Abstracts

International Academy of Cardiology
Annual Scientific Sessions 2017
22nd World Congress on Heart Disease

Vancouver, BC, Canada, July 14–16, 2017

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ABSTRACTS PRESENTED AT THE
INTERNATIONAL ACADEMY OF CARDIOLOGY
ANNUAL SCIENTIFIC SESSIONS 2017
22nd WORLD CONGRESS ON HEART DISEASE

Each abstract was graded by at least seven expert reviewers. Acceptance for presentation was based on the average score of all reviewers. A large number of excellent contributions were received and we thank both contributors and reviewers for their support, interest and effort.

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Chairman

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A BRIEF HISTORY OF THE DEVELOPMENT OF MECHANICAL CIRCULATORY SUPPORT (MCS)

F.A. Arabia
Cedars-Sinai Heart Institute, Los Angeles, CA, USA

**Background:** Congestive Heart Failure (CHF) affects about 5.7 million adults in the U.S. In 2009, 1 out of 9 deaths included CHF as a contributing cause. Approximately 50 years ago, the theoretical management was an artificial heart (TAH). Heart Transplantation became a reality 40 years ago. It currently provides the best therapy for patients with end-stage CHF, however the supply of human donor hearts remains challenging. Medical management has improved but is not sufficient for the deathly ill patient. Ventricular assist devices (VAD) and TAH have continued to evolve and now there is significant experience with the technology. The aim of this study is to examine the development of the technology and how it will influence future devices.

**Methods:** Key scientific manuscripts regarding VAD and TAH outcomes over the past 50 years were reviewed as well as data analysis provided by Intermacs (National MCS Registry). There are over 15,000 devices reported in Intermacs, including outcomes and adverse events (AE) for FDA approved devices.

**Results:** The majority of patients who received a left VAD are usually Intermacs Patient Profile 2 and 3 (IPP). While patients who received a TAH are primarily IPP 1 and 2, a sicker population. The 1-year survival with continuous flow VAD is approximately 80%, for the TAH it ranges 56 – 70%. Approximately 70% of patients who received a VAD or TAH have a readmission during the first year as a result of an AE.

**Conclusions:** MCS technology has made advances to either assist or replace the failing heart. Better understanding of AE will improve patient outcomes and acceptance. Currently there are at least 3 more VAD and 4 more TAH in different stages of development. The evolution of this technology can make a significant impact in the management of advanced CHF.
STEPS FORWARD IN THE MANAGEMENT OF ADVANCED HEART FAILURE

002

IMPROVING QUALITY OF LIFE IN PATIENTS WITH CHRONIC HEART FAILURE:
OVERCOMING EXERCISE INTOLERANCE

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Heart failure (HF) is characterized by poor survival and poor quality of life (QOL); the latter reflected by “exercise intolerance”. Over the past 3 decades, considerable research efforts and treasure were expended toward understanding the pathophysiology of HF and toward the development of new drugs and devices for its treatment. These efforts paid dividends in terms of improved survival but did little to improve QOL. Over the years, most attempts to establish a direct correlation between cardiac function and exercise intolerance in HF failed suggesting a source, other than cardiac output, may be responsible for this maladaptation. These findings were substantiated by an observed lack of appreciable improvement in exercise tolerance in CHF patients who benefited from drugs that extended survival. In recent years, focused research identified abnormalities of skeletal muscle (SM) in patients with HF as potential causes of exercise intolerance. These abnormalities include 1) a reduction in the number of aerobic Type-I, slow-twitch, fatigue-resistant fibers; 2) an increase in the number of glycolytic Type-II, fast-twitch, fibers; 3) functional abnormalities of SM mitochondria (MITO) and 4) a reduced ability of SM MITO to generate ATP commensurate with the demands of working SM. Interestingly, these abnormalities are present in HF despite appropriate SM blood perfusion, normal SM capillary density and SM fiber size. Recent studies in animals with HF showed that elamipretide (ELAM), a mitochondria-targeting peptide, can normalize SM fiber type distribution along with SM MITO abnormalities and maximum rate of ATP synthesis. ELAM also improved SM response to exercise in elderly humans with MITO dysfunction. In a Phase-IIa clinical trial, ELAM improved exercise tolerance in patients with genetic MITO diseases manifesting SM myopathies. These findings, viewed cumulatively, auger well for the use of novel, MITO-targeting drugs, to overcome exercise intolerance and improve overall QOL in patients with chronic HF.
003
ROLE OF ISOLATED ULTRAFILTRATION IN THE MANAGEMENT OF CHRONIC REFRACTORY AND ACUTE DECOMPENSATED HEART FAILURE
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Chronic congestive heart failure (CHF) and acute decompensated heart failure (ADHF) refractory to medical therapy represent therapeutic challenges. In such patients, attempts to reduce pulmonary and systemic congestion frequently produce deterioration of renal function. In studies of patients with chronic severe CHF refractory to medical therapy (including loop diuretics), isolated ultrafiltration was frequently able to relieve congestive symptoms by precise removal of extracellular water and sodium, and in some cases was able to restore responsiveness to loop diuretics. Randomized controlled trials comparing isolated ultrafiltration and medical therapy (mainly loop diuretics) in patients with ADHF failed to demonstrate the superiority of isolated ultrafiltration over diuretic therapy with respect to renal function and mortality. Isolated ultrafiltration reduced length of hospital stay in several studies. At this time, there is insufficient evidence to support the use of isolated ultrafiltration as initial therapy of ADHF.
STEPS FORWARD IN THE MANAGEMENT OF ADVANCED HEART FAILURE

004
TEMPORARY MECHANICAL SUPPORT FOR THE RIGHT VENTRICLE: PRE-IMPLANT PATIENT SELECTION, DEVICE RECIPIENT SURVEILLANCE AND WEANING OF PATIENTS FROM THE SUPPORT SYSTEM

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Because right ventricular failure (RVF) is more likely reversible during short-term mechanical support than left ventricular failure (LVF), temporary RV assist-devices (RVADs) have emerged as a valid therapy for life-threatening RVF. Etiopathogenetically, RVF can be divided into primary (intrinsic) RVF (due to myocardial alterations affecting either the RV alone or both ventricles) and secondary RVF due to excessive pressure and/or volume overloading, which is the leading cause of RVF. Life-threatening congestive heart failure due to primary impaired LV function is the most common indication for RVAD implantation and considerable effort is currently being undertaken to predict, avoid and manage RVF after LVAD implantation. The decision for or against an additional short- or long-term RVAD is challenging and involves echocardiographic, hemodynamic, biochemical and clinical criteria. Preoperative prediction of RV recovery during LVAD support is paramount because both unnecessary RVAD implantation and delayed RVAD implantation increase the postoperative morbidity and mortality of LVAD recipients. Careful pre-operative RV evaluation aiming to distinguish reversible from irreversible RV alterations can spare many patients unnecessary implantation of a permanent biventricular assist-device (BVAD). For decision-making between LVAD, LVAD plus temporary RVAD or long-term BVAD it is more reliable to use both complex quantitative scoring-systems which incorporate measures of different risk factors for post-LVAD RVF and composite variables which include RV geometry, function and load.

Currently there are both surgical and percutaneous options for temporary mechanical support of the RV. Continuous flow RVADs that use percutaneous insertion or cannulation are particularly useful for temporary support in patients for cardiogenic shock as bridge to recovery or bridge to decision. In patients with RV improvement after ≥72 hours of full support and RV stability after gradual reduction of RVAD flow, echocardiography and right-heart catheterization data obtained during “off-pump” trials under adequate anticoagulation, allow decision making in favour of or against RVAD removal.
STEPS FORWARD IN THE MANAGEMENT OF ADVANCED HEART FAILURE

005
DO NEW STUDIES/DEVICES TIP THE BALANCE TO EARLIER LVAD IMPLANTATION?
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The rapidly advancing field of left ventricular assist device (LVAD) use engenders hope that patients with less advanced heart failure might benefit from LVAD implantation. Recent studies provide insight as to whether new management strategies or new devices should change our thinking about how ill a patient needs to be to justify proceeding to an LVAD. The PREVENT trial evaluated whether structured clinical practice (including implant technique, anticoagulation strategy, and pump speed) could improve HeartMate II outcomes. Adopting all proposed management strategies decreased pump thrombosis (from 8.9% to 1.9%, p<0.01) at 6 months. The MOMENTUM 3 Trial showed that the HeartMate III pump reduced reoperations for pump malfunction compared to the HeartMate II device (0.7% vs 7.7%, p=0.002) and no patient with the HeartMate III had suspected or confirmed pump thrombosis. In the ENDURANCE trial of the HeartWare vs HeartMate II LVAD, the HeartWare LVAD was non-inferior to the HeartMate II regarding survival free from disabling stroke or device removal for malfunction/failure. Although the HeartWare patients had a higher risk of stroke, particularly hemorrhagic stroke, this risk was decreased in patients in whom mean arterial blood pressure was 90 mm Hg or lower. Unfortunately, none of the studies showed improvement in gastrointestinal bleeding, right heart failure, or infection, common reasons for readmission following LVAD implantation. The cost-effectiveness of LVADs also needs to be considered. An analysis of Medicare beneficiaries showed that implanting LVADs in less sick, non-inotrope-dependent patients had an unfavorable cost-effectiveness, which could be improved if post LVAD readmission rates decreased. Thus, although the LVAD pumps have improved with fewer pump failures, to justify the use of LVADs in less sick patients, complication rates and the need for hospitalization to deal with complications must decrease.
STEPS FORWARD IN THE MANAGEMENT OF ADVANCED HEART FAILURE

006

VADS IN THE ELDERLY: A VIABLE OPTION

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Objectives: To assess the utility of permanent left ventricular assist devices (LVADS) in patients aged > 80 years.

Background: The gold standard for advanced heart failure is still cardiac transplantation. However with ongoing donor organ shortage LVADS have risen to prominence as bridge to transplantation and as destination therapy. The evolution of mechanical circulatory support systems has increased the possibility of extension of life of the native heart for long periods of time with survival times almost comparable with transplants in the first year. It remains unclear if the survival patterns seen overall would extend to the older populations especially greater than 80 years of age. This work is a systematic review of the morbidity and mortality of mechanical heart therapy in this special population.

Methods: Medline/Google scholar and Cochrane database article search was conducted for the period 2000 and 2016.

Results: The small number of patients in this special group is a limitation but suggests the importance of patient selection, family support and perioperative care in this group particularly to achieve comparable survival rates as seen in the younger populations.

Conclusion: Mechanical support can be successful in older populations if patients are well selected and have adequate family support through their journey with a LVAD.
SODIUM RESTRICTION IN CHRONIC HEART FAILURE: TAKE IT WITH A PINCH OF SALT?
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Background: Sodium restriction is generally recommended in patients with chronic compensated heart failure. However, level of evidence supporting such recommendation is rather weak.

Methods: We will provide a narrated review of the literature addressing sodium restriction in chronic heart failure.

Results: Neurohormonal and hemodynamic studies suggest that sodium restriction may lead adverse changes in neurohormonal and hemodynamic milieu that have been associated with worsening heart failure outcome. Although some observational data suggest that sodium restriction is associated with better outcome, other data suggest the contrary. Small trials from a single center indicate that sodium restriction is associated with worse heart failure outcomes. A recent propensity score matched study of prospective multi-center data of patients with class II and III chronic heart failure suggest that sodium restriction is associated with increased incidence of death or heart failure hospitalization. To date, there are no published high quality, multi-center clinical trials addressing sodium restriction in chronic heart failure. There is one ongoing trial.

Conclusions: Data addressing sodium restriction in patients with chronic heart failure are highly conflicted. A recommendation for sodium restriction in chronic heart failure is not supported by the literature. High-quality multicenter trials dedicated to addressing this important question are sorely needed.
Improving Cardiac Function in Pulmonary Arterial Hypertension: Is There a Role for Exercise Training?

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Exercise training (ET) has preventive and therapeutic effects in several chronic diseases but only recently it started to be recognized as safe and beneficial in pulmonary arterial hypertension (PAH). In fact, PAH treatment guidelines used to advise against physical activity as it could aggravate the disease progression and increase the risk of sudden cardiac death. However, accumulating evidence is showing a positive effect of supervised ET in functional capacity and quality of life, when added to the best standard of care with approved medications, paralleled by a low rate of major adverse events, such right heart failure, mortality and worsening of the disease. Consequently, current guidelines now recommend that PAH patients should be encouraged to be active within symptom limits and, when physically deconditioned, they should undertake supervised ET under medical therapy. Despite consensus in the literature regarding the favorable effects of ET in PAH, the mechanisms underlying these clinical improvements remain to be defined. Existing evidence points for adaptations at the level of skeletal muscle but the impact of ET on right ventricular (RV) function and remodeling cannot be discarded. This would be of great clinical importance as survival is closely related to RV performance. Clinical data is very scarce but there is one pilot study showing increased stroke volume and ejection fraction and one clinical trial showing improvements of cardiac index after a training program, suggesting that ET may indeed improve RV function. Several pre-clinical studies corroborate this impact of ET on cardiac function and show additional improvements in markers of cardiac remodeling, neurohumoral activation, metabolism, oxidative stress and inflammation. While it is tempting to suggest that ET may have a favorable hemodynamic effect in PAH, we still need large multicentre trials, specifically designed to evaluate cardiac function and remodeling, before any final conclusion can be made.
OCT-GUIDED VS IVUS-GUIDED PCI
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Background: Optical frequency domain imaging (OFDI) is a recently developed, light-based, high-resolution intravascular imaging technique. Intravascular ultrasound (IVUS) is a widely used, conventional imaging technique for guiding percutaneous coronary intervention (PCI).

Objectives: We aimed to demonstrate the non-inferiority of OFDI-guided PCI compared with IVUS-guided PCI in terms of clinical outcomes.

Methods: We did a prospective, multicenter, randomized, open-label, parallel group, active-controlled, non-inferiority study to compare head-to-head OFDI versus IVUS in patients undergoing PCI with a second generation drug-eluting stent. Eligible patients from 42 medical centers were enrolled and randomly allocated (ratio 1:1) to receive either OFDI-guided PCI or IVUS-guided PCI. Randomization was performed by a web-based allocation system and was stratified by age, presence of diabetes mellitus, and participating medical centre. The primary endpoint was target vessel failure defined as a composite of cardiac death, target-vessel related myocardial infarction, and ischemia-driven target vessel revascularization until 12 months after the PCI. Primary analysis was based on per-protocol set (non-inferiority margin of 0.07 with a corresponding hazard ratio of 1.85).

Results: Between June 10, 2013, and July 1, 2014, we randomly allocated 829 patients to receive OFDI-guided PCI (n=414) or IVUS-guided PCI (n=415); 791 (95.4%) patients comprised the per-protocol set (OFDI-guided PCI [n=401] and IVUS-guided PCI [n=390]). Target vessel failure occurred in 21 (5.2%) of 401 patients undergoing OFDI-guided PCI, and 19 (4.9%) of 390 patients undergoing IVUS-guided PCI, demonstrating non-inferiority of OFDI-guided PCI to IVUS-guided PCI (hazard ratio 1.07, upper limit of one-sided 95% confidence interval 1.80; p non-inferiority=0.042).

Conclusions: The 12-month clinical outcome in patients undergoing OFDI-guided PCI was non-inferior to that in patients undergoing IVUS-guided PCI. Both OFDI-guided and IVUS-guided PCI yielded an excellent 12-month clinical outcome, with a very low rate of target vessel failure.
INSIGHTS FROM MULTIMODALITY CARDIOVASCULAR IMAGING

010
THE COMPLEMENTARY ROLE OF ANATOMY AND PHYSIOLOGY IN PREDICTING PATIENT OUTCOME: WHERE DO CARDIAC CT AND STRESS MYOCARDIAL PERFUSION IMAGING FIT?

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There has been intense interest regarding the independent and complementary role of anatomic and functional information for predicting patients at risk for cardiac events across the spectrum of coronary atherosclerosis. Stress myocardial perfusion imaging (MPI) remains an important modality for predicting outcome in patients with known and suspected coronary artery disease (CAD) and is applicable to patients with acute chest pain and also in patients with stable chest pain symptoms, and those with known CAD and prior myocardial infarction. Stress MPI combines the presence and extent of myocardial hypoperfusion with extent ischemia and LV functional parameters to successfully define high and low risk groups. Cardiac computed tomography (CT) is useful when performed as a non-contrast and contrast study. Coronary artery calcium score (CACS) predicts outcome but may also determine who requires more aggressive risk factor modification and who might benefit from functional imaging. CT coronary angiography defines the presence and extent of stenosis as well as features such as positive remodeling and low attenuation plaque (a surrogate for a necrotic core). Studies show complementary benefit for predicting risk by utilizing these additional anatomic parameters. Akin to stress MPI, fractional flow reserve (FFR) can assess the functional significance of anatomic stenosis. FFR by CT correlates well with values obtained with invasive coronary angiography. Which test should be utilized in the first line evaluation of symptomatic patients remains unclear based on the recent PROMISE Trial results. The ongoing ISCHEMIA trial should offer new insight regarding the value of functional testing in guiding therapeutics. In addition, the CREDENCE trial which is comparing CT anatomy/FFR results with those of stress MPI may clarify which testing strategy best determines the presence of ischemia using a gold standard of FFR results in the catheterization laboratory.
INSIGHTS FROM MULTIMODALITY CARDIOVASCULAR IMAGING

011
EVALUATION OF CORONARY ARTERY DISEASE IN OBESE PATIENTS. THE ROLE OF NON-INVASIVE CARDIAC IMAGING

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The risk of coronary artery disease (CAD) and subsequent morbidity is increased in obese patients. Furthermore, obesity may mimic or mask manifestation of cardiovascular disease. Evaluation of CAD in obese patients is difficult due to limited value of history and clinical examination, the presence of EKG abnormalities, sleep apnea, left ventricular hypertrophy, poor exercise tolerance and imaging artifacts. Cardiovascular imaging is a vital modality to assess risk in these patients. Available modalities include transthoracic and transesophageal stress echocardiography, myocardial perfusion imaging including PET, Dobutamine MRI and CT angiography. Echocardiography is widely available and does not have weight or torso table limitation of other techniques. PET and MRI imaging provide excellent imaging quality. Increased frequency of artifacts may lead to decreased specificity, repeat testing and unneeded catheterizations. A careful understanding of the advantages and limitations of each imaging technique allows for better resource allocation. More prospective studies are needed to define the merits of these imaging modalities in obese patients.
INSIGHTS FROM MULTIMODALITY CARDIOVASCULAR IMAGING

012

Na\(^+\)-H\(^+\) EXCHANGER 1 DETERMINES ATHEROSCLEROTIC LESION ACIDIFICATION AND PROMOTES ATHEROGENESIS

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The pH in atherosclerotic lesions varies between individuals. Immunoglobulin E (IgE) activates the macrophage Na\(^+\)-H\(^+\) exchanger (Nhe1), acidifies the extracellular milieu, and induces cell apoptosis. The pH-sensitive pHrodo probe identifies acidic regions in human and murine atherosclerotic lesions that colocalize with macrophages, IgE, and cell apoptosis. In apolipoprotein E (ApoE)-deficient mice, inactivation of Nhe1 reduces atherosclerotic lesion size, inflammation, tissue remodeling, and apoptosis. Nhe1 inactivation also blocks lesion acidification in regions rich in macrophages, IgE, and apoptosis. Intravenous administration of a near-infrared (NIR) fluorescent pH-sensitive probe LS662, followed by coregistered fluorescent molecular tomography-computed tomography (FMT-CT) imaging allows detection of acidic regions in atherosclerotic lesions in live mice and isolated thoracic-abdominal aortas. Lesions from Nhe1-inactivated mice have diminished acidity detected by pH-sensitive NIR fluorescence. Ex vivo pHrodo detection and immunohistochemical analysis following FMT-CT imaging establishes the colocalization of acidic regions with areas of macrophage accumulation, IgE expression, and apoptosis in atherosclerotic lesions. This study tests the role of Nhe1 in reducing atherosclerotic lesion pH and in promoting atherogenesis, and proposes a non-invasive and radiation-free imaging approach to localize and monitor the atherosclerotic lesions in live subjects.
INTEGRATED APPROACH TO INTRAVASCULAR IMAGING- CURRENT AND NOVEL TECHNIQUES
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Intravascular imaging is an important tool to guide diagnosis and coronary interventions. These primarily include technologies that are integrated into a catheter delivery system and acquire images of intravascular structures. The more commonly used intravascular imaging solutions are Intravascular Ultrasound (IVUS) that uses ultrasound energy and Optical Coherence Tomography (OCT) that uses infrared energy for image acquisitions. These techniques of imaging delineate anatomical details of the intravascular structures. IVUS has the advantage of more depth of imaging and its ease of use, as opposed to OCT with better image resolution and speed of acquisition. Continuous refinement in these two technologies have allowed both IVUS and OCT to remain in the market as the primary intravascular imaging modalities, often complimenting each other. Most of the therapeutic strategies are based on anatomical, physiological and pathological characteristics of plaque and its effect on blood flow. Hence, any other technology that can provide additional information on physiology of blood flow and pathological characteristics of the plaque would add tremendous value to the currently available techniques of imaging as IVUS and OCT. This has led to development of various technologies that can be integrated with IVUS and OCT that would provide additional information on chemical and cellular characteristics of the plaque as well as other intravascular structures. Near Infrared Spectroscopy, Intravascular Acoustic Imaging, Intravascular Ultrasound Elastography, Time Resolved Fluorescent Spectroscopy, and Fluorescent Lifetime Imaging are various new technologies that can supplement traditional imaging modalities like IVUS and OCT for better delineation of chemical and cellular structure of intravascular structures.
Coronary computed tomography angiography (CCTA) is a non-invasive imaging test to evaluate the burden of coronary artery disease (CAD) and has a high diagnostic accuracy in excluding obstructive CAD in low to intermediate risk patients. However, this test does not determine the functional significance of the lesions identified and remains a fundamental weakness of this test. Less than half of the obstructive lesions identified by CCTA have functional ischemia upon evaluation by invasive coronary angiography (ICA). This therefore may lead to unnecessary ICA and or percutaneous coronary intervention (PCI) in lesions that may not be functionally significant. More recent studies have demonstrated that fractional flow reserve (FFR) is estimable from the CCTA study using novel iteration techniques and can determine the functional significance of coronary stenotic lesions. The CT guided FFR (CTFFR) approach utilizes application of computational fluid dynamics to CCTA images to determine the functional severity of the lesions. CTFFR estimates virtual hyperemia across a lesion by using computational flow modeling without the need for vasodilator agents. Several studies have reported feasibility and diagnostic performance of CTFFR. A meta-analysis to compare the diagnostic performance of CTFFR in comparison to the gold standard FFR observed that the CTFFR performed very well compared to the FFR in diagnosing functional significance of coronary stenosis and more importantly affords a very high negative predictive value. However, the studies did not report outcomes data and therefore it is unclear now if CTFFR strategy can be used to decide about deferred versus immediate revascularization. But it is clear from the results of analysis that CTFFR offers more information than the traditional CCTA alone.
INSIGHTS FROM MULTIMODALITY CARDIOVASCULAR IMAGING

015
DETERMINATION OF OPTIMAL VIEWING ANGLES FOR X-RAY CORONARY ANGIOGRAPHY BASED ON A QUANTITATIVE ANALYSIS OF 3D RECONSTRUCTED MODELS
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Background: Coronary angiography uses expert-recommended viewing angles which is limited by patient variability in vessel foreshortening and overlap. Via 3-D coronary modeling, we propose that a scientifically designed, population-based universal optimal view map (UOVM) may be generated which minimizes these shortcomings. This UOVM would provide quantitatively valid viewing angles for all first and second order coronary arterial segments.

Methods: We analyzed 137 angiograms and created 3D models of each coronary tree which allowed quantitative assessment of vessel foreshortening and generation of patient-specific optimal view maps. From this data, a universal optimal viewing map (UOVM) (Mid-circumflex Fig.) was generated. This permitted a quantitative comparison between traditional and UOVM-derived viewing angles.

Results: In all major vessel segments, the traditional viewing angles provided 17% vessel foreshortening and 13% overlap, while the UOVM provided 5.6% foreshortening and 6.4% overlap, a 60% reduction in foreshortening (P<.05) and a 31% reduction (p=NS) in overlap.

Conclusions: 1) This study demonstrates a scientifically-based method of obtaining optimal view angles 2) UOVM use decreases vessel foreshortening and overlap, i.e facilitating the acquisition of better images with less contrast and radiation. 3) The UOVM permits the design of single injection trajectories for each coronary tree using dual-axis rotational angiography.
Mitral regurgitation (MR), either acute or chronic, can be due to valvular pathology or the supporting apparatus or ventricular pathology. Currently, echocardiography is used in most cases to determine the etiology and severity of MR. Although, semi-quantitative method such as two dimensional color flow jet area is still used for MR assessment, it is less reliable when compared to other quantitative methods integrated with all the available semi-quantitative information. Shape and density of the mitral regurgitation continuous wave Doppler jet signal, mitral and pulmonary vein inflow pattern, size of the left atrium and left ventricle, integrity of the mitral leaflets or the supporting structures when used in conjunction with additional parameters such as width of the vena contracta, regurgitant volume and effective regurgitant orifice area will vastly improve the assessment of MR.

Two dimensional quantitative methods such as continuity method and Proximal Isovelocity Surface Area (PISA) method are clinically more useful given their ability to more precisely determine the MR severity. Specifically, one can precisely estimate the mitral regurgitation volume and effective regurgitant orifice area. When MR volume exceeds 60 mls and effective regurgitant orifice area exceeds 0.4 cm², one is considered to have severe MR based on American society of echocardiography and American college of cardiology guidelines.

Three dimensional (3D) echocardiography now make it possible to not only visualize the mitral valve anatomy better but also measure the vena contracta area and proximal isovelocity surface area without the need for geometric assumptions. Recent studies demonstrated that vena contracta area measurement and 3D PISA measurement using 3D color Doppler echocardiography improved quantitation of MR when compared to 2D dimensional methods or conventional echo-Doppler methods when magnetic resonance imaging was used as gold standard.
Background: Echocardiographic assessment of right ventricular (RV) systolic function is limited by the complex geometric shape of the right ventricle. Reliance on conventional longitudinal measures of RV systolic function (tricuspid annular plane systolic excursion (TAPSE), systolic tissue velocity (S’)) may lead to inaccurate assessment of global RV systolic function. The incremental benefit of RV strain in the assessment of RV systolic function is unclear.

Aims: We investigated whether focused reading sessions would improve correlation of echocardiographic assessment of RV systolic function with right ventricular ejection fraction (RVEF), as quantified by cardiac magnetic resonance imaging (CMR). We also assessed whether incorporating RV strain would incrementally improve echocardiographic assessment of RV systolic function.

Methods: 20 echocardiography readers (7 echocardiologists, 5 fellows, 8 technologists) evaluated 19 randomly selected cases. During the first reading session, standard RV views (parasternal long-axis, parasternal short-axis, apical four-chamber, dedicated RV apical view, subcostal), TAPSE and S’ were shown. The readers categorized RV systolic function into normal, mild, moderate or severe dysfunction. Three weeks later, the readers assessed the same cases again, with the addition of RV global and free wall strain parameters.

Results: RVEF by CMR: 21% to 62% (normal: n=6; mild dysfunction: n=8; moderate dysfunction: n=3; severe dysfunction: n=2). TAPSE: 9 to 32 mm. S’: 5 to 16 cm/second. RV global and free wall strains: -24.5 to -7.7%, and -31.7% to -9.7%, respectively. The original reported grades of RV systolic function: normal (n=15); mild dysfunction (n=2); moderate dysfunction: (n=2); severe dysfunction: (n=0). Correlation of initial grades of RV systolic function with CMR RVEF by Spearman’s rho: -0.59. Following the first focused reading session, correlation with RVEF by Spearman’s rho: -0.67 ± 0.19 (p=0.04). Following the second focused reading session, correlation with RVEF by Spearman’s rho: -0.61 ± 0.10 (p>0.05).

Conclusion: Reading sessions focused on the right ventricle improved correlation of echocardiographic assessment of RV systolic function with RVEF by CMR. Routine incorporation of right ventricular strain parameters did not improve correlation with RVEF by CMR further.
EVIDENCE-BASED USE OF HANDHELD ULTRASOUND IN CLINICAL CARDIOLOGY

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Background: Ultrasound technology is central to diagnosis, treatment, management, and prognosis in the field of clinical cardiology. Applications of cardiovascular ultrasound and vascular ultrasound have long been used as the established standard of care.

Hypothesis: Future uses and expanded applications of the use of current ultrasound technologies are imminent in the field of clinical cardiology.

Current evidence-based uses of handheld ultrasound: The following areas have been demonstrated as evidence-based uses of handheld ultrasound in clinical cardiology:
1. Diagnosis of severe cardiac abnormalities. 2. Diagnosis of pericardial and pleural fluid collections. 3. Prognosis in cardiac arrest patients. 4. Prognosis in outpatient congestive heart failure patients.

Anticipated evidence-based uses: Future incorporations of handheld ultrasound technology are inevitable given the quality and timing of data acquisition – at the point-of-care. As the technology becomes more accessible and it is more incorporated into day to day use and patient care workflows, I anticipate further evidence-based uses in the diagnosis and prognosis of cardiovascular diseases. Since ultrasound gives dynamic imaging data that can be influenced by changes in physiology and treatment, I anticipate future science to discover uses for handheld ultrasound in acute and chronic cardiovascular disease management as well as finding additional prognostic usefulness.
NEW MOLECULAR TARGETS OF VEGF SIGNALING IN CARDIOVASCULAR DISEASE

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Therapeutic angiogenesis is a promising approach to the treatment of ischemic injury. Angiogenesis is a global highlight in the medical field. Many angiogenesis related factors are involved in the development of vessels, in response to physiological or pathological stimuli. VEGF modulates the complex process of angiogenesis and other various aspects of endothelial cell function through either of its two tyrosine kinase receptors, VEGFR1/Flt-1 or VEGFR2/Flk1/KDR via its target protein MAPKinase 2. VEGF mediated angiogenesis signaling is widely accepted however relatively little is known regarding VEGF mediated downstream signaling through Flt-1 and/or Flk-1. The use of Affymetrix gene chip technology in Flk-1+/− knockout (KO) mice allowed us first time to identify several target genes in ischemic preconditioned myocardium. By chip analysis we demonstrated first time down regulation of Pellino-1(Peli1) after ischemic insult to the Flk-1+/− KO mice. Our study showed that overexpression of Peli1 by adeno-Peli1 gene therapy (Ad-Peli1) significantly increased angiogenic effect, increased ejection fraction and reduces ventricular remodeling in myocardial infarction (MI) model. Western blot analysis 24 h after MI revealed increased phosphorylation of Akt, eNOS and MAP Kinase 2 with Ad-Peli1 treatment compared to Ad-LacZ. Immunohistochemical analysis with picrosirius red staining exhibited a decrease in collagen deposition in Ad-Peli1MI group as compared to Ad-LacZMI. Vascular density and connexin-43, a major ventricular gap junction protein was found to be increased in Ad-Peli1MI group compared to Ad-LacZMI. Collectively, our study documents Peli1 as a promising molecule in the treatment of myocardial infarction, which could potentially lead to new therapeutic target.
CELLULAR AND MOLECULAR BIOLOGY TARGETS FOR CLINICAL CARE IN CARDIOVASCULAR DISEASE

020
IMMUNE CELL ALTERATIONS IN HEART FAILURE
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Inappropriately sustained inflammation is a hallmark of chronic ischemic heart failure (HF). Anti-inflammatory strategies, thus far unsuccessful, have focused on the neutralization of pro-inflammatory cytokines, whose levels are influenced by immune cells. Nonetheless, the pathophysiological roles of innate and adaptive immune cells in HF are poorly understood. Our work in mice with chronic HF after coronary ligation has demonstrated that HF is characterized by cardiac and systemic expansion of pro-inflammatory monocytes/macrophages, classical and plasmacytoid dendritic cells, and both CD4+ helper (Th) and CD8+ cytotoxic T-cells. Moreover, we observed profound splenic remodeling in HF with augmentation of the marginal zone and germinal centers, increased expression of alarmins, and expanded antigen-experienced effector and memory CD4+ T cells (among other cell populations). Importantly, the adoptive transfer of unselected mononuclear splenocytes, or splenic CD4+ T-cells, from mice with HF, but not from sham-operated mice, induced long-term LV dilatation, dysfunction, and fibrosis in naive recipients. Naïve mice receiving unselected HF splenocytes also exhibited monocyte activation and splenic remodeling similar to HF mice. Antibody-mediated CD4+ T-cell depletion in HF mice reduced cardiac infiltration of CD4+ T-cells and prevented progressive LV dilatation and hypertrophy. We have also recently shown that chimeric mice with genetic loss of inducible nitric oxide synthase in leukocytes (a key pro-inflammatory gene in M1 macrophages) exhibited improved survival and LV function, and less hypertrophy, fibrosis, oxidant stress, and inflammatory activation than control mice. Hence we propose that ischemic cardiomyopathy is in large part as an immune-mediated disease, activated against as-of-yet unidentified cardiac antigens, and that such immune activation is indispensable for long-term adverse remodeling. These results imply that targeting specific immune cell populations may represent a more fruitful therapeutic immunomodulatory strategy in chronic ischemic HF.
ANGIOGRAPHIC CONTRAST-INDUCED VASCULAR AND RENAL TOXICITY – A NANOMEDICAL APPROACH

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Background: Use of contrast media (CM) in angiography creates a paradoxical dilemma. Adsorption of CM molecules on endothelial cells is necessary to produce an x-ray image of the vasculature, but the adsorption process itself may contribute to cell dysfunction and serious vascular and renal damage. The molecular mechanism of CM induced toxicity is unknown. We hypothesized that CM toxicity can be due to an induced dysfunction of endothelial nitric oxide synthase (eNOS), low levels of cytoprotective NO and high levels of cytotoxic O2- and ONOO-

Methods and Results: A nanomedical approach, utilizing nanosensors (diameter of 150-250nm), was used to monitor the collision/adsorption of contrast molecules (iodixanol and iohexol) with cells and to measure the concentrations of NO, O2-, and ONOO-. Measurements were made at different concentrations of CM and at different incubation times with cellular models of different diseases: diabetes, hypertension and hypercholesterolemia. A ratio of concentrations [NO]/[ONOO-] was used to indicate the level of nitroxidative stress. Initially, the collision/adsorption of CM stimulated NO and ONOO-, peaking at about 400nM NO and 170nM ONOO- and a [NO]/[ONOO-] ratio of about 2.5. The maximal capacity of NO production decreased and ONOO- increased rapidly with time and [NO]/[ONOO-] reached about 0.8 after 2 hours. The decrease in [NO]/[ONOO-] directly correlates with increased incubation time, eNOS uncoupling, dysfunctional endothelium and CM concentration. An elevated glucose, angiotensin II or LDL decreased the [NO]/[ONOO-] ratio. This effect was additive to that observed for CM alone.

Conclusions: CM can hinder cytoprotective NO and increase cytotoxic O2- and ONOO-. It may also diminish the overall function of the vascular and renal system. The negative effect of CM increased in diabetes, hypertension and hypercholesterolemia, but can be mollified by preserving/restoring eNOS function with antioxidants or scavengers of ONOO- and O2- and/or increasing bioavailable NO.
022

VASCULOPROTECTIVE ROLE OF Natriuretic Peptide RECEPTOR C

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VSMC from spontaneously hypertensive rats (SHR) exhibit enhanced proliferation and hypertrophy. We earlier showed that small peptide fragments of cytoplasmic domain of natriuretic receptor-C (NPR-C) attenuate vasoactive peptide-induced hyperproliferation and hypertrophy of VSMC, the key players of vascular remodeling. We undertook the studies to investigate if a specific agonist of NPR-C, C-ANP4-23, could attenuate the VSMC hypertrophy, hyperproliferation as well as hypertension in SHR, and examine the underlying signaling pathways contributing to this inhibition. C-ANP4-23 treatment of SHR attenuated the development of hypertension as well as hyperproliferation of aortic VSMC to control levels. In addition, C-ANP4-23 restored the overexpression of cyclin D1, cyclin A, cyclin E, cyclin dependent kinase 2/4, phosphorylated retinoblastoma protein, Gialpha proteins, peroxynitrite and the decreased expression of p21Cip1 and p27Kip1 exhibited by VSMC from SHR. C-ANP4-23 treatment of VSMC from SHR also attenuated the enhanced protein synthesis (hypertrophy) as well as the enhanced expression of Galpha and PLCbeta1 proteins implicated in hypertrophy. Furthermore, the enhanced phosphorylation of ERK1/2, AKT, EGF-R, PDGF-R, IGF-R and c-Src, enhanced levels of superoxide anion, NADPH oxidase activity, and enhanced expression of Nox1, Nox2, Nox4 and P47phox in SHR were all attenuated by C-ANP4–23 treatment. These results indicate that NPR-C activation by C-ANP4-23 attenuates VSMC hypertrophy, hyperproliferation and hypertension, and suggest that NPR-C has a vasculoprotective role and that NPR-C ligand C-ANP4-23 may have the potential to be used as therapeutic agent in the treatment of cardiovascular complications including hypertension and atherosclerosis.

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ROLE OF APELIN/APELIN RECEPTOR AXIS IN HEART DISEASE: THERAPEUTIC ROLE OF APELIN ANALOGUES

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The apelin peptide system is widely distributed throughout the human body and is a critical mediator of cardiovascular homeostasis. Activation of the apelin receptor by its cognate peptide ligand, apelin, induces a wide range of physiological effects, including vasodilation of cardiac contractility, angiogenesis, and regulation of energy metabolism and fluid homeostasis. The apelin/apelin receptor is also implicated in pathologies including atherosclerosis, hypertension, coronary heart disease, heart failure, diabetes, obesity, and cancer, making it a promising therapeutic target. Considering the potential therapeutic effects by modulation of the apelin/apelin receptor system, research is expanding to develop novel therapies that inhibit degradation of endogenous apelin peptides and augment stable agonists and antagonists to more efficiently interfere in the apelin/apelin receptor system. Given the role of apelin/apelin receptor in cardiovascular diseases, an increased understanding of the cardiovascular actions of apelin/apelin receptor system will help to develop novel therapeutic interventions for cardiovascular diseases. The apelin/apelin receptor signaling represent a relatively new therapeutic axis for the potential treatment of cardiovascular disease. Angiotensin converting enzyme 2 (ACE2) and neutral endopeptidase (NEP) are two key proteases which cleaves and inactivates apelin peptides. The ability of NEP inhibition to can explain the therapeutic benefits of the newly approved heart failure therapy, LCZ696 (EntrestoTM), which includes the NEP inhibitor, sacubitril. We have designed and synthesized novel and potent apelin analogues which are resistant to degradation by proteases as potential drugs for cardiovascular diseases.
CELLULAR AND MOLECULAR BIOLOGY TARGETS FOR CLINICAL CARE IN CARDIOVASCULAR DISEASE

024

ENDOTHELIN-1 AND CORONARY VASOMOTOR DYSFUNCTION: ROLE OF P38 KINASE AND NADPH OXIDASE

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Elevated levels of endothelin-1 (ET-1), a potent vasoactive peptide, are implicated as a risk factor for cardiovascular diseases by exerting vasoconstriction. However, it is unclear whether ET-1, without the participation of its vasoconstrictor action, can influence vasodilation elicited by endothelial nitric oxide (NO) in the coronary microvasculature. To address this issue, porcine coronary arterioles (50-100 micron) were isolated, cannulated and pressurized without flow for in vitro study. The arterioles were challenged with a sub-vasomotor concentration of ET-1 (10 pmol/L) and then the endothelium-dependent NO-mediated vasodilators adenosine and serotonin were examined using a videomicroscope. Arterioles developed basal tone (60±3 micron) and dilated to serotonin (1 nM to 100 nM) and adenosine (1 nM to 0.01 mM) in a concentration-dependent manner. Treating the vessels with a clinically relevant sub-vasomotor concentration of ET-1 for 60 minutes significantly attenuated arteriolar dilations to adenosine and serotonin but not to endothelium-independent vasodilator sodium nitroprusside. The arteriolar wall contains ETA receptors and the adverse effect of ET-1 was prevented by ETA receptor antagonist BQ123, the superoxide scavenger Tempol, the NADPH oxidase inhibitors apocynin and VAS2870, the NOX2-based NADPH oxidase inhibitor gp91 ds-tat, or the p38 kinase inhibitor SB203580. However, ETB receptor antagonist BQ788, H2O2 scavenger catalase, scrambled gp91 ds-tat, or inhibitors of xanthine oxidase (allopurinol), PKC (Go6983), Rho kinase (Y27632), and c-Jun N-terminal kinase (SP600125) did not protect the vessel. Immunohistochemical staining showed that ET-1 elicited Tempol-, apocynin- and SB203580-sensitive superoxide production in the arteriolar wall. Our results indicate that exposure of coronary arterioles to a pathophysiological, sub-vasomotor concentration of ET-1 leads to vascular dysfunction by impairing endothelium-dependent NO-mediated dilation via p38 kinase-mediated production of superoxide from NADPH oxidase following ETA receptor activation.
It is well known that beta-adrenergic stimulation is a significant regulatory mechanism in the heart. Beta3 subtype of adrenergic receptors localized also in the human heart may protect the myocardium against adverse effects of excessive catecholamine stimulation. Stimulation of cardiac beta3-adrenoceptors may lead to a decrease in heart contractility. These receptors mediate lipolysis and thermogenesis in the adipose tissue. The action of catecholamines via beta-adrenoceptors is of particular importance under stress conditions. The sympathetic-adrenomedullary system is one of the two main stress systems. The stress-induced epinephrine and norepinephrine release depends on the type and intensity of the stress stimulus as well as on the actual state of the body. The aim of the present study was to test the hypothesis that stress associated with repeated immune challenge has an impact on beta3-adrenergic receptor gene expression in the adipose tissue and in the brain. Sprague-Dawley rats of both sexes were intraperitoneally treated either with vehicle or lipopolysaccharide (LPS) in increasing doses for 5 days (50-200 microg/kg). Two hours after the last injection, the retroperitoneal adipose tissue and selected brain regions were collected. Repeated LPS treatment was associated with body weight loss and increased anxiety-like behavior. LPS treatment decreased beta3-receptor gene expression in the white adipose tissue with higher values in males compared to females. In the adipose tissue, LPS administration reduced peroxisome proliferator-activated receptor gamma, leptin and adiponectin gene expression, but increased interleukin-6 expression, irrespective of sex. In LPS-treated animals of both sexes, beta3-receptor gene expression was increased in the prefrontal cortex but not the hippocampus. In conclusion, the changes in the gene expression of the regulatory factors in the adipose tissue are likely to contribute to the adaptive processes during stress of repeated immune challenge. Supported by APVV-14-0840.
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REPETITIVE TRANSIENT ISCHEMIA-INDUCED CARDIAC ANGIOGENESIS IS MEDIATED BY CAMKII ACTIVATION

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Background: Coronary angiogenesis is an important protective mechanism in response to myocardial ischemia in coronary artery disease. However, the underlying mechanism remains largely unclear. Here, we investigated the role of CaMKII activation in ischemia-induced cardiac angiogenesis.

Methods and Results: Repetitive transient ischemia model was established in C57/BL6 mice by daily multiple episodes (3 times/day) of short time (5 min) occlusion of the left anterior descending artery for 7 days. Coronary angiogenesis was detected by CD31 immunofluorescence staining. We found that coronary angiogenesis was induced in the border zone of ischemia and suppressed by the chronic intraperitoneal injection of CaMKII inhibitor KN93. RT-qPCR and Western blot analyses showed that myocardial ischemia induced an increased expression and autophosphorylation of CaMKII. VEGF expression was increased in the ischemia model and blunted by KN93. Moreover, KN93 suppressed the proliferation and migration of cardiac endothelial cells in hypoxic condition, in which the expression of CaMKII, p-CaMKII and VEGF were remarkably increased.

Conclusions: CaMKII activation is an important mediator for the ischemia-induced coronary angiogenesis, in which CaMKII-triggered VEGF expression plays a key role.
A NOVEL CELL PENETRATING PEPTIDE, CARDIAC TARGETING PEPTIDE APPEARS TO UTILIZE CARDIAC CHANNELS FOR TRANSDUCTION

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Background: Cell penetrating peptides are small peptides able to carry cargo across cellular membranes resulting in internalization of the intact cargo. A combinatorial in vitro and in vivo approach lead to the identification of a 12-amino acid peptide, APWHLSSQYSRT, which we termed Cardiac Targeting Peptide (CTP), because of its ability to transduce the mouse heart tissue specifically and efficiently after an intravenous injection. CTP has the potential to be a novel delivery tool for the heart for both diagnostic and therapeutic purposes. We now present the result of studies undertaken to elucidate CTP’s mechanism of transduction.

Methods and Results: Neonatal mouse hearts were harvested and cardiomyocytes (CMCs) isolated. Mouse embryonic fibroblasts (MEFs) were used as negative controls. CTP was synthesized dually labeled with 6-carboxyfluorescein and Rhodamine, the latter via an ester link, susceptible to cleavage only by intracellular esterases. Hence, internalization and red fluorescence could not result from membrane attachment or fixation artifact alone. Cells were incubated with 25nM of CTP and showed robust transduction of CMCs within 10 minutes, with essentially no uptake by MEFs. This transduction was statistically significantly enhanced by increasing extracellular K+ ion concentration to 20mM (p-value=0.03;Figure), with this enhancement in uptake abrogated both by calcium channel inhibitor Verapamil (Vpml) and Na-K+-ATPase inhibitor Digoxin (Dgxn). Increased CTP uptake secondary to cell death/apoptosis was ruled out by restoring extracellular K+ concentration to normal levels and resumption of CMC contractile function. Rhodamine with cleaved ester link alone was not internalized by CMCs.

Conclusions: CTP rapidly enters CMCs in a cell specific manner. This transduction is enhanced by increasing the Na-K ATPase pump activity by increasing extracellular K+ concentration, implying that CTP is using this ion channel for cell entry. Further studies, perhaps utilizing mass spectroscopy, are needed to identify the specific binding partner of CTP.
PEROXIREDOXIN1 NORMALIZES MACROPHAGE LIPOPHAGIC FLUX IN ATHEROSCLEROSIS

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Oxidative stress activates autophagy and contributes to atherogenesis via lipophagic flux, a form of lipid removal by autophagy. However, it is not known exactly how endogenous anti-oxidant enzymes are involved in lipophagic flux. Here, we demonstrate that the anti-oxidant Peroxiredoxin1 (Prdx1) has a crucial role in the maintenance of lipophagic flux in macrophages. Prdx1 is more highly-expressed than other anti-oxidant enzymes in monocytes and macrophages. We determined that Prdx1 deficiency induced excessive oxidative stress and impaired maintenance of autophagic flux in macrophages. Prdx1-deficient macrophages had higher intracellular cholesterol mass and lower cholesterol efflux compared to wild-type. This perturbation in cholesterol homeostasis was due to impaired lipophagic cholesterol hydrolysis caused by excessive oxidative stress, resulting in the inhibition of free cholesterol formation and the reduction of NXRalpha activity. Notably, impairment of both lipophagic flux and cholesterol efflux was restored by the 2-Cys Prdx-mimics ebselen and gliotoxin. Consistent with this observation, ApoE ko mice transplanted with bone marrow from prdx1/ApoE dko mice had increased plaque formation compared to ApoE ko BM-transplanted recipients. This study reveals that Prdx1 is crucial to regulating lipophagic flux and maintaining macrophage cholesterol homeostasis against oxidative stress. We suggest that Prdx1-dependent control of oxidative stress may provide a strategy for treating atherosclerosis and autophagy-related human diseases.
THE PROTECTIVE EFFECTS OF EICOSAPENTAENOIC ACID ARE TRIGGERED UNUSUAL MECHANISMS OF CA2+ RELEASE AND CA2+ INFLUX IN MOUSE CEREBRAL CORTICAL ENDOTHELIAL CELLS

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Aims: Eicosapentaenoic acid (EPA), an omega-3 fatty acid abundant in fish oil, protects endothelial cells (EC) from lipotoxicity and triggers EC nitric oxide release, has been demonstrated to have beneficial effects in cardiovascular system and brain protection, but the detail molecular mechanism is unclear and how EPC affects EC Ca2+-signaling and other functions remain largely unexplored. In this work, we investigated the effects of EPA on mouse cerebral cortical endothelial cells (bEND.3 cells) as well as the influence of Ca2+ channel and cytosolic Ca2+ level.

Methods: Brain microvascular bEND.3 cells cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin. Cytosolic Ca2+ in bEND was measured with Fura-2 method. Mitochondria membrane potential (MMP) measured by MMP-Assay Kit. Cell viability was measured by MTT-assay. The p < 0.05 were considered significant (ANOVA).

Results: EPA was shown to cause intracellular Ca2+ release in mouse cerebral cortex endothelial bEND.3 cells; the EPA-sensitive intracellular Ca2+ pool(s) appeared to encompass and was larger than the Ca2+ pool mobilized by sarcoplasmic-endoplasmic reticulum Ca2+-ATPase inhibition by cyclopiazonic acid. EPA also opened a Ca2+ influx pathway pharmacologically distinct from store-operated Ca2+ influx. Additionally, EPA-triggered Ca2+ influx was Ni2+-insensitive; and EPA did not trigger Mn2+ influx. Further, EPA-triggered Ca2+ influx did not involve Na+-Ca2+ exchangers.

Conclusion: EPA caused Ca2+ release and Ca2+ Influx via unusual mechanisms in bEND.3 cells. Given the versatile health effects of EPA, it is interesting and important to study the Ca2+ signaling triggered by this fatty acid in EC and other cell types, whose Ca2+ responses to EPA are very different from those in EC.

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NOVEL APPLICATIONS OF CALCIUM CHANNEL BLOCKERS: A NEW INSIGHT TO CARDIAC DRUGS

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Objectives: To Identify that if calcium channel blockers can be considered as novel preventive or therapeutic agents.

Backgrounds: Calcium channel blockers are widely used in the treatment of cardiovascular diseases. Microbial aggregation and biofilm formation are leading causes of infectious complications in patients with indwelling catheters, central venous catheters and artificial cardiac valves. Calcium homeostasis is critical for multiple functions including motility and biofilm formation in bacteria. We report here that swimming motility in pathogenic Escherichia coli and Proteus mirabilis is inhibited by verapamil, a calcium channel blocker. The central hypothesis for this study is that Calcium channel blockers will prevent bacterial motility and biofilm formation.

Methods: First, we tested the effect of various concentrations of verapamil on growth of common bacterial pathogens E. coli, P. mirabilis and Klebsiella pneumoniae. At high doses (≥12 mM) verapamil was able to inhibit growth of these pathogens. Next, we tested the effect of verapamil, at levels that does not affect bacterial growth (3 and 6 mM), on swimming motility in vitro.

Results: Our results revealed that verapamil inhibits flagella-mediated swimming motility in E. coli (strains CFT073 and UTI89) and also in P. mirabilis.

Conclusion: We identified that verapamil decreases motility of tested bacterial pathogens in a dose-dependent manner. We identified for the first time that calcium channel blockers can be considered as novel preventive or therapeutic agents. Further ex vivo and in vivo experiments are necessary to determine if Calcium channel blockers could be repurposed as therapeutics or prophylactic targets.
BETA-BLOCKER THERAPY IN COCAINE USERS WITH HEART FAILURE: INSIGHTS FROM AN URBAN ACADEMIC CENTER

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Background: Beta-blockers are first line agents for reduction of symptoms, hospitalization and mortality in heart failure patients with reduced ejection fraction (HFrEF). The safety and efficacy of continuous beta-blocker therapy (BBT) in patients who use cocaine remain controversial and available literature is limited. We aimed to evaluate clinical outcomes of BBT among HFrEF patients who use cocaine.

Methods: We conducted a retrospective chart review of 90 patients with a diagnosis of heart failure based on ICD9-CM codes and baseline ejection fraction (EF) <40% who tested positive for cocaine on urine toxicology test at the time of index admission. We included patients age 18 or older with at least 3 months of follow up. Baseline EF was obtained from the earliest available echocardiogram report in 2011 and repeat EF was obtained from follow up echocardiogram reports while on BBT. We described baseline patient characteristics, comorbidities and outcomes (change in EF during study period, re-hospitalizations and mortality).

Results: In our study population (mean age = 56.1 ± 7.8 years), the mean baseline EF was 24.1% (std=9.0). The mean overall change in EF among patients on continuous BBT was 1.9% (std=14.6; p-value=0.2) over a mean follow-up time of 15.5 months (std=8.6). Thirty-nine percent (n=35, mean follow up=15.7 months) of our study population had a decrease in EF (mean change= -10.6%; std=6.8), 22% (n=20, mean follow up=17.4 months) had no change in EF and 39% (n=35, mean follow up=14.3 months) had an increase in EF (mean change= +14.3%; std=7.5). There was an average of 3.2(std=3.3) re-hospitalizations. Ninety-two percent (n=83) were alive at the end of the study period.

Conclusion: Continuous beta-blocker therapy in HFrEF patients who abuse cocaine has variable effects on left ventricular EF. Large observational studies are needed to further elucidate the efficacy and safety of long-term beta-blocker therapy in this population.
RELATIONSHIP BETWEEN ABDOMINAL VISCERAL FAT AND BLOOD PRESSURE RESPONSE DURING EXERCISE IN NORMOTENSIVE POPULATION

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Background: Both obesity and altered blood pressure (BP) responses during exercise have been suggested as cardiovascular risk factors. This study aimed to investigate the relationships of abdominal visceral fat with BP response during exercise in normotensive population.

Methods: Between May 2016 and September 2014, total 604 subjects (260 men and 344 women) with resting blood pressure less than 140/90 mmHg and not taking any medications for hypertension were analyzed. Abdominal visceral fat area (AVFA) was measured by using the dual bioelectrical impedance analysis. Exaggerated BP response (EBR) was defined as >200/100 mmHg at peak exercise in treadmill test.

Results: When the study subjects were divided into quartiles according to AVFA (Q1/Q2/Q3/Q4; lowest/low/high/highest AVFA groups), we found a significant association between AVFA and EBR rate in men (EBR rate (Q1) 5.8%, (Q2) 14.7%, (Q3) 17.0%, (Q4) 25.4%, p=.02). Women showed a trend of the association between AVFA and EBR rate in women (EBR rate (Q1) 7.9%, (Q2) 11.4%, (Q3) 17.3%, (Q4) 21.3%, p=.07). In the multivariate models adjusted for clinical variables, the highest AVFA group (Q4) had more than 3-times higher EBR risk (OR 2.9, 95%CI 1.30-6.50, p<.01).

Conclusion: Even in the normotensive healthy population, higher visceral adiposity augmented blood pressure rise on exercise significantly, especially in men.
MITOCHONDRIAL PROTEIN HYPERACETYLA TION IN SKELETAL MUSCLE IS ASSOCIATED WITH EXERCISE INTOLERANCE IN MURINE MODEL OF POST-INFARCT HEART FAILURE

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Background: Exercise intolerance is a major clinical manifestation in heart failure (HF) patients, due largely to skeletal muscle abnormalities. Protein acetylation on lysine residues is a novel post-translational modification that has been recently emerged as an important contributor to regulating energy metabolism in the skeletal muscle. We thus hypothesized that mitochondrial protein acetylation in skeletal muscle could contribute to exercise intolerance and skeletal muscle abnormalities in a murine HF model after myocardial infarction (MI). We also examined the association between plasma N6-acetyl-lysine level and exercise capacity in patients with chronic HF.

Methods and Results: MI was created in male C57BL/6J mice by ligating the left coronary artery (n=7), and a sham operation was performed in other mice (n=7). After 4 weeks, the work and peak oxygen uptake evaluated by treadmill test with expired gas analysis, was significantly reduced in MI mice compared to sham mice. Acetyl-lysine level of mitochondrial fraction assessed by Western blotting was elevated in the skeletal muscle from MI mice. In accordance with these results, activities of citrate synthase and respiratory chain complexes were significantly decreased in mitochondria from the skeletal muscle obtained from MI mice. In addition, metabolomic analysis of plasma sample from human patients with HF and controls were performed using capillary electrophoresis time-of-flight mass spectroscopy, and revealed that plasma N6-acetyl-lysine level was increased in HF patients compared to controls and negatively correlated with peak VO2 measured by cardiopulmonary exercise test.

Conclusions: Mitochondrial protein hyperacetylation is associated with reduced exercise capacity and skeletal muscle abnormalities in HF. These results provide a novel pathophysiological insight into the mechanism regarding exercise intolerance with HF and also plasma N6-acetyl-lysine might be a novel marker for exercise capacity in patients with chronic HF.
RELATION OF N-TERMINAL PRO B-TYPE NATRIURETIC PEPTIDE AND LEFT VENTRICULAR DIASTOLIC FUNCTION TO EXERCISE TOLERANCE IN PATIENTS WITH SIGNIFICANT VALVULAR HEART DISEASE AND NORMAL LEFT VENTRICULAR SYSTOLIC FUNCTION

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Introduction: An association between N-terminal prohormone brain natriuretic peptide (NT-proBNP) and exercise tolerance in patients with valvular heart disease (VHD) has been suggested; however, there are few data available regarding this relationship. To evaluate the correlation between exercise tolerance and NT-proBNP in patients with asymptomatic or mildly symptomatic significant VHD and normal left ventricular ejection fraction (LV EF).

Methods: A total of 96 patients with asymptomatic or mildly symptomatic VHD and normal LV EF (≥50%) underwent cardiopulmonary exercise echocardiography. NT-proBNP levels were determined at baseline and after exercise in 3 hours.

Results: Patients were divided in two groups based on lower (<26 mL/Kg/min, n=47) or higher (≥26 mL/Kg/min, n=49) peak oxygen consumption (VO2) as a representation of exercise tolerance. In the two groups, after adjusting for age and gender, the NT-proBNP level after exercise in 3 hours, left atrial volume index (LAVI) pre-exercise, right ventricular systolic pressure (RVSP) pre-exercise, E velocity post-exercise, and E/e’ ratio post-exercise varied significantly. In addition, peak VO2 was inversely related to NT-proBNP pre- (r=−0.352, p<0.001) and post-exercise (r=−0.351, p<0.001). The NT-proBNP level pre-exercise was directly related to LAVI, E/e’ ratio, and RVSP pre- and post-exercise. NT-proBNP post-exercise was also directly related to the same parameters. NT-proBNP levels both pre- and post-exercise were higher in the group with lower exercise tolerance.

Conclusion: Through the correlation between exercise tolerance, NT-proBNP, and parameters of diastolic dysfunction, we demonstrated that diastolic dysfunction and NT-proBNP could predict exercise tolerance in patients with significant VHD and normal LV EF.
EXERCISE PHYSIOLOGY; BASIC AND CLINICAL

035
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Objective: To determine if marathon running results in long term or permanent cardiac dysfunction.

Background: Running as a physical activity is generally considered good for health but there is a concern that marathon running can be deleterious to the heart. To clarify this matter we did a literature review on the effects of marathon running on right ventricular(RV) and left ventricular(LV) function, right atrial(RA) and left atrial(LA) function, as well as changes in cardiac biomarkers before and after a marathon.

Methods: A review was performed on major journals and articles that were related to evidence of cardiac dysfunction after a full marathon race. Criteria for inclusion were 1. Studies published after 2005, 2. Full marathon (26.2 miles) reports, 3. Studies that measured RV and/or LV, LA and RA dimension and function using different imaging techniques or measurement of cardiac biomarkers.

Results: 22 studies were found that met the inclusion criteria. They showed transient but reversible RV systolic dysfunction with little or no evidence of LV systolic dysfunction following marathon race. However, there was evidence of transient LV diastolic dysfunction along with RV diastolic dysfunction. The increase in cardiac biomarkers following the race is believed not to be due to cardiac injury as confirmed by imaging, neither did the increase follow a typical cardiac ischemic event. Amateur runners (trained < 35 miles/week) seemed to have a greater increase in the markers compared to trained (> 45 miles/week) individuals. Despite the post marathon race biatrial dilation there was no incidence of atrial fibrillation observed in any of the studies.

Conclusion: Marathon running is an overall safe activity. Although some structural changes are reported at the end of the race it appears as those are physiological adaptations that go back to normal after a short recovery.
Irisin is secreted by skeletal muscle during exercise and influences energy and metabolic homeostasis. This hormone is a cleaved and secreted fragment of fibronectin type III domain-containing 5 (FNDC5).

Elucidation of the FNDC5 gene regulation mechanism is necessary to clarify the function of irisin as a potential therapeutic target in human metabolic diseases. Thus, we investigated the genetic and epigenetic mechanisms that regulate expression of the FNDC5 gene. FNDC5 mRNA was strongly expressed in major energy-dependent human tissues, including heart, brain, liver, and skeletal muscle. Promoter analysis of the FNDC5 gene revealed that the core promoter region of the FNDC5 gene contained one CpG island that was located just upstream of the transcriptional start site for variants 2 and 3. Treatment with the histone deacetylase inhibitor sodium butyrate and the demethylating agent 5-azacytidine increased mRNA expression of FNDC5 in Huh7 cells. Prediction of transcription factor binding sites suggested that the glucocorticoid receptor was involved in the regulation of FNDC5 expression, and indeed, cortisol treatment increased mRNA expression of FNDC5 in Huh7 cells. Collectively, these findings offer insight into the genetic and epigenetic regulation of FNDC5, providing the initial steps required for understanding the role of irisin in the metabolic homeostasis.
Mitochondrial transfer RNA (tRNA) mutation with high-salt stimulation can cause high blood pressure. However, the underlying mechanisms remain unclear. In the present study, we examined the potential molecular mechanisms of cardiac damage caused by mitochondrial tRNA mutation with high-salt stimulation in spontaneously hypertensive rats (SHR). Unanesthetized, 44-weeks-old, male, SHR were divided into four groups: SHR, SHR with high-salt stimulation for 8 weeks (SHR+NaCl), SHR carrying tRNA mutations (SHR+M), and SHR+M with high-salt stimulation for 8 weeks (SHR+M+NaCl). Healthy Wistar-Kyoto (WKY) rats were used as controls. Left ventricular mass and interventricular septum were highest in the SHR+M+NaCl group (P<0.05), while ejection fraction was lowest in the SHR+M+NaCl group (P<0.05). Hematoxylin and eosin staining showed myocardial cell hypertrophy with interstitial fibrosis and localized inflammatory cell infiltration, in the hypertensive groups, particularly in the SHR+M+NaCl group. Electron microscopy showed different degrees of mitochondrial cavitation in heart tissue of the hypertensive groups, which was highest in the SHR+M+NaCl group. In hypertensive animals, levels of reactive oxygen species were highest in the SHR+M+NaCl group (P<0.05). Expression of the voltage-dependent anion channel (VDAC) and the apoptosis regulator Bax were highest in the SHR+M+NaCl group (P<0.05), which also showed evidence of VDAC and Bax co-localization (P<0.05). Overall, these data suggest that mitochondrial tRNA mutation with high-salt stimulation can aggravate cardiac damage, potentially because of increased expression and interaction between Bax and VDAC and increased reactive oxygen species formation and initiation of apoptosis.
SYSTEMIC AND PULMONARY HYPERTENSION

038

POTENTIAL EFFECT OF ALCOHOLIC EXTRACT OF LEAVES OF OCIMUM SANCTUM IN MONOCROTALINE-INDUCED PULMONARY ARTERY HYPERTENSION IN RATS

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Background: Pulmonary hypertension is underdiagnosed and complex disease with features of mPAP above 25mm of Hg and vascular resistance above 3 WU resulting in high mortality if untreated. Cardioprotection using alternative medicine may provide hope.

Objective: To evaluate the effect of ocimum sanctum in MCT-induced PH

Methods: The study was approved by Institutional animal ethics committee, AIIMS, New Delhi, India. Baseline echocardiography was done in 30 rats (n=6). Control rats were injected 1ml/kg normal saline. PAH rats were administered monocrotaline (MCT) 50mg/kg. Sildenafil rats were administered with MCT 50mg/kg and sildenafil (175microg/kg/day) for 25 days. OS100 and OS200 rats were administered with MCT 50mg/kg sc and OS (100 and 200mg/kg/day) for 25 days. Echocardiography measures left ventricular ejection fraction (LVEF), ratio of right ventricular outflow tract to aortic diameter (RVoTD/AoD) and ratio of pulmonary artery acceleration time to ejection time (PAAT/ET). Cardiac catheterization to estimate right and left ventricular systolic pressure (RVSP, LVSP), end diastolic pressure (RVeDP). Heart and lungs were weighed. Lung was preserved for histopathology and western blot analysis for nicotinamide adenine dinucleotide phosphate oxidase (Nox-1). Right ventricular hypertrophy (RVH) and apoptotic markers (Bcl2/Bax).

Results: Monocrotaline induce PAH through oxidative stress (increased TBARS, reduced GSH, SOD and catalase and increased Nox-1). It leads to initiation and progression of pulmonary artery smooth muscle cell proliferation and thus resulting in increased PVR (increased %MWT and decreased PAAT/ET), RV undergo compensatory hypertrophy (increased Fulton index, right ventricular systolic pressure, and RVoTD/AoD). If untreated the cardiac myocytes undergo apoptosis and failure (increased Bax expression and RVeDP). Sildenafil and OS both prevented increased RVSP, RVeDP, RVH, and RVoTD/AoD and apoptosis in right ventricle.

Conclusion: The present study shows cardio protective property of ocimum sanctum in MCT model of PAH in rats, further validation is required through clinical research.
SYSTEMIC AND PULMONARY HYPERTENSION

039

SUBLINGUAL VERSUS ORAL CAPTOPRIL FOR DECREASING BLOOD PRESSURE

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Background: Captopril is a fast acting antihypertensive agent and has been used to decrease blood pressure in emergency department. Sublingual captopril may have a faster onset of action but seems to be less tolerated.

Objective: The present study is performed to make a comparison of efficacy of sublingual versus oral captopril and satisfaction of the patients.

Methods: Hypertensive patients visited in the emergency department, but without indication of intravenous treatment were randomly assigned to receive 25 mg of captopril sublingually or orally. Blood pressure was measured at 30, 45, 60 and 120 min after prescription (Iranian registry of clinical trials # IRCT2015110924963N1).

Results: Mean age of the study group was 59.61 ± 9.34 years and 51 (72.9%) were female. Mean decrease of SBP at 30 min and 45 min was significantly higher in the sublingual group in comparison to oral group (23.20 ± 8.84 versus 18.34 ± 8.50 at 30 min and 25.49 ± 7.97 versus 21.37 ± 9.17 at 45 min, P<0.05), but Mean decrease of SBP at 60 and 120 min and mean decrease of DBP at 30, 45, 60 and 120 min were not significantly different in 2 groups. The scores given by the patient to convenience and their satisfaction was less in sublingual group (6.40 ± 0.88 versus 9.49 ± 0.92, P<0.001).

Conclusions: In the present study, patients reported less satisfaction with sublingual captopril; however it had a faster effective of decreasing SBP at 30 and 45 min in comparison with oral captopril.
040
UNDERLYING RHEUMATIC HEART DISEASE HAD GREATER RISK OF
INFECTIVE ENDOCARDITIS IN TAIWAN DIALYSIS PATIENTS
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Background: The incidence and mortality rate of infective endocarditis (IE) is high in dialysis patients. Limited data are available on the risk factors for IE and long-term outcome after IE among dialysis patients, especially in Asian population.

Methods and Results: This longitudinal cohort study investigated the incidence, risk factors, and outcome of IE in dialysis patients in the Taiwan National Health Insurance research Database between January 1999 and December 2007. The follow-up period was from the start of dialysis to the death, end of dialysis, or December 31, 2008. IE was diagnosed in 502 patients during follow-up (201.4 per 100,000 person-years). Factors increasing IE included Diabetes Mellitus (DM) (HR 1.46, 95% CI: 1.21-1.77), Congestive heart failure (CHF) (HR 1.36, 95% CI: 1.11-1.67), Cerebral vascular accident (CVA) (HR 1.32, 95% CI: 1.03-1.68), and rheumatic heart disease (RHD) (HR 3.07, 95% CI: 1.99-4.75). The cumulative incidence rate of IE of patients with RHD was 1.4% at one year, 2.2% at three years, and 3.9% at five years. Overall in-hospital mortality was 23.5%. The cumulative survival rates after IE was 54.3% at one year, and only 35.3% at five years. Having DM (RR 1.88, 95% CI: 1.13-3.13), and having some in-hospital morbidities after IE, including shock (RR 9.09, 95% CI: 4.91-16.83) and respiratory failure (RR 3.41, 95% CI: 1.87-6.23) were associated with significantly in-hospital mortality.

Conclusion: Dialysis patients had higher risk of IE. Being older and having DM, CHF, CVA and especially RHD were at greater risk. Dialysis patients with IE also had high mortality rate. Having DM and in-hospital comorbidities including shock and respiratory were associated with increased mortality.
CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR DISEASE

041
MECHANICAL DEVICE FOR THE MANAGEMENT OF CARDIO-RENAL SYNDROME
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Cardio-Renal Syndrome (CRS) has been shown to be associated with a significant increase in in-hospital mortality as well as complications, length of stay, and cost. All drug trials have failed to show a significant benefit in this syndrome, and new solutions are needed. The Second Heart Assist Device has been designed and engineered to reverse the adverse physiology of CRS. It consists of a pump mounted on a 13 French stent that is easily placed via a percutaneous femoral artery approach and advanced retrograde into the descending aorta to just above the level of the diaphragm. The shaft of the pump contains a propeller which, when opened, can be spun at adjustable speed to create a significant increase in distal blood flow, especially renal blood flow, to enhance perfusion and filtration leading to marked increase in urine output and renal function. The stent and propeller fill the entire diameter of the aorta, thereby reducing the speed required to generate the increase in blood flow and minimizing the hemolysis reported with other ventricular assist devices. The propeller can be collapsed and the device removed with usual percutaneous closure. In addition, the risk of pump thrombosis will be minimized by use of a new harmonic tuned vibrational energy device placed externally near the device. This mechanical device is easier, quicker, and safer than current devices that require placement across the aortic valve and have less enhancement of renal function. The 2nd generation of the device will include pulsating cuffs to further augment flow and an option to detach the pump within an aortic stent from the catheter with wireless power.
ASSOCIATION OF CORONARY ARTERY CALCIFICATION AND ARTERIAL MICRO-CALCIFICATION OF THE VASCULAR ACCESS IN INCIDENTAL HEMODIALYSIS PATIENTS

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Introduction and Aims: We have reported that arterial micro-calcification (AMC) of vascular access has a negative impact on access patency and cardiovascular mortality in hemodialysis (HD) patients. Reasons behind increased cardiovascular mortality in AMC are not fully understood, but it is believed that aortic stiffness is a major contributing factor. Whereas, coronary artery calcification (CAC) is quite common in HD patients and it is known as predictor of future cardiovascular events and all-cause mortality in HD patients. The aim of this study was to explore the relationship between AMC and CAC in HD patients.

Methods: The AMC was diagnosed by pathologic examination of arterial specimen by von Kossa stain, which was acquired during the operation. All patients underwent a multi-detector computed tomography (MDCT) imaging procedure and coronary artery calcium score (CACS) was calculated. Patients were classified into two groups, according to the CACS, as high (≥100), in 56 patients, and low (<100), in 39 patients.

Results: Patients with high CACS group were older (69.6 ± 9.5 vs. 59.4 ± 14.1, p=0.007), and showed a significantly higher prevalence of diabetes mellitus (75.0% vs. 53.8%, p=0.027). High CACS group showed high incidence of AMC compared to low CACS group (71.4% vs. 33.3%, p<0.001). By binary logistic regression, AMC was independently associated with high CACS (OR: 4.228, 95% confidence interval [CI]: 1.513-11.817, p = 0.006).

Conclusions: The present study suggests that AMC is closely associated with CAC in incident HD patients.
CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR DISEASE

043

MYOCARDIAL ISCHEMIA ASSOCIATED WITH INTER-ARTERIAL VARIANTS OF ISOLATED SINGLE CORONARY ARTERY

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Background. Inter arterial course (between aorta and pulmonary trunk) of anomalous coronary artery may cause myocardial ischemia or sudden death due to compression by great vessels and/or a slit-like anomalous ostium. The latter condition is anatomically absent in isolated single coronary artery (iSCA). We aimed to assess potential contribution of inter-arterial course alone to myocardial ischemia in patients with iSCA.

Methods & Results. Among 713 reported cases of iSCA, 109 had anomalous vessel with inter-arterial course (age 56±14 years, 59% men). Presentation included exertional angina (60%), myocardial infarction (16%), syncope, dyspnea or palpitation (20%) and sudden cardiac arrest (4%). Diagnoses were made by invasive angiography [ICA (39%)], CCTA (10%), ICA+CCTA (31%), autopsy (7%), or combination of modalities (13%). iSCA arose from right (64%) or left coronary sinus. Inter-arterial vessel was left main (47%), right (36%), left anterior descending (17%) or left circumflex (<1%) coronary artery. Among those with angina or myocardial infarction (n=85), atherosclerotic CAD was present in 47 (55%) and among 4 with cardiac arrest, only 1 had atherosclerotic CAD. Stress testing was done in 38 (35%) and was positive in 30. Atherosclerotic CAD was found in 1 of 8 (13%) with and 13 of 30 (43%) without myocardial ischemia on stress testing. Other potential causes of ischemia (intramural course of major coronary artery or coronary vasospasm) were found in 6 patients. Overall, 46 of 109 patients had no other potential explanation for their presenting symptoms than inter-arterial course. Of the latter, 14 underwent CABG, 2 had coronary reimplantation and the remaining were treated medically.

Conclusion. Inter-arterial course of a major coronary artery was present in 15% of those with iSCA. Anomalous inter-arterial vessel was most commonly left main or left anterior descending coronary artery and was the sole cause of myocardial ischemia in >40% of patients.
REABSORBABLE PINS CAN REINFORCE AN EARLY STERNAL STABILITY AFTER MEDIAN STERNOTOMY IN YOUNG CHILDREN WITH CONGENITAL HEART DISEASE
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Background: We evaluated the efficacy of the bioresorbable sternal reinforced device (poly-L-lactide sternal pins) on sternal healing after median sternotomy in young children (body weight less than 10kg) with congenital heart disease (CHD).

Methods: Data from 139 patients who underwent CHD surgery through median sternotomy from October 2016 to January 2017 were collected and analysed. Sternal pins were utilized in 48 patients (10mm x 1mm x 1mm for patients’ body weight less than 5kg, 15mm x 2mm x 2mm for those body weight between 5kg and 10kg) in addition to the standard closure of the sternum with Ethicon PDS TM II running sutures (Group A), and 49 patients received no pins with the standard Ethicon sternal closure (Group B). The occurrence of sternal dehiscence, anterior-posterior displacement and high-low displacement were evaluated by physical examination and three-dimensional computed tomography at one month postoperatively.

Results: There was no anterior-posterior sternal displacement (0%) observed in Group A at discharge. While in Group B, 9 anterior-posterior displacements (18.4%) were observed (P = 0.006). The Figure for sternal high-low displacement in group A and B were 10.4% (5 cases) and 10.2% (5 cases), respectively (P = 0.560). No sternal dehiscence (0%) was observed in Group A. While 4 of the 49 patients (8.2%) in Group B were observed obvious sternal dehiscence (P = 0.009).

Conclusions: The bioresorbable poly-L-lactide sternal pins reduced an anterior-posterior sternal displacement and sternal dehiscence. The pin strengthened an early sternal fixation.
MYOCARDIAL ISCHEMIA CAUSED BY ISOLATED SINGLE CORONARY ARTERY IN PEDIATRIC POPULATION

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Background. Isolated single coronary artery (iSCA) defined as solitary coronary ostium arising from aorta in absence of other major congenital cardiovascular defects is rare (0.024-0.066%) and often discovered incidentally in adults. Certain malignant subtypes of iSCA, however, may present with angina, myocardial infarction (MI) or sudden death. Clinical presentation during childhood is extremely rare and not well studied. We present a summary of reported cases of iSCA in pediatric population.

Methods & Results. Exhaustive literature search identified 18 children with iSCA (age 9±5 years, 67% male). Single coronary ostium was located in right [n=12 (67%)] or left [n=6, (33%)] aortic sinuses. A total of 13 (72%) showed either inter-arterial (n=11) or intra-cristal (n=2) course of anomalous vessel. In addition, 1 (5.5%) patient had hypoplastic (reduced length) of an anomalous left anterior descending coronary artery. Presenting complaints were chest pain in 3, syncope in 4, cardiac arrest in 2 and palpitations and murmur in 3. Method of diagnosis included coronary computed tomographic (CCTA) and magnetic resonance angiography (MRA) in 6 (33%); invasive coronary angiography (ICA) in 3 (17%); autopsy in 4 (22%); and ICG/CCTA/MRA in 5 (28%). Diagnosis of iSCA was made with significant delay in 17%. Major adverse cardiac events included MI [n=5 (28%)]; coronary stenosis at the site of bypass vessel anastomosis [n=2 (11%)]; heart failure [n=2 (11%)] and sudden death [n=3 (17%)]. Surgical management included coronary artery bypass grafting in 2, surgical re-implantation of anomalous coronary artery in 1, surgical coronary unroofing in 1 and translocation of main pulmonary artery to left pulmonary artery in 1.

Conclusion. Malignant subtypes of iSCA may be associated with myocardial ischemia and major adverse cardiac events, including death, in children. A high clinical index of suspicion and timely diagnosis may be important in preventing major complications of malignant iSCA.
GERBODE DEFECT IN AN ADULT PATIENT: A VERY RARE ENTITY

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Background: A communication between the left ventricle (LV) and right atrium (RA) is a rare type of ventricular septal defect (VSD). They are more often congenital than acquired. The incidence of LV-RA communication is 0.08% of all catheterized congenital defects. It was first described in the 19th century and was recognized as the Gerbode defect in 1958 when Gerbode et al. published a series of five patients who underwent successful surgical repair.

Case: 57-year-old male with a past medical history of HTN presented with symptoms of worsening shortness of breath and chest pain. On auscultation was found to have a loud holosystolic murmur in the left lower sternal border. Transthoracic echocardiogram revealed an anomalous left to right shunt. To better characterize the shunt a transesophageal echocardiogram was performed. It revealed a turbulent jet originating from the LV directed to the RA travelling above the tricuspid valve (fig 1). An accurate quantification of anomalous shunt could not be performed due to contamination from tricuspid regurgitation jet. Cardiac catheterization was performed to visualize (fig 2) and precisely quantify the shunt (Qp/Qs 1.9). Patient was referred for surgical closure of the defect.

Conclusion: Gerbode ventriculo-atrial defect is a rare defect that permits shunting from the left ventricle to the right atrium. Anatomically, the defect is characterized as above the tricuspid valve (type I), below the tricuspid valve (type II), or a combination of both (type III). Literature review suggests most of these cases require surgery. Repair of such defects is challenging and requires great expertise.

Fig. 1

Fig. 2
Introduction: Heterotaxy syndrome as the name suggests (from Greek heteros-different and taxis-arrangement) is defined as disorganized arrangement of organs and vessels within the abdominal cavity. There is no single pathognomonic anomaly that characterizes this rare entity and its severity depends on the cardiac manifestation.

Case report: A 46-year old female with history of chronic atrial fibrillation presented to the emergency department with worsening shortness of breath. She reported a 2 year history of shortness of breath that had been progressively getting worse over last month. There was no history of chest pain, palpitation, orthopnea or paroxysmal nocturnal dyspnea. On examination, she was normotensive with a normal resting heart rate with irregularly irregular rhythm. General examination revealed oxygen saturation of 74% on room-air, with cyanotic lips and marked clubbing of the fingers. Cardiovascular exam was positive for a positive jugular venous distension, right parasternal heave, palpable P2 and a holosystolic murmur in the right 4th intercostal space in the mid-clavicular line. Chest X-Ray showed cardiomegaly with apex pointing to the right and stomach bubble to the right. Electrocardiography demonstrated dextrocardia. Laboratory work up suggested polycythemia and thrombocytopenia. Echocardiography confirmed the dextrocardia with severe dilated RA, normal LA, large VSD with bidirectional flow, double outlet RV with severe hypertrophy, severe pulmonary stenosis and aorta to the right of pulmonary artery. CT scan of the abdomen showed left sided liver with right sided polysplenia, IVC on the left side of aorta and malrotation of the gut. Cardiac magnetic resonance(CMR) imaging confirmed the findings.

Discussion: Heterotaxy syndrome includes a wide range of extracardiac manifestations including urinary system, gastrointestinal and hepatobiliary systems. Given the diverse findings in each case, radiological evaluation is an essential tool in the approach of the management of the patient.
EXCEPTIONAL SURVIVAL OF A DOUBLE INLET LEFT VENTRICLE: A RARE CASE
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Background: Double inlet left ventricle (DILV) is a rare anomaly with medial survival of 14 years if not corrected. We present the management of a case of DILV with exceptional survival.

Case Report: A 66-years-old woman was evaluated for management of complex cardiac malformation. She was diagnosed with DILV as a child but no intervention was pursued and she did not have regular cardiac follow-up. She was able to keep up with her peers. In spite of the prohibitive risks, she carried out two full-term pregnancies with no hemodynamic complications. She was able to accomplish her activities of daily living without any cardiac symptoms. Physical examination showed hypoxia (SpO₂ 82%) at room air. There was no evidence of jugular venous distension, lung crackles or peripheral edema. Yet, clubbing and acral cyanosis was seen. Cardiac exam demonstrated a regular rhythm with a 3/6 harsh systolic ejection murmur over left upper sternal border without rubs or gallops.

Decision Making: Echocardiogram revealed DILV with preserved systolic ventricular function and severe pulmonary stenosis. Cardiac MRI revealed DILV with a dilated left ventricle with preserved systolic function, a large bulboventricular foramen, and a rudimentary right ventricle given rise to the aorta without any coarctation. There was a small ostium primum defect with mild atroventricular valve regurgitation. The pulmonary valve was severely stenotic with markedly dilated branch pulmonary arteries. Given asymptomatic status of patient along with a balanced cardiac physiology, no surgical intervention was warranted and it was opted to continue to observe the patient with regular follow-up.

Conclusion: There is a paucity of data for the management of adult patients with unrepaired single ventricle physiology. Our patient has done well without any interventions for almost 7 decades. Late palliative surgery carries high surgical risk and would be deferred in patients with balanced physiology.
MEASUREMENT OF OUTCOME AND QUALITY OF CARDIOVASCULAR CARE

050
PREDICTING HOSPITALIZATION OUTCOMES BASED ON HEART
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Objectives: We assessed the correlation between the HEART score and the hospitalization outcomes to predict the hospital length of stay and the major adverse cardiac events (MACE).

Background: Chest pain is one of the most common presentations in the emergency department (ED) requiring physicians to quickly determine who gets discharged home versus admitted for urgent intervention. Physicians have created various scoring methods to ease the burden of triaging. Most recently in the United States, ED physicians started utilizing the HEART score: history, EKG, age, risk factors, and troponin. The HEART score predicts the 6-week risk of MACE defined as acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), coronary artery bypass surgery (CABG), and death. Despite its common use for triage in the ED, there is a lack of studies analyzing the hospitalization outcomes based on the HEART score.

Methods: We retrospectively analyzed the data in a single center for chest pain admissions by calculating the HEART score and assessing the hospitalization outcomes by the hospital length of stay, AMI, coronary catheterizations with and without PCI, CABG, and death.

Results: 381 patients admitted for chest pain were reviewed. Of the 381 patients, 219 were male and 162 were female patients with an overall mean age of 59.8. They were divided into 4 groups based on the HEART score of 0-1, 2-3, 4-6, and 7-10. The length of stay for each group respectively showed statistical significance with 1.2±0.2, 1.65±0.12, 3.29±0.28, and 7.67±0.57 days (p<0.05). In addition, the rate of MACE during the hospitalization was also statistically significant with 0%, 1.69%, 36.6%, and 96.34%, respectively (p<0.05).

Conclusions: Our study showed that patients with the HEART score of 0-3 required hospitalizations less than 48 hours with significantly fewer MACE, allowing physicians to safely anticipate early discharges.
MEASUREMENT OF OUTCOME AND QUALITY OF CARDIOVASCULAR CARE

051
ORTHOSTATIC VITALS IN THE EVALUATION OF SYNCOPE: KNOWLEDGE, ATTITUDE AND PRACTICE OF HEALTH CARE PROVIDERS (HCPS)
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Background: The approach to syncope by HCPs currently involves utilization of tests with substantial costs but little or no benefit. The guidelines on the other hand, place emphasis on appropriately obtaining orthostatic vitals first. This is because of reduced adverse effects (radiation risks) and high value care (cost effectiveness) of this important step.

Objectives: To assess the Knowledge, Attitude and Practice of Healthcare providers (Medical Residents and Nurses) in orthostatic vitals measurement as part of evaluation for Syncope.

Methods: We administered an eight-item questionnaire based on current guidelines to Nurses and medical Residents in Howard University Hospital. Questions were close-ended and grouped into 3 sections: Provider practice patterns (2), provider attitudes (2) and knowledge (4).

Results: 56 Nurses and 53 Residents were surveyed with a response rate of 61% and 83% respectively. There were discrepant responses regarding attitude and practice amongst HCPs for example, HCPs responses to the questions “how should orthostatic vitals be measured?” showed 53% of respondents got both appropriate responses wrong compared to only 3% who got both right. Stratification by profession revealed that 82% of the nurses, and 54% of the medical residents answered the question incorrectly.

Conclusions: There is inadequate knowledge and practice of appropriate orthostatic vitals by Nurses and Residents. Strong action plan like establishment and enforcement of adherence to standard of care and guidelines is recommended. Continued education could also help bridge this knowledge gap.
CUSTOMIZED QUALITY IMPROVEMENT FOR ECHOCARDIOGRAPHY

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Objectives: To improve our echocardiography lab quality assurance (QA) methodology, making it scalable and searchable in real time.

Background: Spectrum Health is a large healthcare system with 14 hospitals and ambulatory sites providing cardiology imaging services for heart transplant, mechanical circulatory support, and electrophysiology. We employ 49 cardiac sonographers and two advanced cardiac sonographers that provide real time sonographer and physician support, mentoring, and QA.

Methods: We developed an Excel spreadsheet listing pre-identified metrics and accreditation standards such as left ventricular function, Doppler, Simpson’s Biplane, PACS errors etc. Within each column there is a pull-down with multiple choices. Echos are then graded on a 1-5 scale.

Results and Conclusions: By searching this vast array of quantifiable data, we noticed that occasionally we inaccurately measured ejection fractions by Simpson’s Biplane method (figure 1). Once this gap was identified, we focused efforts for improvement. We now have the ability to search and display trends based on specific errors - by sites, sonographers (figure 2), regions, etc. retrospectively and in real time. This helps us to focus efforts and identify education needs for continued quality improvement. As our spreadsheet grows, we foresee many possibilities in improving quality.
MEASUREMENT OF OUTCOME AND QUALITY OF CARDIOVASCULAR CARE

053
MISUSE OF CARDIAC TROPONIN IN THE OUTPATIENT SETTING: A SINGLE-CENTER RETROSPECTIVE ANALYSIS
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Objectives: To evaluate the ordering patterns and intended use of outpatient cardiac troponin orders.

Background: Cardiac troponin (cTn) measurement is useful for diagnosing acute coronary syndromes (ACS), particularly in the inpatient setting. Conversely, the utility of outpatient cTn testing is limited, and little is known regarding cTn ordering patterns in this setting.

Methods: We analyzed 228 patients who had outpatient cTn orders placed at our institution between 1/1/2013-12/18/2015. Data were divided into two cohorts based on intended utility of cTn measurement: orders placed to evaluate for suspected ACS versus orders placed for some other purpose.

Results: Of the 228 patients, 161 were evaluated for suspected ACS. Risk factors (hypertension p=0.32, diabetes p=0.41), coronary disease (p=0.38), heart failure (p=0.098), and chronic kidney disease (p=0.70) were similar between the cohorts. The proportion of females in the suspected ACS cohort was higher (55.9% versus 40.9%, p=0.04). Reasons for cTn testing in the cohort tested for reasons other than suspected ACS included: hyper/hypotension, syncope, tachycardia, atrial fibrillation, evaluating for drug-related cardiotoxicity, and evaluating for cardiac involvement of systemic diseases. In the suspected ACS cohort, an electrocardiogram (ECG) was obtained in only 77% of patients, and only 13.1% were sent to the emergency department (ED) for further evaluation. In this cohort, 17 patients had elevated cTn values: 4 of whom had no further immediate cardiac workup, 7 who were referred for additional outpatient cardiac evaluation, and 6 who were sent to the ED.

Conclusions: Among outpatient cTn orders placed, the majority were intended to evaluate for ACS. ECGs were frequently not ordered and few were sent to the ED for further evaluation. Providers should be encouraged to use cTn testing in a manner that minimizes potential risk to patients with suspected ACS.
PREVALENCE AND PATTERNS OF CARE IN CARDIAC TROPONIN SUPERUSERS

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Objective: To study the patterns of care regarding the small fraction of inpatients who undergo numerous cardiac troponin (Tn) assays during their stay (superusers).

Background: Tn assays are frequently performed serially when evaluating for acute coronary syndrome. For unclear reasons, Tn is sometimes checked excessively during a single hospitalization.

Methods: Data were retrieved from the integrated data repository at our institution for all inpatients with at least one Tn assay between 1/1/2013 and 12/18/2015. We defined a superuser as a patient who had 19 or more assays performed in a single hospitalization. Basic demographics and a selection of conditions, procedures, and outcomes for each encounter were recorded via manual chart review of superusers. We identified clinical factors to explain why numerous troponins were ordered.

Results: Of 43,063 patients, 0.13% (n=56) were identified as superusers. A variety of co-morbidities were observed, including 11 patients with sepsis, 9 with atrial fibrillation, 3 with stroke, and 15 with a recent procedure. 39 had Tn elevation due to suspected causes other than type I myocardial infarction (MI). 22 of these 39 patients had suspected type II MI, while the remaining 17 had chronic/non-specific causes of Tn elevation. MI (any type) was ultimately diagnosed for 31 superusers. Half of superusers (n=28) had notes from cardiology that recommended trending troponins. 13 of these patients were not candidates for invasive angiography due to poor medical status or patient preferences, and thus medical management was the only treatment available.

Conclusions: Among Tn superusers, a recommendation to trend Tn was made by cardiology for half of the cases, despite the fact that additional Tn data often did not alter the course of care or outcomes. Clinicians should reconsider the need to continually trend Tn if the data will not alter clinical decision-making.
CARDIOVASCULAR DISEASE: DIFFERENT STRATEGIES FOR PRIMARY AND SECONDARY PREVENTION

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ASPIRIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE: ADVANCES IN DIAGNOSIS AND TREATMENT
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For the primary prevention of atherosclerotic cardiovascular disease with aspirin therapy, decisions regarding aspirin use should be personalized, balancing the benefit: risk ratio and patient preferences. This presentation will examine advances in cardiovascular and bleeding risk assessment for aspirin use in primary prevention, and review the evidence from a total of eleven randomized clinical trials involving more than 118,000 individuals for the benefits and risks of aspirin use. Recent recommendations will be reviewed, including those of the 2016 U.S. Preventive Services Task Force, regarding the use of low-dose aspirin therapy for the primary prevention of atherosclerotic cardiovascular disease, and secondarily for colorectal cancer prevention. Overall the quality of evidence was high, but important controversies remain unresolved and await several ongoing clinical trials. Individualizing the benefit of aspirin with the risk of bleeding is complex but essential for informed clinical decision making and achieving a net clinical benefit from long-term aspirin therapy for primary prevention. The Aspirin-Guide decision support tool (freely available as an app for mobile devices and also on the web at http://www.aspiringuide.com) is designed to help busy clinicians in shared decision-making discussions with their patients regarding aspirin use for primary prevention.
Cardiovascular Disease: Different Strategies for Primary and Secondary Prevention

056
Optimizing Statin Utilization and Treatment Adherence Among Patients Who Discontinue Statins Due to Adverse Muscle Events

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Statin therapy has been established as first-line therapy for the prevention of atherosclerotic cardiovascular disease (CVD) events in persons who are at high-risk for CVD events based upon either risk estimates that place disease-prone individuals at risk for future CVD events or in patients with clinical evidence of CVD. The reduction in cardiovascular events in participants randomized to statin therapy versus placebo becomes greater with long-term exposure, and these benefits continue to accrue in the ensuing decades after completion of the clinical trial. Under the formal structure of controlled clinical trials, adherence to statins exceeds 90 percent. In less than 5 percent of treated study participants, statins have been discontinued due to perceptions of drug-induced adverse events. In real world studies that comprise data obtained from various sources (surveys, registries and insurance claims), statin adverse events range may be as common as 10 to 20 percent. As adverse events are more common at higher dosages of statins, many patients are unable to continue with evidence-based and guideline-directed high-intensity statin therapy. Among myocardial infarction survivors, patients who down-titrate their statins due adverse events have higher rates of myocardial infarction and other coronary heart disease (CHD) events that result in more hospitalizations and consequently health care expenditures that are 1.5-fold higher in the year after statin downtitration.

Most statin associated adverse events are not life-threatening and may not recur upon challenge with lower doses or other statins. Thus, it is critical to develop a comprehensive strategy designed to improve treatment adherence to statins in patients who perceive that their muscle symptoms are statin-induced. These processes involve a validated tool for assessment of statin associated adverse muscle symptoms, a dechallenge-rechallenge phase, and engagement of the patient who may be resistant to re-challenge with a different statin or reduced dosage of the same statin. Genetic susceptibility to statin muscle symptoms represent potential tools for identification of individuals who may be candidates for non-statin LDL cholesterol lowering therapy.
CARDIOVASCULAR DISEASE: DIFFERENT STRATEGIES FOR PRIMARY AND SECONDARY PREVENTION

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GERIATRIC CARDIOLOGY: OCTOGENARIAN PEARLS

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Approximately 70% of persons older than age 65 in the U.S. have cardiovascular disease, including 85% of those older than age 80. Although adults 75 years and older comprise only about 60% of the U.S. population, they account for > 50% of cardiovascular mortality. Thus the contemporary prototype U.S. cardiology patient is an older adult. Alterations in cardiovascular structure and function with aging substantially impact pathophysiologic mechanisms, predispose to cardiovascular disease, decrease cardiovascular reserve, and increase the risk for adverse outcomes. Cardiovascular disease rarely occurs in isolation at older age, such that management requires consideration of comorbidities as well as geriatric syndromes that include frailty, cognitive impairment, multimorbidity and polypharmacy. Cardiovascular clinical practice guidelines are disease-oriented, with the evidence base deriving from predominantly younger patients. Whereas increased benefit of a favorable intervention may accrue in older adults, given their greater absolute risk of cardiovascular events, this benefit is counterbalanced by the increased risks of adverse effects. Adverse drug events account for about 1/3 of hospital admissions of older adults. There is a transformative effect of aging on cardiovascular disease, including a lesser capacity to tolerate and/or desire medications, devices, or procedures as compared with younger patients. Further, the standard outcome of randomized clinical trials, improved survival, may not reflect the preferences of older adults, whose foremost concerns include improvement or maintenance of function, independence, limitation of symptoms, and decrease in hospitalizations, i.e., improvement in quality of life. Thus geriatric cardiology is the practice of cardiovascular medicine adapted to the needs and complexities of older adults. The emphasis should be on patient-centered outcomes and priorities in contrast to disease-specific outcomes. Patient-centered care is required to embrace this complexity.
Patients with stable angina Pectoris (SAP) seek medical advice primarily for symptom relief and for fear of having a heart attack or dying suddenly. Clinical Guidelines from different countries to treat SAP vary considerably. Guidelines for treating SAP have been derived from randomized clinical trials in patients with documented coronary artery disease (CAD). Despite these facts, current Guidelines do not recommend routine coronary angiography initially, but recommend optimal medical treatment with two or more antianginal medications prior to considering revascularization. Selection of initial class of antianginal drug in the current guidelines is not based on evidence, but is mostly opinion based, as there is lack of data showing that any of the available antianginal medications improve survival in patients with SAP; or that one class of antianginal drug is superior to another class for symptom relief. In the American Society Guidelines, it is recommended that all patients with stable ischemic heart disease, irrespective of the presence or absence of CAD should also be treated with aspirin and a potent statin. In contrast, Guidelines from other countries recommend that patients with CAD should be treated with antianginal drugs and aspirin, and an angiotensin receptor blocker, but the dose of a statin should be titrated to a desirable LDL level. Recommendations for treating patients with SAP who have normal coronary arteries are not evidence based in any of the guidelines.
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COMBINATION THERAPY OF LIPID DISORDERS. CAN WE REDUCE THE RESIDUAL RISK EFFECTIVELY?

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Despite very effective lipid lowering therapy with statins, there is still a large number of patients with residual cardiovascular (CV) risk, which might be between 30 to 70%. Additionally we have been currently challenge with the issue of statin non-response, statin non-adherence as well as statin intolerance. Therefore for last several years different research group have searched for other dyslipidemia therapy, as an add-on to statin therapy. Unfortunately both treatments aimed to lower triglycerides (with fenofibrate - FIELD and ACCORD trials), as well as to increase HDL-C (with niacin - AIM-HIGH and HPS2-THRIVE trials, and with CETP inhibitors - from ILLUMINATE [torcetrapib] to ACCELERATE [evacetrapib] trials) were negative and failed to decrease CV residual risk. It seems that only therapies focused on LDL-C lowering might be effective, and the recent trials with ezetimibe (IMPROVE-IT) and PCSK9 inhibitors (FOURIER). We have been also waiting for new drugs with the effect on different parameters - such as apabetalone or bempedoic acid or with completely new approach of administering - such as inclisiran.
The American Heart Association (AHA) defined seven key metrics of cardiovascular health called "Life’s Simple 7" based on current smoking status, body mass index, physical activity, healthy diet score, total cholesterol, blood pressure, and fasting glucose. Ideal levels of these factors are defined as nonsmoking status (or quit for more than 12 months), BMI<25 kg/m2, physical activity of at least 150 minutes moderate or 75 minutes per week vigorous, at least 4 components of a healthy diet, total cholesterol <200 mg/dl, blood pressure <120/80 mmHg and not on medication, and fasting glucose <100 mg/dl. Data from the Atherosclerosis Risk in Communities and other prospective studies show having all such components in the ideal range to be associated with significantly lower cardiovascular disease (CVD) incidence and other measures. We have also demonstrated lung function measures of FEV1 and FVC to be positively associated with the prevalence of chronic obstructive pulmonary disease (COPD) to be negative related with the number of ideal cardiovascular health factors, although the strong relation of age to several of the cardiovascular health measures as well as to COPD and lung function measures attenuates these relationships. Nevertheless, it is likely that maintaining ideal levels of these cardiovascular health metrics can help delay the onset or progression of COPD as is the case for CVD emphasizing the value of educating patients on these measures.
ACTIVATION OF ADIPONECTIN RECEPTOR INDUCES PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 EXPRESSION BUT AMELIORATES LIPID PROFILES IN MICE

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Objective: The reduced adiponectin levels are associated with type 2 diabetes and atherosclerosis. Adiponectin exerts its functions by activating adiponectin receptor (AdipoR). Proprotein convertase subtilisin kexin type 9 (PCSK9) degrades low-density lipoprotein receptor (LDLR) protein to increase serum LDL-cholesterol levels. PCSK9 expression can be regulated by peroxisome proliferator-activated receptor gamma (PPARgamma) or and sterol regulatory element-binding protein 2 (SREBP2). However, the impact of AdipoR activation on hepatic PCSK9 and LDLR expression and serum lipid profiles remains unknown.

Approach and Results: AdipoR activation by agonists (ADP355 and AdipoRon) induced hepatic PCSK9 expression at the transcriptional level which solely depended on activation of PPAR-responsive element (PPRE) in the PCSK9 promoter. AdipoR agonists induced PPARgamma expression, thus, the AdipoR agonists-activated PCSK9 expression/production was impaired in PPARgamma deficient hepatocytes. Meanwhile, AdipoR agonists transcriptionally activated LDLR expression by activating SRE in the LDLR promoter. Moreover, AMPK was involved in AdipoR agonists-activated PCSK9 expression. Administration of ADP355 to mice increased PCSK9 and LDLR expression and serum PCSK9 levels, but decreased LDL-cholesterol levels.

Conclusions: Taken together, our study demonstrates that although AdipoR activation by agonists increased PCSK9 expression, it activated LDLR transcription directly which can surpass the effect of induced PCSK9 on LDLR degradation, and ameliorated lipid metabolism.
Background: Cardiovascular patients worldwide are becoming elder with larger number of cardiovascular risk factors (CRF). The Framingham risk score (FRS) comprises major CRFs and is commonly used as risk stratification for cardiovascular events.

Objectives: To investigate temporal trends in prevalence of CRFs among contemporary acute myocardial infarction (AMI) patients throughout a decade.

Methods: AMI patients hospitalized in a tertiary medical center, through 2002-2012, were studied. The documented baseline characteristics and CRF included: age, sex, ethnicity, type of AMI (STEMI vs. NSTEMI), chronic ischemic heart disease (CIHD), diabetes, dyslipidemia, hypertension, obesity and smoking as well as blood lipid profile. Personal FRS was calculated for each patient.

Results: a total of 17,780 admissions with AMI were included (mean age 67.8±14.1, 66.6% men, 10.1% Bedouins, 45.1% STEMI). The prevalence of CIHD was 81.9%, diabetes 42.9%, dyslipidemia 66.7%, hypertension 56.0% and smoking 6.1%. The mean FRS was 17.3±4.1. Throughout the investigated decade AMI patients became older, with trends towards higher rate of Bedouins (Muslims minority) and lower rate of STEMI and increased prevalence of CRF. The mean FRS increased from 16.8±4.0 (2002) to 17.3±4.1 (2012) (p<0.001). Multivariate analysis demonstrated a significant increase in FRS among NSTEMI patient and significant decrease for STEMI patients. Additional characteristics related to higher FRS were female sex and absence of CIHD.

Conclusions: During the last decade AMI patients became older with increased prevalence of CRFs. FRS increased among NSTEMI patients and decreased in STEMI patients. These trends are of impact on risk stratification and secondary prevention programs.

Figure. Mean (95%CI) FRS: temporal trends for STEMI and NSTEMI patients.
Assessment of the QT interval is an important marker for drug-induced cardiac toxicity and risk of sudden death. The most frequently used formulae to correct the QT for heart rate (QTc) were developed, almost 100 years ago in 1920 by Bazett (QTcBZT) using the square root of the heart rate and Fridericia (QTcFRD) using the cubed root of the heart rate. These equations are not optimal because (i) they assume a certain formula for the QT-RR relationship that may not be valid across the heart rate range (ii) they poorly correct for the effect of heart rate on the QT interval in large epidemiologic data bases such as the US National Health and Nutrition Examination Survey (NHANES) (iii) data from the same patient with increased heart rate produced by exercise showed discordant changes between QTcBZT and QTcFRD (iv) using QTcBZT or QTcFRD ignores the impact of age on QTc.

A new approach, the spline QT correction, was developed, from 13,627 ECGs in the NHANES data, using a cubic regression spline with four knots with an adjustment for gender and sex. Regression analysis showed the lack of relationship between heart rate and the spline QTc. The spline QTc was superior (significantly more flat i.e. no relationship with heart rate) compared to QTcBZT or QTcFRD. Age and sex factors were built into the new formula, if needed, providing the percentile of the QTc from this population data. Increasing heart rate with exercise showed little effect on QTc spline while QTcBZT increased and QTcFRD decreased with exercise.

Conclusion: It is time to adopt a new modern approach based on a functionally agnostic modeling of population ECG data. QTc spline can be readily applied to a specific patient, considers their age and sex, and indicates the percentile ranking in the population.
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IL-1β INDUCES CARDIAC ARRHYTHMIA IN DIABETES THROUGH ROS REGULATION

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Background: Diabetes is associated with prolonged QT interval and high risk of sudden cardiac death. A recent publication shows that cardiac macrophage-derived IL-1β causes QTc prolongation and increases arrhythmic risk in diabetes. Nevertheless, how IL-1β signals arrhythmic risk is unclear.

Methods and results: C57BL/6J mice were fed with 60 kcal% high fat diet (HFD) for 20 weeks. In comparison to the control mice fed with low fat diet, APD (411±15 ms vs. 61±5 ms, p<0.05) and QTc interval (50.6 ± 1.8 ms vs. 41.5 ± 0.8 ms, p<0.05) were substantially prolonged, and the inducibility of ventricular arrhythmia was significantly higher, while the heart function was preserved. Underlying these electrophysiological changes were alterations in L-type calcium current and Ca²⁺ handling leading to spontaneous sarcoplasmic reticulum (SR) Ca²⁺ releases and early afterdepolarizations (EADs). Cardiac IL-1β was elevated accompanied with upregulated NOX4 and increased mitochondrial reactive oxygen species (mitoROS). Inhibiting IL-1β or mitoROS by treating HFD mice with an IL-1 receptor antagonist (IL-1RA) or mitoTEMPO, respectively, shortened QT interval and APD, reduced calcium sparks and EADs, demonstrating that these electrophysiological changes were mediated by IL-1β and mitoROS. Moreover, inhibiting IL-1β lowered NOX4 and mitoROS, suggesting IL-1β signaled arrhythmia through ROS modulation. Further study revealed increased oxidation of ryanodine receptor and phosphorylation of Calcium/calmodulin-dependent protein kinase II (CaMKII), which was reversed by IL-1RA treatment.

Conclusion: Diabetes associated electrophysiological changes and arrhythmic risk was mediated by IL-1β. ROS, especially mitoROS, may provide a mechanistic link between IL-1β and DM associated arrhythmia.
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NEW ELECTROCARDIOGRAPHIC PREDICTORS OF SUDDEN CARDIAC DEATH
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Each year, sudden cardiac death (SCD) claims the lives of 180,000 to 450,000 Americans. During the past 20 years, strategies for prevention of SCD have focused on a subset of patients with coronary artery disease and have relied on the predictive power of low left ventricular ejection fractions (less than 35%) to determine candidacy for an implantable cardioverter defibrillator (ICD). While this subset of patients is at highest risk for SCD, most patients who die suddenly have more preserved ventricular function or have SCD as the first manifestation of heart disease; and currently are not candidates for primary prevention therapy with an ICD. Accordingly, risk stratification must be more inclusive. Effective, inexpensive, noninvasive, and widely available approaches are needed. Data from the Atherosclerosis Risk in Communities and from the Cardiovascular Health Studies recently reported by Waks and co-workers are noteworthy. The authors calculated five measures (sum absolute QRST integral, spatial QRST angle, spatial ventricular gradient [SVG] magnitude, SVG elevation, and SVG azimuth) of global electric heterogeneity (GEH) from the standard 12-lead ECG obtained in each of 20,177 patients representative of the general population (age range 44-100 yrs, 56% female, 77% white) to see how well GEH identified patients who suffered SCD during a mean follow-up of 14 yrs. After multivariable adjustment, baseline GEH measures and large increases in GEH parameters over time were each independently associated with SCD. When GEH data were added to standard clinical/demographic factors (age, sex, race, diabetes, hypertension, coronary heart disease, and stroke), risk prediction improved significantly. Data from a large set of patients who are representative of the general population demonstrate that measures of GEH are independently associated with SCD. These results set the stage for interventional trials aimed at preventing SCD in a broader set of patients at risk for dying suddenly.
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THE PROGNOSTIC IMPACT OF SINGLE EXTRA-STIMULUS ON PROGRAMMED VENTRICULAR STIMULATION IN BRUGADA PATIENTS WITHOUT PREVIOUS CARDIAC ARREST
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Aims: The prognostic value of programmed electrical stimulation (PES) in Brugada syndrome (BrS) remains controversial. One of the reasons for discrepant results may be due to the selection of stimulation protocol. We evaluated the prognostic value of a positive PES result (PES+) according to the inducible pacing sites and the number of extrastimuli in BrS patients without previous cardiac arrest (CA).

Methods: We enrolled 224 consecutive BrS patients without previous CA (mean age 51±14 years, 209 males), who underwent PES with the identical protocol. Clinical outcomes of development of CA were explored in the patients with and without PES+ according to sites and number of extrastimuli.

Results: During a mean follow-up period of 76 months, 12 cardiac events (CE: sudden cardiac death or documented VF) occurred (8 with and 4 without PES+). The incidence of CE was not different in patients with and without PES+, those with PES+ from RVA (n=72) or RVOT (n=60), and those with and without PES+ by up to 2 extra-stimuli (n=58). However, in patients that were PES+ by single extra-stimulus (n=8) the incidence of CE was significantly higher than in patients without PES+ (8.8 vs 0.6 %/yr, p<0.0001). On univariate analysis, syncope, spontaneous type 1 ECG, and PES+ by a single extra-stimulus were associated with CE.

Conclusions: Details of the stimulation protocol may be important for risk assessment in BrS patients without previous CA. A single extra-stimulus may be useful to distinguish intermediate-from low-risk BrS patients, regardless of choice of sites.
Absence of bystander-initiated resuscitation efforts, survival is rare. Yet the greatest impediment to the initiation of bystander resuscitation efforts is the aversion to or the complicated nature of mouth-to-mouth resuscitation. This is why our group in Arizona has been advocating chest-compression-alone bystander resuscitation since the early 1990s. Since then our group have published six studies that contained data from 169 swine showing that with prolonged cardiac arrest due to ventricular fibrillation, survival is the same with chest-compression-alone resuscitation as with ideal CPR, when chest compressions are interrupted for only 4 s for respiration. The prevalence of bystander-initiated CPR varies but averages somewhere between 20 and 30%. Surveys indicate that prevalence could be markedly increased if bystander chest-compression-alone CPR was advocated for individuals with witnessed unexpected sudden collapse. Chest-compression-alone ‘CPR’ has been advocated since November 2003 in Tucson, Arizona. There are data in humans to support chest compression alone for bystander resuscitation. The investigators from the Kanto area of Japan performed a survey of survivors in a study designated SOS-KANTO. They reported on 9592 out-of-hospital arrests. Of these, 4241 were witnessed. No bystander CPR was provided by 2917 cases (69%) and bystander CPR was provided in 1324 cases (31%). The type of bystander CPR was documented in 1151 cases. Of these, 712 victims (62%) received chest compression plus mouth-to-mouth ventilation and 439 victims (38%) received chest compression alone. Neurologically normal survival at 30 days was greater in those with witnessed arrest with. A large Meta-analysis from 2010 has also shown superiority of CCR vs standard CPR. The technique is ideally taught with emphasis on a metronome-guided rate of 100 per min. Additionally, full chest recoil after each compression is specifically emphasized. This approach can be easily and efficiently taught.
CARDIAC ARRHYTHMIAS AND SUDDEN DEATH

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CARDIAC RYANODINE RECEPTOR CHANNELOPATHY

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In cardiac Ca handling, ryanodine receptor (RyR) channel plays a key role. The channel is encoded by RYR2 gene, encompassing 105 exons on chromosome 1q43, and is expressed on sarcoplasmic reticulum (SR). It collaborates with voltage-dependent L-type Ca channel (LTCC) and releases substantial volume of Ca from the SR, which is a major Ca source for the myocardial excitation-contraction coupling. The channel opening is triggered by intracellular Ca increase through LTCC (Ca-induced Ca release). Since the first discovery of RYR2 mutations as the cause of catecholaminergic polymorphic ventricular tachycardia (CPVT1), several pathologic conditions were shown to be associated with RYR2 mutations.

CPVT is a familial arrhythmogenic disorder characterized by adrenergically-mediated polymorphic VT in the structurally intact heart with onset of manifestations in childhood and adolescence, leading to syncope and sudden cardiac death. Arrhythmias in CPVT are associated with gain-of-function RYR2 mutations and mediated by delayed afterdepolarizations (DADs), oscillations of the membrane potential associated with intracellular Ca-overload. RYR2 mutations are also found in some arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C type 2). More recently, RYR2-associated pathological entity was expanded to the non-compaction of the ventricular myocardium (LVNC), which is referred to as “spongy” myocardium. LVNC is characterized by numerous prominent trabeculations and deep inter-trabecular recesses in hypertrophied and hypokinetic segments of the left ventricle, detected by echocardiography or other imaging modalities. Functional RyR defects are thought to delay embryonic myocardial development with lack of compaction of the loose myocardial meshwork. Finally, several RYR2 mutations are reported to be related with short-coupled variant of torsade de points (ScTdP), characterized by bizarre polymorphic VT triggered by an extremely short coupling interval in the structurally intact heart. Though precise mechanistic link remains unknown, contrary to CPVT, a loss-of-function type mutation was identified in a proband with typical ScTdP phenotypes.
CARDIAC ARRHYTHMIAS AND SUDDEN DEATH

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RISK STRATIFICATION IN PEDIATRIC ASYMPTOMATIC WOLFF-PARKINSON-WHITE PATTERN: THE ONGOING DEBATE

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The risk of sudden cardiac death in asymptomatic Wolff-Parkinson-White pattern and how best to determine that risk have been long debated in both the pediatric and adult electrophysiology fields. Pediatric and Congenital Electrophysiology Society (PACES) guidelines on risk stratification published in 2012 intended to clarify the best practice, but questions remained unaddressed in that document and debate continues today. The utility of exercise tests or the presence of persistent or intermittent pre-excitation as markers of risk is debatable based on current and developing evidence. The use of isoproterenol in risk stratification is inconsistent. Whether or not treatment of asymptomatic WPW is indicated is also widely debated and is a frequent topic in the literature.
AORTIC AND PERIPHERAL ARTERIAL DISEASE: BASIC AND CLINICAL STUDIES

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MOLECULAR REGULATION OF EXTRACELLULAR MATRIX IN VASCULAR AGING
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Epidemiology studies have identified aging as a predominant risk factor that accelerates the pathogenesis of cardiovascular diseases, the leading cause of mortality and mobility in the United States and worldwide. Vascular aging, the age-related structural changes in the blood vessels, not only impair normal vascular contraction and compliance but also increase the incidence of cardiovascular disease, including hypertension, atherosclerosis and heart attack, stroke, and heart failure. We identified increased expression of the Runx2 transcription factor in mouse aortas in an age-dependent manner. In addition, Runx2 upregulation was also demonstrated in an accelerated aging mouse model, the klotho defective mice. Using the smooth muscle specific-Runx2 ablation model, we demonstrated that SMC-specific Runx2 deficiency inhibited aging-associated vascular complications, including neointimal formation, atherosclerosis, and vascular diseases. Mechanistically, we found Runx2 regulated vascular smooth muscle cell senescence and extracellular matrix protein production, two characteristics of vascular aging. These results demonstrating a new role of Runx2 in regulating VSMC aging phenotype and the pathogenesis of vascular aging provide novel insights into the molecular mechanisms underlying vascular aging process, which may lead to identifying new strategies to prevent and treat cardiovascular disease in aging.
cAMP has been shown to inhibit vascular smooth muscle cell proliferation and exerts a vasculoprotective effect. An upregulation of the early growth response protein-1 (Egr-1) expression has been linked with the development of atherosclerosis and intimal hyperplasia. We have recently demonstrated that angiotensin-II (Ang-II) stimulates Egr-1 expression via Ca2+/ERK-mediated cAMP-response element binding protein (CREB) activation. However, whether Ang-II-induced signaling leading to Egr-1 expression is modulated by cAMP remains unexplored. Therefore, in the present studies, we have examined the effect of cAMP on Ang-II-induced expression of Egr-1 and associated signalling pathways. Isoproterenol (ISO) and forskolin (FSK) attenuated Ang-II-induced Egr-1 expression in a dose-dependent fashion. In addition, dibutyryl-cAMP and benzoyl-cAMP, as well as isobutylmethylxanthine, attenuated Ang-II-induced Egr-1 expression. Moreover, inhibition of Ang-II-induced Egr-1 expression was accompanied by an increase in the phosphorylation of the vasodilator-activated phosphoprotein (VASP), and this was associated with a concomitant decrease in ERK phosphorylation. Blockade of PKA using H89 decreased VASP phosphorylation, restored Ang-II-induced ERK phosphorylation, and abolished ISO- and FSK-mediated inhibition of Ang-II-induced Egr-1 expression. In summary, these results suggest that PKA-mediated suppression of Ang-II-induced Egr-1 expression and phosphorylation of ERK may be among the mechanisms by which cAMP exerts its vasculoprotective effects. (Supported by a grant from CIHR)
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ESTIMATION OF IMMEDIATE PRE-DISSECTION AORTIC DIAMETER – IMPORTANT AND SURPRISING INFORMATION
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Background. Multiple studies have quantified the relationship between aortic size and risk of dissection. However, these studies estimated the risk of dissection without accounting for any increase in aortic size from the dissection process itself.

Objectives. This study aims to compare aortic size before and after dissection and to evaluate the change in size consequent to the dissection itself.

Methods. Fifty-five patients (29 Type-A; 26 Type-B) with aortic dissection (AoD) and incidental imaging studies prior to dissection were identified and compared to a control group of aneurysm patients (n=205). Average time between measurement at and prior to dissection was 1.7±1.9 years (1.9±2.0 years mean inter-image time in control group). A multivariate regression model controlling for growth rate, age and gender was created to estimate the effect of dissection itself on aortic size.

Results. Mean aortic sizes at and prior to dissection were 54.2±7.0mm and 45.1±5.7mm for the ascending (AA), and 47.1±13.8mm and 39.5±13.1mm for the descending aorta (DA), respectively. Multivariable analysis revealed a significant dilatory impact by the dissection itself (p<.001) and estimated an increase in size by 7.65mm (AA) and 6.38mm (DA). Thus, 82.8% (AA) and 80.8% (DA) dissected at a size lower than the guideline recommended threshold (55mm).

Conclusions. Aortic diameter increases substantially due to aortic dissection itself and thus, aortas are dissecting at substantially smaller sizes than natural history analyses have previously suggested. These findings have important implications regarding at what size to intervene surgically (suggesting a shift toward smaller aortic sizes).
Intraluminal (mural) thrombus (ILT) is reportedly found in up to 70-80% of patients with abdominal aortic aneurysm (AAA). Statistically, critical occlusion of the aorta and distal thromboembolic events are relatively rare components of the overall threat posed by ILT in AAA. A much more frequent consequence of ILT is its profound local effect on aneurysm progression and rupture. Recent studies have shown that the high concentration of activated neutrophils in the ILT of AAA are associated with high levels of proteolytic enzymes including cathepsins, elastases, collagen proteases, and other metalloproteinases. Marked increases in various reactive oxygen species have also been found at these sites with increased inflammatory cell infiltrates from the adventitia, reduced numbers of viable smooth muscle cells, and progressive degradation and thinning of aortic wall leading to eventual rupture. It was previously thought that ILT of AAA occurs primarily because of pooling or stagnation of blood in areas of aortic out-pouching facilitated by wall damage. In this talk we present the evidence from our laboratory, as well as others, suggesting that ILT can occur at sites of ballooning, curvatures, or branch points even, and perhaps particularly, where the overall rate of flow is not reduced. We show how altered hemodynamic shear forces at such sites, compounded by any of a variety of local or systemic factors, can result in damage to the aortic wall ranging from minimal desquamation of the endothelial lining to marked trans-medial defects followed by platelet deposition and thrombus formation at these sites. We will point out the unexpected similarities to the pathogenesis and consequences of Prinzmetal’s (vasospastic) angina as well as implications of these findings for treatment for prevention of aneurysmal progression and rupture.
AORTIC AND PERIPHERAL ARTERIAL DISEASE: BASIC AND CLINICAL STUDIES

CAN PRESENCE OF AORTIC PLAQUE PREDICT CORONARY HEART DISEASE?

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Carotid arteriosclerosis has been shown to be associated with coronary artery disease (CAD), however, the association does not seem to be very close. On the other hand, presence of aortic plaque (AP) may be associated with generalized arteriosclerosis because arteriosclerosis has been shown to originate from lower aorta. Carotid sclerosis was diagnosed by carotid ultrasonography (US). Aortic plaque was evaluated by US and CT (grading), and aortic valve calcification (AVC) was evaluated by echocardiography. Aortic Calcification was evaluated by CT. Aortic stiffness was calculated by cardio-ankle vascular index (CAVI). In 74 patients with aortic plaque (P patient), 46 patients had CAD (62.1%), 6 had PAD and 10 had CI. In 62 patients without plaque (NP patient), only 6 (9.68%) had CAD, 2 had CI and none had PAD. Incidence of CAD was higher in P patients than that in NP patients (P<0.01). In patients with aortic calcification by CT, CAD was observed in only 16.3%. Aortic plaque grade by CT was associated with presence of CAD (P<0.05). Mean PS in P patients was higher than that in NP patients (P<0.0001). Carotid plaque was not present in 3 of plaque group and in 19 of no plaque group (P<0.05). AVC or AP was an independent predictor of CAD. Presence of both aortic and carotid plaque with aortic valve sclerosis could strongly suggest presence of CAD (sensitivity or specificity > 95%).
THE CLINICAL IMPORTANCE OF CARDIAC CALCIFICATIONS

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Cardiac calcifications are frequently noted on routine clinical echocardiography. They’re particularly common in older patients and those with renal disease. They can involve the aortic root and valve, the mitral valve and annulus, and the sub-mitral apparatus. When severe aortic and/or mitral valve function can be affected. Otherwise they tend to garner little attention. However, they share risk factors with atherosclerosis and have been associated with cardiovascular disease, particularly stroke.

Calcium deposition in cardiac structures and vessels is the result of an inflammatory process that shares many similarities with atherosclerosis and is accelerated by the presence of renal dysfunction. The enzymatic processes involved are highly regulated and, in valvular tissue, can result in lamellar bone formation. While there are currently no effective treatments animal studies suggest possible methods of prevention.

There is no standard way to score echocardiographic calcifications but several semi-quantitative measures have been proposed. These have clinical utility in predicting cardiovascular events and mortality. They can also alert the clinician to the likely presence of chronic kidney disease, conduction disease, and atherosclerosis.

Aside from effects on valvular function calcification of the mitral annulus can be a nidus for infection. Multiple case reports and two case series have documented vegetations arising from the calcified mitral annulus, including an unusual type of large vegetation with a distinctive speckled appearance.

Finally, the distribution, size, and bulk of calcifications have important implications for structural heart procedures. Pre-procedure planning for TAVR and percutaneous mitral valve replacement needs to include careful assessment of calcium deposits in the aortic valve and mitral annulus.
DILATED AORTA: IS IT SAFE TO PERFORM EXERCISE ECHOCARDIOGRAPHY?

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Objective: To assess the safety of exercise echocardiography in patients with dilated thoracic aorta. Methods: We examined 80 patients with hypertension and ischemic heart disease (60 men and 20 women (63.7±8.25 years) with dilated thoracic aorta (sinus of Valsalva and/or proximal ascending aorta). In the study patients with bicuspid- and tricuspid valve were included. We analyzed family history of dilated aorta and persistence or absence of sudden cardiac death. Routine echocardiography was performed with measure the size of aorta, size and volume of the left chambers, grade of aortic insufficiency, aortic stenosis and left ventricular hypertrophy. We estimated the index of BSA: mean index for sinus Valsalva was 21,3±1,64 and for ascending aorta 20.8±1,96 respectively. Exercise echocardiography was performed on treadmill or upright bicycle. We analyzed three criteria of ischemia and all clinical symptoms such as angina, arrhythmias, drop of blood pressure, shortness of breath and syncope.

Conclusion: We did not find any complications during exercise echocardiography for this group of patients with dilated aorta.
AORTIC AND PERIPHERAL ARTERIAL DISEASE: BASIC AND CLINICAL STUDIES

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NOVEL BIODEGRADABLE STENT FOR USE IN CONGENITAL HEART DISEASE
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Current BDS are weaker than similar size metal stents raising concerns for stent collapse when subjected to the elastic forces and other mechanical strain in large vessels like the aorta. Our novel double opposing helical (DH) BDS made of poly-l-lactic acid (PLLA) have the potential for use in CHD and the unique design enables manufacturing to diameters applicable in CHD. Our study aims were: 1. Create a model of coarctation of aorta in minipigs. 2. Evaluate feasibility of stent implantation (DH BDS and metal) and assess mid-term results and inflammatory profile.

Methods: Using left lateral thoracotomy approach, 13 Yucatan minipigs (3-8 kgs) underwent surgical CoA creation with elliptical aortic wall resection. Cardiac MRI was performed to evaluate the CoA followed by cardiac catheterization and implantation of the BDS and metal stents 6-8 weeks from CoA surgery. CoA stents were evaluated with MRI, angiography, IVUS and histopathology at 3, 6, 9 and 12 months after stent implantation.

Results: All 13 animals survived CoA creation surgery. Imaging showed mild to moderate CoA at baseline. Twelve animals underwent successful stent dilation of the CoA with BD (7) and metal (5) stents of 10-12 mm diameters. The remaining 1 animal was followed as control without stent dilation and euthanized after 3 months following sham cath procedure. Five animals had residual CoA after high pressure redilation of the stent. Follow up repeat imaging showed good stent apposition with preserved stent integrity.

Conclusions: A resection CoA model was successfully performed. Feasibility to treat the CoA with DH BDS at diameters 10-12mm is established. The unique design of the BD stents makes it withstand the elastic forces of the aorta in resistant stenotic lesions. Further studies are needed to evaluate long term vessel/stent patency and assess risks associated with stent fragment embolization during the degradation process.
INFLUENCE OF DIASTOLIC BLOOD PRESSURE ON ADVERSE OUTCOMES IN TREATMENT OF HYPERTENSION

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Background: Hypertension is a widely prevalent disease affecting about 1 billion people worldwide. Despite numerous studies, there is limited data and conflicting evidence concerning outcomes pertaining to diastolic blood pressure (DBP).

Objective: To study the influence of DBP on adverse outcomes while treating hypertension.

Methods: This is a retrospective data analysis using the Systolic Blood Pressure Intervention Trial (SPRINT) database. The primary outcome was the composite end-point of myocardial infarction (MI), non-MI acute coronary syndrome, heart failure, stroke or death from cardiovascular causes. Subjects were divided into 3 categories based on their mean DBP: <60 mmHg (group 1), 60-79 mmHg (group 2), >80 mmHg (group 3) and were further classified as systolic blood pressure (SBP) <135 mmHg or SBP >135 mmHg. A total of 8237 subjects were analyzed (814 in group 1, 5882 in group 2 and 1588 in group 3).

Results: The mean DBP for groups 1, 2 and 3 were 55.9, 70.6 and 93.5 mmHg respectively. The primary event occurred in 9.58% subjects in group 1; 5.21% subjects in group 2 and 4.34% subjects in group 3. Patients in group 2 had a statistically significant 28% reduced risk (Hazard Ratio [HR] 0.72, 95% Confidence Interval [CI] 0.55-0.95, p=0.02) and patients in group 3 had 25% reduced risk (HR 0.75, 95% CI 0.5-1.10, p=0.15) of developing the primary endpoint relative to those in group 1. The CI for groups 2 and 3 overlap suggesting no significant difference between the groups. Patients with history of coronary artery disease (CAD) (HR 2.08, CI 1.7-2.5, p<0.05) and increasing age (HR 1.04, CI 1.02-1.05, p<0.05) had a higher likelihood of developing the primary endpoint.

Conclusion: Our results indicate that low DBP is associated with increased incidence of adverse events and the co-existing history of CAD and increasing age contribute to worse outcomes. Moreover, the incidence of primary event in the high DBP group was low; arguing against the J curve phenomenon.
EFFECTS OF ADDING SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS TO STANDARD CARE IN PATIENTS WITH TYPE 2 DIABETES

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Objective: To evaluate the effects of sodium-glucose cotransporter 2 inhibitors (SGLT-2 inhibitor), in addition to standard care, in patients with type 2 diabetes.

Methods: We searched Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials (RCTs) assessing the incremental effect of SGLT-2 inhibitor to standard care, in patients with type 2 diabetes. Endpoints were all-cause mortality, cardiovascular (CV) mortality, myocardial infarction (MI), heart failure (HF), stroke, and renal failure. Event rates were compared using a Forest plot of odds ratio (OR) using a random effects model.

Results: We included 18 RCTs with 17,966 patients for final analysis. There was significant reduction in all cause mortality [OR 0.71 (95% CI 0.59 to 0.85)]; and CV mortality [OR 0.64 (95% CI 0.51 to 0.80)] with addition of SGLT-2 inhibitor to standard of care in patients with type 2 diabetes. However, there was no statistically significant difference in MI [OR 0.86 (95% CI 0.70 to 1.07)]; HF [OR 1.656 (95% CI 0.347 to 7.893)]; Stroke [OR 1.109 (95% CI 0.867 to 1.418)] and renal failure [OR 1.332 (95% CI 0.817 to 2.172)] with addition of SGLT-2 inhibitor. There was no significant heterogeneity among the studies included in the analysis for various end points.

Conclusion: In patients with type 2 diabetes, addition of SGLT-2 inhibitor to standard care, results in a reduction in all cause and CV mortality. Additional studies are indicated to better understand the mechanism of mortality reduction with SGLT-2 inhibitors.
COMPLETE CORONARY REvascularization IN ST ELEVATION
MYOCARDIAL INFARCTION IN HIGH-RISK PATIENTS: DIABETICS WITH
MULTIVESSEL DISEASE
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Introduction: Diabetic (DBT) patients had high prevalence of multivessel disease. The diabetic status and its relationship to the success of complete revascularization (CR) in the setting of STEMI are poorly informed.

Objectives: To determine the clinical outcomes of complete primary coronary revascularization in DBT patients.

Methods: in 433 primary coronary angioplasty, of which 207(48%) had significant coronary multivessel disease were performed. Two groups were defined: group A= Non diabetic group (n=165) and group B= Diabetics (n=42) who had multivessel coronary disease. The baseline characteristics were, groups A and B n(%), respectively: age 58.8 ± 11 vs. 64 ± 9 p=0.005; prior infarction 17 (10) vs 13 (31) p = 0.002; average 53.7 vs 49.9 ventricular function p = 0.05; Killip Kimball to admission no "A" 37 (22) vs 10 (24); anterior infarction 63 (38) vs 13 (31); three-vessel coronary disease 41 (25) vs 13 (31); CR in the same session 49 (30) vs 13 (31); CR same hospitalization 29 (17) vs 9 (21); CR within 30 days 6 (4) vs 1 (2.5), use IIbIIIa 29(17) vs 4 (9); use drug-eluting stents 50 (30) vs 20 (48) p= 0.04; door balloon time 108 ± 57 vs 110 ± 60.

Results: group A and B n(%) respectively: in hospital death cardiovascular 1 (0.6) vs 2 (5); early coronary occlusion 1 (0.6) vs 0; 3 major bleeding (1.8) vs 1 (2.5). At follow-up 12 months cardiovascular mortality in patients with incomplete revascularization was in DBT patients 1 (1.25) vs nondiabetic 3 (15) p=0.02. In DBT patients CR showed relatively fewer deaths (4%) vs patients with incomplete revascularization (15%) although without statistical significance.

Conclusion: At follow-up 12 months complete anatomical revascularization in DBT patients who present with STEMI had lower cardiovascular mortality vs patients with the same glycemic status and residual coronary heart disease.
MANAGEMENT OF HYPERTENSION USING AMBULATORY BLOOD PRESSURE MONITORING, A SAUDI EXPERIENCE

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Background: Hypertension is highly prevalent in general Saudi population and often poorly controlled. Ambulatory blood pressure monitoring (ABPM) record is recommended in clinical practice (for diagnosis and evaluation of blood pressure control). Evidence indicates that target organ damage is more closely related to ABPM measurements than clinic BP measurements.

Objectives: Objective of this study is to assess the utilization of ABPM in management of hypertension at King Abdulaziz Hospital, Al Ahsa. To our knowledge, efficacy of the use of ABPM in adult hypertensive patients has not been previously reported in KSA.

Methods: We conducted a retrospective review of patients above age of 14 who had at least one ABPM from January 1st, 2011 to December 31st, 2015. We defined our primary and secondary objectives. Data was collected from ABPM and medical records on a form and analyzed using SPSS v 23.

Results: 278 ABPM records were identified and analyzed during the study period. 34 records were removed from final analysis due to non-availability of complete data. Results on 243 ABPM patient records are presented here. 54% (n= 127) were male. Mean age was 52.05 ± 13.78 (range 19-83) years. 63% known hypertensive (prior to test) and 29% had diabetes. Main indications for ABPM included suspected masked hypertension (15%), treatment effect evaluation (14%) and uncontrolled hypertension (10%). 58 % of patients were on treatment prior to ABPM. 53% were taking more than two medications. 76% had high BP during test. 46% were poorly controlled previously known and 20% were newly diagnosed hypertensives. As result of the test 32% had no change done in their treatment regime despite high readings. After 3 months follow up study 41% had better BP control, 28% had no change. Yet 22% had no follow up study done.

ABPM is useful tool for hypertensive patients that is underused.
ROLE OF CGRP AND NO IN THE PROTECTIVE EFFECT OF TRANSCUTANEOUS ELECTRICAL STIMULATION IN DEVELOPMENT OF FRUCTOSE-INDUCED HYPERTENSION IN RATS

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Objectives: Sensory neuropeptide calcitonin gene-related peptide (CGRP) and nitric oxide (NO) are the most potent microvascular vasodilators. Transcutaneous electrical stimulation of sensory nerves (TENS) attenuated metabolic disturbances and hypertension. The aim: to evaluate effect of TENS on content of CGRP and NO in the development of fructose-induced hypertension.

Background: Metabolic syndrome (MS) constitutes multifaceted disorders including insulin resistance, glucose intolerance, obesity and hypertension. It is shown that CGRP and NO may be involved in the regulation of vascular responses, however their role in the development of MS-associated hypertension is still unclear.

Methods: Male Wistar rats received either 12.5 percentage fructose solution in their drinking water for 10 weeks or tap water to drink (control). Eight weeks after fructose consumption low-frequency TENS (1mA, 2 Hz, pulse duration 0.5 msec) was given to the paws of rats daily (10 min) for two weeks. Systolic blood pressure (SBP) was measured by non-invasive method (Coda, Kent Scientific, USA). Blood serum content of CGRP was determined with enzyme-linked immunosorbent assay kit Cloud Clon Corp, USA. The blood plasma content of nitrite/nitrate (NO2/NO3) was measured by Griess assay.

Results: Fructose consumption caused a persistent increase of SBP, the decrease in CGRP level and did not affect NO2/NO3. TENS prevented the increase of SBP in rats taking fructose, recovered CGRP content and resulted in the increase of NO2/NO3 level.

Conclusion: The development of fructose-induced hypertension reduces CGRP content in blood. TENS–induced decrease of SBR in fructose rats can be mediated in part by restoration of the reduced level of CGRP and increased activity NO system.
ASSOCIATION OF OBESITY TYPES WITH THE 10-YEAR CORONARY HEART DISEASE RISK IN TIBET AND XINJIANG AREA OF CHINA

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Objective: To investigate the association between types of obesity and 10-year coronary heart disease risk in a Tibetan and Xinjiang population of China.

Methods: Using stratified multi-stage random sampling, 7631 populations aged 35 or older were examined with international standardized examination in 2015-2016. There were 5802 participants eligible for analysis.

Results: The prevalence of general obesity, central obesity, visceral obesity and compound obesity were 0.53%, 12.62%, 10.08% and 42.35%, respectively. Out of all compound obesity, 58.65% (1441/2457) included all types of the obesity in our study. The 10-year coronary heart disease risk of man was higher than woman [(3.05±4.14)% for man and (1.42±2.37)% for woman, respectively], P < 0.0001. Compound obesity (30.16%) had the greatest percent of the highest 10-year coronary heart disease risk than central obesity (28.01%), visceral obesity (18.46%) and general obesity (19.35%). After adjustment for confounding factors, multivariate analysis found compound obesity was associated with the greatest risk to the 10-year coronary heart disease risk (OR, 95%CI: 2.889, 2.525~3.305), moreover people with anomalous BMI and WC had greater risk (OR, 95%CI: 3.168, 2.730~3.677).

Conclusion: Obesity was popular in Tibet and Xinjiang area of China, male and compound obesity (especially both BMI and WC were abnormal) population has a greater risk to 10-year coronary heart disease.
ISOLATED DIASTOLIC WHITE COAT HYPERTENSION

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Introduction: White coat hypertension (WCH) is classically characterized as elevated systolic pressures, with widened pulse pressures, triggered by physician presence. However, in isolated diastolic white coat hypertension (IDWCH), systolic pressures remain relatively unchanged, both in physician’s office and with ambulatory blood pressure monitoring (ABPM), while elevated diastolic pressures are triggered by physician presence. This study reports two IDWCH cases.

Methods: Three decades of ABPM were reviewed to identify IDWCH cases.

Results: Only two patients, with striking similarities, were identified with IDWCH. The first case was a 220 lb, 5’7,” 55-year-old postmenopausal woman presenting with headaches and blood pressures of 120-140/85-100mmHg. Two years before, she had right sided stroke associated with previously undiagnosed atrial fibrillation. She made a complete recovery and continued on lifelong anticoagulation. Headaches continued, eventually, leading to left temporal arteritis diagnosis. ABPM demonstrated diastolic pressures ranging 25-30mmHg lower than reported office values. Systolic pressures remained consistently 120-140mmHg, in office and out. The second case was a 200 lb, 5’5’’ 66 year postmenopausal woman, who presented with an unusual but temporary stroke. Though she could name the letters, her ability to read simple words was impaired. There was no defect in speech and she could read and play sheet music. Blood pressure was 150-155/90-95mmHg. Office pressures remained similarly elevated during her 3-year follow-up. ABPM demonstrated diastolic pressures all below 80mmhg with 60mmHg troughs. As part of a study investigating white coat hypertension triggers, she was wearing an ambulatory blood pressure monitor during a follow up visit, when the diastolic blood pressure drastically rose to 95mmHg.

Conclusion: IDWCH is a rare condition of unexplained cause and unknown significance. Systolic WCH is believed to result from sympathetic and endocrine stimulation. It is not known how diastolic pressures are elevated without systolic elevation, in IDWCH.
INTERVENTIONAL TREATMENT FOR RESISTANT HYPERTENSION: A SYSTEMATIC REVIEW

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Background: Estimates demonstrate that 8 to 15% of hypertensive patients can be considered as being treatment resistant. According with definitions by the American College of Cardiology, resistant hypertension (RH) can be defined as a failure to reach blood pressure (BP) goals despite optimal treatment with 3 or more different antihypertensive drugs, one being a thiazide-like diuretic. RH is associated with higher risk for major cardiovascular events, and new methods of treatment have been evaluated to determine the optimal therapeutic approach.

Objectives: This systematic literature review aims to analyse which interventional therapies are safe and effective in reducing BP in RH.

Methods: This review followed PRISMA statement recommendations, and the article search was performed on PUBMED considering specified inclusion and exclusion criteria.

Results: Eleven articles were included, 9 evaluating renal denervation (RDN), and 2 analysing the implant of a baroreflex activation therapy (BAT). Even though most studies evaluating RDN showed antihypertensive benefit, the only study to include a placebo group, the SIMPLICITY HTN-3 trial, failed to show a significant benefit in reducing BP when compared with a sham-procedure. Concerning the BAT method, the two studies included found benefit in reducing BP with safety.

Conclusions: Considering the results available in literature, there is not enough evidence supporting the use of these two interventional methods for RH treatment in routine care. The SIMPLICITY HTN-3 trial had a great impact in these data, demonstrating that previous data regarding RDN had methodological inadequacies. Concerning the BAT, more studies are needed to conclude its benefit in reducing BP in RH. RDN does not show enough evidence to support its use in typical routine, and studies being performed at the present will confirm or deny this. The BAT could represent a possibility of treatment, and more studies with larger samples are essential to clarify this matter.
PHARMACOKINETIC, SAFETY AND EFFICACY DATA OF CAPRE®, A NOVEL INVESTIGATIONAL OMEGA-3 DRUG DERIVED FROM KRILL OIL

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Objectives: To compare the pharmacokinetic, safety and efficacy data of CaPre with omega-3 prescription drugs containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Background: CaPre is a mixture containing EPA and DHA present as a combination of phospholipid esters and free fatty acids. CaPre is being developed for the treatment of severe hypertriglyceridemia.

Methods: Pharmacokinetic and efficacy data from two Phase 1 trials (single and multiple ascending dose trial along with a comparative bioavailability study against Lovaza) and two Phase 2 dose-finding trials with CaPre were compared to established omega-3 prescription drugs for exposure (AUC⁰⁻⁷₂, C⁰⁻⁷₂) of total EPA+DHA in plasma and lipid profiles.

Results: In fasting conditions, CaPre showed higher AUC⁰⁻⁷₂ and C⁰⁻⁷₂ for total EPA+DHA compared to Lovaza. When following a high fat meal (HF), Lovaza showed higher bioavailability compared to CaPre. Following multiple daily doses, the bioavailability of CaPre is not meaningfully affected by the fat content of the meal consumed prior to dose administration. CaPre presents a more comprehensive effect on lipid markers at various doses by significantly lowering triglycerides and non-HDL cholesterol levels while having either a neutral or a beneficial effect of LDL- and HDL-cholesterol.

Conclusion: The bioavailability of EPA and DHA in CaPre is far less affected when taken on an empty stomach as compared to the Ethyl Ester forms in Lovaza. The bioavailability of Lovaza is maximal following administration with a HF meal which is not suggested for hypertriglyceridermic patients, but is dramatically reduced under fasting conditions. Patients with hypertriglyceridermia adhering to a low fat diet should retain efficacy when taking CaPre in either the fasted state or with a low fat diet. In addition, CaPre may become an interesting clinical option as it appears to provide multiple potential effects on lipid markers such as LDL- and HDL-cholesterol, non-HDL cholesterol and triglycerides.
OBJECTIVE: To compare the effects of pericardium patch and pulmonary patch for treating aortic coarctation (CoA) combining hypoplastic aortic arch in infants, and report the early and mid-term outcomes.

BACKGROUND: The optimal patch material for infants with CoA combining hypoplastic aortic arch is controversial.

METHODS: A total of 57 patients with AC combining hypoplastic aortic arch treated in Fuwai hospital from 2009 to 2014 were retrospectively studied. The patients were divided into 2 groups: Pericardium group (n =26) and Pulmonary group (n =31). The changes of the pressure gradient (PG) and re-stenosis occurrence were compared.

RESULTS: There were 2/57 (3.5%) patients died, 1 in Pericardium group by pulmonary hypertension crisis, the other 1 in Pulmonary group by respiratory distress syndrome. No renal failure or neurological complication occurred in neither group. The cardiopulmonary bypass time, aortic clamping time, ventilator time and ICU stay time were similar between two groups (P>0.05). Selective cerebral perfusion time in Pericardium group was shorter than Pulmonary group (30.5±8.6) vs (35.6±10.3)s, (P <0.05). By echocardiography estimation, the post-operative PG were decreased than preoperaton, as in Pericardium group (9.5±7.5) vs (39.9±15.5) mmHg and in Pulmonary group (11.8±11.3) vs (39.2±14.5)mmHg, (both P<0.05); while post-operative PG were similar between 2 groups, (P>0.05). Follow-up study was conducted in 51 patients for (33.6±16.6) months, two groups both had 6 patients with re-stenosis. Kaplan-Meier curves presented that Pulmonary group was superior to Pericardium group in re-stenosis occurrence during follow-up period.

CONCLUSION: Both pericardium patch aortoplasty and pulmonary patch aortoplasty were effective for treating the patients with AC combining hypoplastic aortic arch, the early post-operative efficacy was similar, while the mid-term follow-up result was better in pulmonary patch aortoplasty.
ATRIAL FIBRILLATION AND STROKE IN PATIENTS WITH REPAIRED TETRALOGY OF FALLOT

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Abbreviations:
AA = atrial arrhythmias
AF = atrial fibrillation
CHD = congenital heart disease
TE = thromboembolic events
TOF = Tetralogy of Fallot

Objectives: This retrospective cohort study investigates the risk factors for AF and its relationship with TE in adults with repaired TOF.

Background: The association between AF and increased stroke risk is well established in the general population. AA are common in adults with CHD and is associated with morbidity and mortality. Validated risk stratification tools such as the CHADS² score may not apply to this unique population.

Methods: We conducted a retrospective cohort study of all TOF patients followed at a tertiary care center to determine the prevalence and predictors of AA and TE risk over long-term follow-up. Univariate and where possible, multivariate analyses were performed to identify predictors and the association between AF and stroke.

Results: Two hundred sixty TOF patients (57.3% female, median age 34) were followed for 5108 patient-years, with median follow-up of 15 years. Sixty-three patients (24.2%) had at least one episode of AF, atrial flutter, and/or focal atrial tachycardia. Twenty-four patients (9.2%) had AF. Factors associated with AF include age ≥54, diabetes mellitus, and hypertension (p<0.001). Twenty-nine patients (11.1%) had TE: 11 had stroke, 8 had TIA, and 10 had peripheral embolisms. Eight of the eleven (72.7%) patients who had strokes had AF. Having AF was a predictor for stroke (p<0.03), however a CHADS² score ≥2 was not statistically associated with stroke (p=0.17). The rate of stroke for the study cohort was 2.15 per 1000 patient-years. Diabetes mellitus, hypertension, and smoking were not associated with stroke (p>0.07).

Conclusions: While having AF was significantly associated with stroke, CHADS² score ≥2 was not, which suggests that this tool may be of limited use in this population. Traditional risk factors like diabetes mellitus, hypertension, and smoking were not associated with stroke. These data support current literature that other factors, such as complexity of congenital disease, may play a role in the relationship between AA and TE in adults with CHD.
UN-ROOFING A MYOCARDIAL BRIDGE
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Background: Myocardial bridge (MB) is defined as a segment of a coronary artery that takes an intra-myocardial course. The presence of MB has been observed in as many as 40%-80% of cases on autopsy, radio-graphically from 0.5% to 16.0%, and often asymptomatic. However, it has been associated with angina, coronary spasm, myocardial infarction, arrhythmias, syncope, sudden cardiac arrest and death. Conflicting opinions exist on the timing of surgical intervention for MB.

Methods: We present an unusual case of a young female, with prior aortic surgery, who had refractory chest pain despite optimal medical therapy. Stress testing revealed anterior ischemia. Cardiac catheterization showed MB of the LAD with significant compromise of blood flow (FFR 0.75 with adenosine). We proceeded with surgery. Intra-operatively, we found an unusually long (10 cm) intra-myocardial segment of LAD which was managed by surgically un-roofing. Post procedure, our patient felt better. Repeat cardiac catheterization showed no further narrowing of LAD with FFR of 0.8 in its distal segment.

Discussion: MB is present mostly in female patients (74.5%), median age at 56.2 years old, and mostly involving the LAD (77.2%). Average length of MB is 21.85±16.10mm (range 5-70 mm). Our case is unique as the involved MB was 10 cm in length, the longest ever reported. Multiple imaging modality revealed significant coronary insufficiency, with subsequent clinical and radiographical improvement upon un-roofing of the culprit coronary vessel.

Conclusion: Management decision on MB remains controversial. This is a case of the longest symptomatic MB, with subsequent improvement post-un-roofing.
Late Presentation of Symptomatic Anomalous Left Main Coronary Artery

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Coronary anomalies carry an incidence of 1.3% in patients undergoing coronary angiography, and vast majority are not clinically significant. However, “malignant anomalies” are associated with an increased risk of sudden cardiac death possibly due to extrinsic compression as they traverse between the major arteries generally at times of high cardiac output.

We present the case of a 65-year-old male veteran brought to our hospital with sudden-onset chest pressure, palpitations, and near-syncopal episode at rest. Electrocardiogram demonstrated ventricular tachycardia associated with hemodynamic instability that was emergently cardioverted to normal sinus rhythm with symptom resolution. He had a questionable history of coronary anomaly without any detailed documentation. Coronary computed tomography angiography demonstrated anomalous aortic origin of the left coronary artery (AAO-LCA) from the right sinus of Valsalva with an inter-arterial course between the right ventricular outflow tract and the aorta.

He had mild elevation of cardiac enzymes and subsequent left heart catheterization failed to demonstrate any coronary obstructive lesion. Exercise nuclear stress test demonstrated mild-moderate anterolateral ischemia. We felt that the coronary anomaly had contributed to his presentation. He then underwent successful transposition of the LCA from the right to left sinus of Valsalva. Subsequent electrophysiology study failed to show any inducible arrhythmias.

This is an exceedingly rare case of myocardial ischemia felt to be secondary to extrinsic LCA compression due to malignant anomaly without evidence of luminal obstruction. Most of the literature on symptomatic the coronary anomalies involves presentations in young adults including risk of sudden death. To our knowledge, late presentation of this particular anomaly in a patient with established military career has never been reported. While bypass grafting or unroofing is an ACC / AHA Grade B recommendation for patients with documented AAOLCA, true evidence-based guidelines for management do not exist due to the rarity of the condition.
PROGNOSTIC VALUE OF RED BLOOD CELL DISTRIBUTION WIDTH IN PEDIATRIC PATIENTS WITH CONGENITAL HEART DISEASE

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Objectives: To evaluate the predictive value of red cell distribution width (RDW) in clinical outcomes after pediatric congenital heart disease (CHD).

Background: Recently, considerable attention was paid to the prognostic value of RDW, and continues studies found the similar association between RDW and various cardiovascular diseases, from myocardial infraction to heart failure. However, the role of RDW has not been elucidated in CHD patients, especially for cyanotic CHD. We conducted the present study with the aim to evaluate the predictive value of RDW in CHD patients.

Method: Between January 2016 and October 2016, 362 pediatric patients underwent complex congenital cardiac surgery were assessed for clinical outcomes and RDW in this retrospective study. Preoperative RDW (normal higher limit value:15%) was considered as a categorical binary variable. Discharge mortality, hospital complications and the duration of mechanical ventilation or ICU, were all compared between high and low RDW group.

Results: Of the 362 patients, preoperative RDW values (mean: 16.3%), was obviously higher than normal value. Among these, 283 cyanotic patients’ mean RDW range 16.6±4.5 % was higher than non-cyanotic patients’ range 15.4 ± 2.7 % (P=0.004). The discharge mortality and complications were all no significant difference between low and high RDW group. However, prolong mechanical ventilation times and ICU stay were associated with higher RDW compared with low RDW group.[(16.5h,[9h-42.3h]) vs (12h, [7h-25h] ), P=0.008] and [(ICU stay 19.3±7.8 days) vs (16.9±5.1 days), P=0.03].

Conclusions: In special CHD populations, the increased RDW is significantly associated with adverse clinical outcomes. The low cost and readily accessible of this laboratory variable may strengthen its usefulness in daily practice, but the potential mechanisms underlying this association still needs exploration.
SPINAL CORD INJURY-INDUCED SYSTOLIC DYSFUNCTION IS ASSOCIATED WITH CARDIOMYOCYTE ATROPHY AND UP-REGULATION OF PROTEOLYTIC PATHWAYS

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Objective: Spinal cord injury (SCI) causes autonomic dysfunction, altered neurohumoral control, profound hemodynamic changes and severe physical deconditioning, which leads to maladaptive cardiac remodeling and subsequent increased risk of cardiovascular disease (CVD). Despite several observational studies reporting a higher prevalence of cardiac dysfunction post-SCI, the underlying mechanisms remain poorly understood. Here we investigated the cellular and molecular mechanisms underlying post-SCI cardiac dysfunction.

Design/Method: We conducted T3 complete SCI in male Lean Zucker rats (SCI, n=9) and compared responses against an uninjured Lean Zucker group (CON, n=9). Cardiac function was examined in vivo using echocardiography and direct left-ventricular catheterization with a pressure-volume conductance catheter. Twelve weeks post-injury, animals were sacrificed. Blood and tissue samples were collected for further histological and gene expression analysis.

Results: Compared to CON, SCI exhibited significant reduction in cardiac structural indices including left ventricular (LV) dimensions and cardiac mass to femur length ratio, indicating the presence of cardiac atrophy post-SCI. Furthermore, cardiac functional indices (i.e., stroke volume, cardiac output and contractility) were significantly reduced post-SCI. Histological analysis indicated a significant decrease in cardiomyocyte length and width in SCI group compared to CON (P<0.05). Cardiac gene expression analysis demonstrated up-regulation of cellular proteolytic pathways (i.e. the ubiquitin–proteasome system (UPS) and autophagy) post-SCI. Lastly; blood profiling revealed a significant decrease in plasma norepinephrine (P<0.0001) and a simultaneous increase in plasma angiotensin II (P=0.012) post-SCI.

Conclusion: SCI is associated with impaired systolic function that is accompanied by cardiomyocyte atrophy, the latter of which occurs in concert with up-regulation of UPS and autophagy, the two main protein degradation pathways in the cell. Atrophy of cardiomyocytes is likely a response to the changes in circulatory profile of norepinephrine and angiotensin II.
MOLECULAR CARDIOLOGY AND VASCULAR BIOLOGY, BASIC RESEARCH

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DPP-4 INHIBITION BY LINAGLIPTIN PREVENTS CARDIAC DYSFUNCTION AND INFLAMMATION BY TARGETING THE NLRP3/ASC INFLAMMASOME

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A recent study suggested that DPP4 inhibition has a direct, GLP-1 independent, effect on the progression of diabetic nephropathy via interaction with integrin-α1. We compared the effects of no treatment, linagliptin (Lina, a DPP4 inhibitor) and direct GLP-1 receptor activation by exenatide followed by exendin-4 in an infusion pump (EX) on infarct size (IS) and post-infarction activation of the inflammasome in wild type (WT) mice and in db/db mice with type-2 diabetes.

Methods: Mice underwent 30min ischemia followed by reperfusion. IS was assessed by TTC at 24h of reperfusion. Cardiac function was assessed by echocardiography 2weeks after infarction. Activation of the inflammasome in the border zone was assessed by rt-PCR 2 weeks after reperfusion.

Results: Lina and EX limited IS in both the WT (23±2% and 32±3% vs. 50±3%) and the db/db mice (29±2% and 29±2% vs. 53±2%). Left ventricular ejection fraction was reduced by infarction (56±1% vs. 81±1% in the WT and 50±1% vs. 78±1% in the db/db mice). Lina and EX improved LVEF without a difference between Lina and EX in both the WT (73±1% and 73±2% vs. 50±3% in the controls) and the db/db (68±1% and 66±2% vs. 53±2% in the controls) mice. Messenger RNA (mRNA) levels of ASC, NALP3, IL-1â, IL-6, Collagen-1 and Collagen-3 were higher in the db/db mice than in the WT mice. Myocardial infarction increased these levels in the WT and db/db mice. Lina more than Ex attenuated the increase in ASC, NALP3, IL-1â, IL-6, Collagen-1 and Collagen-3, especially in the db/db mice. Conclusions: Lina and EX had similar effects on IS and post-infarction function, but DPP-4 inhibition with Lina attenuated the activation of the inflammasome and the upregulation of collagen-1 and -3 more than direct GLP-1 receptor activation by EX.
DOWNREGULATED CAVEOLIN-1 EXPRESSION PLAYS A POTENTIAL ROLE IN CORONARY ARTERY SPASM BY INDUCING NITRIC OXIDE PRODUCTION IN VITRO

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Objective: To investigate the effects of the downregulated caveolin-1 (Cav-1) expression on nitric oxide (NO) and endothelin-1 (ET-1) production in lipopolysaccharide (LPS)-damaged primary human umbilical vein endothelial cells (HUVECs) in a model of the coronary artery spasm (CAS) microenvironment induced by acetylcholine (ACh) treatment.

Methods: Small interfering RNA (siRNA)-mediated Cav-1 downregulation in HUVECs was confirmed by Western blotting. Cell viability and superoxide dismutase (SOD) inhibition in HUVECs incubated with LPS (0, 10, 25, 50, 75, and 100 μg/mL) were measured by CCK8 assay and a SOD kit, respectively. [Ca²⁺]i in Fura4-AM-loaded cells was detected by fluorescence microscopy. NO and ET-1 levels in cell culture supernatants were measured by the nitrate reductase method and ELISA, respectively.

Results: Cav-1 siRNA, especially siCav-1(2), downregulated Cav-1 protein expression. LPS (75 μg/mL) induced a significant decrease in HUVECs/si-NC and HUVECs/siCav-1 viability compared to the other concentrations of LPS. Compared with the effects of untreated cells, SOD inhibition in HUVECs/si-NC and HUVECs/siCav-1 was significantly decreased by LPS (75 μg/mL). ACh stimulation increased [Ca²⁺]i in HUVECs/si-NC more than in LPS-treated HUVECs/si-NC. ACh stimulation induced significantly higher NO levels in LPS-treated HUVECs/siCav-1 than in LPS-treated HUVECs/si-NC cells (P < 0.05). ACh stimulation had no effect on ET-1 levels in any of the groups of LPS-treated cells.

Conclusion: Under the environment with LPS and ACh stimulations, the downregulated Cav-1 expression plays a key role in NO production in an in vitro model of CAS induced by ACh stimulation of LPS-damaged HUVECs.
EFFECTS OF A DISINTEGRIN AND METALLOPROTEASE 10 ON CORONARY ARTERY IN-STENT RESTENOSIS WITH DIABETES
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Objective: To investigate effects of a disintegrin and metalloprotease 10 (ADAM10) on coronary artery in-stent restenosis (ISR) with diabetes.

Methods: Rapamycin-eluting stents were implanted in the coronary arteries of 17 diabetic and 10 normal minipigs, and angiography was repeated after 6 months. The coronary artery tissues of significant ISR and non-ISR segments in both diabetic and normal minipigs were analyzed by western blot analysis. Overexpression and knockdown of ADAM10 were transfected by retrovirus in human aortic smooth muscle cells (HASMC). The proliferation was measured by BrdU and migration was detected by wound-healing. The expression of ADAM10 was analyzed by real-time PCR and western blot after treatment with low glucose, high glucose, advanced glycation end products (AGEs)-bovine serum albumin (BSA), and AGE-BSA-receptor for AGE (RAGE) antibody.

Results: The results showed that ADAM10 levels were significantly increased in ISR tissue compared with non-ISR tissue in both diabetic and normal minipigs, and even higher in diabetic ISR tissue than that in non-diabetic ISR tissue. In vitro, overexpression of ADAM10 significantly induced proliferation and migration in HASMCs, on the contrary, which were attenuated by knockdown of ADAM10. The HASMCs proliferation in high glucose culture was significantly increased compared with in low glucose culture in both overexpression and knockdown of ADAM10. The cell migration distance in high glucose culture was significantly longer compared with in low glucose culture in both overexpression and knockdown of ADAM10. The relative expression quantity of ADAM10 mRNA and ADAM10 protein were significantly higher in high glucose culture and AGE-BSA than in low glucose culture, while that were significantly lower in AGE-BSA+RAGE antibody than in AGE-BSA.

Conclusions: ADAM10 is significantly increased in coronary artery ISR segments of diabetic minipigs. Increased ADAM10 expression promotes the proliferation and migration of HASMC. ADAM10 may be involved in the development and progress of diabetic ISR.
DIFFERENTIAL ROLES OF THE FULL-LENGTH AND N-TERMINAL FRAGMENT OF SERUM RESPONSE FACTOR ON CARDIOMYOCYTE DIFFERENTIATION FROM CARDIAC STEM CELLS

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Background: Cardiac stem cells (CSCs) have been shown to contribute to myocardial regeneration after ischemia injury. Yet, the molecular mechanism by which CSCs differentiation into cardiomyocytes remains unknown. In this study, we tested different roles of both the full-length serum response factor (SRF-full) and its N-terminal fragment (SRF-N) on CSCs differentiation.

Methods: Neonatal Sprague Dawley (SD) rat cardiomyocytes were maintained under a hypoxia condition (2% O₂) for 3 days to detect the expression of SRF-full and SRF-N by immunoblot analysis. CSCs were isolated from SD rat hearts, and the c-kit⁺ subtypes were obtained using the magnetic activated cell sorting method (MACS). Following infection of CSCs with the lentivirus overexpression of SRF-Full or SRF-N, cells were induced to differentiate by TGF-β1 (10 ng/ml) for 7 days. Immunofluorescent staining and real-time quantitative RT-PCR were used to assess cardiomyocyte, smooth muscle cell (SMC), and endothelial cell lineage related markers. Cotransfection of the myocardin plasmid with the cardiac homebox protein Nkx2.5 promoter luciferase reporter vector (Nkx2.5-PG04) was performed to SRF-Full or SRF-N stably expressed NIH-3T3 cells, and then the Nkx2.5 promoter activity was assessed using the dual-luciferase reporter assay. Results: TGF-β1 (10 ng/ml) was sufficient to induce the expression of the markers for cardiomyocyte (Nkx2.5, GATA4, cTnI) and SMC (SM22α), but not for endothelial cell differentiation-related gene (vWF) in c-kit⁺ CSCs, which accompanied by the up-regulation of myocardin. Transfected CSCs with SRF-Full overexpressing lentivirus promoted TGF-β1-induced differentiation, while SRF-N attenuated such effects of TGF-β1. Both qRT-PCR and immunofluorescent staining yielded the same conclusion. Further, SRF-Full combined with myocardin significantly improved the activity of Nkx2.5 promoter, whereas SRF-N inhibited the Nkx2.5 promoter activity. Conclusion: Hypoxia stimulation led to fragmentation of SRF-full into SRF-N. While SRF-full promoted CSCs differentiation into cardiomyocyte-like cells, SRF-N attenuated such differentiation.
ROLE OF VASCULAR AUTOPHAGY IN HYPERTENSION AND HYPOTENSIVE EFFECTS OF TETRAHYDROXYSTILBENE GLYCOSIDE IN OBESE RATS

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Objectives: We wished to ascertain: (i) the role of autophagy in obesity-induced hypertension and the underlying mechanisms; (ii) whether 2,3,5,4’-tetrahydroxystilbene-2-O-beta-D-glycoside (TSG) influences endothelial dysfunction and obesity-associated hypertension.

Background: Obesity is a major risk for cardiovascular diseases including hypertension. Endothelial dysfunction contributes to increased peripheral vascular resistance and subsequent hypertension. However, whether autophagy is related to endothelial dysfunction and hypertension in obesity remains largely unclear. Moreover, TSG is the main bioactive ingredient extracted from the traditional Chinese medicinal herb Polygonum multiflorum Thunb used safely for approximately two millennia with a wide spectrum of pharmacologic functions including improving blood flow and protecting against oxidized LDL-induced vascular dysfunction. But little is known about the effects of TSG on endothelial dysfunction in obesity.

Methods and Results: Twelve-week-old male obese Zucker diabetic fatty (ZDF) rats were used. Compared with their lean counterparts, obese ZDF rats exhibited hypertension and mesenteric artery endothelial dysfunction (n=6, P<0.05), along with impaired Akt/mechanistic target of rapamycin (mTOR) signaling and upregulated expression of beclin1, LC3II/I, p62, ATG5 and ATG7 in mesenteric arterioles (n=6, P<0.05), suggesting increased and impeded autophagy in mesenteric arteries from ZDF rats. Two-week TSG administration (100mg/kg/day) by gavage significantly decreased blood pressure (BP) and improved microvascular endothelial function (n=6, P<0.05), reactivated Akt/mTOR pathway and decreased endothelial autophagy in obese ZDF rats (n=6, P<0.05). Rapamycin pretreatment blocked the hypotensive effect of TSG in obese ZDF rats. Suppression of Akt and mTOR expression with siRNAs significantly blunted the anti-autophagic effect of TSG in cultured human umbilical vein endothelial cells as evidenced by abnormal autophagic flux and increased expression of autophagy-associated proteins, respectively (n=3, P<0.05).

Conclusions: Microvascular endothelial dysfunction in obese rats is partially attributable to excessive autophagy. TSG improves endothelial function and exerts hypotensive effects via inhibiting endothelial autophagy (supported by the National Natural Science Foundation of China, No.81670449).
OBJECTIVE: Mannan A, immunomodulator of polysaccharide origin, has been shown to produce hypolipidemic effect and stimulate macrophages in vivo through its interaction with the mannose receptor (Korolenko et al., 2016). The aim: to evaluate the activity of serum chitotriosidase (CHIT1) and CHIT1 expression in a murine model of acute lipemia in which mice were pretreated with hypolipidemic drugs.

Background. The involvement of elevated serum level of CHIT1 in a variety of inflammatory diseases and in atherosclerosis has previously been shown. The primary sources of secreted CHIT1 into the serum are activated macrophages after toll-like receptor stimulation, stimulation with IFN-γ, TNF-α, GM-CSF.

Methods. Poloxamer 407 (P-407) was administered to CBA/Lac mice as a single intraperitoneal injection (300 mg/kg). Mannan of Candida albicans serotype A (Institute of Chemistry, SAS, Slovakia) was evaluated for the hypolipidemic potential. Serum CHIT1 activity was determined against 4-methylumbelliferyl-beta-D-N-N'-N''-triacetylchitotrioside as a substrate using fluorescent assay (Guo et al., 1995). Expression of CHIT1 was determined in mouse liver using RT-qPCR.

Results. Acute lipemia in mice induced by P-407 was accompanied by an increase in serum CHIT1 activity at 24 h post-dosing. Mice pretreated with mannan A before the induction of hyperlipidaemia with P-407 showed a significant reduction in the serum concentration of atherogenic lipids and in liver (cholesterol, TG). The activity of serum CHIT1 was found to be significantly increased in P-407-induced hyperlipidaemic mice pretreated with mannan A compared with mice administered P-407 only. Mannan A treatment in mice was shown to significantly increase CHIT1 expression in the liver of both non-hyperlipidaemic and P-407-induced hyperlipidaemic mice.

Conclusion. Mannan A revealed hypolipidemic effects in a murine model of acute lipemia. Increased serum CHIT1 activity was a result of increased expression of CHIT1 in the liver, as well as the activation of macrophages following overloading of lysosomes with lipids.
Aortic valve replacement with sutured stented valve is the treatment of choice in patients with severe aortic valve stenosis. This surgical approach has shown excellent mortality, morbidities and long-term survival. Nevertheless, this procedure has been often denied to the high-risk patients with severe aortic stenosis due to the advanced age, numerous comorbidities and poor predicted outcomes. In this setting, transcatheter aortic valve implantation (TAVI) has been considered a valid option in the treatment of high-risk patients, as it has shown to be superior to medical therapy and not inferior to conventional surgery in terms of mortality and early survival. These enthusiastic results have brought the cardiac community to increase the number of TAVI procedures, with the aim of decreasing the invasiveness of surgical operations even in lower risk patients. However, it has been reported that TAVI was associated with higher incidence of neurological events, vascular complications and paravalvular leakages when compared with the conventional surgery.

From the dualism between the surgical and transcatheter approaches, a new valve technology has been developed as an additional treatment option to the high-risk patient undergoing aortic valve replacement to simplify and standardize the surgical procedure and facilitate the minimally invasive approach. The sutureless and rapid deployment aortic valves have been designed to avoid or minimize passing stitches through the annulus and suture knotting to decrease the surgical trauma to the aortic annulus and consequently reduce the operative times. Many studies have reported excellent clinical results in terms of postoperative outcomes, hemodynamic performances, structural valve deterioration and freedom from reoperation up to 5 years. These results have been confirmed even in the setting of minimally invasive surgery. As consequence, these valves have been recommended for those patients belonging to the “gray zone” between TAVI and conventional surgery.

The potential benefits of sutureless and rapid deployment valves when compared with TAVI are the decreased paravalvular leak rate and decreased need for postoperative pacemakers. Furthermore, the surgical approach has the advantage of removing the calcified stenotic valve, a possible cause of neurological events. A large European study reported excellent outcomes, hemodynamic results and 1 year survival with sutureless and minimally invasive aortic valve replacement with the sutureless valve through a right minithoracotomy approach or ministernotomy. These outstanding results have raised the hypothesis that the combination of minimally invasive surgery with the sutureless technology might be considered the “real alternative” to the TAVI technology in intermediate and high risk operable patients. In this setting, a recent meta-analysis has shown that sutureless valves are associated with a 70% reduction of early mortality and 90% reduction of postoperative paravalvular leakage. Paravalvular leakage is now considered a negative outcome, because it has been demonstrated that even mild regurgitation is associated with lower survival at 2 and 5 years. More studies and a proper randomized trial are required to confirm these data.

In conclusion, based on the current literature data, TAVI is recommended for inoperable and very high-risk patients whereas sutureless and rapid deployment valve in combination with any minimally invasive approach are advised for medium risk operable patients. The low risk patients may benefit of a minimally invasive approach but still with a conventional sutured valve. In this setting, the role of the “heart team” is essential for the correct indication, minimizing the potential risks. While we are waiting some robust data and recommendations from the American and European Societies, we will expect that the future be without suture!!!
TRANSCATHETER AORTIC VALVE IMPLANTATION FOR PURE AORTIC REGURGITATION

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The incidence of noncalcific pure aortic regurgitation (AR) is much lower than that of calcific aortic stenosis (AS). Conventional aortic valve surgery is the gold standard for the treatment of pure AR. However, a number of patients with AR have been declined for open-heart surgery because of age and other significant comorbidities. Although transcatheter aortic valve implantation (TAVI) is now a standard treatment for calcific AS in high risk patients, TAVI remains an investigational therapy for pure AR. This is because the majority of transcatheter heart valves (THV) require calcification of the aortic valve for their anchoring. A lack of calcification can result in a high incidence of valve migration and paravalvular leak. The Edwards SAPIEM valve is generally avoided in patients with pure AR. However, this valve with a dock device was successfully used in the treatment of pure AR in a small number of patients. The Medtronic CoreValve has been used with some success in patients with pure AR, but this is associated with high incidences of valve migration and paravalvular leaks. Some THVs, such as Direct Flow THV and Acurate THV, incorporate self-seating geometry that facilitates optimal positioning at the aortic annulus. A few case reports have showed the feasibility of these valves in the treatment of pure AR. Other valves, such as Engager, JenaValve and J-Valve THVs, have further incorporated design elements, such as 3 “arches”, 3 “feelers”, and 3 “graspers”, respectively, which facilitate both self-positioning and anchoring at the aortic valve. Clinical experience has suggested that these valves are probably more suitable for the treatment of pure AR. Excellent outcomes with minimal paravalvular leaks and 30-day mortality rate have been reported following TAVI with the use of J-Valve in patients with pure AR.
VALVULAR AND STRUCTURAL HEART DISEASE – ASSESSMENT AND NOVEL TREATMENTS

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VALVE PROSTHESIS - PATIENT MISMATCH: AN UPDATE - CLEAR THE CONFUSION AND SIMPLIFY

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The clinical problem of Valve Prosthesis-Patient Mismatch (VP-PM) was first defined in 1978 and has become an integral part of medicine. There is confusion and it is time to identify the myths to clear this up. Some people use the term PPM (Patient-Prosthesis Mismatch), but that terminology has existed for permanent pacemakers. To avoid confusion, one should use the abbreviation VP-PM. The diagnosis is usually made by use of Echocardiography/Doppler and is expressed as Effective Orifice Area Index (EOAi). Since VP-PM is related to left ventricular outflow obstruction and is similar to aortic stenosis, the criteria of severe VP-PM should be less than 0.6cm²/m² and mild as greater than 0.9cm²/m². Various techniques of predicting VP-PM have been described but are not reliable. Therefore, it is best to measure the EOAi in each individual patient. After insertion of prosthetic heart valve (PHV), there are 4 phases of physiologic healing which takes place over a period of 6 months. From a clinical point of view, one needs to know the EOAi of an individual patient at 6 to 12 months. To simplify this in the clinical setting, the surgeon should place the largest PHV that can be inserted safely and effectively. The measurement of EOAi is best done initially at 6 months. Subsequently, the EOAi can be determined at routine annual followup or earlier if there is a clinical indication to do so.
WHEN ANSWERS CANNOT BE FOUND IN THE TEXTBOOK – MAKING DECISIONS IN CHILDREN WITH PROFOUND DISABILITIES

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We present the cases of 4 children with major congenital heart diseases, in whom the cardiac anomaly was only part of a serious debilitating congenital condition with overall poor prognosis. These children are barely communicative or responsive, with profound mental and physical disability, and their life expectancy is limited.

1. A 19 month old child with trisomy 13 (including anophthalmia, renal and limb anomalies) and tetralogy of Fallot.
2. Tetralogy of Fallot with small pulmonary arteries in an infant with Goldenhar syndrome (extreme cleft palate, microtia).
3. Severe obstructive hypertrophic cardiomyopathy in a child with hydrocephalus and profound mental retardation and developmental delay.
4. Complex heart defect (including multiple ventricular septal defects, severe pulmonary stenosis and patent ductus arteriosus) in a trisomy 18 infant with severe epilepsy and recurrent aspiration pneumonias.

Managing the treatment in these special patients requires not only medical assessment but also ethical and practical considerations. An open, sincere discussion with the families has to take place in order to ascertain that they fully understand the child's condition and also to appreciate their wishes. Some of these patients may not withstand cardiopulmonary bypass. Low-risk Palliative procedures rather than complete surgical correction may be favored in select cases as compassionate measures in view of the grave prognosis.
Recent epidemiological studies have revealed the risk factors associated for vascular atherosclerosis, including male gender, smoking, hypertension and elevated serum cholesterol, are similar to the risk factors associated with development of calcific aortic valve disease (CAVD), calcific aortic disease (CAD) and coronary artery calcification (CAC). The results of the experimental and clinical studies demonstrate that traditional risk factors initiate early atherosclerosis which over time differentiates to form bone in the heart causing, clinical CAVD, CAD, and CAC. It is critical to understand the cellular mechanisms of cardiovascular calcification, the end stage process of the atherosclerosis, to define the critical time point to modify this cellular process before it is too late. Experimental models suggest that medical therapies may have a potential role in patients in the early stages of this disease process to slow the progression of disease. To date, randomized clinical trials in this field have not demonstrated medical therapy can slow progression. Therefore, ongoing studies are necessary to translate cellular biology to turn basic science into future clinical success. This review will summarize the role of Wnt Signaling in osteocardiology to unravel the dilemma of the proper timing of therapy- the Go/ No Go timepoint to slow progression of cardiovascular calcification.
TAVR FOR ALL COMERS WITH AORTIC STENOSIS: A DESTINATION TOO FAR?

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Transcatheter Aortic Valve Replacement (TAVR) has revolutionized the treatment of symptomatic aortic stenosis (AS) with several randomized trials demonstrating efficacy in inoperable AS patients and equivalence to conventional surgical aortic valve replacement (SAVR) for high and intermediate surgical risk patients. In addition, transfemoral TAVR has demonstrated mortality and stroke benefit compared to SAVR in high surgical risk AS patients prompting a large increase in the number of TAVR procedures being performed both in North America and elsewhere. Furthermore, there have been significant advances in TAVR technology and procedural techniques over the last few years with development of smaller delivery catheters and improved valve design. This technological and procedural optimization has improved the safety of TAVR procedures and reduced the rates of paravalvular regurgitation. However, important issues have been identified from the observational and randomized studies of TAVR raising caution for an unrestricted application of TAVR in all patients with AS. The most pertinent of these concerns include high pacemaker rates post TAVR, unknown long term durability of transcatheter heart valves (THV) and subclinical thrombus formation on THV leaflets. Although, there is great enthusiasm for a less invasive approach such as transfemoral TAVR compared to conventional valve surgery, the clinicians anxiously await the results of ongoing studies examining latest iterations of TAVR technology in low surgical risk patients. In addition, long term follow up on THV hemodynamics and the optimum anticoagulation strategy to prevent subclinical THV thrombosis are required before TAVR can be expanded to all comers aortic stenosis.
Pericardial cyst (PC) is usually an incidental finding and commonly left as a footnote unless associated with symptom. PC is a rare congenital anomaly and symptoms mostly related to compression were described. PC were documented to rupture spontaneously, shrink by Trans thoracic aspiration or eliminated by surgery. We present here a new aspect of PC. We have been following a female with a known PC since 1998, located in the left hilar area along the left heart border proximal to the left atrial appendage. Paroxysmal atrial fibrillation (Afib) started in 2003 and was treated with anti arrhythmic drugs. Afib became persistent and in early 2016 PC was larger than its original size 77X45mm vs. 50/15mm. An ablation attempt was unsuccessful. A subsequent electrocardioversion (ECV) was unsuccessful. Imaging showed shrinkage and disappearance of the PC. Afib persisted but heart rate control was more manageable. Free of PC she is ready now for another ablation attempt. Our local review found 10 patients with a PC, consisting of 7 males and 3 females. The mean age at detection was 64.4 years standard deviation SD = 13.9, with range = 34 to 80mm; 5 were 65 or older. All 10 patients were asymptomatic and the cyst was an incidental finding on a CT scan. Seven were located on the right, 3 on the left, and 1 was central. The largest linear dimension had a mean of 33 mm SD = 10 mm, ranging from 10 to 43 mm. Follow-up CT was available on 8 patients. On follow-up, the largest dimension had a mean of 38 SD = 3 mm, with range = 30 to 40 mm.

We believe that the disappearance of a PC post ECV is a phenomenon not previously documented. The disappearance may be attributed to collateral damage from the ECV energy.
DA VINCI AORTIC AND NON-AORTIC SURGERY
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Objectives: The feasibility of laparoscopic aortic surgery has been adequately demonstrated. Our clinical experience with robot-assisted aortoiliac reconstruction for occlusive diseases, aneurysms, endoleak II treatment, robotic median arcuate ligament release and hybrid procedures performed using the robotic system is herein described.

Methods: Between November 2005 and June 2016, we performed 363 robot-assisted vascular procedures. 256 patients were prospectively evaluated for occlusive diseases, 77 patients for abdominal aortic aneurysm, four for a common iliac artery aneurysm, 7 for a splenic artery aneurysm, one for an internal mammary artery aneurysm five for hybrid procedures, four for median arcuate ligament release and nine for endoleak II treatment post EVAR. The robotic system was applied to construct the vascular anastomosis, for the thromboendarterectomy, for the aorto-iliac reconstruction with a closure patch, for dissection of the splenic artery, and for the posterior peritoneal suture.

Results: 348 cases (95.8%) were successfully completed robotically, one patient's surgery (0.3%) was discontinued during laparoscopy due to heavy aortic calcification. In 14 patients (3.8%) conversion was necessary. The thirty-day mortality rate was 0.3%, and early non-lethal postoperative complications were observed in 7 patients (1.9%).

Conclusions: Our experience with robot-assisted laparoscopic surgery has demonstrated the feasibility of this technique for occlusive diseases, aneurysms, endoleak II treatment post EVAR, for median arcuate ligament release and hybrid procedures. The robotic system facilitated the creation of the aortic anastomosis, and shortened the aortic clamping time as compared to purely laparoscopic techniques.
INFLAMMATION AND CARDIOVASCULAR DISEASE: FROM PATHOGENESIS TO THERAPEUTIC TARGET

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REGULATED EXOCYTOSIS IN ENDOTHELIAL CELLS: BIOLOGY AND CLINICAL IMPLICATIONS

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The exocytosis of endothelial cells (ECs) is one of the first lines of defense against vascular injury. ECs are equipped with specific secretory granules known as Weibel-Palade bodies (WPBs) in which various bioactive molecules are stored, including von Willebrand factor (VWF) and P-selectin. In the past few years, the mechanisms that control WPB exocytosis in the final stages (including the docking, priming and fusion of granules) have been revealed gradually, providing potential therapeutic targets for treating related diseases. In this oral presentation, we will demonstrate the importance of endothelial exocytosis in vascular homeostasis and related pathogenesis. In addition, we will use our recent data as an example showing how a new regulator of endothelial exocytosis is identified and what the new regulator is implicated in understanding the pathogenesis of vascular thrombosis and inflammation as well as in exploring potentially new therapeutic targets. Our study also demonstrates a good combination of a genetic/protein screen, high resolution imaging, and an animal model where a known protein is shown to be critical to an important physiological process using totally new mechanism---Namely, that the focal adhesion protein zyxin is involved in actin coat formation around exocytic vesicles in endothelial cells.
INFLAMMATION AND CARDIOVASCULAR DISEASE: FROM PATHOGENESIS TO THERAPEUTIC TARGET

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BEYOND SLICING AND DICING: CYSTEINE PROTEASE CATHEPSIN K A NOVEL TARGET FOR CARDIOMETABOLIC DISEASE
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Cathepsin K is a lysosomal cysteine protease with potent collagenolytic and elastolytic properties. Elevated levels of cathepsin K have been reported in both human and animal models of heart failure. Studies from our lab have demonstrated that global deletion of cathepsin K attenuates cardiac hypertrophy and contractile dysfunction in a variety of animal models of cardiac dysfunction including high-fat diet feeding, pressure overload, diabetic cardiomyopathy, alcoholic cardiomyopathy and ageing. Recently we have generated a cardiomyocyte-specific knockout of cathepsin K using the Cre-Lox system and found that this knockout protects mice against doxorubicin-induced cardiotoxicity. Cathepsin K knockout alleviates hyperglycemia and improves whole-body glucose disposal in both streptozotocin-induced and obesity associated diabetic mice. At the molecular level, cathepsin K knockout attenuated oxidative stress and inhibited mitochondrial apoptosis and attenuated oxidative stress. Excessive oxidative stress associated with cardiac pathology results in impairment of lysosomal membrane stability that causes the release of cathepsin K into the cytoplasm where it triggers mitochondrial apoptosis. Cathepsin K knockout also augmented autophagic flux and inhibited calcineurin/NFATc signaling. The molecular studies suggest that cathepsin K may be playing a nontraditional role in the context of the pathophysiology of cardiovascular disease. Cathepsin K thus represents a novel, bona-fide, pharmacological target for treating cardiometabolic complications.
INFLAMMATION AND CARDIOVASCULAR DISEASE: FROM PATHOGENESIS TO THERAPEUTIC TARGET

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IL-10 AND TOLL LIKE RECEPTORS 2 AND 4 IN CARDIAC STRESS CONDITIONS

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Aims: It has been suggested that TLR4 promotes IL-10-mediated cardiac cell survival while TLR2 is detrimental. However, the role of these TLRs and their downstream signaling molecules in response to different stresses is not completely known. This study reports a differential role of TLR4 and TLR2 in IL-10 knockout (IL-10 KO) mice and global ischemia/reperfusion (I/R) injury in rat hearts.

Methods and Results: Adult rat ventricular cardiomyocytes as well as cardiac tissue from wild type and IL-10 KO mice (strain C57BL/6) were used. Increase in TLR2 in IL-10 KO hearts indicated its negative regulation by IL-10. Circulating and myocardial levels of TNF-alpha were higher in IL-10 KO hearts. The ex-vivo I/R caused a marked upregulation of TLR2. However, 40min reperfusion with IL-10, triggered an increase in TLR4 expression. Increase in interleukin-1 receptor-associated kinase-M (IRAK-M) and IRAK-2 activity during I/R injury suggested their role in TLR2 signaling. Inhibition of TLR4 activity as a consequence of RNAi-mediated suppression of MyD88 suggests a MyD88-dependent activation of TLR4. IL-10 significantly downregulated the expression of IRAK-2 and TRAIP as well as TGF-beta and its receptor TGF-beta1. IL-10 mitigation of these changes suggests that IL-10 stimulation through TLR4 signaling, dissociates IRAK-4 into IRAK-1 instead of IRAK-2.

Conclusion: Under conditions of stress, an increase in TNF-alpha and upregulation of TLR2 mediated activation of IRAK-M and formation of IRAK-2 from IRAK-4, results in apoptosis and fibrosis. IL-10 significantly reduced TNF-alpha receptor-associated apoptosis during I/R injury and IL-10 KO which reduced TGF-betaRI expression and had an anti-fibrotic action via increase in IL-1beta activity. These data suggest that IL-10, through TLR4 induced innate signaling, restores heart health under conditions of stress due to I/R and a drop in IL-10 in its gene knockout mice.

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110 ACUTE CORONARY SYNDROMES: A ROLE FOR INFLAMMATION AND ITS RESOLUTION
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Inflammation contributes to many of the characteristics of plaques from nascent lesions to rupture of fibrous cap that precipitate acute coronary syndromes (ACS). Substantial evidence supports that inflammatory pathways govern the collagen metabolism, macrophage polarization, generation of lipid/necrotic core, microscopic calcification and outward remodeling, characteristic features of the unstable plaque. Plaque rupture triggers thrombus formation, accumulation of neutrophils at culprit lesions, which can facilitate entrapping leukocytes and propagation of thrombosis. Elevated plasma levels of neutrophil-derived myeloperoxidase predict adverse outcomes in patients with ACS. Limiting excessive inflammatory responses requires countervailing mechanisms. Indeed, the inflammatory reaction normally also involves a resolution phase governed by specialized pro-resolving mediators (SPMs). The SPM families include annexin A1 and IL-10, as well as lipid mediators, such as lipoxins, resolvins, and maresins arising from omega-3 polyunsaturated fatty acids. These mediators can efficiently inhibit inflammatory cell influx, reduce production of pro-inflammatory mediators and oxidative stress, and restore defective efferocytosis and fibrous cap thinning. Thus, the risk of ACS depends critically on the prevailing balance between pro-inflammatory and resolution pathways. An emerging concept is that resolution mechanisms are defective in coronary artery disease, thereby aggravating ACS risk. Lower plasma levels of aspirin-triggered lipoxin A4 increases the risk for atherosclerosis and high fat diet associates with defective inflammation resolution. Conversely, therapeutic administration of resolvins decreases leukocyte trafficking into injured arteries, and dietary omega-3 fatty acid supplementation or overexpression of 12/15-lipoxygenase, a key SPM biosynthetic enzyme results in better cardiovascular outcomes. Thus, promoting resolution of inflammation represents a promising novel therapeutic approach for reducing ACS risk or for the treatment of acute coronary artery disease. (Grant support: CIHR).
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INFLAMMATION, AUTOPHagy AND MYOCARDIAL ISCHEMIA

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Inflammation is present in the heart soon after acute myocardial infarction and continues during the chronic stage. Autophagy is a physiologic process for tissue survival. We hypothesized that inflammation may promote cardiomyocyte autophagy and protect cardiomyocytes from death during the ischemic process. To address this hypothesis, we used the myocardial infract mouse model (total left coronary artery occlusion) to investigate the relationship between inflammation and autophagy at different time points after. Our data showed that inflammation (TNF-α and IL-6) and autophagic (LC-3 and Beclin-1) responses were strongest during the first week, and then declined over the next 3 weeks. The maximal increase in inflammation and autophagy was in the border zone. To elucidate the role of inflammation in cardiomyocyte autophagy and its impact on cardiac function, we treated mice with TNF-α inhibitor during the first week after total left coronary artery occlusion, and measured infarct size, cytokine release and autophagy. We observed that anti-TNF-α treatment markedly reduced leukocyte infiltration and pro-inflammatory cytokine levels in the heart and sera (all P<0.05). The infarct size was somewhat increased, and autophagy signals were diminished compared to controls (P<0.01). Most importantly, cardiac function measured by echocardiography (FS and EF) was modestly but significantly (P<0.05) decreased. Our findings indicate that inflammatory responses may be protective in the early stage of myocardial infarction by stimulation of cardiomyocyte autophagy, and anti-inflammatory therapy at this stage may be harmful.
OXIDIZED LIPIDS HAVE LONG BEEN IMPLICATED IN SYSTEMIC INFLAMMATION AND THE RESULTING CARDIOVASCULAR COMPLICATIONS. ONE OF THE POTENT METABOLITES DURING LIPID OXIDATION IS LYSOPLASMATIDIC ACID (LPA). LPA HAS BEEN KNOWN TO BE A POTENT GROWTH PROMOTOR AND MORE RECENTLY IT WAS SHOWN TO BE AN ATHEROGENIC MOLECULE. WE HAVE STUDIED LPA IN PRECLINICAL TRIALS TO DETERMINE THE MODE OF GENERATION OF THIS MOLECULE IN THE INTESTINE AND IN THE LIVER BY FEEDING HIGH CHOLESTEROL, HIGH DIET (WESTERN DIET, WD) AND THE EFFECT OF AGE AND GENDER ON ITS REGULATION. WE HAVE ADDitionally STUDIED THE EFFECT OF THE INHIBITORS OF ENZYMES INVOLVED IN THE FORMATION OF LPA NAMELY AUTOTAXIN. IN OTHER STUDIES WE HAVE INVESTIGATED THE EFFECT OF FEEDING LPA TO LABORATORY ANIMALS ON THE FORMATION OF LIPID OXIDATION PRODUCTS IN THE INTESTINE, IN THE CIRCULATION AND IN THE LIVER DETERMINING THE RESULTING EFFECTS ON CARDIOVASCULAR SYSTEM. OUR GROUP, IN SEPARATE STUDIES, HAS LOOKED INTO THE EFFECT OF LPA IN TUMORIGENESIS IN THE INTESTINE AND METASTASIS TO THE LUNGS. WE ARE EXPLORING THE PATHWAYS THAT CONTRIBUTE TO BOTH ATHEROGENESIS AND TO CANCER THROUGH THE ACTIONS OF LPA.
MODIFIED MYXOMAVIRAL SERPIN REACTIVE CENTER LOOP (RCL) PEPTIDE IMPROVES SURVIVAL AND OUTCOMES IN AN ACCELERATED LEthal MOUSE INFEnMATory vASCULITIC SYNDROME MODEL

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Introduction: Inflammatory vascular syndromes (IVS), giant cell arteritis and Takayasu’s disease, are rare but devastating arterial disorders. Mouse gamma herpesviral (MHV68) infection in interferon gamma receptor knockout mice (IFNγR−/−) is a model for a lethal IVS. The role of the bacterial microbiome in IVS and treatment remains undefined. In prior work, Myxomavirus-derived serine protease inhibitor (serpin), Serp-1, and a Serp-1 RCL-derived anti-inflammatory peptide, S-7 (G305TTASSDTAILIPR319), significantly improved survival and reduced aortic inflammation in MHV68-infected IFNγR−/− mice.

Method: We examined survival and disease progression in 56 MHV68-infected IFNγR−/− mice with and without Serp-1 or serpin peptide (S-2, S-7, S-8, or two modified S-7 peptides designed for enhanced function in silico) treatments, with and without oral antibiotics. We also assessed microRNA responses to Serp-1 by qPCR and potential plasma protein targets for S-7 by mass spectrometry.

Results: Depletion of gut bacteria accelerated MHV68-induced IVS markedly, increasing early mortality and reducing survival from 60 to 20 days (P<0.036). Suppression of gut bacteria also reduced Serp-1 and S-7 treatment efficacy, decreasing survival from 70% at 150 days to 20% at 30 days for Serp-1 (P<0.0028) and 0% at 30 days for S-7 (P<0.0001). S-2 was inactive and S-8 treatment trended towards improved survival with antibiotic treatment (N=14), while treatment with two modified S-7 peptides (N=10) optimized for serpin blockade retained efficacy and improved survival in MHV68-infected mice (P<0.001). Mass spectrometry revealed S-7 bound to numerous plasma proteins including complements C1S and C3, plasminogen, fibrinogen, antithrombin, and antitrypsin. Antibiotics suppressed aerobic stool bacterial growth and phage counts without alteration of Serp-1 inhibition of uPA. Serp-1 significantly decreased miRNAs 126 and 136 and increased miRNA 335.

Conclusion: Myxomavirus-derived Serp-1 protein and RCL peptide S-7 improve survival in a lethal MHV68 infection in mice. Suppression of gut bacteria both accelerates MHV68 infection and blocks Serp-1 and S-7 peptide treatment efficacy, suggesting microbiome-mediated modulation of serpin treatment in herpes infection. Modified S-7 peptides restored therapeutic benefit in antibiotic-treated MHV68-infected mice. The collective microbiome, or specific microbial sub-populations, may play a central role in viral sepsis, IVS, and modulation of treatment response.
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UPSTREAM MEDIATORS OF INFLAMMATION AND THE POTENTIAL TO UNLOCK PARADOXES OF AGE-RELATED DISEASE

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The extent to which specific inflammatory pathways might serve as key mechanistic drivers of disease and, in turn, as potentially high-yield therapeutic targets has been unclear. Accumulating data now suggests that upstream mediators of inflammation are likely to play a causal role in disease pathogenesis and, thus, serve as effective therapeutic targets. The upstream initiation of inflammation in humans is governed primarily by small molecule effectors of polyunsaturated fatty acid metabolism, termed eicosanoids. These bioactive lipid effectors of both pro- and anti-inflammatory activity include prostaglandins, lipoxins, and leukotrienes. Until recently, interactions between eicosanoid pathways and age-related diseases including cardiovascular disease (CVD) remain poorly understood. Small molecule profiling methods now allow for the rapid and accurate quantification of >150 upstream eicosanoid mediators representing multiple enzymatic origins. Emerging evidence now points to distinct profiles of pro- and anti-inflammatory eicosanoids as being related to cardiometabolic and specifically CVD risk as well as risk for other age-related diseases in the community. In some cases, very significant albeit paradoxical associations are observed, underscoring the potential for certain eicosanoids to exert pro- or anti-inflammatory activity in a time and context dependent fashion. Intriguingly, certain eicosanoids also appear progressively or chronically altered in the setting of statin and RAA modulating medication use. Further work is needed investigate the efficacy of therapies, including both existing and novel agents, for modulating variation in distinct eicosanoids as well as outcomes.
THE UTILITY OF ECHOCARDIOGRAPHY IN SYNCOPE EVALUATION

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Objective: To evaluate the utility of Echocardiography (ECHO) in syncope work-up.

Background: The American College of Cardiology guidelines include syncope without evidence of cardiovascular disease as an appropriate indication for ECHO but this has been widely challenged. The study is not recommended for lightheadedness, dizziness, or vertigo, collectively defining “presyncope.” We reviewed the incidence and value of echocardiograms ordered, at Richmond University Medical Center, for the work-up of syncope between June and November 2016.

Methods: 1658 echocardiograms, recorded from June to November 2016, were reviewed. 174 were ordered for syncope (148) and presyncope (26). Electronic medical records were reviewed for history, examination, and electrocardiogram (EKG). Data was examined to confirm diagnosis and determine echocardiogram value in elucidating cause of syncope.

Results: Only 5 patients in the syncope/presyncope group were found to have echocardiographic explanations for transient loss of consciousness. 3 had various severity of pulmonary hypertension and 2 had severe aortic stenosis. 27 other patients had echocardiographic abnormalities but none of these could be etiologically linked to syncope.

Of the 174 patients, ECHO was of no etiological value in 43 who had no cardiovascular comorbidities, 51 who had normal EKGs, and in 26 “presyncope” patients.

Conclusion: Syncope leads to approximately 1 million ER visits a year. ECHO provided a diagnostic explanation of syncope in only 5 of 174 patients and only 3 in whom the clinical diagnosis would have been difficult to determine. Only 1 patient was discharged with a syncope diagnosis that relied on ECHO findings. ECHO cannot be recommended as a diagnostic test for syncope. It was not helpful in any patient with “presyncope,” those with normal EKG findings, and those without cardiovascular comorbidities. Adoption of these recommendations would save time, unnecessary testing, and considerable cost in the work-up of syncope.
Assessment of Left Ventricular Segmental Mass in Hypertrophic Cardiomyopathy by Three Dimensional Echocardiography

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Objectives: Our aim was to assess the distribution of left ventricular (LV) segmental mass in patients with hypertrophic cardiomyopathy (HCM).

Background: Hypertrophic cardiomyopathy is defined echocardiographically by unexplained left ventricular wall thickening. Left ventricular segmental mass, measured by 3-D echocardiography, has not been systematically assessed in this cardiac disease.

Methods: In 53 HCM patients (age 43 ± 17 years; 65% men), endocardial and epicardial borders were traced manually using 3-D echocardiography to measure LV myocardial volume. By multiplying myocardial volume in a constant number (1.05), LV myocardial mass was calculated. The mass values for each cardiac segment were automatically given by the software. All the values were indexed by body surface area, and compared with that in 59 healthy control subjects.

Interobserver and Intraobserver Variability: Interobserver measurement variability was determined by a second independent blinded observer in 15 randomly selected patients. The first observer who measured the data in all patients re-measure parameters in 10 patients 1 month apart to achieve intraobserver variability.

Results: The LV mass index in HCM patients significantly exceeded that of control subjects (122 ± 45 g/m2 vs. 74 ± 16 g/m2 with p < 0.001). However, values were within the normal range (≤ mean +2 SDs for control subjects) in 6 patients (11%), and only mildly increased (mean +2 to 3 SDs) in 3 (5%). The LV mass index showed a modest relationship to maximal LV thickness (r2 ± 0.28 and p < 0.001). Segmental values showed distributed hypertrophy in all segments.
SAFETY PROFILE OF ECHOCARDIOGRAPHIC CONTRAST AGENTS
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Introduction: Echocardiographic contrast agents (ECAs) are often utilized to enhance the image quality, however, the concern for adverse reactions may limit their use. Moreover, these agents had been either contraindicated or are labeled with a warning in patients with intracardiac shunts because of a theoretic risk of systemic microvascular obstruction. This labeling was recently removed in the United States, but data in these patients is lacking. Herein, we reviewed and compared the safety profile of ECAs used at our center.

Methods: Over a 15-month period, patients receiving 3 different FDA-approved ECAs were prospectively evaluated for clinically significant adverse events (AEs) defined as either anaphylactoid reactions (rash, back pain, dyspnea, wheeze), or true anaphylaxis. Incidences of AEs were compared between the ECAs using a Chi-square test.

Results: A total of 5506 contrast administrations were performed (Definity: 3306, Lumason: 2137, Optison: 78). There were 14 AEs (%) reported (Lumason: 0.04% [n=1] vs. Definity: 0.39% [n=13], p= 0.02), and all were classified as minor. Back pain was the most common complaint (n=9), with headache, rash and dyspnea also reported. Of the 33 patients noted to have intracardiac shunts, none experienced any AE. Known right-to-left shunts with positive saline bubble study were present in 20 of the patients (Lumason: n=9, Definity: n=11). Left-to-right atrial shunts based on color Doppler were present in 10 patients (Lumason: n=5, Definity: n=5). 3 patients were known to have ventricular septal defect with left-to-right flow (Definity: n=2, Optison: n=1).

Conclusion: AEs were significantly higher with Definity, however, overall the incidences were low, and were minor. Furthermore, there were no AEs reported in patients with known intracardiac shunt. Our study shows a good safety profile of ECAs, and should be afforded to all appropriate patients, including those with known intracardiac shunts.
CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY AS A COST-EFFECTIVE TEST FOR CORONARY ARTERY DISEASE

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Background: Recent studies have demonstrated the clinical benefits of coronary computed tomography angiography (CCTA) as a gatekeeper to invasive coronary angiography (ICA) in suspected coronary artery disease (CAD). In the context of value-based care, an ideal first-line investigation is essential for superior health and economic outcomes.

Objectives: To evaluate the cost-effectiveness of CCTA in the cardiac care algorithm leading to ICA for symptoms suggestive of CAD.

Methods: Two pathways involving initial or secondary usage of CCTA or stress myocardial perfusion imaging (SMPI) were compared (CCTA-SMPI-ICA vs. SMPI-CCTA-ICA) in a model population of 1000 symptomatic patients with an intermediate risk of CAD (40% prevalence). Cost of care was determined based on diagnostic performance (sensitivity, specificity), counts of possible outcomes (true positives/negatives, false positives/negatives), per-diagnostic test fee, and overall net differences. Values were obtained from existing meta-analyses and United States Medicare payer data. An identical hypothetical model eliminating procedural cost differences was constructed.

Results: Ordering CCTA prior to SMPI and ICA (CCTA-SMPI-ICA vs. SMPI-CCTA-ICA) reduced estimated first-line costs by $829,000 USD and overall diagnostic expenses by $450,996 or 19.7%. After eliminating cost differences between diagnostic tests, a net savings of $14,000 was associated with using CCTA as a primary mode for risk stratification without altering clinical performance. This is largely due to a greater number of patients receiving a differential diagnosis prior to downstream ICA.

Conclusions: Reducing the number of ICA procedures to rule out possible CAD has notable potential to generate cost savings and improve resource utilization across the care pathway. CCTA has a higher diagnostic accuracy and is relatively cheaper to perform than SMPI. The model presented in this study highlights that ideally a single first-line CCTA test can potentially lower the number of investigations, patient burden, and overall costs of CAD detection in patients with intermediate disease risk.

Figure: A comparison of total costs in US dollars with a different order of investigations (CCTA-SMPI-ICA vs SMPI-CCTA-ICA) in the detection of CAD in symptomatic patients without known heart disease, assuming costs of $356 for CCTA, $1,185 for SMPI, and $2,549 for ICA. Sensitivity/specificity values for CCTA and SMPI were 99%/88% and 89%/76%, respectively.
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DOES MORPHOLOGY AND FUNCTION OF THE LEFT ATRIAL APPENDAGE CHANGE AS A RESULT OF MITRAL REGURGITATION?

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Background: Left atrial appendage (LAA) morphology is known to change in patients with atrial fibrillation (AFib). However, there is little data available regarding the relationship of LAA morphology and degree of mitral regurgitation (MR). The current study assesses LAA morphology and function in patients with varying degrees of MR.

Methods: Data was retrospectively collected from electronic medical records for 17 patients (mean age 62.18 ± 15.38, range 22-93 years, 12 males (70.6%)) who underwent a transesophageal echocardiogram (TEE) at our institution and were found to have MR. Indications for TEE in these patients were moderate to severe MR (n=8, 47.1%), bacteraemia (n=6, 35.3%), exclusion of cardiac source for thromboemboli (n=2, 11.8%), and quantification of aortic stenosis (n=1, 5.9%). We excluded patients with current or past history of AFib or intracardiac thrombi. Patients were stratified to three groups: mild (n=6), moderate (n=6), and severe MR (n=5). In all patients we evaluated by TEE maximal length of LAA (mm), number of lobes, diameter of LAA mouth (mm), shape of the LAA, emptying velocity (cm/sec), and presence of thrombus.

Results: Maximal length of LAA increased with increasing MR severity and was 33.7±5.4, 40.7±7.9, and 46.6±2.5 mm for mild, moderate, and severe MR, respectively (p=0.0092 one-way ANOVA). In the same three groups, the mean number of LAA lobes was not significantly different (1.8, 1.7, 1.6, respectively; p=0.81). The mean diameter of the mouth of the LAA was significantly larger as the degree of MR increased – 14.0±3.0 mm (mild), 18.7±2.5 mm (moderate), and 22.8±5.3 mm (severe MR) (p=0.0052). The “chicken wing” shape of the LAA was most common in all three groups (50%, 100%, 80%, respectively) followed by the “windsock” shape (33% in mild and 20% in the severe MR groups), while the “cauliflower” shape was seen only in one patient (5.9%) from the mild MR group. The emptying velocity of the LAA was 0.49±0.16, 0.37±0.18, 0.48±0.19 cm/sec for the mild, moderate, and severe MR groups, (NS p=0.47). None of the patients were found to have thrombus in the LAA.

Conclusions: The morphology of the LAA changes with increase in MR severity: LAA elongates and its mouth diameter increases. However, the function of the LAA, represented by emptying velocity, does not change significantly.

LAA morphology may provide an additional guide to MR severity, once these findings are confirmed in large numbers of patients.
QUANTIFICATION OF PLEURAL EFFUSIONS BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY
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Background: Pleural effusion (PLE) is a common occurrence in patients with heart disease, often incidentally detected on transthoracic echocardiograms. A method for echocardiographic quantification of PLE has not been developed to date, and thus considerable variability exists in its reporting. Our aim was to determine whether PLE measured from routine TTE views correlate with the amount visualized on CXR.

Methods: A retrospective analysis of 204 patients (mean age 71.5 years, 53% men) who underwent clinically indicated TTE at a large tertiary center between 1/2015-1/2017. Inclusion criteria included presence of PLE indicated by the final TTE report, and upright CXR performed ±2 days. Linear measurements of the largest PLE pocket were obtained from parasternal long axis (PLAX), apical 4 chamber, and subcostal views. The strength of association between TTE and CXR measures of PLE was assessed by fitting a proportional-odds model to predict the PLE size category from CXR; p-values from Wald test. The ability of TTE to predict “large” PLE on CXR was assessed using AUROC with cut points for estimating accuracy defined by the Youden criteria.

Results: There are statistically significant associations between PLE size assessed by TTE by certain views and CXR: Apical, PLAX (Depth), and PLAX (Length), all P<0.05. AUROC for Apical Left, Apical Right, and PLAX (Depth) were 0.68 (95% CI [0.47,0.89]), 0.67 [0.46,0.88], and 0.612 (95% CI [0.35,0.88]). Optimal TTE thresholds for predicting ‘large’ PLE on CXR were 2.25cm (accuracy=40%), 2.3cm (43%), and 9cm (48%).

Conclusions: Despite a strong association, TTE is not a reliable predictor of the degree of PLE measured by CXR. The best thresholds for predicting large left PLE >2.3cm from apical 4 chamber view on left and >9cm depth from PLAX, and >2.3cm from apical 4 chamber view for right pleural effusion) is associated with 40-48% accuracy.
AUTONOMOUS HEART MURMUR DETECTION IN THE ELDERLY WITH VALVE DEFECTS
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Objective: Evaluate clinical performance of a new heart murmur detection algorithm on an elderly population through a blinded trial.

Background: Algorithms that autonomously detect heart murmurs have the potential to improve auscultation accuracy, but their practical application has been hampered by lack of blinded clinical testing.

Methods: Using an electronic stethoscope, 57 digital heart sound recordings (one per patient, 20 seconds each) were acquired from elderly in-patient subjects (mean: 72.4 years, SD: 13.6 years) admitted to the Division of Cardiology, University Hospital Graz, Austria. All patients had known pathological murmurs caused by multiple valve defects, confirmed by gold standard echocardiography. Defects were interpreted by the cardiologist as “low, medium or high” severity. Altogether, 155 valve defects were observed, including insufficiencies of the aortic (15%), mitral (32%), tricuspid (23%), and pulmonary (6%) valves; and stenosis of the aortic (21%) and mitral (3%) valves. Recordings were fully blinded before undergoing one-time automated analysis. Algorithm results for each recording included: AHA classification (I “pathologic” versus III “innocent/no murmur”), murmur timing, murmur grade, heart rate and S1/S2 identification. Two-sided 95%-confidence intervals (CI) for sensitivity were calculated.

Results: The algorithm’s sensitivity for autonomous detection of pathologic murmurs was 89% (CI: 78-96%). Two of the six false negatives (FN) were detected as innocent murmurs, no murmur was detected in the other four. Of the six FN, two were diagnosed by the cardiologist as medium and four as low severity. No high severity cases were missed by the algorithm.

Conclusion: In this blinded clinical trial, the algorithm performed with high sensitivity in the detection of pathological murmurs. Further, it yielded accurate heart rate estimation and S1/S2 detection, despite the presence of significant environmental noise. Results are consistent with this algorithm’s clinical performance data from large-scale prospective studies on pediatric populations with congenital heart disease.
SYSTEMATIC REVIEW OF USING SIMULATION TO TEACH ECHOCARDIOGRAPHY

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Background/Objective: Over the past several years, high fidelity simulators for teaching echocardiography skills have been developed and manufactured. These simulators are increasingly used to train students and physicians with varied backgrounds and echocardiography experience. We conducted a systematic review of educational literature to describe how simulation is being used to teach echocardiography.

Methods: We searched the MEDLINE (PubMed), Web of Science, Cochrane Central Register of Controlled Trials, and ERIC databases for search terms related to: echocardiography, simulation, and education. Our initial search yielded 294; after review of the abstracts 67 were selected for full text review. Duplicate publications were excluded. After full text review, 24 studies were included. Two reviewers independently extracted all relevant data fields with discrepancies resolved by a third reviewer.

Results: A total of 503 learners were exposed to simulation in 24 studies. Study designs included cohort trial (n=4), Pre-post comparison (n=10), and randomized trials (n=10). Outcomes varied, ranging from surveys of self-confidence (Kirkpatrick level 2a) to improved diagnostics on real patients (Kirkpatrick level 4b). The majority of studies (n=22) demonstrated efficacy associated with simulation-based training. Educational theories for adult and experiential learning were rarely applied. Studies including medical students (n=1) and attending physicians (n=3) were uncommon; the remainder were focused on housestaff trainees (n=20). Studies of cardiology fellows represented a minority (n=3 studies versus n=11 in anesthesiology and n=9 other specialties). The literature indicated that both transthoracic and transesophageal techniques were taught; the majority (n=22) used a hands-on simulator for training.

Conclusion: The use of simulation to teach echocardiography is effective in a variety of settings and learners. Robust study designs were frequently used however most described low Kirkpatrick outcomes. Future investigations should apply educational theory and focus on demonstrating whether simulation can improve care delivery and patient outcomes.
CARDIOVASCULAR ABNORMALITIES IN HIV PATIENTS AND THEIR ASSOCIATION WITH DURATION OF HAART AND CD4 COUNT

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Background: Cardiovascular abnormalities are common in HIV patients but often go unrecognized resulting in increased cardiovascular related morbidity and mortality. The prevalence of cardiac involvement has been reported to range between 28 and 73 percent depending on the screening methods selected, population studied and the definition of cardiac abnormality. Our aim was to study the prevalence of cardiac abnormalities in HIV patients admitted to a tertiary care center.

Methods: Hospital based observational cross sectional study conducted in the Department of Medicine, King George’s Medical University, Lucknow, India. A total of 75 patients were enrolled after taking informed consent and cardiac evaluation was done using clinical examination, Chest Xray, Electrocardiogram (ECG), transthoracic Echocardiography (ECHO) and serum NT proBNP levels. The duration of study was 1 year.

Results: Cardiomegaly on X ray chest were found in only 11 percent of HIV patients while ECHO showed abnormality in 52 percent mainly comprising diastolic dysfunction, dilated cardiomyopathy and pericardial effusion. These abnormalities were more in the group with duration of HAART greater than 6 months as compared to the group with no treatment or less than 6 months. This was not statistically significant except for Regional wall motion abnormality (RWMA) which was significantly higher with longer duration of therapy in low CD4 count. RWMA on ECHO, with ECG changes indicative of ischemia was found in 5 cases with mean age group of 36.2 years. Low HDL was seen in 4 out of these 5 patients but no other risk factor was present. NT proBNP levels were raised in 12 percent of patients. These patients were following National AIDS Control Organisation, Government of India protocol for HAART and none of them were on protease inhibitors.

Conclusions: Cardiac abnormalities in admitted HIV patients, as assessed by ECHO, were 52 percent and were more prevalent with longer duration of therapy and low CD4 count.
Lifestyle factors such as smoking and drinking habits, regular physical activity (in older studies at work, nowadays as leisure) and maintenance of a certain level of leanness in the elderly without body overweight or obesity are associated with lower mortality risks from all-cause, cardiovascular (CVD), coronary (CHD) and cancer specific causes. This is so in conjunction with a healthy diet meaning substantially high intake of plant foods (including vegetables, fruits, nuts, legumes, whole grains and starch), moderated in animal foods and alcohol intake and rich in fish, thus resembling what was called a Mediterranean Diet. However, few studies investigated these factors in combination and fewer addressed the problem of life-long projection of healthy versus unhealthy lifestyle habits in terms of relative risk (RR) and years of life saved.

The existing evidence accumulated in observational population studies and excluding intervention trials and Guide Lines enables to conclude that comparing healthier versus unhealthier lifestyles, RR range from 0.14 to 0.75 depending on the outcome type considered (higher for CVD than cancer or all-cause mortality) and likely duration of follow-up. There is in general a great advantage at long-term (around 15 to 20 years) with 4 to 12 years of life saved. Considering CHD in 50 years, RR range from 0.19 to 0.47 for incidence and 0.27 to 0.72 for mortality.

Behavioral and social science research on interventions for these risks should be strengthened which may be facilitated by the fact that many prevention and primary care policy options are available now to act on key risks. Acting effectively on smoking habits, physical activity, body weight and dietary habits should be a good starting point for cardiovascular (and CHD, in particular) and overall disease-burden prevention and accordingly for life prolongation.
Cardiovascular diseases (CVD) including heart disease, stroke and other vessel-related diseases are the leading global cause of death, accounting for more than 17.3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030. Many traditional risk factors are associated with CVD including hypertension, smoking, hypercholesterolemia, diabetes, physical inactivity, unhealthy diet and obesity as well as family history. However, these factors cannot account for the entire risk for incident diseases. Many other potential risk factors have been identified such as aldosterone, autoantibodies, brain natriuretic peptide (BNP), fibrin D-dimer, Willebrand factor (vWF), trimethylamine-N-oxide (TMAO), homocysteine, C-reactive protein, antiretroviral therapy drugs, adipokines, soluble CD40L, nitrotyrosine, chlorotyrosine and serum uric acid. For example, several recent large clinical studies have confirmed that hyperuricemia is a significant and independent risk factor for CVD including hypertension, ischemic heart disease, and heart failure, after an extensive adjustment for almost all of the possible confounding conditions. Hyperuricemia contributes to the progression of CVD through oxidative stress, systemic inflammation, and endothelial dysfunction. We showed that the treatment with clinically relevant concentrations of uric acid caused the downregulation of endothelial nitric oxide synthase (eNOS) in human endothelial cells by a unique mechanism of MAPKs (p38 and EKR1/2)-mediated signal transduction and GATA4-mediated eNOS promoter inhibition. Hyperuricemia-related endothelial dysfunction has been observed in rats and humans. Accordingly, xanthine oxidoreductase (XOR) inhibitors improve endothelial functions. We showed that hyperuricemia of uricase-/- mice caused downregulation of eNOS in the mouse aorta; while new XOR inhibitors as well as Allopurinol successfully inhibited eNOS downregulation in uricase-/- mice. These studies may suggest new strategies to prevent and treat CVD.
PARADOXICAL HOOKAH SMOKING-INDUCED AUGMENTATION OF ENDOTHELIAL FUNCTION

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Hookah tobacco smoking is a new global phenomenon among youth. The World Health Organization wants to prohibit claims that hookah is less harmful than cigarettes but scientific data are sparse. Because hookah tobacco traditionally is heated with charcoal, the smoke delivers “tar” and nicotine plus charcoal combustion products, including carbon monoxide (CO) and carbon-rich nanoparticles that increase oxidant stress. Hookah smoke induces acute dysfunction of human endothelial cells in culture but whether it impairs human endothelial function in vivo is unknown.

To address this question, in 23 healthy young adults who smoke hookah but not cigarettes (age 25±1 years, mean ±SE), we measured plasma nicotine, exhaled CO, and brachial artery flow-mediated dilation (FMD) before and after ad lib hookah smoking. The same measurements were performed before and after eight age-matched cigarette smokers smoked one cigarette and nine of the hookah smokers smoked the same hookah tobacco heated with an allegedly healthier electronic heat source rather than charcoal.

Nicotine levels increased similarly with the three types of smoking, while exhaled CO increased 8.3-fold more after smoking charcoal-heated hookah tobacco than after cigarette smoking and 12.5-fold more than after smoking electrically-heated hookah tobacco. The major new finding is that FMD was not acutely impaired by traditional hookah smoking but instead was augmented by 50±9% (p<0.001). In contrast, FMD was acutely impaired after either cigarette smoking (by 36±4%, p<0.001) or smoking electrically-heated hookah tobacco (by 27±5%, p=0.001).

Thus, unlike cigarette smoking: 1) hookah smoking acutely augments, rather than impairs, brachial artery endothelial function in young adults; and 2) the augmentation is caused by CO or other charcoal combustion products and masks the impairment caused by hookah tobacco toxicants. Further research is warranted to test acute and chronic effects of hookah smoking on the coronary circulation and on atherosclerotic cardiovascular disease risk.
IDENTIFICATION AND MODIFICATION OF NOVEL RISK FACTORS FOR CARDIOVASCULAR DISEASES

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CARDIOVASCULAR RISKS OF RECREATIONAL MARIJUANA USE

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Social acceptability, availability, and regional legalization of recreational marijuana (cannabis) have caused a dramatic increase in its use across the United States. In 2014, ~22.2 million individuals aged 12 years and older were considered current users of marijuana and 4.2 million met the diagnostic criteria for abuse of or dependence on cannabis in the United States. According to the 2014 National Survey on Drug Use and Health (NSDUH), marijuana remains the most commonly used illicit drug. The sharp rise in recreational marijuana use has paralleled increased reporting of serious cardiovascular adverse events related to this substance in younger individuals. Marijuana smoking is a recognized trigger for myocardial infarction (Figure). Other cardiovascular complications have included ischemic stroke, cardiac arrhythmias and stress cardiomyopathy. Marijuana-related complications appear to be pathophysiologically related to the absolute and relative contents of psychoactive [tetrahydrocannabinol (THC)] and non-psychoactive [cannabidiol (CBD)] cannabinoids and their interaction with endocannabinoid and autonomic nervous systems. National and local debates, among health professionals and policy makers, on the merits of legalization of marijuana continue and appear to be primarily centered on a perception of the safety of the drug. Awareness and acknowledgement of serious complications of unregulated marijuana use and their potential public health implications should be included in discussions of legalization and widespread availability of this “recreational” drug.
Nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed frequently. By 2005 observational studies and small randomized trials suggested excess cardiovascular (CV) adversity with some NSAIDs. Rofecoxib, a COX-2 selective NSAID, reportedly caused relatively frequent CV adversity; effects of celecoxib, also COX-2 selective, were unclear. However, no study had prospectively assessed NSAID effects specifically on CV adversity. Therefore, the USFDA mandated a prospective comparison of CV (and GI and renal) adversity with celecoxib versus the non-selective ibuprofen and naproxen. The resulting Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (PRECISION) trial included 24,081 arthritis patients with known or high risk for coronary artery disease (CAD), given either celecoxib (200-400mg daily), ibuprofen 1800-2400mg daily or naproxen (750-1000mg daily). Approximately half received low dose aspirin; most received antacid drugs. Mean exposure (months) to celecoxib was 20.8±16.0, to naproxen 20.5±15.9 and to ibuprofen 19.6±16.0. The hazard ratio (HR [95% CI]) and noninferiority P-values for the primary ITT analysis were 0.93 (0.76,1.13), P<0.001 for celecoxib versus naproxen and 0.85 (0.70,1.04), P<0.001 for celecoxib versus ibuprofen. On-treatment, HR for celecoxib versus naproxen was 0.90 (0.71,1.15), P<0.001, and versus ibuprofen was 0.81 (0.65,1.02), P<0.001. Celecoxib caused the fewest CV events, the least hypertension and the fewest serious GI and renal events among the NSAIDs. The rate of CV death was lower for celecoxib versus ibuprofen (on-treatment population), HR 0.64 (95% CI 0.42 to 0.99), P=0.04; all-cause mortality was lower for celecoxib versus naproxen in the ITT population, HR 0.80 (95% CI 0.63 to 1.00), P=0.052. In summary, in arthritic patients with or at high risk of CAD, to minimize CV, GI and renal adversity, celecoxib at anti-arthritis doses is relatively favorable compared with ibuprofen and, to a lesser extent, naproxen. COX-2 selectivity appears NOT to confer excess CV (or GI or renal) risk compared with non-selectivity.
IDENTIFICATION AND MODIFICATION OF NOVEL RISK FACTORS FOR CARDIOVASCULAR DISEASES

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NON-PLATELET THROMBOXANE GENERATION AS A NOVEL PREDICTOR OF MORTALITY

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Thromboxane A2 (TXA2) is a signal-activated eicosanoid generated from the metabolism of arachidonic acid by the cyclooxygenase (COX) and thromboxane synthase enzymes. In healthy individuals, TXA2 is predominantly produced in platelets where it mediates platelet activation and local vasoconstriction. Aspirin (ASA) exerts its principle cardioprotective effect by suppressing platelet TXA2 synthesis via irreversible inhibition of platelet COX-1. Unfortunately 25-50% of patients with cardiovascular disease (CVD) on ASA therapy continue to generate substantial amounts of TXA2 that originate from non-platelet sources. Dysfunctional endothelial cells under oxidative stress may be a potentially major source of non-platelet TXA2 generation in patients with CVD, though leukocytes may also be a significant source in conditions of extreme inflammation. Recent outcome studies have identified non-platelet TXA2 generation as an independent risk factor for adverse events and long-term mortality in patients with CVD. The mechanism by which this occurs is unknown but does not appear to be due to increased platelet reactivity. Compelling evidence suggests that non-platelet TXA2 generation may promote atherothrombosis via alterations in endothelial function. As standard ASA therapy is incapable of suppressing non-platelet TXA2 formation, alternative strategies will need to be identified to modify this novel cardiovascular risk factor and improve outcome.
IDENTIFICATION AND MODIFICATION OF NOVEL RISK FACTORS FOR CARDIOVASCULAR DISEASES

HEALTHY WEIGHT, HEALTHY EATING AND ACTIVE LIFESTYLE REDUCE THE RISK OF HEART DISEASE AND STROKE

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Developed and developing countries are facing epidemic increase in cardiovascular diseases (CVDs), obesity, diabetes mellitus, arthritis, degenerative disorders of CNS, respiratory illnesses and cancer. The burdens of premature mortality and morbidity due to heart disease and stroke are escalating worldwide. Though CVDs and obesity generally manifest in middle age and beyond, it is now recognised that risks of these diseases originate from fetal programming and are manifested in childhood and adolescence. The conventional risk factors of CVD consist of hypertension, hyperlipidemia, atherosclerosis, and hyperglycemia. Lifestyle factors including tobacco use, lack of exercise, unhealthy dietary habits, and low socioeconomic status contribute heavily to the development of obesity, diabetes and CVD in children and adults. Sugar-loaded beverages and excessively salted foods are also potential risk factors. Diets rich in whole grains, fruits and vegetables, olive/flaxseed/perilla oils, fish and omega-3 fatty acids, low-fat dairy products, and moderate wine consumption are linked with lower incidence of CVDs. Lifestyle modifications such as regular physical activity (about 30 min/day), restriction of caloric and sodium intake, smoking cessation and moderate alcohol consumption are recommended for improving cardiovascular health and quality of life. Ingestion of functional foods, vitamins, minerals, and amino acids assist to improve overall health beyond basic nutritional functions. Emerging evidence suggests that dietary supplements containing flavonoids, carotenoids, and antioxidants modulate gene and protein expression and thereby modify endogenous metabolic pathways and homeostasis, and consequently reduce the risk of CVD and chronic diseases multifactorial in origin. Given the scope and prevalence of CVDs, a cost effective population health strategy - 'prevention is better than cure' - would be the most appropriate model to adopt to reduce CVD-related mortality and morbidity.
IDENTIFICATION AND MODIFICATION OF NOVEL RISK FACTORS FOR CARDIOVASCULAR DISEASES

A CURRENT UPDATE ON INFLUENZA AND CARDIOVASCULAR DISEASES

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Much emphasis has been placed on the role of chronic risk factors leading to development and progression of atherosclerosis over years. However, newer studies show an important role for triggers of acute coronary syndromes (ACS). Triggers can cause a rapid transition of stable plaques into unstable plaques which are the culprit pathology for ACS. Influenza has been established as a clinically relevant, yet preventable ACS trigger. In over 35,000 autopsies over 8 years, we showed that each and every influenza epidemic is associated with a sharp rise in number of cardiovascular death. In apo-E knockout hypercholesterolemic mice, we have shown that influenza infection can cause a marked increase in inflammatory cells in atherosclerotic plaques leading to focal inflammation in synergy with profound systemic inflammation. Multiple retrospective, prospective, and clinical trial studies in various patient groups showed that influenza vaccination is associated with a significant reduction in risk of myocardial infarction, sudden cardiac arrest, stroke, and hospitalization for cardiac causes. Based on these, American Heart Association and American College of Cardiology secondary prevention guidelines recommend influenza vaccination for all patients with cardiovascular disease (CVD). Unfortunately, the vaccine usage in patients with CVD remains less than 65% in US, and is even lower in most other countries. Efforts are needed to increase vaccination rate in cardiac patients. Most recent studies have also demonstrated that influenza can increase the risk of supraventricular and ventricular arrhythmias. These studies suggest an important role for influenza in pathogenesis of acute cardiovascular events and call for multi-disciplinary efforts to improve vaccination rates in high risk subjects.
BIG DATA IN CARDIOLOGY - WHERE WE SHOULD BE GOING AND WHY?

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Big data collection, analysis and analytics are changing the modern world. In healthcare, medical and cardiovascular research, the concept of big data is in its infancy. I am the founder of the ACALM (Algorithm for Comorbidities, Associations, Length of stay and Mortality) and we have been utilising the concepts of big data especially in the cardiovascular field over the last decade. Existing research utilising big data (including ACALM) will be discussed and the full potential of big data going forward with the potential to transform cardiovascular research and clinical practice will be highlighted with real clinical examples and scenarios.
HEMODYNAMICS, INTERVENTIONAL CARDIOLOGY AND SURGICAL TREATMENT

HEMODYNAMIC SUPPORT FOR HIGH RISK PCI AND CARDIOGENIC SHOCK: FINDING THE SWEET SPOT

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Hemodynamic support (HD) requires decision-making related to device, timing of use, and appropriateness of use. Appropriate use is critical. Adopting a “wait and watch” or "getting by" philosophy potentially leads to less optimal results. The real risk of "getting by” reduces late outcomes despite acceptable immediate results.

In Cardiogenic shock, device choice is based on effectively increasing cardiac output (CO) as well as limiting ischemia by reducing preload. IABP and Impella devices both increase blood pressure but Impella more effectively increases CO while decreasing preload. Earlier support, before reperfusion and/or high dose inotropes yields excellent late results. Impella 2.5 in AMI/CS in the USPella Registry demonstrated that Impella 2.5 was associated with improved survival: pre PCI Impella group had a hospital survival of 65.1% compared to 40.7% survival for later support. (p=0.003).

In High-risk PCI (HRPCI) appropriate HD requires low LVEF, and/or severe, complex coronary anatomy and/or general patient risk. Device choice again favors Impella for its ability to provide CO during sudden loss of LV contractility. Importantly, getting out of the lab is feasible without support in many cases but late outcome is enhanced by better initial lesion results. The PROTECT II Trial randomly compared pre-procedure IABP vs. Impella 2.5 support for patients requiring prophylactic hemodynamic support during non-emergent, HRPCI. Impella support had more extensive rotational atherectomy use, greater revascularization but shorter support times post procedure with numerically lower MACCE at 30 days (p=NS) but significantly lower 90 day MACCE rates (p<0.023) and less repeat hospitalizations over 90 days compared to the IABP arm supporting the importance of an better initial result leading to better late results.

In conclusion, HD decisions are important. Hitting the "sweat spot" is critical to limit risk while achieving optimal acute and late results. Early and effective support supports improved outcomes.
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THE IMPORTANCE OF POST-PCI FFR: “IT'S NOT OVER ‘TIL IT'S REALLY OVER”

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The value of fractional flow reserve (FFR) in determining whether an intermediate stenosis lesion causes ischemia is well documented. Treating lesions with an ischemic FFR and deferring lesions with a non-ischemic FFR have been shown to improve long-term outcomes. As a result, use of FFR in evaluating angiographic intermediate lesions has a Class I recommendation by the European guidelines and a Class IIa recommendation by the American College of Cardiology (ACC)/American Heart Association (AHA). The guidelines are, however, silent on the value of measuring FFR after an angiographically successful percutaneous coronary intervention (PCI). We propose that measuring FFR post-PCI is valuable and will improve long-term outcomes.

Although one might conclude that an angiographically normalized vessel after PCI will have a non-ischemic FFR, this is not always the case. There are at least three major reasons for a persistently ischemic FFR in this setting: 1) unmasking the ischemia-potential of a second unimpressive angiographic lesion, 2) underexpansion of stented areas, and 3) the presence of diffuse disease. The level of post-PCI FFR is a major predictor of long-term outcome. In three large studies comprising over 2500 patients, the level of post-PCI FFR predicted long-term outcome in each study.

In a series of 664 lesions, we noted an incidence of 21% of post-PCI ischemic FFR. The two most important associated characteristics were the presence of diffuse-but not severe-angiographic disease and a lesion in the left anterior descending artery. In our study the best cutoff point by ROC analysis for good outcome after PCI was an FFR of 0.87 or higher. In a study by Li et al, the cutoff point was 0.88. We also addressed the issue as to whether a low post-PCI FFR is simply a marker of more extensive atherosclerosis or whether the FFR can be improved by further intervention. We demonstrated that in the 137 lesions which had a relatively low FFR (0.78±0.08) and underwent subsequent intervention, FFR improved significantly (p<0.001) to 0.87±0.06. Furthermore, of the 21% of lesions with an angiographically satisfactory PCI result and FFR< 0.80, further intervention decreased the incidence of ischemic FFR (<0.80) to 7%. Subsequent interventions included post-dilatation of the stent with a non-compliant balloon (42%), use of addition stenting in 33%, and both in 18%. In 9% the vessel was imaged with either IVUS or OCT, but due to diffuse disease was not further treated. We also demonstrated that measuring post-PCI FFR and performing additional interventions were not associated with any significant complications. Prospective studies are necessary but based on current data optimization of FFR after PCI may result in improved outcomes.
DURAGRAFT VASCULAR GRAFT TREATMENT IN THE PREVENTION OF PATIENTS UNDERGOING CABG

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Background: The principal mechanism thought to limit the benefits of CABG is saphenous vein graft disease leading to vein graft failure (VGF). Injury to the saphenous vein graft (SVG) endothelium during harvesting and implantation promotes inflammation and neointimal hyperplasia that can lead to subsequent graft atherosclerosis and occlusion. We investigated the beneficial impact of a novel formulation SOMVC001 (DuraGraft) for intraoperative SVG treatment on angiographic early (4-6 weeks and 3 months) graft wall thickness and late (12-month) lumen loss in patients undergoing CABG

Methods: This is an ongoing prospective randomized, double-blinded study designed to compare within patient the impact of DuraGraft vs. the standard of care heparinized dose saline (SOC). The early endpoint evaluates the magnitude of change in the mean wall thickness of paired grafts within patients at 4-6 weeks and 3 months after CABG. The late endpoint evaluates the change from 4-6 weeks to 12 months in mean lumen diameter over each graft plus the lumen diameter at maximal stenosis within-person following CABG surgery. Graft structural changes are evaluated using 64-slice or better multi-detector computed tomography (MDCT) angiography.

Results: Enrollment of 119 patients who received treatment (mITT population) at 7 investigational sites was completed. Baseline procedural characteristics are representative of a population of subjects undergoing initial CABG with at least two SVG (Fig. 1). MDCT angiographic follow-up showed the proportion of patients with mean reductions or no change in wall thickness at 4-6 weeks and 3 months after CABG was greater in the DuraGraft treated group when compared to SOC: 70.3% (95% CI: 62%-79%, p<0.0001) 67.0% (95% CI: 58%-76%, p<0.0003), respectively. Conclusion: These results support the hypothesis that pretreatment of SVG with DuraGraft prevents early increased wall thickness as an expression of intimal hyperplasia. Evaluation of DuraGraft at 12 months and its potential to prevent graft lumen loss as an expression of VGF in patients undergoing CABG surgery is pending.
HOW TO PREDICT THE LONG-TERM OUTCOME OF NEW STENTS?

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It is well known that the short-term clinical outcome cannot predict the long-term outcome of drug-eluting stents (DES) from the experience of head-to-head comparison between Cypher and Endeavor stents, in which 1-year results were better for Cypher but 5-year results were extremely better for Endeavor stent. On the other hand, angioscopy revealed the terrible appearance of Cypher stent at 1-year follow-up having unhealed ruptured plaque, thrombus, and poor neointima coverage. Furthermore, the early formation of yellow plaque (neoatherosclerosis) at 1 year was also detected after Cypher stent implantation, which was not detected after bare metal stent (BMS) implantation. However, Endeavor stent had adequate white neointima coverage that was similar with BMS. Recently, DESNOTE study demonstrated that the presence of yellow plaque in the stented segment at 1-year follow-up was associated with the higher risk of very-late stent failure (VLSF). The use of statin and the larger reduction of serum LDL-cholesterol were associated with the lower risk of VLSF. Therefore, the DES with adequate neointima coverage without yellow plaque at 1-year follow-up would have a good long-term outcome. Aggressive LDL-cholesterol lowering therapy may also contribute to reduce the incidence of VLSF. Taking these into consideration, we should judge if a new DES is better than the previous ones by both the early clinical outcomes and early findings from the intra-coronary imaging and pathological studies. We should regard the findings from imaging and pathological studies as of same or of more important value as the early results of clinical trials. The long-term clinical outcome over 30 or 50 years may be real evidence, but 1-year clinical outcome may not worth surrogate endpoint. Looking for the imaging or pathological findings at short-term period to speculate the future clinical outcome should be more important than satisfying with the good short-term clinical outcome.
LEFT MAIN CORONARY ARTERY DISEASE TREATMENT IN 2017:
PCI vs CABG

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European and U.S. guidelines currently recommend that the majority of patients with unprotected left main coronary artery disease (UPLM) undergo coronary-artery bypass grafting (CABG). Percutaneous Coronary Intervention (PCI) should be considered in patients with UPLM and favorable coronary disease (ie, in the absence of complex and diffuse lesions). The guidelines are substantially based on the 705 patient subgroup with UPLM in the SYNTAX trial, and on the findings of some randomized trials, LE MANS (100 patients), PRECOMBAT (600 patients), and Boudriot et al (201 patients). Of note, after the publication of the Guidelines, two large randomised controlled trials, the NOBLE and the EXCEL, and long term data of the previous studies have been published providing further evidences and possibly challenging the Guidelines. Indeed, a recent meta-analysis suggest a substantial equivalence of the two strategies in terms of hard end point at both short and long term follow up, although differences have been observed for the rate of stroke (favoring PCI at short term) and the rate of new revascularization (favoring CABG at short and long term FU). Yet, in some patient and doctors view, along with the longer stay in hospital, the risk of reoperation for bleeding and infection, a longer recovery time, pursuing the surgical approach might not be worth the lower risk of repeat revascularisation as no difference in mortality and MACEs can be detected. Accordingly, we believe that all patients with complex multivessel coronary artery disease involving the LM should be reviewed and discussed by a clinician, a cardiac surgeon and an interventional cardiologist to reach consensus on optimum treatment, considering the conundrum of clinical setting, anatomy, physiology, technical challenges and operators/center experience as well as patient preferences.
ECMO is extracorporeal life support to augment oxygenation, ventilation, and cardiac output. Veno-arterial ECMO used in critical cardiac care in Refractory Heart Failure and managing cardiac arrest non responsive to conventional CPR. V-V ECMO mainly useful for managing advanced respiratory failure. VAECMO used as a bridge to recovery or for subsequent VAD or cardiac transplantation. Cardiogenic shock trial and CHEER trial have shown survival benefits with ECMO. Also beneficial in accidental hypothermia and cardiac arrest due to intoxications. Major complications are thrombosis and local vascular problems and infections. To sum up, ECMO is a temporary heart lung machine and its use in refractory cardiogenic shock and both in hospital and out of hospital cardiac arrest is rapidly increasing as it improves survival benefits in these other very hopeless medical conditions.
COMPREHENSIVE MULTIMODAL INTRA-VASCULAR OPTICAL IMAGING WITHOUT EXOGENOUS CONTRAST AGENT

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Intravascular optical coherence tomography (IV-OCT) is an imaging catheter that visualizes three-dimensional microstructure of arterial walls. With unprecedented high-resolution IV-OCT for cardiovascular imaging, clinicians can identify key features associated with high-risk lesions within the blood vessels. While grayscale IV-OCT allows a clear visualization of high-risk lesions, it cannot provide comprehensive information on atherosclerotic plaques, such as biochemical compositions and inflammation. Therefore, we have developed an algorithm to measure the lipid content of atherosclerotic plaques by analyzing spectral information from IV-OCT images. The algorithm utilizes the IV-OCT images, thus it does not require any hardware modification. Additionally, we have developed a multimodal intra-vascular optical imaging technology that combines OCT with fluorescence lifetime imaging (FLIM). Since FLIM provides multichannel fluorescence intensity as well as lifetime of the fluorophore, the biochemical composition of the plaque can be analyzed quantitatively. In particular, the FLIM signal can be obtained from the autofluorescence of the tissue itself, thus no exogenous contrast agent is needed. By providing comprehensive information of the arteries, these new imaging technologies can provide new opportunities to investigate vascular biology and stent pathobiology and to identify high-risk plaques.
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DEVELOPMENT OF BIODEGRADABLE NANOFIBROUS DRUG-ELUTING STENTS: CHALLENGES AND OPPORTUNITIES
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Drug-eluting stents are implanted for opening up narrowed or blocked arteries to restore blood flow. Coronary heart disease and acute myocardial infarction are often treated by catheterization and stenting prior to the open-heart bypass surgery. Surgical stenting opens up arteries blocked with plaque, esophageal cancer, airways blocked due to lung cancer, and weakening of the vessel wall. Relatively less hospital cost, low risk of stenting, and quick patient recovery are well recognised, as opposed to the higher risk and prolonged rehabilitation after open-heart surgery. Several varieties of stents have been developed and are available for clinical use. The Global Cardiovascular Implants Market is poised to grow around 4.5% over the next decade. Currently, the US market share for coronary stent devices is nearly 40%, while European share is around 37%. Drug-eluting stents not only reduce early and delayed complications with stenting, but also restenosis rate by 80%. However, there are challenges to minimise the potential risks of stenting: namely restenosis of arteries due to in-stent thrombosis, growth of scar tissue caused by in-stent-restenosis, migration of stent due to insufficient radial stretch, inflexibility and mechanical mismatches between stented and non-stented vessels, and shortening of in-stent length. To overcome these difficulties, development of biodegradable nanofibrous drug-eluting stents is warranted to enhance the long-term safety and mechanical effectiveness of stents. This presentation will focus on the fabrication of nanofibrous stents with targeted drug delivery system. Hopefully, biodegradable nanofibrous drug-eluting stents would overcome the mechanical challenges as well as early and delayed complications of stenting.
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PERCUTANEOUS HEMODYNAMIC SUPPORT DEVICES IN THE CURRENT DAY
CATH LAB

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There has been a significant progress in the field of interventional devices that have improved the success rate of cardiac procedures dramatically. Cardiologists are willing to tackle more complex cases, thanks to these innovations. Hemodynamic support devices are commonly used in patients presenting with acute myocardial infarction in cardiogenic shock, acute decompensated heart failure or high-risk percutaneous coronary intervention (PCI). The ideal hemodynamic support device should satisfy the following criteria: easy to insert, simple to use and maintain and provides maximal coronary support. Since its inception in 1968, intra aortic balloon pump (IABP) has been the only device available to support these patients, but in the past few years, devices that provide more support such as Impella™, Tandem Heart™ and veno arterial extra corporeal membrane oxygenation (ECMO) have been introduced. One must have a sound physiologic knowledge to understand the clinical application of these devices. Despite the lack of prospective randomized trials supporting the use of these devices, the interventional field has seen a tremendous increase in the implantation of these devices. The “true believers” of this technology argue that the trials consisted of a very heterogeneous population and had significant limitations. It is generally accepted that in patients with cardiogenic shock hemodynamic support is beneficial, although the timing of placement of the device (before or after PCI) is controversial. High risk PCI is currently the most common indication for hemodynamic support, but the definition of high risk is debatable. These devices are not without complications, although with continued innovation their incidence has diminished. One has to look beyond the randomized trials and have to rely on observational and registry data to support its use. Professional societies have published guidelines to help clinicians make better therapeutic decision.
IMPROVING UNDERSTANDING, TREATMENT AND OUTCOME IN ATRIAL FIBRILLATION

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CELLULAR ELECTROPHYSIOLOGICAL MECHANISMS OF PAROXYSMAL ATRIAL FIBRILLATION IN PATIENTS

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Atrial fibrillation (AF) is the most prevalent arrhythmia that presents a wide range of therapeutic challenges. AF usually begins in a self-terminating paroxysmal form (pAF) and tends to become persistent (non-terminating within 7 days) or permanent in a large proportion of patients. There are important differences between pAF and persistent AF forms in terms of clinical features, in particular the responsiveness to antiarrhythmic drugs and ablation therapy. Here, I will carefully examine the available data regarding the electrophysiological basis for pAF occurrence and maintenance, as well as the molecular mechanisms forming the underlying AF-promoting substrate. I will first consider the mechanistic insights that have been obtained from studies in human atrial samples from patients with persistent (chronic) AF. Then I will move on to discuss the information about underlying molecular mechanisms that has been obtained from atrial samples from pAF patients, focusing on the potential role of delayed afterdepolarization-mediated ectopic (triggered activity) and the related underlying molecular mechanisms. pAF patients shows dysfunctional (leaky) ryanodine-receptor channels and calcium overloaded sarcoplasmic reticulum, both supporting the occurrence of delayed afterdepolarizations and triggered action potential that may be the correlates of focal ectopic firing. Finally, I will discuss the information available about the putative role of reentry-related mechanisms (APD shortening, connexin remodeling) and structural remodeling (heterogeneous atrial fibrosis) in the pathophysiology of pAF. I will conclude by identifying and discussing questions that I consider particularly important to address through future research in this area.
IMPROVING UNDERSTANDING, TREATMENT AND OUTCOME IN ATRIAL FIBRILLATION

IMPROVEMENT IN QUALITY OF CARE FOR ATRIAL FIBRILLATION IN GET WITH THE GUIDELINES—ATRIAL FIBRILLATION (GWTG-AFIB)

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Get With The Guidelines (GWTG) is a quality improvement program that has demonstrated improvement in the management of heart failure, myocardial infarction, and stroke. Recently, GWTG developed an atrial fibrillation (AF) module that has been adopted by 79 hospitals across the U.S. We sought to determine if participating in GWTG-AFIB would be associated with high rates of compliance with anticoagulation using the new ACCF/AHA AF performance measure definitions.

Methods: We included GWTG-AFIB patients with a primary or secondary diagnosis of AF at centers with >90% complete data. Patients with documented absolute contraindications to oral anticoagulation were described but not included in the primary analysis. Adherence to the ACCF/AHA performance measures for AF was reported and the adjusted association with adherence and outcomes was determined.

Results: The cohort included 20,342 AF admissions. The median age was 71, 48% were female, and the median CHA2DS2-VASc score was 4. The distribution of first-detected/paroxysmal/persistent/long-standing persistent AF was 27%/47%/15%/11%. Contraindications to oral anticoagulation were documented in 3678 patients (19%). Rates of oral anticoagulation at hospital discharge in eligible patients (no contraindications) with a CHA2DS2-VASc ≥2 was 92.3% in the total population. Rates of anticoagulation were similar by race and coronary artery disease status. However, anticoagulation was more frequent in men (p<.001), those with heart failure (p<.001), age <75 (p=0.007), prior AF ablation (p<.001), and rhythm control (p<.001). Utilization of oral anticoagulation at discharge in eligible patients improved to >90% after the 2nd year of the program and is now 95.6% in the last quarter of enrollment.

Conclusions: Among hospitals participating in GWTG-AFIB, use of stroke prevention therapy at discharge in eligible guideline-indicated patients was high and improved over time. This national practice quality improvement registry demonstrates that a high degree of adherence to stroke prevention and AF quality measures is achievable and sustainable.
IS IT TIME TO RETHINK OUR MODEL OF ATRIAL FIBRILLATION AND STROKE?

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Atrial fibrillation is the most common sustained arrhythmia in clinical practice and the leading cause of disabling strokes in developed countries. The CHADS2 and CHA2DS2VASc scores are intended for patients with atrial fibrillation (AF) as a tool for assessing stroke risk. These scores summate risk factors of an advancing disease state. These scores also predict dementia risk, cardiac and total mortality and have similar utility in patients without AF. AF is an additive risk factor when applied to score models of all people. Critical to current treatment strategies to reduce stroke in AF patients is the mechanistic role of the arrhythmia for the genesis of thromboembolism. Traditionally the prevalent mechanism considered is that of atrial fibrillation onset, local stasis, hypercoagulability, and inflammation in the left atrium and left atrial appendage, followed by formation of thrombus. If this mechanism is a dominant cause of stroke then local therapies such as left atrial appendage occlusion or ligation, durable rhythm control approaches, and pill-in-the-pocket anticoagulation strategies should lower risk. Recent data from implantable cardiac devices have raised significant questions regarding this mechanism as a dominant cause of stroke. In light of these emerging data, we must ask the question of if it is time to rethink our model of AF and stroke? Critical to these data is understanding the degree to which AF is a risk factor of stroke and if it is modifiable versus a risk marker of systemic disease severity. In addition, when AF is considered in the setting of a systemic disease state that evolves, what temporal and dynamic tools can offer benefit to give insight into the disease severity and risk?
TREATMENT OF ARRHYTHMIAS IN THE ELDERLY: SPECIFIC AGE RELATED CONSIDERATIONS

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The increasing pressure of caring for an aging population has an enormous impact on the health community. Atrial fibrillation – the arrhythmia of the elderly and interventional therapy like catheter ablation, ICD implantation in elderly and battery replacement in patients older than 85 years will concern us more and more in the future. The benefits of these interventional treatment strategies for elderly patients (> 80 years of age) with respect to mortality, morbidity and stroke reductions remain unclear. The question how old is too old for these interventions has to be asked. An accurate assessment of biological age and quality of life is important in the assessment of elderly patients referred for these complex interventions. The assessment of frailty is emerging as an important marker for prognosis in cardiovascular disease. No randomized studies exist for the patient population. Several small studies demonstrated that elderly patients with AF benefit from AF-ablation, which is safe and effective in maintaining sinus rhythm and is associated with lower mortality and stroke risk. Similar findings were obtained regarding ICD Therapy. ICD therapy may remain effective in highly selected elderly patients at high risk of arrhythmic death. Biological rather than chronological age per se should be the decisive factor in making a decision on ICD selection or indication for AF ablation for survival benefit and improvement in quality of life.
IMPROVING UNDERSTANDING, TREATMENT AND OUTCOME IN ATRIAL FIBRILLATION

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ARE LOW DOSES OF DIRECT-ACTING ORAL ANTICOAGULANTS JUSTIFIED AND APPROPRIATE IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION? NONVALVULAR ATRIAL FIBRILLATION?

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The novel direct-acting oral anticoagulants (NOAC) (dabigatran, rivaroxaban, apixaban and edoxaban) overcome most drawbacks of vitamin K antagonists and have proven efficacious and safe in well-designed multicenter randomized clinical trials. Therefore, various cardiology societies recommend NOAC as the first-choice oral anticoagulants in patients with nonvalvular AF.

However, the four pivotal NOAC trials in patients with AF have very important differences in design, doses, population, and results. Importantly, in the trials different subgroups of patients received reduced doses of NOAC with different criteria. In the RELY trial, all patients randomized to either dose of dabigatran received the full dose, whereas in the ROCKET-AF (with rivaroxaban), ARISTOTLE (with apixaban) and ENGAGE-AF (with edoxaban) trials, the dose of NOAC was reduced at baseline (after randomization to NOAC) in 20.7%, 4.7%, and 25.4% of the patients, respectively. Subgroup analyses of low-dose regimens in the pivotal studies of NOAC in nonvalvular AF revealed no alert signs versus the higher dose (non-significant interaction p-value).

Nevertheless, physicians should be aware that only limited numbers of patients received the reduced doses of rivaroxaban, apixaban, and edoxaban in the pivotal studies.

In summary, low-dose NOACs are justified in patients who present a high risk of bleeding for any reason. However, the reduction of hemorrhagic risk comes at the cost of lower antithrombotic protection. Therefore, patients must be carefully evaluated before being prescribed low-dose NOACs and reevaluated during the follow-up. Inappropriate application of low-dose NOAC regimens will probably lead to worse thromboembolic results than those observed in the large randomized clinical trials and will probably compromise patient safety. As is true for all drug classes, clinicians need to be educated in all aspects of NOAC treatment, from choosing the most appropriate drug and dose to managing possible complications.
IMPROVING UNDERSTANDING, TREATMENT AND OUTCOME IN ATRIAL FIBRILLATION

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UTILIZATION OF 3-D MAPPING FOR SUCCESSFUL ABLATION OF TYPICAL ATRIAL FLUTTER

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Objectives: Achieving bidirectional isthmus block (BIB) along the cavo-tricuspid isthmus (CTI) is crucial for successful atrial flutter (AFL) ablation and also to prevent recurrence. BIB can be demonstrated by utilizing intra-cardiac electro grams while pacing on both sides of the presumed isthmus block. 3-D mapping is a complementary tool for testing of BIB.

Background: Typical AFL is defined by CTI dependent counterclockwise or clockwise macro-reentry involving the right atrium. Catheter ablation carries high procedural success rate and creation of BIB along the CTI predicts long-term success. Isolated unidirectional isthmus block may rarely occur during AFL ablation. Utilization of 3-D mapping is an important tool to demonstrate absence of BIB and to prove BIB after further ablation.

Methods: Between July 2009 and March 2017, 105 AFL ablations were done at our institution. I herein report utilization of 3-D mapping in these procedures.

Results: We had 100% success rate and 1 recurrence in 105 AFL ablations. We demonstrated persistence of BIB with 3-D mapping in 102 patients. Although we demonstrated unidirectional medial to lateral isthmus block in 3 patients; lateral to medial conduction remained intact in these patients. Further radiofrequency applications were delivered lateral to the first ablation line, while pacing the low right atrial free wall. 3-dimensional mapping confirmed achievement of BIB.

Conclusions: Even with successful termination of AFL during ablation, meticulous testing by pacing medial and lateral to the line of block should be done to confirm BIB. 3-D mapping is a great complementary tool to prove BIB.
Autonomic nervous system plays a critical role in atrial fibrillation (AF) arrhythmogenesis. Current experimental data regarding autonomic stimulation in AF are mainly derived from normal animals, indicating that vagal nerve stimulation (VS) is more arrhythmogenic than sympathetic stimulation (SS) in AF arrhythmogenesis. Heart failure (HF) results in sympathetic activation and vagal withdrawal, and is associated with an increased AF incidence. In this study, we specifically investigated whether failing hearts, compared to normal controls, respond differently to autonomic stimulation in AF arrhythmogenesis. By using a rat myocardial infarction (MI)-HF model, HF was induced in 9 rats 2 months after MI surgery. Sham-operated animals (n=10) served as controls. AF inducibility was augmented in both groups by autonomic stimulation. However, the increased magnitude was less in the MI-HF group (49±31% in MI-HF versus 80±33% in control, P=0.029) under VS, but was significantly more in MI-HF hearts under SS (53±24% versus 6±21%, P<0.001), compared with sham-controls. In light of the presence of ryanodine receptor dysfunction in HF, we further investigated whether stabilizing ryanodine receptors with dantrolene can decrease SS enhanced AF inducibility in HF. This part was done in 17 MI-HF animals, randomized into 2 groups: control (vehicle treated, n=9) and dantrolene (10mg/kg, IP, n=8) groups. AF inducibility under SS were studied in all animals 30-min after the respective treatments. Compared with controls, dantrolene treatment significantly reduced AF inducibility and AF duration under SS. Thus, in contrast to normal controls, failing hearts are less sensitive to VS, but more vulnerable to SS induced AF. Dantrolene treatment, by stabilizing ryanodine receptor, can significantly attenuate SS enhanced AF inducibility in HF, indicating that ryanodine receptor dysfunction may play a critical role in enhancing AF in HF under SS, and stabilizing ryanodine receptor may be a new treatment option in reducing AF in HF.
ATRIAL FIBRILLATION AND GERIATRIC SYNDROMES

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Atrial Fibrillation (AF) is the commonest arrhythmia seen in the elderly and incidence increases with aging. Although rate, rhythm control and anticoagulation are similar for young and older adults, elderly AF subjects present also with geriatric syndromes and multiple chronic conditions. Geriatric syndromes such as cognitive impairment, falls, incontinence, depression and polypharmacy add to the complexity of caring for older adults with AF. AF has been associated with Mild Cognitive Impairment and dementia, even though the association was not consistent across studies. Recent studies had shown that AF can cause cognitive decline even in the absence of stroke. One of the common reasons for withholding anticoagulation is frequent falls, so understanding the relationship between falls and AF is important. Overall, assessing for geriatric syndromes as part of the evaluation in AF may help to provide the complex care in elderly as well as to provide opportunities to prevent complications.
Pacemakers require contiguous electrical wires from energy source to induce cardiac stimulation resulting in cardiac contraction. The battery source and electronic circuitry are in a far away location from the heart due to the utility of the leads. Leads themselves are subject to cardiac motion, creating stress, which in turn can test their structural or functional integrity. Leadless pacemakers, by integrating power source, electronic circuitry and stimulating electrodes into one single unit, facilitate intra cardiac placement of these devices. At this time, single chamber leadless pacemakers are available and multi-chamber pacemakers are in development.
FUNCTIONAL CHARACTERIZATION OF RARE VARIANTS IMPLICATED IN SUSCEPTIBILITY TO LONE ATRIAL FIBRILLATION

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Background: Many variants in ion channel genes have been identified in monogenic AF families. To elucidate the molecular mechanisms of AF may allow a mechanism-based approach to treatment: for example, patients with gain-of-function ion channel variants are likely to benefit from a drug that selectively blocks mutant channel complexes. We here sought to determine the clinical impact of rare variants in AF-associated genes in patients with lone AF and characterized these variants electrophysiologically.

Methods and Results: We screened all coding regions in 10 AF-associated ion channel genes in 90 patients with lone AF, with an onset of 47 ± 11 years (66 men; mean age: 56 ± 13 years), by high-resolution melting curve analysis and DNA sequencing. The potassium and sodium currents were analyzed using whole-cell patch clamping. In addition to using four individual in silico prediction tools, we extended those predictions to an integrated tool (Combined Annotation Dependent Depletion, CADD). We identified seven rare variants in eight patients: H463R and T527M in KCNA5, L492_E493 ins DL in KCNQ1, T436M and T895M in KCNH2, R986Q in SCN5A, and T189M in SCN1B. Probands with both KCNH2 variants had a family history of AF. Electrophysiological studies revealed KCNA5_H463R and SCN5A-R986Q showed a loss-of-function, and KCNA5-T527M, KCNH2-T436M, KCNH2-T895M, and SCN1B-T189M showed a gain-of-function. Five of six variants with electrophysiological abnormalities were predicted as pathogenic by CADD scores. Two probands with SCN1B T189M, showed paroxysmal AF that was controlled well by pilsicainide.

Conclusions: In our cohort of lone AF patients, seven rare variants in cardiac ion channels were identified in eight probands, with a prevalence of approximately 9%. More than half of AF-associated rare variants showed gain-of-function behavior, which may be targeted using genotype-specific pharmacological therapy.
PROGNOSTIC IMPACT OF LEFT VENTRICULAR REMODELING IN ARTERIAL HYPERTENSION: AN ECHOCARDIOGRAPHIC STUDY

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Introduction: Hypertension has a high prevalence in the general population and is one of the most important cardiovascular risk factors. This pathology can lead to the development of heart failure through pathological phenomena such as myocardial infarction or the onset and progression of hypertensive heart disease, in which the cardiac remodeling process has a prominent role.

Purpose: The aim of the study was to evaluate the prognostic impact of the Complex Remodeling Classification (CRC), which describes ventricular remodeling using indexed left ventricular mass, relative wall thickness and indexed left ventricle end-diastolic volume in patients with hypertension.

Methods: A group of 749 hypertensive subjects was followed over a period of 60 months and evaluated both clinically and by echocardiography. We considered a composite end-point: total mortality, myocardial infarction, coronary revascularization, cerebrovascular events and acute pulmonary edema. Echocardiographic analysis revealed the presence of 102 patients with concentric remodeling, 29 patients with eccentric remodeling, 11 patients with mixed hypertrophy, 52 patients with dilated hypertrophy, 36 patients with eccentric hypertrophy and 157 patients with concentric hypertrophy.

Results: At the end of follow-up, Kaplan-Meier analysis showed that there was a different distribution of survival (p = 0.0001) for the remodeling pattern in accordance with the CRC and in the analysis of multiple Cox regression (adjusted for age, sex, blood pressure levels, smoking, family history, diabetes mellitus, dyslipidemia, obesity, remodeling drug therapy and classical classification) the CRC is demonstrated to be an independent predictor for the endpoint (p = 0.01, OR = 1.85, 95% CI 1.20 2.86). These data were confirmed by logistic regression (p = 0.016).

Conclusion: CRC can provide additional information to the prognostic stratification of hypertensive patients.
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RELATIONSHIP BETWEEN CARDIOMEGALY BY CHEST X-RAY AND LEFT VENTRICULAR SIZE BY ECHOCARDIOGRAPHY

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Background: The diagnostic accuracy of cardiothoracic ratio (CTR) on chest x-ray to detect left ventricular enlargement has been criticized due to low sensitivity and specificity when TTE is used as a gold standard. Indexed LVEDD, routinely assessed in all echocardiogram studies, is an independent predictor of mortality in a number of cardiac conditions. Our aim was to investigate the correlation between CTR and LVEDD indexed, and to determine the predictive value of CTR to detect enlarged LV (defined by >30mm/m2).

Methods: Consecutive patients who underwent transthoracic study at tertiary care hospital 1/2015-1/2017 and also had a posteroanterior CXR within 60 days were identified. Using the parasternal long-axis view, LVEDD (mm) was measured by standard techniques according to the recommendations of the American Society of Echocardiography and indexed to BSA (m2). Cardiothoracic ratio was calculated by dividing maximum transverse diameter of the heart shadow by the maximum transverse diameter of right and left lung boundaries. Pearson correlation was used, with ability of CTR to predict ventricular enlargement (LVEDD indexed) >30mm/m2 assessed using the AUROC with cutpoint for accuracy defined with the Youden criteria.

Results: A total of 187 patients (mean age 68.5±12 years, 51% men) were reviewed. There was a weak (r=0.215), but statistically significant (p=0.043) correlation between CTR and indexed LVEDD. The ability of CTR to predict LV enlargement (LVEDD indexed >30mm/m2) was also minimal with an ROC area under the curve of 0.58 (95%CI 0.48, 0.68) and accuracy of 59% with a CTR cutpoint of 0.55.

Conclusions: CTR is weak predictor of LV enlargement, even though the correlation did reach statistical significance. The finding of cardiomegaly on CXR should not be equated as enlarged left ventricle.
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EXERCISE INDUCED REGIONAL WALL MOTION ABNORMALITIES IN
SIGNIFICANT AORTIC REGURGITATION: VOLUME OVERLOAD, DIRECTION OF
AR JET OR CORONARY ARTERY DISEASE
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\textit{Background:} Significant aortic regurgitation (AR) is sometimes accompanied with regional wall motion abnormalities (RWMA) in exercise stress echocardiography. The aim of this study was to evaluate the meaning of regional wall motion change after exercise, as if related with coronary artery disease (CAD) or volume overload in the presence of significant AR.

\textit{Method:} We retrospectively reviewed 166 patients (69.9\% males, 55±13 years) with significant AR who underwent exercise echocardiography. In addition, we investigated the patients who underwent coronary angiography (CAG) or coronary computed tomography angiography (CCTA) and diagnosed as CAD. The patients were divided into 2 groups according to presence of RWMA after exercise: RWMA group (n=41) and No-RWMA group (n=125).

\textit{Results:} In RWMA group, 30 patients (73.2\%) were performed with coronary artery evaluation by CAG or CCTA. Two patients were diagnosed as real CAD with percutaneous coronary intervention. The patients were older (61.3±10.7 vs. 52.3±13.3, \textit{p}<0.001), more patients had symptoms related AR (36.6\% vs. 20.0\%, \textit{p}=0.037), severe AR (56.1\% vs. 36.8\%), and underwent aortic valve replacement (AVR) (39.0\% vs. 14.4\%, \textit{p}=0.001) in the RWMA group than the No-RWMA group. As compared with two groups, exercise duration was shorter (487.6±179.3 vs. 606.7±145.8 [sec], \textit{p}<0.001), difference of pre and post-exercise ejection fraction was bigger (-7.57±8.57 vs. 3.12±6.21 [%], \textit{p}<0.001), and difference of pre and post-exercise indexed LV end-systolic volume (LVESV) was smaller (2.06±16.21 vs. -13.60±10.44 [mL/m\textsuperscript{2}], \textit{p}<0.001) in the RWMA group than the No-RWMA group. Mostly wall motion changes were seen in lateral and inferior segments. The location of wall motion changes was relatively consistent with the directions of AR jet.

\textit{Conclusion:} Observed magnitude of change in wall motion from rest to exercise in significant AR did not seem to be related with CAD, but to severity of volume overload and exercise-induced changes of preload, additionally the direction of AR jet.
OUTCOMES OF ACUTE MYOCARDIAL INFARCTION IN CENTENARIANS

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Background. Number of centenarians (CN) have been on the rise and >50% have ischemic heart disease (IHD) at autopsy. Clinical trial data is unavailable for management of acute or chronic IHD for CN. We sought to evaluate recent trends in hospitalization, management and outcomes of acute STEMI and NSTEMI in CN.

Methods. Nationwide Inpatient Sample database 2003-2011 contains 7579 CN (age 101±2 years, 79% women, 81% white, 62% hypertensive, 40% prior IHD, 13% diabetic, 13% hyperlipidemic, 2% smoker) hospitalized for STEMI (n= 2427) or NSTEMI (n=5152).

Results. Annual number of admissions remained stable over study period (OR=0.994; 95% CI=0.985-1.003). Reperfusion therapy was performed in 1.2% either percutaneously (0.9%: 0.5% bare metal, 0.4% drug eluting stents), surgically (0.1%) or with fibrinolysis (0.2%). In-hospital mortality was 19%. Other major events included renal failure (18%), respiratory failure (8%), CHF (4.5%), ventricular arrhythmias (4%), cardiogenic shock (3%), cardiac arrest (2%), acute stroke (2%) and complete heart block (0.8%). Mechanical ventilatory (5.4%) or circulatory (0.2%) support (intra-aortic balloon pump) or pacemakers (0.9%) were infrequently used. STEMI and NSTEMI cohorts were similar in age (mean age 101 years) and race but those with NSTEMI were more often men (22%-vs-19%; p=0.017) and had more comorbid conditions [hypertension (63%-vs-57%), IHD (41%-vs-37%), diabetes (13%-vs-12%), hyperlipidemia (15%-vs-8%), congestive heart failure (2.8%-vs-1.2%) [p<0.001 for all]. Revascularization including percutaneous coronary intervention (2%-vs-0.5%) and coronary bypass grafting (0.2%-vs-0%) was more often performed in STEMI [p<0.001 for both]. In hospital mortality (32%-vs-13%, p<0.001) and other adverse events were higher in the STEMI group [Cardiogenic shock (6%-vs-2%), cardiac arrest (4%-vs-1.3%), respiratory failure (10%-vs-7.4%), ventricular fibrillation (2.4%-vs-0.4%), complete heart block (1.5%-vs-0.5%), acute renal failure (17%-vs-3%), cardiopulmonary resuscitation (3%-vs-0.4%), ventilatory support (8.3%-vs-4%) or temporary pacing (0.9%-vs-0%) [p<0.001 for all], circulatory support (0.4%-vs-0.1%, p=0.004)] with exception of acute CHF (5.2%-vs-3%,) which was higher in NSTEMI (p<0.001).

Conclusions. CN admitted with acute myocardial infarction are infrequently revascularized but when performed receive percutaneous intervention with bare metal stents. CN with NSTEMI have more comorbidities but more favorable in-hospital outcomes compared to STEMI.
ACUTE MYOCARDIAL INFARCTION, REPERFUSION THERAPY

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EFFECT OF TAILORED USE OF TIROFIBAN IN PATIENTS WITH NON-ST-ELEVATION ACUTE CORONARY SYNDROME UNDERGOING PERCUTANEOUS CORONARY INTERVENTION
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Background: We conducted a randomized controlled trial to investigate whether an additional platelet inhibition with tirofiban, would reduce the myocardial damage and periprocedural myocardial infarction (PMI) in patients with Non-ST-elevation acute coronary syndrome (NSTE-ACS) with a high residual platelet activity (HPR).

Methods and Results: Patients with NSTE-ACS eligible for an early conservative strategy were enrolled. Patients with an HPR, defined as P2Y12 reaction unit (PRU) >230, were randomly assigned to group A (tirofiban treatment, n=30) or group C1 (n=30) and patients without a HPR to group C2 (n=78). Periprocedural myocardial damage was assessed using the area under the curve (AUC) of serial cardiac enzyme levels from the time of procedure to post-36 h. PMI incidence was evaluated on the basis of the 2012 Third Universal Definition of Myocardial Infarction. The troponin I AUC was not different between the groups (A: 351.1±514.1, C1: 234.8±352.2, C2: 325.8±495.8 h∙ng/mL; p=0.586). The results did not change when the baseline levels were adjusted (365.3 [279.5, 451.1], 293.0 [207.1, 379.0], and 298.0 [244.7, 351.3] h∙ng/mL; p=0.487). The PMI event rates were also not different between the groups (53.0% vs. 50.0% vs. 33.3%, p=0.092). The CK-MB isoenzyme analysis showed similar results. No difference in complications was noted.

Conclusion: Additional tirofiban administration was not beneficial to patients with NSTE-ACS even with an HPR during the early conservative management.
ACUTE MYOCARDIAL INFARCTION, REPERFUSION THERAPY

AMI IN PATIENTS WITH NON-OCCLOSIVE CORONARY ARTERY DISEASE. A SINGLE CENTER EXPERIENCE IN SINGAPORE
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Background: In great majority of the cases, acute myocardial infarction (AMI) is due to atherosclerosis, resulting in critical coronary occlusion usually with plaque rupture. However, Non-obstructive may be found at angiography in minority of patients presenting with AMI.

Objective: To give an overview of the clinical characteristics and possible etiologies of AMI patients with non-occlusive coronary artery in Singapore.

Method: This is a single center, retrospective, descriptive study of all patients who presented clinically with AMI (STEMI and NSTEMI) from January 2014 to January 2016 who had non-occlusive coronary arteries on coronary angiogram. Clinical profiles of these patients were retrieved from hospital records.

Results: Of the 1,404 patients admitted for NSTEMI and STEMI, 46 patients were included, giving a prevalence of 3.28%. Of these, 23 are male and 23 are females. Most are of Chinese descent (41%) followed by Malays (28%) and Indians (20%). Average BMI was 25.6+/-5.5. None had renal failure, 46% have hyperlipidemia, 39% with hypertension, and 20% with diabetes mellitus. Only 10% have a history of IHD and/or angioplasty, 17% had family history of CAD and 19% had reduced ejection fraction. Of those with non-occlusive coronary arteries, 37% have normal coronaries while 63% have minor CAD. Being a smoker, hyperlipidemic, hypertensive, diabetic, and having past history of IHD didn’t point to a predilection towards having a non-occlusive CAD. Minor CAD patients are significantly older and all those with history of ethanol use belong to normal coronary group. Cardiomyopathies were attributed in 20% of patients, 15% to coronary spasm, 10% to muscular bridging and 2% to myocarditis/myopericarditis, while in majority (52%), the cause is unknown.

Conclusion: Non-occlusive CAD in coronary angiogram, though infrequent, can be observed in patients who present with AMI. Hypertension, hyperlipidemia, diabetes mellitus were not significantly associated with non-occlusive CAD in AMI.
ACUTE MYOCARDIAL INFARCTION, REPERFUSION THERAPY

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DIDO TIMING FOR A SECONDARY CARE HOSPITAL FOR STEMI PT. A SAUDI EXPERIENCE

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STEMI patients are usually treated with primary PCI in hospitals with a cath lab. ACC/AHA guidelines suggest for hospitals with no cath lab to transfer patient to a cath lab equipped facility if primary PCI can be offered with in 120 minutes of First medical contact (FMC), with "Door-in-Door-out" (DIDO) time of not more than 30 minutes at receiving facility. Most of data for STEMI patient in Saudi Arabia come from centers that have Cath Lab onsite. Few (if any) data is available from secondary or no cath lab equipped hospitals. We report an experience of STEMI patients presenting to a secondary care hospital in Alhasa, Saudi Arabia with no Cath lab onsite. A near by cardiac center is a referral site for such cases. It is only 15 minutes drive away. We evaluated the DIDO time (among other parameters) for these patients. Data for consecutive 54 patients with STEMI (who were eligible to either PCI or thrombolytic therapy) was collected to assess these parameters, including DIDO.

Results: 2 patients were excluded as they faced long stay in ER (5 and 11 hours as secondary screening to rule out MERSCoV infection was requested by referral center). 52 patients were transferred to the cardiac center for Primary PCI after diagnosis of STEMI was established. The DIDO time ranged between 13 and 286 minutes. Average time was 157 minutes. Cardiology team response time was less than 10 minutes in all cases once notified by ER doctors. Time between cardiology notification and door out averaged 92 minutes (Range: 13-416 minutes).

Conclusion: Despite the presence of geographically close cardiac center, patient with STEMI faced significantly long time in transfer for primary PCI that negates the benefits of PCI over thrombolytic therapy. Such patient may benefit from thrombolytic therapy as initial treatment method.
POSSIBLE DIFFUSE ALVEOLAR HEMORRHAGE FROM BIVALIRUDIN USE

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Diffuse alveolar hemorrhage (DAH) is a rare but potentially fatal complication of anti-coagulant or anti-platelet use.

A 61-year old man with no known cardiac disease was admitted for ST elevation myocardial infarction after he was resuscitated and intubated for pulseless electrical activity. Emergent coronary angioplasty was performed with placement of 2 stents. However it was complicated with ventricular tachycardia and hypotension requiring defibrillation and intravenous (IV) amiodarone. IV Bivalirudin was used, but IV eptifibatide was added due to no reflow after the first stent. Unfortunately, oxygen saturation started declining about 15 minutes after bivalirudin bolus. Active bleeding from endotracheal tube was observed with more profound desaturation about 30 minutes after IV bivalirudin and 15 min after IV eptifibatide. He also became much more tachypneic. IV Bivalirudin drip was immediately discontinued. No additional antiplatelet agent was given. Of note, IV eptifibatide drip was never initiated. Impella CP® device was placed, but he continued to deteriorate and unfortunately passed away within 36 hours after initial presentation.

We report a possible association between DAH and bivalirudin use. Thus far, there has been no report of DAH as a complication of bivalirudin use. Although, our patient did receive a standard bolus dose of eptifibatide, we believe that the hemorrhagic process was mostly triggered by bivalirudin based on the fact that hypoxemia and tachycardia occurred prior to administration of eptifibatide and only the bolus dose of eptifibatide was given without any subsequent infusion. Furthermore, his baseline and immediate post-procedure platelet counts were also normal.

Thus, a low threshold of clinical suspicion must be maintained to initiate proper management of the potentially fatal disease. However, no definitive therapy has been established for anti-thrombotic agent induced DAH, which is worth further study.
SPONTANEOUS CORONARY ARTERY DISSECTION: A CASE REPORT AND BRIEF REVIEW OF LITERATURE

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Introduction: Spontaneous coronary artery dissection (SCAD) is a non-traumatic and non-iatrogenic separation of the coronary arterial wall. It causes 0.1 to 0.4% of cases of acute coronary syndrome (ACS) in the general population and up to 25% cases of ACS in women aged < 50 years. We present a case of SCAD which presented as non-ST-elevation myocardial infarction (NSTEMI) requiring coronary artery bypass graft (CABG) surgery.

Case Report: A 52-year-old female presented in 2016 with several days of nausea, dizziness and palpitations without chest discomfort. EKG showed sinus rhythm with bifascicular block and ventricular bigeminy. Peak troponin-I was 40 ng/mL. Cardiac catheterization in 2009 for evaluation of NSTEMI had shown total occlusion of distal left circumflex artery and second obtuse marginal with well-developed right-to-left collaterals. The patient was nonsmoker and was physically active. She had been on daily aspirin, atorvastatin, lisinopril, and metoprolol. Urgent cardiac catheterization showed left main coronary artery dissection with Thrombolysis in Myocardial Infarction (TIMI) 3 flow and dissection of right coronary artery with sluggish flow in distal vessels. Left ventricular ejection fraction was 35%. She underwent CABG surgery complicated by bleeding which required repeat surgery. She was discharged home in stable condition three days later and participated in cardiac rehabilitation.

Conclusion: SCAD may be due to an intimal tear of vasa vasorum with intramedial hemorrhage. Fibromuscular dysplasia (FMD), postpartum status, multiparity, systemic inflammatory conditions, and hormonal therapy are some predisposing factors. 20% of cases are idiopathic. SCAD may clinically present as ACS. Angiographically, the classic lesion is a non-iatrogenic dissection plane without coronary atherosclerosis. SCAD is a rare cause of ACS. Awareness of the predisposing risk factors is important. Ideal management may be conservative, especially in the setting of TIMI 3 flow. If intervention is required, surgical revascularization is likely superior to percutaneous revascularization.
ACUTE MYOCARDIAL INFARCTION, REPERFUSION THERAPY

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TRAZODONE INDUCED VASOSPASTIC ANGINA MIMICKING WITH ST-ELEVATION MYOCARDIAL INFARCTION
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Objectives: To report rare association of trazodone intoxication with coronary vasospasm and ST segment elevation.

Introduction: Vasospastic angina is a syndrome of chest pain caused by myocardial ischemia secondary to reversible coronary artery vasospasm. It is characterized by transient elevation of ST-segment in presence of angiographically normal coronary arteries. Although tricyclic antidepressants and antipsychotics have been previously associated with coronary vasospasm, trazodone’s association has not been previously reported.

Case Presentation: We present a case of a 29-year-old Caucasian male who presented to the emergency after suicidal ingestion of 25 tablets of Trazodone 50 mg. His initial electrocardiography revealed 3 mm ST-segment elevation in leads II, III and aVF along with reciprocal ST-segment depression in anterior wall leads. He was immediately taken to cardiac catheterization laboratory on account of acute infero-posterior wall ST-segment elevation myocardial infarction. Coronary angiography revealed normal epicardial coronary arteries. His subsequent electrocardiograms showed resolution of ST segment changes. He was treated with vasodilator therapy using topical nitroglycerin paste along with supportive measures. He had an uneventful cardiovascular recovery and antidepressant regimen was changed to Mirtazapine.

Conclusion: Trazodone is a serotonin antagonist and reuptake inhibitor and is regarded as the least cardiotoxic antidepressant. QT prolongation and risk of ventricular arrhythmias are well known cardiac side effects of tricyclic antidepressant and selective serotonin reuptake inhibitors. Increased serotonergic effect of Trazodone at toxic levels may be a possible cause of coronary vasospasm.
VARIATIONS IN CARDIAC CATHETERIZATION PROCEDURE IN ST-ELEVATION MYOCARDIAL INFARCTION

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Objective: To devise a safe, timely, and cost effective strategy based on the current available literature for directing cardiologists to adopt the most appropriate approach while treating patients with ST-elevation myocardial infarction (STEMI).

Background: The field of interventional cardiology is changing dynamically with the advent of newer devices, newer techniques, and the goal of rapid revascularization. Percutaneous coronary intervention (PCI) can now be utilized to treat coronary artery disease and structural heart diseases. Guidelines to reduce patient morbidity and mortality are becoming stricter leading to interventional variations while performing PCI in patients with STEMI. These variations include preference in choosing peripheral access artery (radial vs. femoral) and timing and performance of complete angiography including left ventriculography, prior to or after intervening on the culprit vessel.

Method: We sought to review the current literature to determine the various techniques that are adopted by interventionists in performing primary PCI in patients with STEMI. We studied how each of these techniques were performed and the advantages and disadvantages related to them. We also attempted to identify the reasons the interventionists preferred to perform a particular technique and the outcomes associated with each of these techniques.

Results: Wide variations were observed in the preferences of cardiologists when it came to selecting approaches for primary PCI. EKG guided culprit vessel angiography was preferred due to increased demands to reduce door-to-balloon times, although the clinical significance of this reduction is questionable. Performing complete angiography or left ventriculography increased the door-to-balloon time and did not provide an additional advantage over EKG guided culprit vessel angiography.

Conclusion: A revision of PCI guidelines for cardiologists treating STEMI patients that address the most appropriate approach is needed. Such approach should not only reduce the time taken to establish flow and have proven benefits but also be safe.
PERICARDIAL DISEASE

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CARDIAC TAMPOONADE SECONDARY TO PURULENT PERICARDITIS IN A PATIENT WITH LUDWIG’S ANGINA AND LEMIERRE’S SYNDROME

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Introduction: Purulent pericarditis is a rare cause of pericardial effusion which requires emergent intervention and intravenous antibiotics. We present a case of a 51-year-old male with Ludwig’s angina and Lemierre’s syndrome who developed cardiac tamponade secondary to purulent pericarditis.

Case Presentation: A 51-year-old male presented to the emergency department with five days of right-sided cheek and neck swelling with pain. Magnetic resonance imaging (MRI) head and neck were negative for drainable fluid collection, and the patient was discharged home with antibiotics. He improved however returned in four days with shortness of breath and dizziness. Electrocardiogram (ECG) demonstrated sinus tachycardia with diffuse ST elevation and PR depression. A portable chest radiograph showed widened cardiome diastinal silhouette. Computed tomography (CT) and MRI now revealed extensive Ludwig’s angina. Incision and drainage was performed followed by intravenous steroids and antibiotics. Emergent echocardiography revealed a large pericardial effusion with right ventricular diastolic collapse consistent with cardiac tamponade. Emergent pericardiocentesis was performed yielding 590 mL of fluid and a pericardial drain was placed. Due to his worsening clinical status, further imaging was obtained and showed progressing infection including infectious thrombus in his right internal jugular vein. He remained in the hospital for further treatments and his pericardial drain was removed without complication or need for further cardiac intervention.

Discussion: Purulent pericarditis accounts for less than one percent of cases of pericarditis. The incidence of cardiac tamponade in purulent pericarditis is unclear and reportedly ranges from 42% to 77%. If left untreated it is fatal and therefore early recognition and aggressive treatment is essential. As many as 85% of patients with purulent pericarditis who have received comprehensive therapy will survive with good long-term outcomes. Physicians recognize and appropriately manage rare causes of cardiac tamponade, a life-threatening condition, such as purulent pericarditis due to Ludwig’s angina.
PERICARDIAL DISEASE

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SUDDEN CARDIAC DEATH DUE TO FOCAL PERICARDITIS INDUCED ANEURYSM FOLLOWING PERCUTANEOUS CORONARY INTERVENTION
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Objectives: Increase provider awareness regarding the rare diagnosis of focal pericarditis in order to improve appropriate therapy initiation and overall morbidity and mortality outcomes.

Background: A 75 year old female presented complaining of shortness of breath with severe back pain. She was one week status post acute inferior lateral myocardial infarction with subsequent percutaneous coronary intervention and stent placement to the left circumflex and right coronary arteries. An electrocardiogram (ECG) was significant for V4-V6 ST-segment elevations and the patient underwent immediate left heart catheterization which showed patent stents as well as new moderate to severe left ventricular (LV) hypokinesis involving the apical and anteroapical segments plus moderate ballooning of the associated LV wall. Her ejection fraction was additionally decreased to 40-45% from 55-60% seven days earlier. These findings were confirmed via transthoracic echocardiogram which found a 1.27 aneurysmal, akinetic LV apex and apical lateral wall segment. Given presenting symptoms, additional ECG findings of reciprocal PR depression, and positive inflammatory markers on admission, it was presumed this patient developed acute cardiomyopathy secondary to focal pericarditis. She was initiated on Toradol with improvement in her symptoms and was eventually discharged home. Of note she additionally developed new onset atrial fibrillation which was stabilized prior to discharge. Unfortunately, shortly thereafter the patient developed ventricular fibrillation cardiac arrest and was unable to be resuscitated.

Conclusion: Although no prior cases have been reported in the literature, rarely reported focal pericarditis appears to be a possible cause of aneurysm and cardiomyopathy and should therefore be included in post coronary intervention differentials to hopefully decrease negative outcomes in the future.
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LONG-TERM CLINICAL BENEFITS OF TWO-INCISION TECHNIQUE FOR SUBCUTANEOUS IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

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Background: The subcutaneous implantable cardioverter-defibrillator (S-ICD) is a well-established therapy for primary and secondary prevention of malignant ventricular arrhythmias in patients that do not require pacing. The S-ICD implantation technique initially involved three incisions with one incision at the left mid-axillary line and two incisions along the sternum. The newly adapted technique only involves two incisions by forgoing the incision by the sternal notch. It may offer benefits such as lower rates of infection and discomfort. However, due to its relatively recent utilization in practice, there are limited data on the clinical benefits of the two-incision technique.

Objective: The purpose of this retrospective study was to analyze the clinical benefits of the two-incision S-ICD implantation techniques.

Methods: We retrospectively analyzed data in a single center regarding the demographics, safety, and long-term follow-up in patients who underwent two-incision and three-incision techniques from April 2011 to April 2016.

Results: 110 patients with the S-ICD had a median follow-up of 340 days (IQR 68-696). Of the 110 patients, 49 patients (69% male, mean age 52.64) had two incisions and 61 patients (59% male, mean age 54.75) had three incisions. The average procedure times for two incisions and three incisions were 48.22±8.87 minutes and 66.98±12.84 minutes, respectively (p-value < 0.001). 1 inappropriate shock was found in patients with two incisions compared to 8 inappropriate shocks in patients with three incisions (p-value 0.04). There was 1 infection in the two-incision arm and 3 infections in the three-incision arm (p-value 0.62).

Conclusions: While there was no significant difference in the rate of infection between the two techniques, the two-incision technique had a significantly shorter procedure time and a lower rate of inappropriate shocks compared to the three-incision technique. This data provides evidence of the long-term clinical benefits of utilizing the two-incision technique.
Mutations in hERG cause long QT syndrome type 2 which is characterized by a prolonged QT interval on electrocardiogram and predisposition to life-threatening ventricular tachyarrhythmia, syncope, and sudden death. hERG-G572S induces trafficking defects of hERG channel protein from Golgi to the plasma membrane and results in a dominant negative suppression of hERG current density. As an accessory beta subunit, KCNE2 promotes hERG migration from Golgi to cellular membrane. In this study, we investigated the rescue effect of KCNE2 in a G572S mutation of hERG. Transfection was performed into HEK293 cells. Patch clamp technique, western blotting analyses and confocal microscopic examination were used. Results showed that KCNE2 had a significantly enhanced effect on G572S mutation current. The increase of current was largest at KCNH2:KCNE2 of 1:3. Confocal images showed co-expressing G572S and KCNE2 could cause a substantial up-regulated membrane protein (155 kDa) expression. Expression of membrane protein accumulated markedly with increasing ratio of KCNH2:KCNE2. G572S defective mutant could be restored by both KCNE2 and lower temperature (27 degree centigrade), which suggested that the lower temperature could be the favorable circumstances for the rescue function of KCNE2. In this study, we successfully set up “the action potential” on the HEK 293 cells by genetically engineered to express Kir2.1, Nav1.5, and Kv11.1, wherein on reaching over an excitation threshold by current injection. The results suggested that KCNE2 could shorten action potential duration which was prolonged by G572S. These findings described electrophysiological characteristics of the LQT2 syndrome mutation KCNH2-G572S and regulation by accessory protein KCNE2, and provided a clue about LQT2 and relative rescue mechanism.
INCIDENCE AND TIMING OF RECOVERY OF CONDUCTION IN POST-CORE VALVE IMPLANTATION HEART BLOCK

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Background: CoreValve (CV) Trans-catheter Aortic Valve Replacement is associated with a high rate of post procedural complete heart block (CHB). The optimal timing of pacemaker (PM) implantation in these patients is not defined.

Objective: We examined patients who developed CHB post CV for rate and timing of recovery of conduction.

Methods: A chart review of patient’s status post CV implantation was undertaken. CHB was further defined as intermittent or persistent after 24 hours. PM dependency was defined as no underlying rhythm with pacing at 30 beats per minute. Definite or probable ongoing pacing need was defined as persisting 2nd or 3rd degree atrioventricular block, PR interval >250msec or atrial fibrillation with pacing burden over 40%.

Results: Between June 2011 and October 2016, 170 patients received a CV. 42 of them had pre-implanted devices and were excluded. CHB developed in 39 patients, in 10 cases this was initially intermittent and in 29 cases persistent. At a median duration of 2.3 days post CV implantation, 37 patients underwent PM implantation. At their most recent follow up, (median follow up 123.5 days), 13 patients were PM dependent, 10 patients had definite or probable ongoing pacing need, 7 patients had no definite ongoing need for pacing and 7 patients had no follow up. Of the 23 patients with initial persistent CHB who met follow up criterion, only 1 (4.3%) had no clear definite pacing need at follow up. Of the 9 patients with initial intermittent CHB who underwent PM implantation, 6 (66.6%) had no definite pacing need at follow up.

Conclusion: In patients who develop CHB post CV, those with intermittent CHB often had no clear long-term pacing need, requiring further study. In those with persistent CHB >24 hours, there is a low rate of conduction recovery, and a high rate of PM dependency at follow up.
**168 PERMANENT HIS BUNDLE PACING (PHBP) WITH CLS OUTPERFORMS ACCELEROMETER-BASED RATE-RESPONSIVE PACING**

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**Background:** PHBP represents the most physiologic strategy for ventricular pacing. Closed Loop Stimulation (CLS) may provide the most physiologic rate responsive pacing, and is based on contractility-based impedance changes measured at the lead-tissue interface in the RV apex. It is uncertain whether contraction dynamics at the His bundle position are adequate for CLS.

**Objective:** To compare accelerometer-based rate responsive programming (VVIR) with CLS (VVI-CLS) in a patient with ventricular pacing dependence treated with PHBP.

**Methods:** N/A

**Results:** An 89-year-old male with moderate cardiomyopathy (LVEF 45-50%), permanent atrial fibrillation, and profound bradycardia was treated with PBHP using a single chamber BIOTRONIK pacemaker (Eluna model). Programming was VVIR for 8 weeks followed by VVI-CLS for 8 weeks (50-130 bpm, nominal settings for each), with >90% ventricular pacing for each setting. Rate histograms for each pacing mode were compared (Figure). Rate variability was greater with CLS, with 28% at 50 bpm, 40% at 60 bpm, 18% at 70 bpm, and 14% >80 bpm. Rates were more restricted with VVIR, with 70% at 50 bpm, 16% at 60 bpm, 9% at 70 bpm, and 5% >80 bpm. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) demonstrated improved quality of life with CLS (0 vs 4 /150).

**Conclusion:** This is the first case where PHBP was combined with CLS. CLS derived from the His-bundle position outperformed accelerometer-based rate-response, and achieved greater patient satisfaction (quantified with the MLHFQ). PHBP with CLS may represent the most physiologic system for rate responsive ventricular pacing presently available.
A RARE CASE OF PROGRESSIVE HEART BLOCK WITH X-LINKED RECESSIVE INHERITANCE

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Introduction: Several genetic mutations have been associated with atrioventricular (AV) block. A recent study by Esposito et al. (2013) discovered a unique Australian pedigree in which progressive AV block co-segregates with focal segmental glomerulosclerosis (FSGS) in an X-linked recessive inheritance. Affected individuals share a mutation in the NXF5 gene. Our case reports an encounter with a member of this most rare pedigree.

Case Presentation: A 38-year-old Australian man presented to our hospital with dyspnea on exertion and pressure-like chest pain for one day. He reported a family history of cardiac conduction defects and renal disease in numerous male relatives on his maternal side. Several of his family members had been diagnosed with a rare mutation in the NXF5 gene. Six years ago, he tested homozygous for the mutation, and was found to have a first-degree AV block and mild proteinuria on screening tests. On presentation, he had a heart rate of 46/minute and a blood pressure of 135/63 mmHg. Physical exam was significant for bradycardia. Laboratory results were normal, except for trace proteinuria in the urinalysis. An electrocardiogram revealed a second-degree AV block with 2:1 conduction, which prompted his admission to the cardiac care unit. Ten hours later, he progressed to complete AV block, requiring transvenous pacing. After ruling out reversible causes of conduction defects, he underwent placement of a permanent pacemaker. His symptoms improved with pacing, and he was discharged with electrophysiology and nephrology follow-up.

Conclusions: The pathogenesis of the conduction defect in patients, like the one described, is purported to be the same mechanism responsible for the destruction of renal tubular podocytes in FSGS. The case highlights a rare and complex inherited disease with life-long implications for the patient. Furthermore, it represents an opportunity for physician scientists to study the potential co-inheritance of seemingly independent but comorbid conditions.
ELECTROPHYSIOLOGY, SUDDEN DEATH, ARRHYTHMIAS AND DEVICE THERAPY

BILATERAL SYMPATHECTOMY AS A TREATMENT MODALITY FOR TREATMENT REFRACTORY VENTRICULAR TACHYCARDIA

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Background: Ventricular tachycardia (VT) is seen in patients with ischemic and non-ischemic cardiomyopathy (NICM), often requiring anti-arrhythmics, ablation or advanced circulatory support. Few patients have life-threatening VT that is refractory to these therapies. Cardiac sympathetic denervation (CSD) can be considered as an option to reduce the occurrence of these fatal arrhythmias by essentially inhibiting the sympathetic outflow to the cardiac tissue.

Case: A 69-year-old man with a 14-year history NICM with a left ventricular ejection fraction (LVEF) of 30% with a bi-ventricular implantable cardioverter defibrillator (ICD) presented to the hospital after multiple ICD discharges for VT which eventually required external defibrillation. Over the year prior to admission, patient had over 15 ICD discharges and numerous hospitalizations for refractory VT despite being on anti-arrhythmics and undergoing ablations. During present admission, two morphologies of monomorphic VT (MMVT) were noted on ICD interrogation for which he underwent cardiac mapping and ablation. A total of 5 different MMVTs were induced, with only two thought to be clinical. Of those two, only one was acutely successfully ablated. MMVT recurred within 24 hours of ablation. After a multidisciplinary discussion, decision was made to undergo a bilateral video-assisted thoracoscopic surgery (VATS) with T1-T4 sympathectomy. Following surgery, patient had no new ventricular arrhythmic events and was discharged on Amiodarone, Mexiletene and Metoprolol succinate. At six month follow up, patient remained shock-free.

Conclusion: CSD has been used as an effective treatment in patients with long QT syndrome and Catecholaminergic polymorphic ventricular tachycardia. Role of CSD in other substrates is less clear. From literature review, 5 other patients with refractory VT in NICM have been treated with CSD with successful results reported in 60% of the cases. CSD can be considered in management of patients when other treatment modalities have been exhausted.
TRENDS IN PERMANENT PACEMAKER IMPLANTATION IN THE UNITED STATES FROM 2004-2011

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Objective: The study sought to assess the national trends in Cardiac resynchronization therapy (CRT) device implantation by analyzing the National Inpatient Sample (NIS) database.

Background: Limited data exist regarding temporal trends in CRT implantation. In 2008, The American College of Cardiology/ American Heart Association/Heart Rhythm Society issued revised guidelines for cardiac pacemakers and anti-arrhythmic device implantation. We hypothesized that these guidelines have significantly influenced CRT-D and CRT-P implantation rates over the last few years.

Methods: We queried the Nationwide Inpatient Sample to identify CRT-D and CRT-P implantations between 2004 and 2011 using the International Classification of Diseases-Ninth Revision-Clinical Modification procedure codes for CRT-D and CRT-P. Annual device implantation rates were analyzed. All trend analyses were conducted using SAS 9.4. Yearly weighted frequencies for each procedure were generated using the ‘trendwt’ variable included in the data. The effect of 2008 HRS guidelines was assessed by grouping years 2004-2009 and 2010-2011, and then testing for mean difference.

Results: Over 7700 CRT-P devices were placed in the United States in 2004. This rate remained relatively steady over the years and in 2011 around 6600 devices were placed. Between 2004 and 2009, the mean number of CRT devices with pacemaker (CRT-P) per state procedures was 174 (95% CI 151, 197). After publications of revised guidelines in 2008 the mean number of procedures per state was 162 (95% CI 127, 199). Assuming equal variance between the two groups (Folded F p value 0.5149) this decline was not significant at alpha=0.05 (p value = 0.5950). However, CRT-D Devices had a higher implantation rate. In 2004, over 34,000 implantations took place. By 2011, the implantation trend declined to under 31,000 devices per year. Across all states, the mean number of cardiac resynchronization therapy with pacemaker (CRT-D) procedures between 2004 and 2009 was 1147 (95% CI 995, 1300) per state. After publications of revised guidelines, the mean procedure volume per state dropped to 816 (95% CI 638, 995). Assuming unequal variance between the two groups (Folded F p value = 0.0003) this drop was significant at alpha=0.05 (p value = 0.0056).

Conclusion: These results suggest a significant impact of 2008 Heart Rhythm Society guidelines on CRT-D implantations and negligible impact on CRT-P implantations. These trends have important health care policy implications.
AN UNUSUAL CAUSE OF SYNCOPE: BRUGADA SYNDROME

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Case Presentation: A 26 year old Hispanic man with no past medical history and no reported medication use presented to the hospital after a syncopal episode. The patient reports mowing the lawn when he felt sudden onset of chest discomfort and palpitations followed by dizziness and loss of consciousness. There were no witnesses but the patient estimated he was unconscious for about ten minutes. In the emergency department the patient had a negative urine toxicology screen, but an ECG (Figure 1) was obtained demonstrating ST segment abnormalities and pseudo-right bundle branch block pattern in the precordial leads concerning for Type 1 Brugada pattern. The rest of his workup was unremarkable. Given his clinical presentation along with characteristic ECG findings he was subsequently diagnosed with Brugada Syndrome. He was admitted to the hospital and had a subcutaneous implantable cardiac defibrillator (ICD) implanted for secondary prevention of sudden cardiac death. In addition to performing a thorough family screening, the patient was referred for genetic testing.

Discussion: The exact prevalence for Brugada syndrome in the general population is not well known though most estimates are less than 1%. Several gene mutations, mainly involving sodium channels, have been found to be associated with this syndrome. It is important to distinguish patients with Brugada pattern from those with Brugada syndrome. Brugada pattern refers to a set of characteristic EKG findings in asymptomatic individuals. When individuals experience clinical events (sudden cardiac death or malignant arrhythmias) they are deemed to have Brugada Syndrome. It is important to screen patients for medications (anti-arrhythmic, psychotropic, calcium channel blockers), toxins (alcohol, cocaine), and fever as these can be inducers of the Brugada pattern. Treatment is aimed at preventing sudden cardiac death and terminating malignant arrhythmias.

Figure 1. ECG demonstrating ST-segment abnormalities and pseudo-right bundle branch block in precordial leads.
A NEW SOLUTION TO AN OLD PROBLEM FOR CARDIAC DEVICE HYPERSENSITIVITY

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Objective: Introducing a new potential solution to cardiac device hypersensitivity.

Background: Allergy to a Cardiovascular Implantable Electronic Device (CIED), though uncommon, can occur. Treatment typically consisted of avoiding nickel placement, if patient has a known allergy, or replacement with a gold-plated device with lead change. We report a case of an allergy to an implantable cardiac defibrillator (ICD), with recurrent fluid accumulation in the device pocket that was successfully treated after coating the device with an antibiotic envelope.

Method: An ICD generator was entirely coated with an antibiotic envelope in order to prevent device-tissue interaction.

Results: A 60 year-old male, following ICD placement, presented with painless fluid accumulation to ICD pocket site. No local or systemic signs of infection were present. Over 3 months, 140 cc was aspirated from the pocket, twice. Each time, pocket fluid would re-accumulate within a day. Further, fluid analyses yield no signs of infection. Skin patch test revealed sensitivity to nickel. An attempt to implant a gold-plated generator was made. However, due to subclavian vein thrombosis and concerns of complications, such as pneumothorax, the procedure was aborted and right side implantation was planned for a later date. Meanwhile an antibiotic coated envelope was used on the ICD to prevent device-tissue interaction. Follow up at 1 week, 4 weeks, and 3 months, showed no re-accumulation of fluid and patient continued to be completely asymptomatic.

Conclusion: This case demonstrates that fluid accumulation that does not resolve after repeated aspiration could be indicative of hypersensitivity to a component of the ICD such as nickel in this case. Entirely coating the device with antibacterial envelope is an effective way to treat this condition, as can be seen in the case of our patient.
ATRIAL FIBRILLATION AND SUPRAVENTRICULAR ARRHYMIA

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COMPARISON OF OUTCOMES AFTER RHYTHM OR RATE CONTROL STRATEGY FOR THE NEW ONSET ATRIAL FIBRILLATION IN CRITICALLY ILL SEPSIS PATIENTS

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Background: Data regarding effective rhythm or rate management for new onset atrial fibrillation (AF) in critically ill sepsis patients managed in the medical intensive care unit (MICU) are sparse. Objective: We tried to compare the outcomes after rhythm or rate control strategy in these patients.

Methods: A total of 5,383 sepsis patients were managed in MICU of Asan Medical Center from 2007 through 2015. Among these patients, 482 experienced new-onset AF, and the medical records of them (mean 68.2 years old, 68.9% male, median CHADS2VASC score 3, median APACHEII score 24) were reviewed. After exclusion of 34 patients who underwent urgent electrical cardioversion, patients were divided into two groups (rhythm control, 43.5%; rate control group, 56.7%) according to the initial management strategy. The main outcomes of the current study were rate of mortality, thromboembolism, and sinus conversion at 28 days after AF onset.

Results: ICU interventions such as mechanical ventilator, inotropics or vasopressor, and renal replacement treatment were applied in 84.5%, 59.9%, and 26.8% of the patients at the time of AF onset. Amiodarone was predominantly used as a rhythm control measure (95.4%). After propensity matching, patients managed by rhythm control strategy showed higher sinus conversion rate compared to those with rate control strategy (39.8% vs. 19.8%, p<0.001). However, mortality rate (54.9% vs. 49.3%, p=0.529) or thromboembolic events (5.5% vs. 7.6%, p=0.635) were not different between the two groups.

Conclusion: Early rhythm control strategy could facilitate the sinus conversion. However, it did not provide additional benefits over rate control strategy in terms of hard outcomes.
ATRIAL FIBRILLATION AND SUPRAVENTRICULAR ARRHYTHMIA

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WHO WATCHES THE WATCHMAN, AND HOW OFTEN?

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Percutaneous left atrial appendage occluders such as the WATCHMAN device are treatment alternatives for patients with atrial fibrillation who cannot tolerate lifelong anticoagulation. We present a patient with recurrent thrombosis after WATCHMAN placement.

62 year old male with ischemic cardiomyopathy, atrial fibrillation with two prior cerebral vascular accidents, and recurrent severe epistaxis necessitating multiple transfusions and nasal artery embolization while on anticoagulation. The WATCHMAN was offered and was implanted without immediate complications. Aspirin and warfarin was prescribed for 6 weeks. Transesophageal echocardiogram (TEE) done at 45 days after implantation showed stable device placement but with layered thrombus formation upon the device. Warfarin therapy was extended for a total of 4.5 months. A repeat TEE after 4 months revealed resolution of the thrombus. Since he was 6 months post implant, his warfarin was stopped and he was treated with aspirin 325mg daily per protocol. Follow-up TEE 1 month later demonstrated recurrent thrombus formation again layered on top of the WATCHMAN where the device meets the limbus. The patient was reinstated on warfarin with planned reevaluation in another three-months time.

Thrombus formation at 6 weeks post WATCHMAN implant is unusual, and when it does occur it is usually attached to the central insert from where the device was previously attached and released. In our case, there was recurrent layered thrombus on top of the entire device.

There is a lack of guidance and data on patients with recurrent device related thrombus post WATCHMAN implant. We suggest more frequent INR monitoring with goals at the higher end of the 2-3 range. Longer warfarin duration for these patients may also be required. Alternatively, use of a NOAC can be considered, however, data on the treatment of recurrent thrombus post WATCHMAN implant is limited and is an area that should be studied further.
WOLFF-PARKINSON WHITE CAUSING ELECTRICAL ALTERANS ON ECG

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Introduction: Wolff-Parkinson White Syndrome (WPW) is the presence of an accessory pathway conducting faster than the His-Purkinje system, known as pre-excitation. We report a case of WPW alternans, where every sinus beat is followed by a pre-excited beat in an alternating pattern.

Case Description: 59 year old male with history of schizoaffective disorder, tobacco abuse, hypertension, hyperlipidemia and chronic kidney disease presented to the emergency department with transient loss of vision. Medications included clozapine, metoprolol and valproate. Ischemic workup was started. The electrocardiogram (ECG) showed sinus tachycardia. Troponin was mildly elevated at 0.103ng/mL. Myocardial perfusion imaging was negative for ischemia. Subsequent EKG (Figure 1) revealed WPW alternans, a known but rare phenomenon. Metoprolol was increased on discharge to lower his resting heart rate.

Case Discussion: WPW is a phenomenon of pre-excitation caused by alternate conduction through an accessory pathway. It is estimated that around 0.2% of the population has WPW, more commonly males than females. In 40-80% of patients, WPW is often diagnosed initially as an incidental finding of paroxysmal sinus tachycardia. In our patient the accessory pathway was expressed on every other beat, a phenomenon known as WPW alternans. This is a known but rare condition, thought to be caused by a long refractory period of the accessory pathway, preventing conduction through the accessory pathway on every beat. Presence of the refractory period makes it less likely to degenerate into a reentrant tachycardia. To differentiate WPW alternans from electrical alternans one should identify changes in PR interval from beat to beat with consistent PP interval. Delta waves may be seen.
PERIPHERAL ARTERY DISEASE AND AORTIC DISEASE

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STRICT CONTROL OF RISK FACTORS MAY NOT PREVENT PROGRESSION OF ARTERIOSCLEROSIS

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We compared preventive effect on progression of arteriosclerosis between strict and standard control of risk factors.

Methods: The progression of carotid atherosclerosis was evaluated by ultrasonography and carotid plaque score (PS) and mean intima-media thickness(m-IMT) were calculated. Cardio-ankle vascular index(CAVI) was also for evaluation of arterial stiffness. Hypertension, diabetes mellitus, dyslipidemia and smoking were considered to be risk factors. In strict control group, systolic blood pressure(SBP) was less than 130 mmHg and LDL-cholesterol(C) was less than 80 mg/dl. In standard group, SBP was less than 140 mmHg, and LDL-C was less than 140mg/dl. HbA1c was less than 6.5% in strict control group, and less than 7 % in standard control group. All patients were followed for more than 7 years.

Results: In 64 patients with strict control group (mean age 71.50 years old), mean SBP was 121.23mmHg±6.15 (mean±standard deviation) and mean LDL-C was 75.4±5.99 mg/dl. In 95 patients with standard control group (mean age 72.46 years old), mean SBP was 135.83 mmHg and mean LDL-C was 133.95±5.95 mg/dl. Mean Hb A1c was 6.11±0.43% in patients with strict control group, and 6.9±0.83 in standard control group. PS increased from 4.95±2.13 to 6.03±2.72 in standard group(P<0.005), and from 4.10±2.35 to 4.74±2.10 in strict group(P<0.005). Mean IMT increased from 0.93±0.10 to 0.99±0.11 mm in standard group(P<0.001), and from 0.94±0.10 to 0.91±0.11 mm in strict group(P<0.005). In all patients, mean CAVI decrease from 9.49±0.95 to 9.30±0.94 (P<0.05).

Conclusions: Even with strict control of risk factors for arteriosclerosis, progression of carotid sclerosis cannot be prevented, however, progression may be very slow. CAVI cannot predict progression of carotid arteriosclerosis.
ASSOCIATION BETWEEN SYMMETRIC BICUSPID AORTIC VALVE PHENOTYPES AND PATTERN OF VALVULAR DYSFUNCTION AND AORTIC CONFIGURATION
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Objectives: To characterize aortic valve dysfunction and aortic configuration over patients with symmetric bicuspid aortic valve (BAV) using transthoracic echocardiography (TTE), multidetector computed tomography (MDCT), gated coronary computed tomography angiography (CCTA) and surgical findings.

Background: An association between symmetric BAV phenotypes and the pattern of valvular dysfunction or aortic configuration has yet to be definitely established.

Methods: The study retrospectively collected 136 symmetric BAV patients (79 men, age 59.26 ± 11.07 years) who underwent TTE, MDCT and gated CCTA from February 2010 to February 2017. BAVs were classified as anterior-posterior (BAV-AP) or lateral (BAV-LA) orientation of the cusps. Thoracic aortic dimensions from the aortic root to the descending aorta were measured by gated CCTA at six levels.

Results: The prevalence of BAV-LA and BAV-AP was 80.6% and 19.4%, respectively. Comparing BAV-LA and BAV-AP, no differences in age, in the prevalence of male sex or in the prevalence of moderate-to-severe aortic regurgitation were determined. However, significant differences in the valvular dysfunction pattern were noted, with moderate-to-severe aortic stenosis predominating in patients with BAV-AP (77.9% vs. 52% in BAV-LA; p =0.009). Except ascending aortic dilation, dilation of proximal aortic arch was significantly more frequent in BAV-LA patients (76.69% vs. 56.0% in BAV-RL; p =0.035).

Conclusion: The patterns of valvular dysfunction and aortic configuration differed significantly between the 2 symmetric BAV phenotypes, suggesting the possibility of etiologically different entities. Symmetric BAV patients have a very high incidence of aortic valve stenosis rather than aortic valve insufficiency, especially in patients with BAV-AP.
PERIPHERAL ARTERY DISEASE AND AORTIC DISEASE

PERIPHERAL INTERVENTIONS AND ANTIPLATELET THERAPY: WHERE DO WE STAND IN AN ERA OF GUIDELINE BASED THERAPY?
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Objective: Review the evidence on revascularization strategy, the role and duration of antiplatelet and anticoagulant therapy in re-vascularized peripheral artery disease (PAD) patients.

Background: PAD is a significant risk factor for cardiovascular mortality, however there is paucity of clinical information on its optimal management. There has been a threefold increase in endovascular procedures and 42% decrease in bypass surgeries between 1996 and 2006.

Methods: All relevant studies published in PUBMED, EMBASE, Google scholar were identified using specific keywords. Additional manual searching of bibliographies of included reports was performed.

Results: While the efficacy of aspirin monotherapy and aspirin-clopidogrel is limited in preventing major adverse cardiac events (MACE), clopidogrel monotherapy is effective. Ticagrelor was not superior to clopidogrel in preventing MACE. Voraxapar reduced limb ischemic events and repeat revascularization, but effect was upset by higher intracranial hemorrhage. Warfarin is associated with lower rate of vein-graft occlusion in surgical bypass. Cilostazol improved the maximal and pain-free walking distance in patients with intermittent claudication. Aspirin-Dipyridamole improves post femoro-popliteal angioplasty patency, and Aspirin-Clopidogrel reduced prosthetic graft failure, target lesion revascularization and improved patency. It also improves functional outcome and it is the most commonly used after endovascular therapy. No data on Prasugrel, and studies on direct-acting oral anticoagulants are on-going.

Conclusion: While the long term patency of open surgical and endovascular modalities for PAD treatment continues to improve, there is an emerging consensus that endovascular therapy, when feasible should be attempted first, on a case-by-case determination. Post-intervention use of Aspirin-Clopidogrel is common, but the duration of therapy is highly variable without a strong recommendation in practice guidelines. Additional studies are needed to assess the optimal medical treatment and duration of medical therapy across the spectrum of PAD.
QUICK SEPSIS-RELATED ORGAN FAILURE ASSESSMENT (QSOFA) SCORE PREDICTS ADVERSE EVENTS IN PATIENTS WITH INFECTIVE ENDOCARDITIS

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Background: In 2016, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total Sepsis-related Organ Failure Assessment (SOFA) score more than 2 points consequent to the infection. The quick Sepsis-related Organ Failure Assessment (qSOFA) score with four scales was introduced as a simplified version of SOFA score. The qSOFA score is more accurately identifies patients at high risk of adverse outcome with an infection than the systemic inflammatory response syndrome (SIRS) and SOFA score in non-ICU patients. Infective endocarditis (IE) is life-threatening disease characterized by persistent bacteremia. However, there is still no data about the association with IE and qSOFA score.

Objectives: The purpose of this study was to elucidate the relationship between qSOFA score and adverse events, such as in-hospital mortality, cardiac and embolic complications in patients with IE.

Methods: This study enrolled patients who diagnosed with IE in our hospital from January 2006 to December 2016. We diagnosed with IE as based on the Duke criteria. We divided patients with IE into two groups based on qSOFA scores (qSOFA more than 2, qSOFA less than 1).

Result: Consecutive 79 patients were retrospectively reviewed after excluding 26 patients due to data deficits (age 62 plus-minus 17 years, male 69.6 percent). Patients with qSOFA more than 2 were observed in 11 (13.9%) out of 79 patients. Sepsis group had a higher in-hospital mortality compared to non-Sepsis group (n equals 68) (45.5 percent versus 4.4 percent, p-value lower than 0.01). Furthermore, the incidence of stroke detected by imaging study was significantly higher in Sepsis group compared to that in non-Sepsis group (90.9 percent versus 38.2 percent, p-value lower than 0.01).

Conclusion: qSOFA score is considered to be useful in risk stratification of patients with IE.
THE RELATIONSHIP OF HEART DISEASES, AUTONOMIC IMBALANCE AND PSYCHOLOGICAL FUNCTIONING

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Cardiovascular disease, especially coronary artery disease, hypertension (AH) and cardiac arrhythmias (CA), due to the prevalence and negative social and economic effects, belong to a group of civilization diseases. Previous research suggests comorbidity of heart diseases, mood disorders and impaired cognitive functioning. Those researches indicate also, the need of holistic assessment of the quality of life of patients with such diseases. Aim of this study is evaluation of psychological aspects of cardiovascular diseases. Studied groups included 65 women with primary hypertension, cardiac arrhythmias and hypertension with concomitant heart rhythm disturbances. All patients underwent cardiological diagnostics and psychological assessment, that included questionnaires in order to assess quality of life, personality traits and cognitive functioning. All of them had 24-hour ECG monitoring with Holters method in order to evaluate the autonomic activity based on heart rate variability (HRV). Patients with AH and CA exhibit the highest intensity of neuroticism and conscientiousness in comparison with the others groups. Individuals with AH declared decreased quality of life, in connection with major somatic complaints, but also receive most public support. Also, AH, characterized by the highest levels of anxiety and anger, paradoxically, has the greatest satisfaction with life. Decrease in cognitive functioning was associated with the occurrence of hypertension in the group with isolated AH and AH with CA. The highest scores in cognitive tests received people with CA. In patients with hypertension, the highest total daily HRV power spectrum and a higher power component in the low frequency band compared to other groups have been found. 1. Type of cardiovascular disease determines the assessment of quality and satisfaction with life. 2. Disorders in the autonomic nervous system depended on the type of disease and affect the severity of negative emotions, cognitive functioning and negative internal representation of the disease.
A CASE OF INCIDENTAL CORONARY ARTERY ECTASIA

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Case: A 62-year-old man, with history of type 1 aortic dissection status post Bentall’s procedure and mechanical aortic valve, presented with staphylococcus lugdunensis blood stream infection, endocarditis, and aortic root abscess formation. He underwent coronary catheterization as part of pre-surgery evaluation prior to aortic valve and aortic graft replacement. It demonstrated diffuse ectasia of multiple coronary arteries and mild coronary artery disease (CAD). CT angiography demonstrated ectasia in the common iliac and common femoral arteries. There was no evidence of intracranial aneurysm. Patient's history and physical exam showed no evidence of collagen vascular disease, neurofibromatosis, vasculitis or history of Kawasaki disease. Screening syphilis and rheumatologic studies were negative. Family history is significant for early onset cardiovascular disease and sudden cardiac death, suggesting a potential genetic disposition. Genetics has been consulted for possible SMAD3-related disease or other genetic conditions.

Discussion: Coronary artery ectasia (CAE) is defined as dilation more than 1.5 times compared to normal adjacent artery. It has 1.2-8% prevalence and a male predominance. It can be diffuse or localized, and tends to affect right coronary artery. Etiologies include atherosclerosis (50%), congenital abnormalities (20-30%), vasculitis or connective tissue diseases (10-20 %). It has been associated with increased ischemic events and higher rate of three vessel coronary artery disease. Anti-platele therapy and anticoagulation are sometimes recommended for prevention of ischemic events. However they remain controversial as large trials have not demonstrated risk reduction. Nitrates should be avoided as they can lead to further dilation.

Conclusion: In patients who presents with CAE, it is important to consider uncommon etiologies, such as vasculitis and genetic disorders, in addition to atherosclerosis. We also recommend evaluating for evidence of ectasia/aneurysm in other arteries. In addition to CAD treatment, anti-platelet therapy and anticoagulation could be considered to prevent cardiovascular events.
ATTEMPTING TO CLEANUP A RIGHT ATRIAL MASS IN A 20 YEAR OLD FEMALE WITH ANGIOVAC

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Case: 20-year-old female presented with chief complaint of left sided non-radiating chest pain for one day duration. Physical exam showed sinus tachycardia, systolic murmur at right lower sternal border. Electrocardiogram lacked any signs of acute ischemia. The patient had past medical history of type 1 diabetes mellitus, hypertension, hyperlipidemia and morbid obesity. The patient had a ST elevation myocardial infarction at 18 years of age and had percutaneous coronary intervention. Extensive workup did not reveal the cause of early onset CAD. Transthoracic echocardiogram demonstrated a large mobile mass in the right atrium (RA) straddling the tricuspid valve. Transesophageal echocardiogram further revealed a long stalk RA mass connecting to the vena cava. After a multi-disciplinary assessment that included cardiothoracic surgery and cardiology it was agreed that an attempt should be made to remove the mass percutaneously with the AngioVac® device. Despite multiple attempts with good engagements, conversion to open cardiac surgery was necessary. The mass was successfully removed and histologically identified as an organized thrombus. Patient was discharged home on oral anticoagulation.

Discussion: The differential diagnosis of RA masses includes tumors, thrombi, and vegetation. RA masses are often asymptomatic, we report the atypical presentation of RA mass with chest pain. The mass had a unique stalked appearance akin to a myxoma but location was atypical. It is unusual to develop an intra-cardiac well-organized thrombi without any coagulopathies. As imaging was inconclusive a novel minimally invasive approach with the AngioVac® was attempted. This device is approved as a venous drainage cannula during extracorporeal bypass for removal of deep venous thrombi. Its use for minimally invasive removal of vegetations and cardiac masses has been reported. This case serves as a unique learning opportunity and will aid in refinement of this new technique that may serve as a valuable diagnostic and therapeutic cardiac tool.
HYPERTENSION, OBESITY, DIABETES MELLITUS AND CARDIOVASCULAR DISEASES, PREVENTION, RISK REDUCTION AND TREATMENT

PROTECTION OF DIABETIC HEART WITH PDE5 INHIBITION AND HYDROXYCHLOROQUINE
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Diabetes is associated with high risk of ischemic heart disease. We previously showed that phosphodiesterase 5 inhibitor - tadafalil (TAD) induces cardioprotection against ischemia/reperfusion (I/R) injury in diabetic mice. Hydroxychloroquine (HCQ) is a widely used antimalarial and anti-inflammatory drug, which was reported to reduce hyperglycemia in diabetic patients. Therefore we hypothesized that combination of TAD and HCQ may induce synergistic cardioprotection in diabetes. We also investigated the role of insulin-Akt-mTOR signaling, which regulates protein synthesis and cell survival. Adult male db/db mice were randomized to receive vehicle, TAD (6 mg/kg), HCQ (50 mg/kg), or TAD+HCQ daily by gastric gavage for 7 days. Hearts were isolated and subjected to 30-min global ischemia followed by 1-hour reperfusion in Langendorff mode. Cardiac function and myocardial infarct size were determined. Plasma glucose, insulin and lipid levels and relevant pancreatic and cardiac protein markers were measured. Treatment with TAD+HCQ reduced myocardial infarct size (17.4±4.3% vs. 37.8±4.9% in Control group, P<0.05) and enhanced production of ATP. The TAD+HCQ combination treatment also reduced fasting blood glucose, plasma free fatty acids, and triglyceride levels. Furthermore, TAD+HCQ increased plasma insulin levels (513±73 vs. 232±30 mU/L, P<0.05), with improved insulin sensitivity, larger pancreatic beta-cell area and pancreas mass. IGF-1 levels were also elevated by TAD+HCQ (343±14 vs. 262±22 ng/mL, P<0.05). The increased insulin/IGF-1 resulted in activation of downstream Akt/mTOR cellular survival pathway. These results suggest that combination treatment with TAD and HCQ could be a novel and readily translational pharmacotherapy for reducing cardiovascular risk factors and protecting against myocardial I/R injury in type 2 diabetes.

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Purpose: We assessed whether 1) Dapagliflozin (Dapa, an SGLT2-inhibitor) attenuates the deterioration of heart function and inflammasome activation in diabetic mice. 2) the effects can be augmented with saxagliptin (Saxa), a DDP4-inhibitor. 3) Dapa effect is possibly SGLT2-independent on cardiofibroblasts in-vitro.

Methods: Type-2 diabetic (BTBR ob/ob) and wild-type (WT) mice received vehicle, Dapa or Dapa+Saxa for 8 weeks. Glucose tolerance test and echocardiogram were performed. Cardiofibroblasts from WT and BTBR hearts were incubated with Dapa and exposed to LPS.

Results: Left ventricular ejection fraction (LVEF) was 81±1% in the WT and 53±1% in the T2D-cont mice. Dapa and Dapa+Saxa improved LVEF to 68±1% and 74.6±1% in the BTBR mice (p<0.001). The mRNA levels of NALP3, ASC, IL-1β, IL-6, Caspase-1 and TNFα were significantly higher in the BTBR compared to the WT hearts; and Dapa and Dapa+Saxa significantly attenuated these levels. Collagen-1 and -3 mRNA levels significantly increased in the BTBR mice and these increases were attenuated by Dapa and Dapa+Saxa. The in-vitro study showed that NALP3, ASC, IL-1β and Caspase-1 mRNA levels were higher in the BTBR cardiofibroblasts and attenuated with Dapa. The effect was AMPK-dependent and SGLT1-independent.

Conclusions: Dapa attenuated the activation of the inflammasome, fibrosis and deterioration of LVEF in BTBR mice. The anti-inflammatory, anti-fibrotic effects are likely SGLT2- and glucose-lowering-independent, as they were replicated in the in-vitro model. The effects on remodeling were augmented when Saxa was added to Dapa. Yet, adding Saxa to Dapa did not result in a greater effect on myocardial fibrosis and collagen levels.
CO2 WATER-BATH AS A NOVEL THERAPY FOR THE TREATMENT OF PERIPHERAL ARTERY DISEASE IN DIABETES

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Background and Objectives: Peripheral artery disease is commonly seen in diabetic subject; however, no satisfactory intervention is available for its treatment. This study examined the effects of CO2 water-bath therapy on blood flow in the ischemic hind limb of diabetic animals.

Methods: Diabetes in rats was induced by streptozotocin (65 mg/kg) and two weeks later, ischemia in the limb was induced by ligating the femoral artery for a period of 2 weeks. Diabetic ischemic animals were subjected to water-bath (37°C) treatment with or without CO2 therapy for 6 weeks (30 min/day for 5 days/week). Diabetic ischemic animals without water-bath treatment served as control. Blood flow in the ischemic hind limb was measured by the Pulse Wave Doppler System whereas angiogenesis in the skeletal muscle was evaluated histologically.

Results and Discussion: Both peak and mean blood flow in the ischemic limb were increased by the CO2 water-bath therapy without any changes in the minimum blood flow. Furthermore, angiogenesis was markedly promoted by the CO2 water-bath treatment. These alterations by CO2 bath therapy were not associated with any changes in heart rate as well as plasma glucose, cholesterol, triglyceride and high density lipoprotein levels. The depressed levels of plasma oxidized low density lipoproteins (Ox-LDL) were further decreased whereas the elevated levels of plasma NO were further increased without any changes in the increased plasma levels of malondialdehyde by CO2 water-bath treatment. Conclusions: These results indicate the improvement of blood flow and development of angiogenesis in diabetic ischemic limb by CO2 water treatment were associated with increase in the formation of NO as well as reduction in the level of Ox-LDL. It is suggested that CO2 water-bath therapy is beneficial for the treatment of peripheral artery disease in diabetes. (Infrastructure support for this study was provided by the St. Boniface Hospital Foundation)
Type 2 diabetes (T2D) is associated with decreased exercise capacity (EC). Decreased EC in T2D is important because it confers increased risk for premature mortality and may represent very early evidence of cardiovascular (CV) impairment. Our lab has identified cardiac and peripheral causes of the abnormalities but the relative importance of the various abnormalities has not been well integrated. Current data suggest preliminarily that the defect is greater in women than men with T2D. Our long-term goal is to understand the abnormalities and their greater presence in women, to develop strategies to restore EC and thereby improve CV health in T2D by understanding and targeting pathogenic drivers of this impairment. New MRI based non-invasive imaging offers a quantitative, sensitive and reproducible opportunity to define early pathogenic cardiac and vascular changes contributing to EC decrease in T2D. We have shown that

- EC impairment in T2D is associated with both cardiac and vascular dysfunction.
- EC and associated cardiac and vascular dysfunction are more pronounced in T2D women than men.

This collaborative research employs state of the art cardiac and vascular imaging, developed by our team, to quantitatively characterize CV systemic structure and function in men and women with T2D compared to non-diabetic controls. With these new methods, we are able to simultaneously integrate functional exercise capacity measurements with early cardiac and vascular structural and functional measurements. Understanding the cardiac and vascular abnormalities associated with EC may enable us to target novel therapeutic approaches.
AGING AND OBESITY

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The population of elderly (defined as age ≥ 65 years) people with obesity (defined as body mass index [BMI] ≥ 30) has been increasing worldwide. Concurrently, the prevalence of type 2 diabetes (T2DM) and heart failure (HF) from hypertension (HTN) and myocardial infarction (MI) has been rising. Since both aging and obesity increase health care costs, prevention of obesity and associated comorbidities is becoming recognized as a priority among many developing and developed nations. The relationship between aging and obesity and associated comorbidities appears to be complex. In the U.S. where elderly persons are projected to double by 2050, more than one-third of the elderly are obese based on NHANES data. While obesity raises mortality risk, the relationship between BMI and mortality appears to be U-shaped. Increased fat mass and reduced muscle mass with aging, partly due to physical inactivity and poor diet, seem to promote the metabolic syndrome in elderly people with sarcopenic obesity compared to those with isolated sarcopenia or obesity based on data in Asians. Data in Canada underscores the risk of diabetes, heart disease and stroke besides depression and cancer with aging and obesity. Data from India suggest that the prevalence of T2DM will more than double by 2030 with aging and obesity. Recent US data on odds ratios showed that aging and obesity had larger effects on heart disease, hypertension and diabetes than smoking and alcohol consumption. Longitudinal population data underscore the harmful effects of obesity during aging from childhood through adulthood and the elderly thereby underpinning the need for early prevention. Short-term studies suggest that diet and exercise can reverse T2DM. Future research may clarify biochemical and molecular mechanisms that explain the interactions between aging and obesity and identify key pathways that can be targeted for reducing mortality and morbidity.
ROLE OF THE ADIPOKINE OMENTIN IN CARDIOVASCULAR DISEASE

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Obesity, particularly excessive visceral fat accumulation, is closely linked with the progression of cardiovascular disease. Adipose tissue produces various secretory factors, also known as adipokines or adipocytokines, which directly affect nearby or remote tissues. Accumulating evidence indicates that dysregulated production of adipokines under conditions of obesity participates in the development of metabolic and cardiovascular disorders. Omentin is a circulating adipokine that is expressed abundantly in human visceral fat tissue. Plasma levels of omentin are reduced in association with obese complications including coronary artery disease. Omentin ameliorates myocardial injury in response to ischemia-reperfusion in mice. Omentin also prevents neointimal formation in mice after vascular injury. Furthermore, omentin attenuates atherosclerotic lesion formation in a mouse model of atherosclerosis. These data suggest that omentin functions as a crucial adipokine that plays protective roles in regulation of obesity-linked cardiovascular disease.
HYPERTENSION, OBESITY, DIABETES MELLITUS AND CARDIOVASCULAR DISEASES, PREVENTION, RISK REDUCTION AND TREATMENT

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REVASCULARIZATION IN PATIENTS WITH DIABETES MELLITUS: OPTIMAL APPROACH IN 2017
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Background: Diabetes mellitus is a growing worldwide problem, affecting 28 million patients in the US, with another 80 million at risk due to obesity and related disorders. Diabetes mellitus is associated with significant health and social costs, with an estimated annual economic toll of $322 billion dollars in the US. In addition, surgical and percutaneous revascularization outcomes are impaired in the setting of diabetes mellitus, requiring careful individualized consideration of the need and optimal choice of revascularization strategy.

Results: Diabetes mellitus is associated with a 2-5 fold increased risk of premature, diffuse coronary disease resulting in an increased risk of acute coronary syndrome and death. A disadvantageous metabolic milieu creates an environment hostile to favorable long-term revascularization results with an increased risk of lesion development, progression and restenosis. Optimal medical therapy and risk factor modification has been shown to significantly improve cardiovascular outcomes independent of the choice of revascularization strategy. Compared with percutaneous revascularization (PCI), coronary bypass grafting (CABG) is associated with reduced MACE in higher risk patients with multivessel disease despite an increased early risk of stroke, particularly in patients with LM disease and more complex anatomy.

Conclusion: In asymptomatic or minimally symptomatic diabetic patients with coronary artery disease, optimal medical therapy remains the preferred initial treatment strategy and the foundation of sound management. Patients at higher risk due to multivessel disease and large ischemic burden may benefit from early revascularization. An individualized, patient-centric heart team approach, including consideration of coronary anatomy, risk profile, presentation features and patient preference is essential. Ongoing medical, surgical and percutaneous developments require continuous reassessment of relative risks and benefits associated with these modalities to ensure optimal outcome in patients with diabetes mellitus.
During physical work or exercise, systolic blood pressure (SBP) rises progressively with increased workload and plateaus at approximately 180-200 mm Hg, while diastolic BP remains close to or even lower than resting levels. However, in some individuals with prehypertension and established hypertension, SBP rises disproportionately to the workload, achieving levels >200 mm Hg even during sub-maximal exercise. This exaggerated BP response to exercise has been associated with future hypertension, left ventricular hypertrophy (LVH) and cardiovascular disease morbidity and mortality. However, others reported that an exaggerated BP response at peak exercise was associated with lower likelihood of angiographically-determined severity of coronary artery disease and lower mortality rates. This paradoxical finding may be explained by subclinical coronary artery disease (CAD). In the absence of subclinical CAD, myocardial perfusion is preserved even at peak exercise workload, myocardial contractility is sustained and relatively high exercise BP levels are achieved.

Conversely, in individuals with subclinical CAD, myocardial ischemia at peak workload is likely to ensue, leading to an attenuated inotropic response, lower exercise BP and termination of exercise. Workloads of 4-5 METs reflect most daily activities. Thus, the BP response at these workloads reflects daytime BP. We examined the clinical significance of BP response at the workloads of 4-5 METs in 790 middle-aged, pre-hypertensive individuals. We found a strong association between SBP and LVH. Individuals with SBP >150 mm Hg at the exercise workload of 4-5 METs had a significantly higher LVM index compared to those with systolic BP below this level. The risk of having LVH increased 4-fold for every 10-mm Hg rise in SBP beyond the threshold of 150 mm Hg. Thus, the SBP-LVM association at submaximal workloads suggests that daily exposure to relatively high SBP may provide the impetus for an increase in LVM even at the pre-hypertensive stage.
MTOR SIGNALING IN DIABETES AND MYOCARDIAL INFARCTION

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Mammalian target of rapamycin (mTOR), a conserved serine/threonine kinase, plays a crucial role in integrating cellular and environmental cues that modulate cell metabolism, growth, proliferation, survival and homeostasis. Deregulation of mTOR signaling has been implicated in many human diseases, including cancer, obesity, diabetes, pulmonary hypertension, cardiovascular diseases and neurodegeneration. Considering its pathophysiological importance, the mTOR signaling pathway has attracted broad scientific and clinical interest as a potential therapeutic target to treat a variety of diseases including patients with metabolic abnormalities and myocardial infarction. mTOR interacts with several proteins to form two functionally distinct complexes known as mTOR complex 1 (mTORC1) and complex 2 (mTORC2). There has been growing interest in investigating the role of mTOR inhibition in protecting the heart against ischemia/reperfusion (I/R) injury. Studies have shown that pharmacological inhibition of mTOR with rapamycin exerts preconditioning-like effect in the murine heart through activation of JAK-STAT3 signaling. Rapamycin attenuates cardiomyocyte necrosis and apoptosis as well as reduces tissue damage after myocardial infarction. mTOR inhibition prevents adverse cardiac remodeling and improves cardiac function following chronic myocardial infarction. Reperfusion therapy with rapamycin also protects the murine heart against I/R injury by selective activation of mTORC2 and ERK with concomitant inhibition of mTORC1 and p38. Moreover, a persistent hyperactivation of mTORC1 has been implicated in obesity-related metabolic pathologies. Specific inhibition of mTORC1 activity with simultaneous activation of mTORC2 provides beneficial effect of cardioprotection in diabetic mouse heart. Chronic treatment with rapamycin improves metabolic status and prevents cardiac dysfunction in diabetic mice through attenuation of oxidative stress as well as alteration of contractile and glucose metabolic proteins. Rapamycin also protects diabetic mouse heart against myocardial reperfusion injury through STAT3 signaling. Therefore, selective targeting of mTOR subcomplexes may hold therapeutic promise to combat myocardial infarction and improve prognosis in diabetic patients.
LOW DOSE IGF1 FOR CARDIAC CYTOPROTECTION AND REPAIR FROM MOUSE TO MAN

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IGF1 is an endogenous pro-survival peptide within the adult heart. We have previously identified low dose IGF1 (LD-IGF1) as a potent paracrine factor secreted from endothelial progenitor cells known to facilitate cardiac repair post myocardial infarction (MI). We have also demonstrated in a murine MI model that low concentrations of IGF1 secreted via modified RNA promote a cardiac survival pathway in the 24-48 hours post therapy. Moreover, in a porcine MI model of human scale we have shown that cognate IGF1 receptor signalling occurs within 30 mins of intracoronary injection of LD-IGF1 in the setting of ischemia-reperfusion. Specific receptor activation promotes acute cardiomyocyte survival in the infarct and border zones with medium term improvement in ventricular function, cardiac remodelling and scar formation. More recently in a phase I/II randomised placebo controlled clinical trial we have shown that specific doses of LD-IGF1 are safe and have a beneficial effect on cardiac remodelling assessed by MRI in the setting of large ST elevation myocardial infarcts associated with moderate LV dysfunction. This latter effect is most likely driven by acute reduction in infarct size and limitation of ventricular chamber expansion.
WHERE ARE WE WITH BONE MARROW CELL THERAPY FOR HEART REPAIR?

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Numerous clinical trials of bone marrow cell therapy for heart repair have been completed in the past 15 years. These early trials included relatively small numbers of patients and injected widely variable numbers of cells using different routes at various time-points after myocardial infarction (MI). Understandably, the outcomes of BMC therapy in these trials have been disparate. Because of significant inter-study variability in observations, pooled data from these studies have been subjected to numerous meta-analyses over the past several years. Although these meta-analyses included variable combinations of trials and patients, the results indicate that BMC therapy in patients with acute MI and chronic IHD produces modest improvements in left ventricular function and structure. BMC therapy also appears to be safe. Moreover, these analyses identify significant improvements in important clinical outcomes during follow-up of BMC-treated patients. Nonetheless, a number of significant challenges remain to be overcome in order to realize the full potential of BMC therapy in clinical practice. The purpose of this talk is to summarize the emerging clinical evidence regarding the efficacy and safety of therapeutic cardiac repair with adult BMCs, and to discuss insights from meta-analyses on this topic.
WHAT YOU SHOULD KNOW ABOUT CARDIAC REMODELING

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The "Age of Cardiac Remodeling" began in the mid-1990s with the realization that drugs leading to improved ventricular remodeling were doing something remarkable in cardiac patients. This created an experimental need for high quality assessment of changes in cardiac tissue composition, including myocyte shape, myocardial fibrosis/collagen, and vascular remodeling. Many working in the field today have little or no training related to recognition of fixation artifacts or common errors associated with quantitative morphology. Unfortunately, such skills had become somewhat of a lost art during the ages of cardiac physiology in the mid-20th century and molecular biology, gaining prominence by the mid-1970s. Consequently, cardiac remodeling studies today are often seriously flawed to the point where data are not reproducible and subsequently researchers may be chasing the molecular basis of a non-existent or erroneous phenotype. The current unacceptably high incidence of irreproducible data is a serious waste of time and resources as noted recently in comments by the NIH Director. The goal of this talk is to improve the ability of clinicians/scientists to better evaluate accuracy of the remodeling literature and to provide practical solutions for improving the quality of remodeling data. The goal of researchers in the field should be to routinely publish highly reproducible morphologic data that stand the test of time and contribute to our fundamental knowledge of cardiac remodeling and the molecular mechanisms that drive it. A review article on this topic can be found at the following web site.

PLAQUE ANGIOGENESIS IN HUMAN ATHEROSCLEROSIS: A SYSTEMS MEDICINE APPROACH

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Background: Unstable plaques are hallmarked by the abundant presence of imicrovessels, supplying oxygen, nutrients, but also immune cells and lipoproteins to the central atheroma of the plaque, and as such are promoting plaque expansion and inflammation. However the molecular pathways, which regulate microvessel expansion in human atherosclerotic plaque remain elusive. In this paper we present a novel strategy to dissect critical pathways in human atherosclerosis.

Methods & Results: mRNA expression profiles of a cohort of human carotid artery plaque segments, classified as stable were compared versus segments from the same plaque classified as ruptured (IPH or thrombotic) (n=32). Expression data were analysed by weighted gene coexpression network analysis, to identify coexpressed gene sets. Subsequently, candidate genes were selected according to their tight co-expression with CD31+ microvessel density (as assessed by immunohistochemistry on an adjacent plaque section), leading to the identification of 4 candidate regulators of plaque angiogenesis. All candidates showed selective expression by human endothelial cells. Two candidates, Zeb1 and SPTBN1, appeared to be critical for angiogenesis in vitro (tube formation, proliferation). As Zeb1 has recently been implicated in tumor angiogenesis, we zoomed in on SPTBN1. Knockdown of SPTBN1 expression led to profound tight junction loss, and we were able to pinpoint this to a cytoskeleton defect. In vivo, SPTBN1 morphants had clear defects in venous ISV and CVP formation, once more implicating SPTBN1 as critical regulator of angiogenesis.

Conclusion: Collectively, our findings support a role of SPTBN1 and ZEB1 as novel gene regulators of plaque angiogenesis and microvessel dysfunction, identifying them as targets for intervention.
Ischemic heart disease continues to have tremendous impact on public health, shortening lifespan and impairing quality of life. The inability of the adult human myocardium to undergo regeneration after myocardial infarction has inspired research using cell therapy for myocardial repair. However, clinical trials to date have shown modest or no benefit, suggesting the need to consider other cell sources and approaches. In large animal models, derivatives of human pluripotent stem cells have provided promising results, but the grafts have generally been small, transient, and of limited functional benefit. Additionally, important questions remain regarding cardiac cells derived from iPSCs, including optimal delivery strategy, immunogenicity, maturity, and ability to couple effectively to native myocardium without causing arrhythmias. Human induced pluripotent stem cells (hiPSCs) must be fully differentiated into specific cell types before administration, but conventional protocols for differentiating hiPSCs into cardiomyocytes (hiPSC-CMs), endothelial cells (hiPSC-ECs), and smooth muscle cells (SMCs) are often limited by low yield, purity, and/or poor phenotypic stability. We are now investigating a novel study of generation of hiPSC-CMs, -ECs, and -SMCs that are substantially more efficient than conventional methods, as well as a method for combining cell injection with a cytokine-containing patch created over the site of administration. Conventional 3D-printing techniques cannot produce structures the size at which individual cells interact. In these studies, we used multiphoton-excited, 3-dimensional printing (MPE-3DP) to generate native-like, extracellular matrix (ECM) scaffold with submicron resolution; then seeded the scaffold with cardiomyocytes (CMs), smooth-muscle cells (SMCs), and endothelial cells (ECs) that had been differentiated from human induced-pluripotent stem cells to generate a human, iPSC-derived cardiac muscle patch (hCMP), and subsequently evaluated in a murine model of myocardial infarction. The novel MPE-3DP technique produces ECM-based scaffolds with exceptional resolution and fidelity, and hCMPS fabricated with these scaffolds may significantly improve recovery from ischemic myocardial injury.
HISTONE DEACETYLASE INHIBITORS PREVENT CARDIAC HYPERTROPHIC REMODELING AND DYSFUNCTION IN NPR1 HAPLOTYPE MICE

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Objectives: The goal of the present study was to investigate the role of genetically determined differences of Npr1 gene copies on the expression of proinflammatory mediators, cardiac hypertrophic markers, and matrix metalloproteinases (MMPs) on cardiac dysfunction in the Npr1 gene-targeted mouse models. Introduction: Atrial and brain natriuretic peptides (ANP, BNP) bind guanylyl cyclase/natriuretic peptide receptor-A (GC-A/NPRA), stimulate the generation of the second messenger cGMP, thereby regulate blood pressure and cardiovascular homeostasis. We determined whether all-trans retinoic acid (RA) and sodium butyric acid (SB), histone deacetylase (HDAC) inhibitors suppress the expression of cardiac disease markers in Npr1 (coding for GC-A/NPRA) gene-disrupted mouse models.

Methods and Results: The Npr1 gene-disrupted haplotype (Npr1+/-, 1-copy), wild-type (Npr1+/+, 2-copy), and gene-duplicated (Npr1++/+, 3-copy) mice were treated intraperitoneally with RA, SB, and a combination of RA/SB hybrid drug (HB) for 16 days. Untreated 1-copy haplotype mice showed significantly increased heart weight/body weight (HW/BW) ratio, hypertrophic markers, including beta-myosin heavy chain (beta-MHC), activating protein-1 (AP-1) proto-oncogenes (c-fos and c-jun), nuclear factor kappa B (NF-êB), and MMPs (MMP-2, MMP-9) by almost 4- to 6-fold as compared with 2-copy and 3-copy mice. The treatments with RA, SB, or HB exhibited significantly reduced expression levels of beta-MHC, NF-êB, AP-1 (c-fos, c-jun), and (MMP-2, and MMP-9) by approximately 60-70% in haplotype 1-copy mice. In drug-treated animals, the activity of HDACs was significantly reduced and histone acetyltransferase activity was increased. The drug treatments markedly increased the fractional shortening and decreased the cardiac systolic and diastolic dysfunctions in haplotype Npr1+/- mice.

Conclusions: The present findings suggest that a decreased Npr1 gene copy number greatly enhances the expression of hypertrophic markers and proinflammatory mediators; however, on the contrary, an increased Npr1 gene-copies and treatments with RA, SB, and HB repress the cardiac disease markers and protect the heart from the hypertrophic stimuli in a Npr1 gene-dose-dependent manner.
Heart diseases are still the leading cause of morbidity and mortality in the western world. Cell therapy has made significant progress to treat various cardiovascular diseases such as myocardial infarction, cardiomyopathy and heart failure. We have shown that transplanted pluripotent embryonic stem cells can engraft and differentiate into heart cell types to regenerate the injured myocardium. However, embryonic stem cells have a characteristic to form teratoma following transplantation that limits its use in the clinical applications. Recently, we have developed a cell free source from embryonic stem cells called exosomes. These exosomes contain specific miRNA that inhibits cell death and cardiac remodeling in the injured myocardium. Our data suggest that exosomes could be a potential for future cell therapy to treat various heart diseases compared with the embryonic stem cells that may carry a risk of teratoma formation.
One of the biggest limitations to the benefit of stem cell therapy for organ regeneration is the very brief time (hours to days) that cells remain in the target organ post delivery. The body has a number of electrical fields as evidenced by an EKG. Bioelectric stimulation is a growing field that takes advantage of manipulating these fields by non-invasive stimulation of the target tissue at very precise frequencies. Decades of research has led to identification of the precise frequency that is the signature of a large number of proteins in the body. Stimulation at this precise signal can induce the controlled expression and upregulation of up to 13 targeted proteins in the heart and other tissues that have each been shown to be beneficial in organ regeneration. This includes SDF-1, which is one of the most potent stem cell mobilizing proteins in the body, as well as multiple growth factors such as IGF, HGF, PDGF, EGF, HGF, and VEGF, and other proteins such as eNOS, Tropoelastin, and Follistatin. The stimulator used is programmable and delivers each of the signals at specific duration and strength for that protein, and in any sequence selected. This strategy much more closely mimics the multiple proteins involved in native tissue repair.

A second major problem that is that all cell therapy to date has utilized only a single delivery. The Leonhard strategy is that the local expression of each of the target proteins are stimulated in repetitive cycles to continually drive native tissue repair. These proteins can also be delivered directly into the target tissue to enhance the effect of the biostimulation, either alone or in combination with repeated delivery of stem cells and other substances shown to be beneficial such as matrix, exosomes, and hydrogels. This novel approach addresses most of the deficiencies in the field and promises to markedly enhance the possibility of organ regeneration.
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A NOVEL MECHANISM CONTROLLING VASCULAR REMODELING

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Vascular remodeling due to smooth muscle cell (SMC) proliferation and neointima formation is a major medical challenge in cardiovascular intervention. However, anti-neointima drugs often indistinguishably block re-endothelialization, an essential step for successful vascular repair, because of their nonspecific effects on endothelial cells (ECs). Using both rat balloon injury and mouse wire injury models, we identified CTP synthase 1 (CTPS1) as a novel target for developing better therapeutics for treating proliferative vascular disorders. CTPS1 was induced in proliferating SMCs in vitro and neointima SMCs in vivo. Blockade of CTPS1 expression by small hairpin RNA or activity by cyclopentenyl cytosine suppressed SMC proliferation and neointima formation. Surprisingly, cyclopentenyl cytosine had much less effect on EC proliferation. Of importance, blockade of CTPS1 in vivo sustained the re-endothelialization due to an induction of CTP synthesis salvage pathway enzymes nucleoside-diphosphate kinase A and B in ECs. Diphosphate kinase B seemed to preserve EC proliferation by using extracellular cytidine to synthesize CTP. Indeed, blockade of both CTPS1 and diphosphate kinase B suppressed EC proliferation in vitro and the re-endothelialization in vivo. Our study uncovered a fundamental difference in CTP biosynthesis between SMCs and ECs during vascular remodeling, which provides a novel strategy by using cyclopentenyl cytosine or other CTPS1 inhibitors to selectively block SMC proliferation without disturbing or even promoting re-endothelialization for effective vascular repair after injury.
EMERGING ROLE OF CELLULAR THERAPY (STEM CELL THERAPY) IN CORONARY ARTERY DISEASE

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The regenerative potential of stem cells offers an enormous impact on clinical applications in the management of cardiovascular diseases. There are multiple factors for success of cellular therapy for coronary artery disease or cardiomyopathy such as mode of delivery, retention of stem cells in ischemic tissue, microvascular plugging, bio-distribution, homing to ischemic tissues and paracrine function of stem cells. Atherosclerotic disease is associated with obstructive coronary artery disease and microvascular dysfunction. While coronary artery interventions address the obstructive coronary artery disease, cellular therapy may improve the healing process in acute and chronic coronary artery disease at cellular level. Repair of damaged myocardial tissue occurs by virtue of proliferation of cells capable of restoring the injured tissue and regeneration and healing of a damaged tissue is critical to survival. The ability of stem cells to repair tissue is dependent upon the intrinsic ability of tissues to proliferate such as embryonic stem cells giving rise to virtually any type of tissue. The ability to convert adult stem cells into pluripotent cells that resemble embryonic cells, and to transplant those in the desired organ for regenerative therapy is one of the goals of cellular therapy. This has lead to the exploration of innovative treatments for cardiovascular diseases. However one of the key concepts is homing of desired cell to the target injured tissue for enhancing the desirable paracrine function. The race is on to find an ideal stem cell, delivery strategies, retention of stem cells in target tissue and other factors for successful homing of such cells.
Macrophage accumulation in the myocardium is critical for the clearance of necrotic cardiomyocytes and orchestration of cardiac repair. Key macrophage scavenging receptors facilitate clearance and also trigger intracellular signaling and immune cell metabolism that culminates in resolution of cardiac inflammation and deposition of collagen and scar formation. The efficiency of macrophage-mediated cardiac repair is modulated by disease risk factors and low oxygen supply. Basic understanding of these pathways is permitting a focused targeting of macrophage scavenger receptor pathways to limit reperfusion-associated injury and infarct expansion.
THE VALUE OF INCORPORATING THE LEFT ATRIAL SIZE TO THE CURRENT STROKE RISK SCORING SYSTEMS FOR ATRIAL FIBRILLATION.
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Objective: To evaluate the potential additive role of left atrial size in predicting cardio-embolic stroke in atrial fibrillation.

Background: Stroke is associated with significant morbidity and mortality. Atrial fibrillation is associated with a fivefold increase in risk of cardio-embolic stroke. Clinicians rely on risk scoring systems to predict stroke risk in patients with atrial fibrillation. Left atrial size is not utilized in any stroke risk scoring system to stratify patients at risk for cardio-embolic stroke.

Methods: A systemic review encompassing stroke risk scores was performed. Clinical studies reported in the English Literature during the period January 1, 1985 to December 31, 2015, were identified through a computerized search using the search terms Atrial fibrillation, Stroke and Atrial size utilizing the Medline (PubMed) and Cochrane electronic databases. Reference lists of retrieved articles were scanned for additional reports.

Results: There is a significant amount of literature emphasizing left atrial size, including diameter, volume, and left atrial volume index, as a predictor of stroke. In recently published studies that address a relationship of left atrial size with CHADS2 and CHA2DS2-VASc scores to aid in stroke risk assessment. It was noted that the combination of the CHA2DS2-VASc and identification of left atrial remodeling was able to distinguish between low and moderate risk patients for stroke. On the other hand, CHADS2 had the potential to identify left atrial remodeling in patients that are high risk of stroke. Moreover, it was found that higher thromboembolic risk associated with CHADS2 and CHA2DS2-VASc scores were significant in patients with left atrial enlargement.

Conclusion: Scoring system that incorporates both the best available stroke risk scoring systems and the left atrial size, may provide a better stroke risk stratification and management of atrial fibrillation.
EFFECT OF ATRIAL FIBRILLATION ON THE IN-HOSPITAL MORBIDITY AND MORTALITY TRENDS OF TAKOTSUBO CARDIOMYOPATHY

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Background: Incidence of Takotsubo cardiomyopathy has gradually increased through the recent years. Though considered a reversible disease with good prognosis, it can be associated with significant morbidity and mortality due to arrhythmias. The main objective of our study was to assess the effect of atrial fibrillation on the morbidity, length of stay (LOS) and hospital outcomes in patients with Takotsubo cardiomyopathy.

Methods: Using National Inpatient Sample (NIS) from 2007-2012, Takotsubo cardiomyopathy was identified with International Classification of Diseases, 9th Revision (ICD-9-CM) code 429.83 as the principal discharge diagnosis who underwent diagnostic coronary angiography. National estimates were calculated according to NIS-complex-survey-design weights and predictors of hospital outcomes were estimated using mixed-effects regression models.

Results: A total of 21596 patients were identified to have Takotsubo cardiomyopathy during the period of 2007-2012. Atrial fibrillation was considered a secondary discharge diagnosis in 2397 cases with increasing annual incidence (p<.001). In-hospital mortality, age and hospitalization costs did not show any significant trend. The mean hospitalization costs and LOS were 12349 USD and 3.6 days respectively. Atrial fibrillation as well as men, history of heart failure, pulmonary hypertension and alcohol consumption significantly predicted a higher risk of inpatient mortality (p<0.05). Atrial fibrillation was also a significant predictor of increasing LOS (p=0.002) and hospitalization costs (p=0.003).

Conclusion: We found an overall occurrence of concomitant atrial fibrillation in 11.1% of Takotsubo cardiomyopathy. Atrial fibrillation as a secondary diagnosis is significant positive predictor of inpatient mortality, extended length of stay and increasing hospital cost in patients with Takotsubo cardiomyopathy.
ASSOCIATION OF CHA2DS2-VASC AND R2CHADS2 SCORES WITH LEFT ATRIAL VOLUME INDEX: A RETROSPECTIVE STUDY OF STROKE PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION (NVAF)

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Introduction: Atrial fibrillation is the most common rhythm disorder responsible for 1 of 5 strokes. CHA2DS2-VASC and R2CHADS2 are used for anticoagulation recommendation in NVAF, but do not take into consideration objective parameters, such as left atrial volume index (LAVI). Studies have identified LA diameter’s association with a 39% increased risk for AF. LA volume is superior to LA diameter for predicting outcomes in AF. Despite this, the LA is not included in scoring. The aim of our study was to understand the association of LAVI with R2CHADS2, CHA2DS2-VASC, and renal function in stroke patients with NVAF.

Methods: 91 adult patients admitted over two years with AF and stroke diagnosis were reviewed. Data variables included admitting diagnosis, renal function, and CHA2DS2-VASC/R2CHADS2 scores. For assessing the LA size and remodeling, indexing of LA volume to body surface area is recommended by the American Society of Echocardiography (ASE) and the European Association of Echocardiography. Echocardiographic measurements of the LA using the biplane disk summation technique were performed in the apical 4 chamber and 2 chamber views. Measurements >34ml/m2 were quantified as enlarged.

Results: Comparison of LAVI+R2CHADS2 to CHA2DS2-VASC, LAVI+CHA2DS2-VASC and R2CHADS2, and LAVI+ R2CHADS2 to LAVI+ CHA2DS2-VASC revealed a positive and significant correlation [(R=0.4624, p <0.00001), (R= 0.5144, p<0.0001), (R=0.8119, p<0.00001)]. LAVI and GFR revealed a weak negative, but significant correlation (R= -0.2076, p<0.05).

Conclusion: LA enlargement is a known risk factor for AF; however, parameters of LA are not in decision-making for anticoagulation. We found a positive and significant association when LAVI was added to CHA2DS2-VASC and R2CHADS2 scores. This objective finding can help predict higher thromboembolic risk in patients with AF. There is an inverse relationship between worsening renal function and enlargement of LA diameter, which can help predict patients at risk for developing AF.
INFERIOR VENA CAVA DIAMETER BY HAND HELD ULTRASOUND PREDICTS ATRIAL FIBRILLATION RECURRENTNESS AFTER CARDIOVERSION

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Background: Ultrasound measurements of the inferior vena cava (IVC) are commonly used to estimate right atrial pressure. Atrial fibrillation (AF) recurrence after successful direct current cardioversion (CV) is common, and additional clinical predictors may be useful. Objective: We sought to evaluate the risk of early AF recurrence according to IVC measurements by hand-held ultrasound (HHU) at the time of CV.

Methods: Using a HHU device (Vscan, GE Healthcare), the maximum IVC diameter (IVCd) and collapsibility with inspiration were measured in 117 patients immediately before and after successful CV for AF. Patients were followed by chart review for 30 days for recurrence of AF.

Results: Mean IVCd was 2.14cm in AF pre-CV and 1.99cm in sinus rhythm post-CV (p<0.0001). AF recurred within 30 days of CV in 28 of 117 patients (23.9%). Mean IVCd pre-CV was 2.20cm in patients with AF recurrence, and 2.12cm in patients without recurrence (p=0.40). However, among patients with IVCd ≤2.1cm pre-CV and any decrease in IVCd post-CV, AF recurrence rate was 9.1%, compared to 29.8% in patients not meeting these parameters (OR 0.24, p=0.03). This association persisted after adjustment for a history of persistent AF, ejection fraction, left atrial dilation, and anti-arrhythmic drug therapy (adjusted OR 0.20, p=0.02). Among patients in whom IVCd post-CV was ≤1.7cm, AF recurrence rate was 10.8%, compared to 31.3% in patients not meeting this parameter (OR 0.28, p=0.03). This association remained significant in the adjusted model (adjusted OR 0.17, p=0.01).

Conclusion: The presence of a normal-sized IVCd pre-CV that becomes smaller post-CV and the presence of a small IVCd post-CV are each independently associated with reduced likelihood of AF recurrence. Therefore, HHU assessment of the IVC at the time of CV may be useful to identify patients at low risk of early recurrence of AF after CV.
ARRHYTHMIA I: DIAGNOSIS, DRUG THERAPY, ABLATION

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PVI WITHOUT FLUOROSCOPY IS AS SAFE, EFFICIENT, AND EFFECTIVE AS TRADITIONAL FLUOROSCOPIC TECHNIQUES

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Objectives: To determine the safety, efficacy, and procedural efficiency of zero fluoroscopy pulmonary vein isolation (PVI).

Background: PVI is a common procedure for treating symptomatic atrial fibrillation (AF). Traditionally, significant fluoroscopy is needed to aid in transseptal access and catheter manipulation. With advanced 3D mapping systems and intracardiac echocardiography (ICE), PVI is possible without fluoroscopy.

Methods: This retrospective study compared 34 patients undergoing PVI utilizing a zero fluoroscopy (ZF) technique to a control group of 42 patients undergoing PVI by conventional technique (CT). ZF procedures were performed utilizing the Carto 3D EAM system and ICE. A single experienced operator performed all procedures.

Results: Both groups did not differ significantly except that the ZF group had a greater percentage of persistent AF (66% vs. 17% p<0.01) and number of failed antiarrhythmics prior to ablation (1.3±1.0 vs. 0.7±0.76 p=<0.01). The procedural time was similar among groups (ZF: 127.9±33.9 vs. CT: 134.7±35 min, p=0.39). No major complications were observed in either group. One patient in the ZF group had issues with a venous sheath limiting use of ICE, therefore it was converted into a conventional approach. As expected, radiation dose (55658±42755 vs. 556±3185 mGycm² p=<0.01) and fluoroscopy time (9.3±6.3 vs. 0.2±1.3 min, p<0.01) were much greater in the CT group compared to ZF technique. The acute procedural success rate was the same in both the ZF and CT groups (100% vs. 100%). The rate of recurrences was similar between ZF and CT groups (17% vs. 33% p=0.133) however, mean follow up time was shorter in the ZF group (44±38 vs. 203±92 days, p<0.01).

Conclusion: PVI utilizing a zero fluoroscopy technique is feasible. This technique is as safe, effective, and efficient as conventional techniques while exposing the patient and operator to significantly lower doses of ionizing radiation.
AV NODAL REENTRANT TACHYCARDIA OF THE SICK
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Background: AVNRT is the most common paroxysmal supraventricular tachycardia. It is more likely to occur in young adults but may also begin in elderly. Symptoms are usually brought by minimal exertion or even at rest. AVNRT of the Sick has not been previously reported in the literature.

Objective: We report our single center experience of AVNRT of the Sick in 13 consecutive patients who were admitted to the hospital with acute illness and developed a short RP SVT between January, 2014 and September, 2016.

Methods: Retrospective chart review of all patients who developed SVT in the setting of acute illness between January of 2014 and December of 2016. ECG diagnosis of typical slow-fast AVNRT was made with a short RP interval of 80 milliseconds or less.

Results: None of the patients had prior history of AVNRT or any other arrhythmia. Majority of the patients were males (77%) with a mean age of 59 ± 12. Among those patients, 46% had HTN, 31% had DM, 8% had CHF, 8% had CAD and 54% had active cancer. Reason for admission was cancer related surgery in 62%, chemotherapy in 31%, and sepsis in 38%. All patients developed symptomatic AVNRT during the hospitalization. None of the patients were hemodynamically unstable. Patients were successfully treated with Amiodarone (69%), metoprolol (23%) or diltiazem (15%). Patients were followed for at least 3 months after the resolution of the acute illness. Amiodarone was discontinued at 1 month follow-up in all patients. None of the patient had recurrence of AVNRT and required ablation.

Conclusion: AVNRT of the Sick has not been previously described in the medical literature. Increased adrenergic tone and electrolyte abnormalities during the acute illness can be the potential causes. Further research is required to delineate the exact mechanism.
INTER-OBSERVER RELIABILITY OF TWO-DIMENSIONAL SPECKLE-TRACKING DERIVED GLOBAL LEFT ATRIAL STRAIN MEASUREMENTS IN PATIENTS WITH SLEEP DISORDERED BREATHING AND PAROXYSMAL ATRIAL FIBRILLATION: RESULTS FROM THE SAFEBEAT STUDY

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Background: Global left atrial (LA) strain has proven clinical utility, including predicting the maintenance of sinus rhythm following catheter ablation for atrial fibrillation (AF). Sleep disordered breathing (SDB) is associated with the onset of AF. Reliability data on LA strain measurements in patients with SDB and paroxysmal AF (PAF) are limited. The clinical utility and inter-observer reliability of LA strain measurements in patients with SDB and PAF are unknown.

Methods: SAFEBEAT (NCT number: 02576587) is a prospective, multi-site, case-control study examining the relationship between SDB and PAF in 317 subjects. To assess the inter-observer reliability of LA strain measurements in patients with SDB and PAF, two blinded echocardiologists assessed global LA strain in 19 randomly selected subjects using velocity vector imaging (Siemens Medical Solutions, Mountain View, CA). Intra-class correlation coefficients (ICC) were calculated to assess inter-observer reliability.

Results: 18 subjects (8 cases with PAF; 10 controls without PAF) comprised the final analytic sample (one subject excluded due to sub-optimal imaging): age: 60.4±12.6 years; 83.3% male; body mass index: 31.2±4.9; body surface area: 2.2±0.25 m²; LA volume index: 31.0±8.6 mL/m² for cases; 29.7±9.4 mL/m² for controls; global LA strain: 35.3±9.7% (Table 1). The overall ICC for global LA strain was good (0.70, 95% confidence intervals (CIs): 0.16 – 0.89). The ICC for global LA strain for the 8 cases with PAF was good (0.69, 95% CIs: -0.09 – 0.94). The ICC for global LA strain for the 10 controls was excellent (0.79, 95% CIs: 0.39 – 0.94).

Conclusion: Global LA strain can be reliably measured by two-dimensional speckle-tracking in patients with SDB, with comparable results between subjects with and without PAF. These findings suggest that LA mechanics may be useful in elucidating the changes in LA function in SDB, and may help unravel the links between SDB and PAF.
ARRHYTHMIA I: DIAGNOSIS, DRUG THERAPY, ABLATION

ASSOCIATION OF BRAIN NATRIURETIC PEPTIDE AND ATRIAL FIBRILLATION RECURRENCE AFTER SUCCESSFUL ELECTRICAL CARDIOVERSION: A MULTIVARIATE ANALYSIS INCLUDING DIASTOLIC DYSFUNCTION

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Introduction: N-terminal pro-b-type natriuretic peptide (NT-proBNP) and BNP have been inconsistently associated with atrial fibrillation (AF) recurrence after electrical cardioversion (ECV). BNP has also been linked to structural remodelling in both systolic and diastolic dysfunction. Most studies excluded systolic dysfunction in assessing BNP as a predictor of AF recurrence. However, this association does not appear to have been studied independent of diastolic dysfunction.

Objective: Assess whether BNP predicts AF recurrence independent of diastolic dysfunction.

Methods: A retrospective analysis compared persistent AF patients maintaining sinus rhythm 3 months after ECV versus those who reverted to AF. Exclusion criteria were left ventricular ejection fraction less than 50%, severe mitral regurgitation, moderate to severe mitral stenosis, left atrial thrombus, previously failed ECV, and atrial size more than 5cm. BNP levels were obtained from hospital records before ECV. Both univariate and multivariate analysis of BNP with AF recurrence incorporating diastolic dysfunction were conducted.

Results: Included were 61 patients (41% male, 59% female) with no significant differences between AF recurrence (n = 29) and non-recurrence (n = 29) groups in terms of gender (31% vs 28% female and 18% vs 23% male), age (71.80 +/- 10.42, 73.13 +/- 10.45, p 0.62), BMI (30.18 +/- 7.14, 30.79 +/- 6.75, p 0.75), creatinine (1.11 +/- 0.72, 0.99 +/- 0.37, p 0.39), and BNP (309.52 +/- 190.15, 334.48 +/- 270.27, p 0.67). No significant univariate correlation was found between BNP and AF recurrence (Spearman’s rho 0.02, p 0.88). In multivariate analysis stratified by diastolic dysfunction (22 positive, 32 negative), BNP remained non-predictive of AF recurrence (299.55 +/- 194.09, 329.06 +/- 243.29; p = 0.76).

Conclusions: BNP prior to ECV was not a reliable predictor of AF recurrence irrespective of diastolic dysfunction. Prior association of BNP with diastolic dysfunction likely confounded the positive results of previous studies.
ARRHYTHMIA I: DIAGNOSIS, DRUG THERAPY, ABLATION

ASSESSMENT OF SAFETY OF BOLUS INJECTION OF PROTAMINE AFTER PULMONARY VEIN ISOLATION

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Background: Pulmonary vein isolation (PVI) is becoming a standard therapeutic procedure for drug resistant symptomatic atrial fibrillation. During PVI, continuous heparin infusion was performed and ACT was monitored during whole procedure for prevention of systemic embolism. On the other hand, hemorrhagic side effect is a problem. It has been reported that without discontinuation of direct oral anti-coagulation (DOAC) or warfarin during PVI is acceptable outcome but there was 7% incident of minor bleeding including hematoma greater than 5 cm or pericardial effusion in DOAC continued PVI.

Objectives: Our purpose is to assess safety of protamine bolus infusion for prevention of hemorrhagic complication.

Method: We reviewed the patients who received protamine bolus administration after PVI or cavo-tricuspid isthmus (CTI) ablation in our institute. Between 2014 to 2016, 411 atrial fibrillation (AF) or atrial flutter (AFL) ablation were conducted in our institute. After the procedure, 50 mg of protamine was administered with bolus injection.

Result: PVI was 393 cases (95.6%) and total case of CTI were 50 (12.1%). The patients with paroxysmal atrial fibrillation (PAF) were 228 cases (55.5%) and persistent or longstanding persistent atrial fibrillation (PeAF) were 165 cases (40.1%). The patients with AFL only were 18 cases (4.4%). There were no cases which developed hypotension or shock. Our complication rate including hemorrhage and cardiac tamponade was 1%.

Conclusion: Protamine administration could reduce bleeding complication and safety of bolus injection was ascertained.
RAMP™ SHEATH DECREASES THE NUMBER OF RADIOFREQUENCY ABLATION APPLICATIONS FOR BIDIRECTIONAL ISTHMUS BLOCK IN TYPICAL RIGHT ATRIAL FLUTTER

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Background: The RAMP™ sheath is used in right atrial flutter ablation (RAFA) to guide catheter placement on the tricuspid valve annulus and provide catheter stability as needed. There is no literature on the utilization of RAMP sheath in RAFA.

Objective: To compare the number of RAFA applications to reach bidirectional isthmus block (BIB) with the use of the RAMP™ sheath from the start versus without the use of the RAMP™ sheath. Methods: A retrospective chart review of all patients who underwent RAFA either with or without the RAMP™ sheath between January 2010 and November 2016 was done. A total of 104 patients’ data were reviewed. We compared the average number of RAFA applications required to achieve BIB in either group. BIB was demonstrated in all patients. A statistical analysis compared the two values and illustrated the data using a boxplot.

Results: The average numbers of RAFA applications to achieve a BIB without the RAMP™ sheath utilization was 11.27 ± 0.72. With the introduction of the RAMP™ sheath from the start, the average number of RAFA applications decreased by 2.78 ± 1.2 (p=0.019). There were no complications associated with RAMP™ sheath use. Conclusion: The use of RAMP™ sheath in RAFA procedures from the start led to fewer RAFA applications in order to achieve BIB as compared to RAFA procedures that did not use a RAMP™ sheath.
CONVERSION OF ISOLATED UNIDIRECTIONAL ISTHMUS BLOCK TO BIDIRECTIONAL BLOCK BY ABLATING A DIFFERENT LOCATION IN THE CAVO-TRICUSPID ISTHMUS FOR THE TREATMENT OF TYPICAL ATRIAL FLUTTER

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Objectives: Achieving bidirectional block along the cavo-tricuspid is crucial to atrial flutter ablation success and we seek to optimize this success by re-evaluating testing of the bidirectional isthmus block.

Background: Typical atrial flutter is defined by cavo-tricuspid isthmus (CTI) dependent counterclockwise or clockwise macro-reentry involving the right atrium. Catheter ablation carries high success rate and creation of bidirectional block along the CTI predicts long-term success. However, isolated unidirectional isthmus block may rarely occur during ablation.

Methods: Between July 2009 and July 2016, 72 ablations were done for the treatment of typical atrial flutter at the University of Arkansas for Medical Sciences. We herein report three cases of isolated unidirectional isthmus block.

Results: During an atrial flutter ablation, we demonstrated persistence of unidirectional medial to lateral isthmus block; however, lateral to medial conduction remained intact in three patients. Further radiofrequency applications were delivered lateral to the first ablation line in the seven o’clock position in a lateral oblique view, while pacing the low right atrial free wall. Bidirectional block was achieved and confirmed with 3-dimensional mapping.

Conclusions: Even with successful termination of atrial flutter during RF ablation, meticulous testing by pacing medial and lateral to the line of block should be done to confirm bidirectional block, as this is an important end point for long-term atrial flutter ablation success.
ASSOCIATION OF SERUM FERRITIN WITH CARDIOVASCULAR DISEASE INCIDENCE AMONG AFRICAN AMERICANS: A JACKSON HEART STUDY

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Objective: To evaluate the association of serum ferritin with incident CHD, incident stroke and subclinical measures of atherosclerosis among African Americans (AA)

Background: There has been conflicting results regarding the role of ferritin, a nonspecific marker of systemic inflammation, in the development of coronary heart disease (CHD). To our knowledge, there are no studies that have exclusively evaluated the association of serum ferritin levels with incident CHD among African Americans.

Methods: We utilized data from the Jackson Heart Study for our retrospective cohort study. Eligible participants (N= 4,679) were enrolled between year 2000-2004, their baseline serum ferritin level were obtained, and they were followed for an average of 7 years to identify incident CHD events and stroke. We used a multivariate linear regression and cox proportional hazard models to evaluate the associations of serum ferritin with incident CHD events and incident stroke. The age-adjusted correlations between ferritin and specific study covariates including carotid intima-media thickness, coronary artery calcium, and abdominal aortic calcium were obtained.

Results: During an average of seven years of follow-up, 158 incident CHD events and 116 incident stroke events were documented. There was no significant association between ferritin levels and incident CHD events (P=0.54 in males; P=0.31 in females) or incident stroke (P=0.17 in males; P=0.56 in females). Ferritin was significantly correlated with abdominal aortic calcium (r 0.09; P=0.0005) in women but not in men.

Conclusion: In the African American population, a higher serum ferritin level is not associated with an increased risk of incident CHD events or incident stroke. Our study suggests that serum ferritin levels cannot be used as an independent predictor of incident CHD or stroke in African Americans. Larger observational studies may be needed to further elucidate the association between serum ferritin and abdominal aortic calcium among African American women.
Objective: We examined the association of CVH metrics to social isolation (SI) in US adults.

Background: SI predicts cardiovascular risk; however, there are limited data regarding its relation to global cardiovascular health (CVH).

Methods: Using the US National Health and Nutrition Examination 2007-2008 Survey of noninstitutionalized adults aged >=40 we examined the association of SI, defined by a lack of emotional support with the American Heart Association’s Life’s Simple 7 (LS7) CVH components (smoking, body mass index, physical activity, total cholesterol, diet, blood pressure, fasting blood glucose). The sum of the components (each scored 1 for poor, 2 for intermediate, and 3 for ideal) created a composite global CVH score categorized as poor (<10), intermediate (11-15) and ideal (16-20). ANOVA compared the composite CVH score in those with and without SI, adjusting for age, gender, and ethnicity and logistic regression the odds of SI according to the composite CVH score and its components.

Results: We studied 3528 adults aged >=40 (50.9% females, 18.8% African American, 26.2% Hispanics) representing 126 million persons. The mean adjusted composite CVH score was 14.32 in those without vs. 14.05 in those with SI (p=0.02). The adjusted odds ratio (OR) (95% CI) of SI was less in those with intermediate (OR= 0.62 [0.33, 1.16]) and ideal (OR= 0.45 [0.22, 0.93]) vs. poor global CVH scores. The individual metrics (OR’s for ideal vs. poor) contributing to this were: smoking: 0.57 (0.39, 0.85), physical activity: 0.53 (0.37, 0.76), and fasting glucose: 0.65 (0.47, 0.91).

Conclusion: Our study shows higher levels of CVH to relate to lower odds of SI, with nonsmoking status and ideal physical activity and glucose components important contributors to this. These findings may help to explain the link between SI and elevated cardiovascular disease risk, but further study is warranted to confirm this.
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CARDIORESPIRATORY FITNESS ATTENUATES THE RISK OF CONGESTIVE HEART FAILURE IN HYPERTENSIVES

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Introduction: Hypertension is one of the most common risk factors for congestive heart failure (CHF). Evidence suggests that increased fitness may attenuate the risk for CHF in the general population. However, the association between fitness and CHF incidence in hypertensive patients has not been assessed.

Methods: A total of 8,725 hypertensive men (mean age 60±10) from Washington DC and Palo Alto Veterans Affairs Medical Centers underwent routine exercise tolerance testing. Peak workload was estimated in metabolic equivalents (METs). We established five fitness categories based on age-stratified quartiles of peak metabolic equivalents (MET) achieved: Least-fit (4.3±1.18 METs; n=1,643); Low-Fit (5.8±1.10 METs; n=1,926); Moderately-Fit (7.2±1.2 METs; n=1,771); Fit (8.4±1.2 METs; n=1,931) and Highly-Fit (11.2±2.2 METs; n=1,455). Cox proportional hazard models were applied after adjusting for age, BMI, race, family history of CV disease, CV/antihypertensive medications, and risk factors. P-values <0.05 using two sided tests were considered statistically significant.

Results: During a mean follow-up period of 10.7±6.5 (median 10.4), there were 654 incidences of CHF (7.5%) or 6.7 events per 1000 person-years of follow-up. The association between new onset CHF risk and fitness was inverse and graded. For every 1-MET increase in exercise capacity, the risk was lowered by 16% (HR=0.84; CI: 0.81-0.87; p<0.001). When compared to the individuals in the Least-Fit category, the risk for developing CHF was progressively lower, ranging from 32% (HR=0.68; CI: 0.55-0.84; p<0.001) for the next fitness category (Low-Fit) to 70% those in the highest fitness category (HR=0.30; CI: 0.23-0.41; p<0.001).

Conclusions: Increased cardiorespiratory fitness is associated with lower risk for developing CHF in hypertensive patients.

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A FEASIBILITY STUDY ON 10-YEAR CVD RISK ASSESSMENT AS A SECONDARY PREVENTION TOOL FOR CARDIOVASCULAR DISEASE

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Background: China National Center for Cardiovascular Disease launched a guideline-based 10-year risk assessment of cardiovascular disease (CVD) phone APP, and created a heart age index to visualize the CVD risk to public. This is the first time using totally Chinese local database which includes 40,000 people following up 10-15 years to assess CVD incidence risk. We assessed the self-test effect of the app in China and the feasibility of promoting the app as a secondary prevention tool for CVD by government.

Method: Media and government projects encouraged people spontaneously using the app and answering 8 CVD risk factor’s questions. We analyzed the current status of cardiovascular risk in Chinese residents, the prevalence of hypertension, hyperlipidemia, diabetes, the distribution of heart-age and so on by SPSS.

Finding: During 5 months, 18,214 people (39.7% of men, 60.3% of women) used the app around the whole country. The mean age was 55.9 years, the mean heart-age was 64.8 years, and the mean 10-year CVD risk was 4.1%. For hypertension, hyperlipidemia and diabetes patients, the mean 10-year CVD risks were 8.7%, 7.1%, and 9.5% respectively. Prevalence of hypertension (SBP over 140 mmHg or DBP over 90 mmHg), hyperlipidemia (total cholesterol>6.2mmol/L) and diabetes mellitus were 15.8%, 14.4% and 8.5%, respectively. Among hypertensive patients, 33.4% had hyperlipidemia at the same time, and 10.5% of diabetes patients had hyperlipidemia. The correlation coefficient between hypertension and hyperlipidemia was 0.101 (P<0.001), between hyperlipidemia and diabetes was 0.022 (P=0.003), and between hypertension and diabetes was 0.038 (P<0.001).

Conclusion: The 10 years CVD risk evaluation app can be a primary prevention tool for CVD in China. For Chinese population, heart-age is 10 years older than actual age. Hyperlipidemia is highly associated with hypertension and diabetes, so it’s necessary for Chinese government to include blood lipid management in its national policy.
PATIENT CENTERED SPECIALTY PRACTICE: THE PROVIDENCE EXPERIENCE

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Background: Over the last decade, significant transformation has occurred in primary care to provide team-based, comprehensive care to optimize clinical outcome and contain cost. Yet little has been done to update specialty care to better meet the needs of patients and referring providers. Providence Heart Clinic at Gateway was the first Cardiology Practice in the nation to achieve Patient Centered Specialty Practice (PCSP) recognition by the National Committee on Quality Assurance (NCQA). We have since expanded PCSP across 15 Providence Heart Clinic sites in Oregon. Through this transformative project, we have seen improvement in access, care coordination, quality and patient satisfaction.

Methods: An interrupted time series design to measure patient access (new and follow up patient seen), care coordination (completeness and timeliness of referral), quality (setting and achieving quality metrics), and patient satisfaction (CG-CAHPS survey).

Result: Implementing PCSP standards have resulted in improvement of specialty care quality with better access with a 24% increase in the number of new patients seen comparing 2016 to 2014. We have standardized result reporting and communication with better care coordination as tracked through chart review. There was improved operational efficiency for our outpatient practice. We standardized referral response and documentation to improve billing accuracy and show a 6% increase in work RVU production/encounter. Achieving PCSP allowed us to qualify for the maximum score for the clinical practice improvement domain of the Merit-based Incentive Payment System of The Medicare Access and CHIP Reauthorization Act (MACRA).

Conclusion: PCSP is a set of national standards to guide specialty practice improvement. By transforming our operations and achieving NCQA recognition for PCSP, we achieved improvement in access, care coordination, patient experience and production.
PREVALENCE OF ASYMPTOMATIC PERIPHERAL ARTERIAL DISEASE BY ANKLE BRACHIAL INDEX AND ITS CORRELATION TO ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) RISK ESTIMATE AMONG PATIENTS IN A PRIVATE TERTIARY HOSPITAL IN PASAY CITY, PHILIPPINES: A PROSPECTIVE ANALYTICAL STUDY
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Introduction: Peripheral Arterial Disease (PAD) is a form of atherosclerotic disease that confers a cardiovascular (CV) risk equivalent to that of coronary heart disease and is associated with increased risk of amputation, major cardiovascular events and even deaths. Majority of population is asymptomatic, hence usually under diagnosed. Objective: To determine the prevalence of PAD among asymptomatic patients at Private Tertiary Hospital in Pasay City and to describe the Atherosclerotic Cardiovascular Disease (ASCVD) Risks Estimate and its correlation with severity of PAD using Ankle Brachial Index (ABI).

Methods: This is a Prospective Cross-Sectional Study of Outpatient and Admitted Patients at Private Tertiary Hospital in Pasay City from March 1, 2016 - October 31,2016. Demographic profile, co-morbidities and CV risk determined. Measurement of ABI using Doppler Ultrasound was done and correlated to the patients ASCVD Risk Estimate.

Results: A total of 138 subjects were included in the study, 20.3% (n=28) had PAD, 39% (n=18) had mild to moderate PAD and 22% (n=10) had non-compressible arteries. Mean age was 56.68 years and most of them were females (55.8%). Patients aged >75 showed three-fold increase in the incidence of PAD. The most common comorbidities noted were hypertension (72.3%) and diabetes (38.9%), but none of the risk factors showed positive correlation with PAD. ASCVD Risk Estimate (10 year risk) of patients was significantly higher among patients with PAD than those without PAD with 28% and 17.9% respectively.

Conclusions: The study showed that prevalence of asymptomatic PAD is 20.3% using ABI. There was a significant direct correlation between the presence and severity of PAD with ASCVD Risk Estimates. No noted significant correlation between PAD and Cardiovascular Risk factor in this study. Incorporating the ABI into routine screening might help address the problem in under-diagnosing the population that is high risk for major cardiovascular events.
MAKING THE DECISION TO QUIT SMOKING: IMPACT OF INTERACTIVE AND EDUCATIONAL VIDEO APPLIED IN POPULATION WITH MULTIMORBIDITIES

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Introduction: The epidemiological transition has progressively made the most prevalent chronic diseases over the last century, with cardiovascular diseases, diabetes mellitus and neoplasias with smoking as a preventable risk factor. Brazil has a prevalence of 12.9 to 25% of its smoking population, which increases the risk of morbidity and mortality and reduces life expectancy. In this scenario, encouraging smokers to quit is one of the most cost-effective interventions available in clinical practice.

Objectives: To evaluate intervention through an electronic tool, designed to motivate smokers to make the decision to stop smoking.

Methodology: Prospective, randomized study evaluating patients in the waiting room of the Hiperdia Minas Center in Juiz de Fora/ Brazil, aimed at the care of hypertensive, diabetic and chronic renal patients with high cardiovascular risk, from 05/2016 to 02/2017, in your initial consultation in the service. In those who reported being smokers, two groups were divided: Intervention Group (GI), using an interactive and educational video about smoking and Control Group (CG), using a basic approach to smoking. All participants were invited to participate in smoking cessation groups in the service (UAI-T).

Results: Sixty-six smokers, 50% in GI and 50% in GC, 64.7% of them female; 63.5%, with a low level of schooling. Regarding smoking history and comparing GI with CG, we observed that users smoked significantly more cigarettes/ day (p <0.005) in the GI, and there were no statistical differences between the interest and the confidence to stop the addiction in both groups. When assessing decision making in seeking help for cessation, GI tended to be more significant (p = 0.067), compared to CG.

Conclusion: Alternative interventions to increase motivation to quit smoking should be encouraged and show promise for reaching this goal.
Background: Reciprocal inferior ST depressions in patients with ST elevation anterior wall myocardial infarction have been correlated with the severity of anterior wall ischemia in patients with proximal LAD obstruction. Alternatively, inferior ST depressions may reflect inferior wall ischemia due to co-existing RCA disease. We investigated the relationship between ST depression with the location and severity of luminal narrowing in the LAD, and associated RCA or dominant Cx obstructive atherosclerosis.

Methods: 89 patients with anterior wall myocardial infarctions who underwent coronary angiography within 14 days were selected and admission ECGs were examined. Angiography was evaluated for the location (proximal, mid, or distal) and degree (mild, moderate, or severe) of luminal narrowing. Chi-square test and unpaired t-test were used for statistical analysis.

Results: In our study cohort of patients with anterior ST elevation myocardial infarction, 30 patients (33.7%) presented with inferior ST depression and 22 (24.7%) had severe (~70%) proximal LAD occlusion. Patients with the inferior ST depression were significantly more likely to have a severe proximal LAD luminal narrowing than individuals without ST depression (p=0.013, OR=3.26). Inferior ST depression has a sensitivity of 44.9%, specificity of 80%, and PPV of 73.3% for a proximal LAD occlusion. In contrast, only 10 patients with inferior ST depression had co-existing severe RCA and/or Cx occlusion, which was a much lower probability when compared to patients without ST depression (p=0.43, OR=1.47). Inferior ST depression has a sensitivity of 40%, specificity of 68.8%, and PPV of 33.3% for severe RCA and/or Cx occlusion. There were no significant differences in age (p=0.15), gender (p=0.81), tobacco use (p=0.65), hypertension (p=0.15), or diabetes (p=0.07) between groups.

Conclusion: Inferior ST depression observed in patients with ST elevation anterior myocardial infarction is a stronger predictor of severe proximal LAD luminal narrowing than co-existing RCA and/or Cx disease.
WOMEN FAIL TO RECOGNIZE SYMPTOMS OF MYOCARDIAL INFARCTION LEADING TO DELAYS IN HOSPITAL PRESENTATION

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Objectives: To investigate the reasons for delayed hospital presentation in acute ST segment elevation infarction (STEMI).

Background: Previous studies in patients presenting with an acute STEMI have shown that delays from symptom onset to hospital presentation occur more frequently in women than men. It is not clear whether atypical symptoms and/or a lack of recognition account for the delay seen in women.

Methods: Consecutive patients referred for primary angioplasty for the treatment of an acute STEMI at four New York City Hospitals were interviewed after discharge from the hospitals.

Results: A total of 218 patients were examined (24% female; Women: 68.7 +/- 13.1 years and men: 60.7 +/- 13.8 years). A significantly larger percentage of women than men had atypical symptoms (62% vs 36%, p=0.001). Overall a smaller percentage of women compared to men thought they were having a myocardial infarction (MI) (15% vs 34%, p=0.01). Among patients with atypical symptoms, only 12 (13%) thought they were having an MI. This finding was numerically lower in women than men (6% vs 17%, p=0.14). Furthermore, when examining patients with typical symptoms, only 30% of women compared to 42% of men thought they were having an MI (p=0.30). A total of 97 (46%) of patients had a delay of >120 minutes from symptom onset to hospital presentation (S2P time). A larger proportion of women than men had S2P time >120 minutes (57% vs. 41%, p= 0.04). Women were more likely than men to attribute their delay to a lack of recognition that they were having an MI (74% vs 48%, p=0.02).

Conclusions: Educational campaigns should emphasize the importance of recognizing both typical and atypical symptoms of MI in women, with the goal of shortening S2P times.
TYPE II MYOCARDIAL INFARCTION AND THE RISK OF READMISSION

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Background: Readmission of patients with Type II myocardial infarction (T2MI), an imbalance between oxygen supply/demand in the presence or absence of atherosclerosis, is common, costly, and perhaps preventable. To our knowledge, characteristics associated with readmission of patients with T2MI have not been previously investigated.

Objective: To identify the characteristics of patients readmitted with T2MI.

Methods: We retrospectively studied patients older than 18 years who presented to our health care facilities between 9/2011-12/2015. All patients diagnosed with T2MI (i.e., if the patient had an elevated troponin greater than or equal to 0.05 ng/mL or diagnosis of demand ischemia) were included. We excluded those with troponin greater than 20.0 ng/mL, ST-elevation MI diagnosis, cardiogenic shock, or non-ST-elevation MI with percutaneous coronary intervention, or coronary artery bypass surgery. Logistic regression, two-sample t-test, Chi-square and Fishers exact tests were used for statistical analysis. All tests were performed at a 5% level of significance.

Results: Readmission rate in this cohort of 21,139 was 5,066 (24%). Univariate analysis showed older age and White race (P’s<0.0001), and additionally, increased BMI (P=0.0146), were associated with readmission. Multivariate analysis showed that risk of readmission was significantly more likely in patients with a history of congestive heart failure [OR=3.13, 95%CL(2.88 -3.41),P<0.0001] coronary artery disease [OR=1.90, 95%CL(1.58 -2.29),P<0.0001], chronic obstructive pulmonary disease[OR=1.86, 95%CL(1.66 -2.09),P<0.0001], atrial fibrillation[OR=1.80, 95%CL(1.65 -1.96),P<0.0001], stroke[OR=1.69, 95%CL(1.51 -1.89),P<0.0001], diabetes[OR=1.21, 95%CL(1.11 -1.31),P<0.0001]. Other factors associated with a higher readmission rate were hypertension, hyperlipidemia, anemia, chronic kidney disease, and left ventricular hypertrophy (all P’s<0.0001). Readmission within 30 days of an index episode of T2MI was associated with a higher mortality (22.7% vs. 7.2%, P<0.0001) with OR=3.36, 95%CL (3.07-3.67).

Conclusion: Patients diagnosed with Type II MI are more likely to be older, White, and with multiple co-morbid conditions. Readmission within 30 days of an index event is associated with high mortality.
THE HIGH-DEGREE ATRIOVENTRICULAR BLOCK REMAINS A SEVERE PROGNOSTIC MARKER IN THE PRIMARY PERCUTANEOUS CORONARY INTERVENTION ERA, THE NEXT STEP

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We collected a group of 15 patients with a transvenous temporary atrioventricular sequential cardiac pacing (TAVSCP), all patients suffered an acute myocardial infarction (MI) complicated by a high-degree atrioventricular block (HAVB). We assessed a hemodynamic effect of TAVSCP compared to a ventricular cardiac pacing. The cardiac output (CO), cardiac index (CI) was measured by thermodilution in 7 patients. TAVSCP hemodynamic results: CO = 4.19 ± 0.74 L/min, CI = 2.19 ± 0.31 L/min/m2. Ventricular pacing hemodynamic results: CO = 3.57 ± 0.91 L/min, CI = 1.86 ± 0.40 L/min/m2. TAVSCP resulted in a significantly higher CO by 17%, p < 0.0005, CI was higher by 18%, p < 0.002. HAVB results: CO = 3.40 L/min, CI = 1.76 L/min/m2.

We tested one patient to detect and assess changes in sympathovagal balance caused by the loss of atrioventricular sequence because of complete heart block (CHB). We recorded the intra-cardiac ECG record of consecutive atrial potentials during TAVSCP and CHB, we performed the spectral analysis of atrial heart rate variability: CHB resulted in decrease in vagal activity, Power HF component decreased from 104.0 to 10.3 ms2; Relative Power HF decreased from 63.3% to 35.3%; Ratio LF/HF increased from 0.2381 to 1.1081; Relative Power LF increased from 16.1% to 39.3%.

The restoration of atrioventricular sequence resulted in prompt change in sympathovagal balance, Power HF component increased from 10.3 to 378.4 ms2. Relative Power HF increased from 35.3% to 52.1%, Ratio LF/HF decrease from 1.1081 to 0.5618, Relative Power LF decreased from 39.3% to 29.3%.

Conclusion: TAVSCP is hemodynamically superior to ventricular pacing. CHB produced low CO and changes in sympathovagal balance. These findings deserve further investigation in view of the high in-hospital mortality. I propose to monitor plasma catecholamine levels and measure CO in patients with an acute MI complicated by HAVB.
ONE-YEAR MORTALITY IN TYPE 2 MI: PATIENT CHARACTERISTICS FROM A LARGE CLINICAL SERIES

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Background: Type 2 MI is caused by an imbalance in oxygen supply/demand. Little is known about the patient characteristics associated with Type 2 MI.

Objective: This study aimed to define patient characteristics of Type 2 MI.

Methods: We retrospectively studied patients older than 18 years presented to our health care facilities between 9/2011-12/2015. All patients determined to have Type 2 MI (i.e., if the patient had an elevated troponin greater than or equal to 0.05 ng/mL or diagnosis of demand ischemia) were included. We excluded those with troponin greater than 20.0 ng/mL, ST-elevation MI diagnosis, cardiogenic shock, or non-ST-elevation MI with percutaneous coronary intervention, stent placement, or coronary artery bypass surgery. Hospice discharges were also excluded. Cox proportional hazards model, Chi-squared and Fisher's exact tests were used for statistical analysis for one-year mortality. Hazard ratios (HR) and associated 95% confidence intervals (CI) were also computed.

Results: A total of 21,139 patients [mean age 71 +/- 16 years, females 10,565(49.9%)] fulfilled the study cohort. Univariate analysis showed that one-year mortality (28.5%) was high and associated with older age and White race (P's<0.0001). A history of diabetes (P=0.037), aortic aneurysm (P=0.0008), congestive heart failure, atrial fibrillation, anemia, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD; P's<0.0001) were also associated with one-year mortality. One-year death rate was lower in patients with known history of coronary artery disease (CAD; P's<0.0001). Multivariate analysis showed that anemia (P=<0.0001; HR=1.29, CI[1.22-1.38]), COPD (P=<0.0001; HR=1.26, CI[1.16-1.37]), CKD (P=<0.0001; HR=1.16, CI[1.08-1.24]), and diabetes (P=0.012; HR=1.08 CI[1.02-1.15]) were significantly associated with one-year mortality. Additionally, a five year increase in age increases the risk of one-year mortality (HR=1.15, CI[1.14-1.16]).

Conclusion: Patients with Type 2 MI have several common characteristics which increases their likelihood of one-year mortality and a history of CAD is somewhat protective.
ACUTE MYOCARDIAL INFARCTION AND CHRONIC TOTAL OCCLUSIONS: A NOT SO INNOCENT SILENT GUEST

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Introduction: During acute myocardial infarction (AMI), the presence of chronic occlusive lesions as non-culprit lesions may not provide additional collateral circulation supply to the affected territory and possibly compromise the compensatory contractile activity.

Objective: to evaluate the clinical, procedural characteristics in pts with AMI with multiple vessel disease and at least one non-culprit chronic total occlusions.

Materials and Methods: Between May 2001 and November 2016, 481 primary coronary angioplasty procedures were performed, of which 231 patients (48%) had multiple vessel diseases. They were excluded for the analysis pts with acute coronary syndrome epiphenomenon and those admitted with signs of shock.

Patients who underwent complete revascularization (n= 108, RC group) and patients with incomplete revascularization (n= 79, RIE group) due to stenosis lesions and pts with incomplete revascularization due to chronic occlusive lesions (n= 25, RIO group). The baseline characteristics were RC, RIE and RIO, n(%) respectively: age 58.7±10 vs 60.9±11 vs 61.08±10; female 12(11) vs 6(7) vs 2(8), diabetes 23(21) vs 15(19) vs 4(16); prior infarct 13(12) vs 11(14) vs 5 (20); prior CABG 1(0,9) vs 5(6) vs 4(16) p=0,004; left ventricular function 54,8±0,3 vs 52,7±14 vs 46,9±15 p=0,001; prior PTCA 11(10) vs 10 (13) vs 3 (12); IIbIIIa use 14(13) vs 15(19) vs 4(16), three vessels disease 20(18) vs 25(32) vs 11 (44) p=0,01; anterior infarct 45(42) vs 24(30) vs 8(32); radial access 56(52) vs 9(11) vs 4(16) p=0,002.

Results: at follow up 38,4±32 months was obtained RIE and RIO, n(%) respectively: total mortality 2(1,8) vs 5(6)vs 4(16) p=0,01; cardiovascular mortality 1(0,9) vs 3(4) vs 2(8) p=0,09; re infarct 2(1,8) vs 0 vs 0; coronary re-intervention 15(14) vs 25(32) vs 6(24) p=0,006.Conclusion: patients with AMI and presence of chronic total occlusion as non-culprit lesions presented worse clinical and angiographic profile and at follow-up they obtained higher major adverse cardiovascular events.
OBJECTIVES: To elucidate cardioprotective effects of postconditioning with lactate-enriched blood (PCLeB) in patients with ST-segment elevation myocardial infarction (STEMI).

BACKGROUND: No approach has proven successful in preventing reperfusion injury in clinical settings. We recently reported that PCLeB can be a new approach for preventing reperfusion injury in STEMI patients.

METHODS: Methods: Our modified protocol consists of intermittent reperfusion and timely coronary injections of lactated Ringer’s solution. The duration of each brief reperfusion was prolonged stepwise, from 10 to 60 s. Lactated Ringer’s solution (20-30 mL) was injected directly into the culprit coronary artery at the end of each brief reperfusion. Each ischemic period lasted 60 s. After 7 cycles of balloon inflation and deflation, full reperfusion was performed, followed by stenting.

RESULTS: We treated 66 consecutive STEMI patients (mean age, 65.9 ± 14.1 years, 78.8% men) using PCLeB within 12 h of symptom onset. No patient experienced ventricular tachycardia/fibrillation during reperfusion. The last 11 patients with non-inferior STEMI underwent Holter electrocardiogram during and after reperfusion, which revealed that the mean premature ventricular contraction (PVC) count during the first hour of reperfusion was <4 counts/h without emergence of multiple PVCs. Resumed coronary blood flow was augmented, as indicated by the mean corrected TIMI frame count of 19.7 ± 9.7 (normal value, 21). The mean peak creatine kinase (CK) and CK-MB levels were 2640 ± 2062 and 265 ± 171 IU/L, respectively. No patient died or experienced worsening/new-onset heart failure at 30 days after the onset. Moreover, no patient required continued oral diuretic or inotropic therapy for heart failure upon discharge, including those who required temporary use of a diuretic during the early admission period.

CONCLUSIONS: PCLeB abolished reperfusion-induced arrhythmia, induced augmented microcirculation recovery, and led to zero mortality and no overt heart failure at 30 days after the onset of STEMI.
ACUTE CORONARY SYNDROME: DETECTION, PREVENTION AND TREATMENT

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STRESS-INDUCED THROMBUS: ROLE OF ANTICOAGULATION IN TAKOTSUBO CARDIOMYOPATHY
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Objectives: To determine and compare the incidence of left ventricular (LV) thrombus in patients diagnosed with Takotsubo cardiomyopathy to the rate of stroke in patients with atrial fibrillation, as well as possible need for prophylactic anticoagulation in this patient population.

Background: Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy has a favorable prognosis with expected recovery in weeks. Left ventricular (LV) thrombus is a known complication of Takostubo cardiomyopathy, which can lead to embolization and potentially a stroke. The incidence of LV thrombus and the role of anticoagulation have yet to be fully defined in this condition.

Methods: We performed a search of published literature through SCOPUS, which identified 282 patients with Takotsubo cardiomyopathy in whom the incidence of LV thrombus was reported. In order to contrast this to the current anticoagulation strategy of atrial fibrillation, the occurrence of LV thrombus was compared to the adjusted stroke rate using the CHADS2 score.

Results: Of the 282 patients identified through a literature search, 26 (9.2%) were noted to have a LV thrombus in the setting of Takotsubo cardiomyopathy. The incidence of LV thrombus ranged from 5.3% to as high as 14.0%. When compared to the CHADS2 score the average incidence of LV thrombus in our study equated to a score between 4 and 5.

Conclusion: While the occurrence of LV thrombus in Takotsubo cardiomyopathy is variable among studies, the average incidence remains relatively high. Thus, making LV thrombus a significant complication of stress-induced cardiomyopathy. Prophylactic anticoagulation until recovery may have a role in reducing the rate of LV thrombus. Further studies will be needed to determine the rate of embolization and utility of anticoagulation in Takotsubo Cardiomyopathy.
STEMI IN A PATIENT WITH HIV ASSOCIATED CORONARY ARTERY DISEASE
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Introduction: The exact pathophysiology of atherosclerosis and Premature Coronary Artery disease in HIV patients remains controversial. Multiple hypotheses have been proposed including inflammation from immune activation, direct endothelial damage from viremia, direct effects from antiretroviral therapy itself, and higher prevalence of traditional atherosclerotic risk factors. We report a case of acute MI in an otherwise healthy young patient with HIV secondary to acute coronary thrombus.

Case Description: A 50-year-old Caucasian male with history of HIV on HAART treatment and unremarkable cardiovascular history presented to a tertiary care facility after an episode of syncope. Patient had to be intubated for airway protection. Shortly afterwards he became hypotensive and went into Pulseless Ventricular Tachycardia, requiring multiple shocks with Return of Spontaneous Circulation. While being brought back from an urgent head CT, patient once again became hypotensive shortly followed by sustained pulseless Ventricular Tachycardia. Cardiopulmonary resuscitation was started and patient received multiple rounds of shock therapy. During the code, as a last resort, he received intravenous lytic therapy (tPA). Patient’s rhythm stabilized and a subsequent 12 lead EKG showed 2 mm ST elevation in the anterior precordial leads. Emergent cardiac catheterization via right radial approach was performed. Patient was found to be having a critical mid Left anterior descending artery (LAD) stenosis secondary to coronary thrombus (figure 1). After mechanical catheter based thrombus aspiration a stent was placed in the mid LAD. He was extubated the next day with subsequent discharge home 1 week later.

Discussion: This case illustrates importance of early recognition of Coronary Vasculopathy in HIV patients on HAART therapy. This therapy has been associated with increased inflammation and coagulation disorders. We recommend aggressive treatment for CAD risk factors in such patients as they are at significantly increased risk of MI especially if their CD4 cell count is <200 cells/mm3.
ARRHYTHMIA II: SUDDEN CARDIAC DEATH / ADVANCES IN IMPLANTABLE RHYTHM DEVICE THERAPY

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A NOVEL RYR2 P.R420W MUTATION CAUSING SUDDEN CARDIAC DEATH IN FAMILIES WITH CPVT
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Objective: To determine the effect of the RYR2 p.R420W mutation on survival in a three pedigree population.

Background: Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a cause of sudden cardiac death (SCD). We have ascertained a putative founder mutation in RYR2 (p.R420W).

Methods: Retrospective chart review of individuals with RYR2 p.R420W mutation and family members. Individuals born at a-priori 50% risk from three pedigrees segregating RYR2 p.R420W were ascertained (n=79). Individuals were included if disease status of ≥50% of their sibship was known (n=66). Affected individuals included mutation positive, obligate carriers (OC) and/or documented SCD <50 years. Unaffected status was defined as mutation negative. Remaining individuals were unknown (UK). All genetic and clinical data available on included individuals was collected. Of 66 included individuals, 33 (50%) were affected (16 mutation positive, 6 OC and 11 SCD) and 26 (39%) were unaffected. Time to death was compared using Kaplan-Meier time-to-event analysis and multivariate Cox regression.

Results: Affected status was significantly associated with mortality: RR = 4 (95% CI: 1.1-14.5) and affected males died earlier than females RR=7 (95% CI: 1.5-34.5). When infant deaths are included mortality is increased in the affected group: RR=6, (95% CI:1.7-20.4). Median survival in males with RYR2 p.R420W was 50 years (95% CI: 5.5-94.5), when infant deaths are included survival was 19 years (95% CI: 14.1-24.1). Median survival in females with RYR2 was 76 years (95% CI: 37.7-115.2). Six deaths under age 10 were found.

Conclusions: The RYR2 p.R420W mutation significantly affects mortality, with a clear sex-influence. Survival in affected males is significantly decreased compared to affected females. Deaths under age 10 raise concern for this mutation as a cause of sudden infant death.
OUTCOMES IN QUADRIPOLAR VS BIPOLAR LEFT VENTRICULAR LEADS IN CARDIAC RESYNCHRONIZATION THERAPY (CRT): A META-ANALYSIS OF SEVEN STUDIES
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Introduction: Traditionally, CRT has been performed with use of a bipolar left ventricular (LV) lead. Recent technological advances have led to the development of a quadripolar LV lead to allow multi-point pacing (MPP). The objective of our meta-analysis is to compare outcomes for bipolar Vs quadripolar left ventricular lead for CRT.

Methods: PubMed database was searched through December 2016. Two randomized controlled trials (RCTs) and five studies (n= 25,949) comparing CRT with Quadripolar lead (QL) (n=19,798) Vs Bipolar lead (BL) (n=6151) for CRT were included. End points were mortality, LV lead issues (replacement, repositioning, deactivation), phrenic nerve stimulation, procedure failure, and fluoroscopy time. The odds ratio (OR) or mean difference (MD) with 95% confidence interval (CI) was computed and p<0.05 was considered as a level of significance.

Results: Mortality was significantly lower for QL compared to BL (OR 0.60, CI 0.54-0.67, p < 0.00001. LV lead issues were significantly lower with QL (OR 0.54, CI 0.35-0.84, p = 0.007). Phrenic nerve stimulation was noticeably lower in QL with OR 0.40, CI 0.15-1.09, p=0.07. Procedure failure was not significantly different for QL compared to BL (OR 0.74, CI 0.48-1.12, p=0.16). Fluoroscopy time was lower for QL with MD 2.91, CI -6.01-0.18, however did not achieve statistical significance with p=0.07.

Conclusions: With the development of quadripolar lead to allow multi-point pacing for CRT, there is increasing interest towards the comparison of these left ventricular leads. The results of our meta-analysis showed significantly reduced mortality and lower left ventricular lead issues with quadripolar left ventricular leads. Phrenic nerve stimulation, procedure failure and fluoroscopy time were also lower for QL, however did not achieve statistical significance.
ARRHYTHMIA II: SUDDEN CARDIAC DEATH / ADVANCES IN IMPLANTABLE RHYTHM DEVICE THERAPY

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BETTER THAN YOU THINK: APPROPRIATE USE OF IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS AT A SINGLE ACADEMIC CENTER

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Background: Some are concerned about overuse of implantable cardioverter-defibrillators (ICD); one estimate suggested that 23% of primary prevention ICDs were not evidence based. Appropriate use criteria (AUC) for ICD implantation have since been published, however the data on application of AUC to real-world patient populations are sparse.

Objective: To determine the prevalence of rarely appropriate ICD implantation at our facility and compare this to previously published estimates.

Methods: We reviewed 286 patients undergoing ICD implantation between March 2013 and March 2016. Appropriateness of each ICD implantation was rated based on AUC.

Results: Of 286 ICDs implanted, 90% were “appropriate”, 6% “may be appropriate”, 1% “rarely appropriate” and 3% had no listed indication. Patients with secondary prevention indications were more likely to go unrated (9.0% vs. 3.5% overall, p=0.038) due to unique situations like transplant vasculopathy and rare genetic disorders.

Conclusion: Compared to prior registry data reports, the prevalence of rarely appropriate ICD implantation at our facility was very low. The AUC could be improved by adding additional secondary prevention indications. Our comparatively high appropriate use rate may be explained by improved patient selection after the AUC release or more likely that the existing evidence-based guidelines do not adequately reflect current accepted electrophysiology practice.
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SUDDEN CARDIAC DEATH (SCD) AND SUDDEN UNEXPLAINED DEATH (SUD) IN NEWFOUNDLAND AND LABRADOR: A 10 YEAR RETROSPECTIVE STUDY
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Background: Sudden cardiac death (SCD) is the unexpected termination of life in previously healthy individuals, in which autopsy confirms a cardiac etiology. Sudden unexplained death (SUD) has negative autopsy findings, where malignant arrhythmias remain the most likely cause. All these cases are referred to the medical examiner (ME), which in Newfoundland and Labrador (NL) is a centralized system with full ascertainment. SCD/SUD in young people is a catastrophic event and is likely related, at least in part, to the action of underlying mutations. Several founder mutations in multiple genes which cause SCD, have been identified in NL.

Objectives: a) create a database with all deaths referred to the medical examiner (ME) in NL between 2-50 years during the period 2004-2013, excluding homicide and suicide; b) classify the SCD/SUD cases based on sex, age and cause of death; and c) determine the incidence of SCD and SUD.

Methods: This is a retrospective population-based study in NL for ME cases between the years (2004-2013) categorized as “natural”, “accident”, or “undetermined”, all of which were ascertained, reviewed and classified by the research team.

Results: Out of a total of 1152 ME cases, 386 SCD/SUD cases were ascertained. The annual incidence rate was 12 per 100,000 person-years (approximately three SCD/SUDs per month), with a male to female ratio of 3:1 (p<0.0001). The incidence of SCD/SUD gradually increased with age. The incidence of SUD was 2 per 100,000 persons-years, and accounted for most of these deaths in people ≤29 years (p<0.0001) while coronary artery disease was predominant among people ≥30 (p<0.0001).

Conclusion: In the NL cohort of deaths (between 2-50 years) reported to the ME, high incidence rates of SCD and SUD were reported. There was a trend towards more arrhythmogenic deaths in the young which may reflect underlying cardiac mutations in NL.
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STAPLING FOR WOUND DEHISCENCE AFTER CARDIAC IMPLANTABLE ELECTRONIC DEVICE IMPLANTATION

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Background: Wound dehiscence (WD) has been reported as a complication in 0.3% of Cardiac Implantable Electronic Device (CIED) procedures. Stapling has not been reported as a treatment modality for WD.

Objective: We report our single center experience of WD 759 cardiac device procedures between 2009 and 2016.

Methods: Retrospective chart review of all patients who underwent CIED implantation between 2009 and 2016.

Results: There were a total of 10 patients with WD (1.1%), majority (80%) were female. 4 (40%) had diabetes and one patient was immune-compromised due to recent chemotherapy. WD occurred in 6 patients after generator change, 2 patients after a biventricular device upgrade, 1 patient after biventricular ICD implantation and in 1 patient after subcutaneous ICD implantation. Median time to WD was 5 weeks post procedure (3-11 weeks). In all patients, wound stapling was performed under sterile conditions after administering intravenous narcotic analgesics. 6 patients received intravenous antibiotics and all patients received at least two weeks of oral antibiotics. Blood cultures were negative in all patients. However, wound cultures in 5 patients were positive. Staples were removed in two weeks in all patients. Figure 1 demonstrates WD (Fig 1A), staples covering the dehiscence (Fig 1B) and complete wound healing (Fig 1C). All of these patients were successfully treated with stapling and none of the devices required extraction.

Conclusion: Stapling under sterile conditions may be an acceptable treatment strategy for management of device WD. This procedure can be performed as outpatient and can help avoid unnecessary device extraction.
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2 CASES OF PACEMAKER DERMATITIS INDUCED BY BACKPACK STRAP FRICTION
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The cause of pacemaker dermatitis is regarded as compression of the skin by generator itself. There are very few reports of pacemaker dermatitis apparently caused by external stimuli such as seatbelt injury. We previously reported pacemaker dermatitis on patient with no obvious risk factors and dermatitis was caused by backpack strap friction. Careful observation of patients of pacemaker infection who referred to our institute for device explantation, we found another pacemaker dermatitis with backpack strap friction. The patient was 71 year-old female without risk factors which previously reported such as diabetes, hypertension, dyslipidemia, chronic kidney disease or thin skin. Her device was almost completely exposed from pocket. Her injury site resembled our former reported case. Both cases had similar episode which they used heavy backpack in daily life. First case he used 5 to 10 kg backpack while walking 3 times in a week. Second case she was carrying 5kg of rice bag in few months each when she went shopping at supermarket. Both patients had similar alignment of injury which was upper site of device and lateral to bottom part of pocket where the backpack strap across.
There were no reports except ours about influence of backpack strap on pacemaker implanted patients. Here we report 2 cases of pacemaker dermatitis induced by backpack strap friction due to its clinical importance. It is astonishing that patient’s daily habit could cause serious complication after pacemaker implantation even in remote period. We should pay more attention to patient’s daily habits to avoid this preventable complication.
ARRHYTHMIA II: SUDDEN CARDIAC DEATH / ADVANCES IN IMPLANTABLE RHYTHM DEVICE THERAPY

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Background: Temporary cardiac pacing is a life-saving maneuver in patients with severe conduction abnormalities. Non active-fixation leads placed on the right ventricular endocardium have been used for many years for trans-venous pacing. Patients have to remain on telemetry and ambulation is restricted due to the potential for loss of capture. More recently researchers adapted screw-in leads (first report in 1999 by Martin et al) for temporary pacing. This is known as a temporary-permanent pacemaker (TPPM) or semi-permanent pacemaker, and appears to minimize loss of capture.

Methods: We performed a literature search using PUBMED, Google scholar and Clinical Key. Most articles found were case reports and case series. The keywords used for our search were temporary permanent pacemaker, external permanent pacemaker, active fixation lead, hybrid pacing, temporary permanent generator, prolonged temporary trans-venous pacing, and semi-permanent pacemaker.

Results: 24 studies with 770 patients were included in our review. The age group was primarily above the sixth decade of life. Only 2 studies had a control group. Indications for pacing included device infection, sick sinus syndrome, atrioventricular block, ventricular tachycardia, and bradyarrhythmias associated with systemic illness. The duration of use of TPPM varied from a few days up to 336 days. A total of 18 (2.3%) TPPM-related infections were reported. Loss of capture was documented in only 8 patients (1.0%). Death occurred in 84 patients (10.9%), and all appeared secondary to underlying critical illness. Complication rate varied from 0 to 30.6%, with the highest rates reported in studies that used femoral venous access.

Conclusions: The compilation of data suggests that TPPM are a safe approach to trans-venous pacing with a low incidence of infection and loss of capture. Mortality rate seems to be driven by the underlying illness. When possible screw-in lead pacemakers should be used for temporary pacing.
ARRHYTHMIA II: SUDDEN CARDIAC DEATH / ADVANCES IN IMPLANTABLE RHYTHM DEVICE THERAPY

TORSADES DE POINTES IN THE SETTING OF IVABRADINE
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Introduction: Ivabradine is indicated for treatment of chronic angina and heart failure. We report polymorphic ventricular tachycardia occurring in a patient on ivabradine hypothesized to be secondary to medication interactions.

Case Description: A 29 year old female with post-partum dilated cardiomyopathy, persistent NYHA class III symptoms, reduced ejection fraction of 15% despite optimal medical treatment underwent an ICD implantation. Medications were lisinopril, metoprolol, furosemide and spironolactone. Symptomatic angina and sinus tachycardia continued. Ivabradine was initiated and later increased for better heart rate control. One month later she presented after two syncopal events, chest pressure and dyspnea. Cardiac enzymes were 0.361 ng/ml. (reference <0.034 ng/ml.) Cardiopulmonary arrest occurred from ventricular fibrillation, requiring resuscitation. Investigation revealed normal coronaries and appropriate ICD discharges. ICD tracings showed pauses of 1200-1500msec associated with a prolonged QT interval causing torsades de pointes (TdP) degenerating to ventricular fibrillation. It was felt that ivabradine caused TdP due to medications that enhanced its arrhythmogenic effect (furosemide), and slowed the heart rate further (beta blocker).

Case Discussion: Ivabradine acts on If channels in the sinus node. Being voltage dependent, it’s more effective at faster rates. Because of its selectivity for If, it has no effect on P, PR or QRS duration. While it effects QT interval during bradycardia, the corrected QT (QTc) remains unchanged. Case reports exist of torsades when ivabradine was administered with QT prolonging medications. Prolonged QT can lead to premature ventricular contractions and when occurring on a proceeding T wave, cause compensatory pauses that precipitate torsades. Studies of If inhibitors show proarrhythmic effects at higher doses. Furosemide increases the arrhythmogenic property of ivabradine by preventing its metabolism and causing electrolyte imbalance. Our patient experienced polymorphic ventricular tachycardia, degenerating into ventricular fibrillation due to a prolonged QTc from concomitant use of ivabradine, metoprolol and furosemide.
RECURRENT CONTACT DERMATITIS SECONDARY TO ADHESIVE TAPE AND DERMAFOND USE AFTER PACEMAKER PROCEDURE

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Introduction: Contact dermatitis (CD) has been reported as a result of reaction to pacemaker components and/or silicon leads. We present a case of recurrent CD as a result of reaction to adhesive tape (AT) and Dermabond.

Case presentation: An 81-year-old woman with a dual-chamber pacemaker underwent generator change. Dermabond was applied after wound closure as well as Medipore AT. At 1 week wound check, she reported pruritus and redness (Fig 1A), similar to a reaction following initial implant 5 years ago. 2.5% hydrocortisone cream was started with the presumptive diagnosis of CD. The wound soon developed hemorrhagic crusting with serous discharge (Fig 1B). Due to concern for wound infection, she was hospitalized and started on IV antibiotics. Dermatology felt this was CD due to AT used after surgery and exam findings were a result of the healing process with low likelihood of infection. Cultures were negative and incision improved with Triamcinolone ointment and Vaseline (Fig 1C). However, Dermabond was later re-applied after suture removal, causing recurrence of CD (Fig 1D). 2.5% hydrocortisone cream was continued for 1 more week leading to complete resolution and a well-healed incision site (Fig 1E).

Discussion: AT is notorious for causing CD. However, Dermabond induced CD has been sparsely reported, as 2-octyl-cyanoacrylate, which is contained in Dermabond, degenerates slowly, unlike short-chained formulations. In our patient, Dermabond definitely caused the second flare of CD because AT was not re-applied. With increasing use of Dermabond, providers should be aware of this allergic reaction and limit repetitive application of this agent.
VENTRICULAR FIBRILLATION STORM: AN UNCOMMON PRESENTATION OF IDIOPATHIC HEART BLOCK

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Introduction: Ventricular fibrillation (VF) is known to occur commonly in the setting of organic heart disease most often, myocardial infarction resulting from coronary stenosis. However, recurrent VF is less frequently encountered with heart block. We present a case of recurrent VF in a middle-aged female with idiopathic second degree atrioventricular block (AVB) without coronary artery disease.

Case Presentation: A 48-year-old African-American female with a medical history of hypertension presented to the emergency department following a syncopal episode. During her hospital stay, she had repeated episodes of VF, cardiopulmonary resuscitation and achieved return of spontaneous circulation each time. Her electrocardiogram showed sinus rhythm with 2:1 AVB. She had no electrolyte abnormalities. Echocardiogram showed normal left ventricular systolic function. Cardiac catheterization showed normal coronary arteries. Electrophysiology study, cardiac magnetic resonance imaging and a cardiac biopsy did not reveal any abnormalities. She eventually had a dual chamber automatic implantable cardioverter-defibrillator (AICD) placed with pacing set at 60 bpm. She had complete resolution of her VF. On follow up, she had no further episodes of VF on AICD interrogation.

Discussion: Our patient had recurrent VF arrest due to bradycardia resulting from 2:1 AVB. She had an exhaustive work-up that revealed no abnormalities. Her AVB was surmised to be idiopathic as no clear cause was found.

Conclusions: VF storm is a potential but rare occurrence in patients with idiopathic AVB. Prompt identification of VF arrests and early institution of resuscitative measures can be lifesaving. Transcutaneous and transvenous pacing are temporary measures to control the heart rate and should only serve as a bridge to definitive therapy which includes permanent pacemaker or ICD implantation.
MECHANISMS AND MANAGEMENT OF HEART FAILURE IN 2017: HOW CAN WE DO BETTER?

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DIASTOLIC HEART FAILURE AND ATRIAL FIBRILLATION, THE TWIN-EVIL EPIDEMIC IN THE ELDERLY

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Diastolic heart failure and atrial fibrillation, the twin-evil epidemic in the elderly
Left ventricular diastolic dysfunction (LVDD) and atrial fibrillation (AF) are becoming increasingly prevalent in the elderly population. Furthermore, LVDD and AF act as co-conspirators to perpetuate the vicious cycle of diastolic heart failure and contribute to significant morbidity and mortality. This ‘twin-evil’ have become the bane of the aging population affected by diastolic heart failure. Left atrial enlargement associated with LVDD has been reported as an independent predictor of atrial fibrillation. Oftentimes, these patients with AF and LVDD have severe bi-atrial dilatation surpassing the size of ventricles. Mitral and tricuspid regurgitation and pulmonary hypertension are frequently associated with these patients. Thus, their cardiac output is significantly reduced despite their normal LV contractility and therefore the intractable heart failure. While drug therapy has a modest role, newer treatment strategies are being actively explored. Genetic substrate may make certain populations vulnerable to LVDD and AF. However, preventive life style measures with diet and regular exercise at a younger age may prevent these conditions. Among those patients with diastolic CHF associated with LVDD and AF, simple catheter based AF ablation to maintain sinus rhythm or alternatively AV nodal ablation with biventricular pacer implantation have been reported to improve their morbidity and prognosis.
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BLOOD UREA NITROGEN REFLECTS THE COMPLEXITY OF CARDIORENAL INTERACTIONS IN HEART FAILURE

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The non-osmotic release of arginine-vasopressin, concurrent with activation of the sympathetic nervous system and renin-angiotensin-aldosterone system are thought to represent the maladaptive response that is central to the pathophysiology of heart failure (HF). The degree of neurohormonal activation correlates with the severity of the disease and can predict the outcome. However, quantification of components of neurohormonal axis (e.g. serum arginine vasopressin level) is mainly reserved for research purposes rather than routine practice. The results of several recent HF trials have shed light on the differential role of blood urea nitrogen (BUN) and creatinine in predicting the outcomes. These studies suggest that BUN could indeed represent a surrogate marker for “renal response” to neurohormonal activation in this setting, beyond and above its role in estimation of renal function. In this talk, the relevant physiologic mechanisms underlying urea transport in the kidney are first reviewed. Then the activation of neurohormonal axis and the impact of its components on renal urea transport, independent of changes in renal function, are explained. A number of more recent studies that have evaluated the differential role of BUN as a prognostic marker will be discussed. Finally, the unique role of BUN as a biomarker of neurohormonal activation in the setting of HF, and the potential clinical implications of this novel concept is emphasized.
Several new treatments and management strategies have been developed for heart failure in the last 10 years and are now approved for use in many countries. These therapies (sacubitril/valsartan, pulmonary pressure sensor monitoring and ivabradine) now have recommendations for use in clinical practice guidelines. New and improved versions of ventricular assist devices are also now available. However, the cost of these therapies is higher than established heart failure treatments, and it is unclear if the benefit is worth the cost. Cost-effectiveness studies based on clinical trial data suggest that these therapies vary markedly in their cost-effectiveness (between US$ 50,000 to 200,000 per life-year gained). The World Health Organization recommends labeling treatments as poor value if they cost more than 3 times a country’s gross domestic product (GDP) per capita ($57,000 in the US). Many countries would consider these treatments a poor value. In contrast, most established therapies (e.g. beta-blockers, angiotensin converting enzyme inhibitors and mineralocorticoid antagonists are now so inexpensive that they are a high value for almost all health systems.
STATIN MODIFIES THE ASSOCIATION OF FISH CONSUMPTION WITH RISK OF HEART FAILURE: THE PHYSICIANS’ HEALTH STUDY

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Background: While previous studies have reported a lower risk of heart failure (HF) with fish intake or omega-3 fatty acids, it is unclear whether statin modifies the fish-HF relation.

Objective: To test the hypothesis that statin modifies the association of fish consumption with HF risk in male physicians.

Methods: A prospective cohort of 19,020 participants from the Physicians’ Health Study. Frequency of fish consumption was assessed between 1999 and 2002 using a food frequency questionnaire and HF was ascertained through annual follow-up questionnaires with validation in a subsample. We used Cox regression to estimate multivariable adjusted hazard ratios of HF.

Results: During a median follow-up of 11.3 years, 930 cases of HF occurred. The mean age at baseline was 66.4 ± 8.4 years and 34.7% of subjects were using statin. Fish intake was associated with a lower risk of HF only in men using statin: multivariable adjusted hazard ratios (95% CI) were: 1.0 (ref), 0.63 (0.42-0.96), 0.55 (0.37-0.82), and 0.54 (0.36-0.81) for fish consumption of <1/Mo, 1-3/Mo, 1/week, and 2+/week, respectively, among men receiving statin treatment (p for linear trend: 0.015), after adjustment for age, BMI, alcohol use, smoking, exercise, and history of coronary artery disease, hypertension, diabetes, and atrial fibrillation (p interaction statin x fish intake 0.009). In a secondary analysis, we observed an inverse and nonlinear relation between dietary marine omega-3 fatty acids with HF [HR (95% CI): 1.0 (ref), 0.70 (0.50-0.99), 0.89 (0.64-1.23), 0.68 (0.48-0.96), and 0.78 (0.56-1.07) across consecutive quintiles of dietary omega-3 fatty acids] among men using statin and no relation in men not using statin (p interaction statin x dietary omega-3 = 0.08).

Conclusions: Our data suggest that statin modifies the association of fish consumption and dietary marine omega-3 with HF risk by statin in US male physicians.
Hypertrophic obstructive cardiomyopathy is an inherited myocardial disease defined by cardiac hypertrophy (wall thickness >15mm) that is not explained by abnormal loading conditions, and left ventricular obstruction >30mmHg. Typical symptoms include dyspnoea, chest pain, palpitations, and syncope. The diagnosis is usually suspected on clinical examination and confirmed by imaging. Some patients are at higher risk of sudden death, heart failure, and atrial fibrillation. Patients with a higher risk of sudden death undergo cardioverter-defibrillator implantation, in patients with severe symptoms related to obstruction, septal reduction therapy (myectomy or alcohol septal ablation) is recommended, and a life-long anticoagulation is indicated after the first attack of atrial fibrillation.
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KETOGENIC SIGNALING AND BDH1 AS EARLY BIOMARKERS OF DCM

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The myocardium is designed to utilize distinct substrates to generate energy in the form of ATP to support function. While in the normal adult myocardium fatty acids account for greater than 70% of substrate fuel, the heart has a remarkable capacity to adapt and utilize glucose, lactate or ketones depending on conditions and substrate availability. Certainly, changes in fatty acid oxidation and glucose metabolism have been noted in heart failure although the underlying causes to these changes remain multifactorial. Recent data indicate enhanced ketone body oxidation in mouse models of heart failure. Further, in human heart failure an increase in the utilization of the ketone beta hydroxybutyrate as well as an increase in the expression of the gene encoding the ketogenic enzyme beta-hydroxybutyrate dehydrogenase (BDH1) was evident. Thus it appears that ketone metabolism is enhanced in heart failure and this may be an important adaptation to support function. Interestingly, in a mouse model of dilated cardiomyopathy (DCM) we noted ~900% increase in the protein levels of BDH1 as early as postnatal day one while it was undetectable at this age in myocardium from wild type (wt) littermates. Further, BDH1 protein levels were similar in adult myocardium from DCM and normal mice although the DCM mice were exhibiting heart failure. It is notable that ketones can serve in cell signaling to modulate expression of enzymes and proteins involved in communication. The levels of connexin 43 which is involved in cardiomyocyte communication were much reduced at postnatal day one in DCM mice. We suggest that the early postnatal upregulation of BDH1 impacts ketone signaling to deregulate connexin 43 levels leading to the observed DCM. Hence BDH1 may be an important early biomarker for DCM.
SEX DIFFERENCES IN BIOMARKERS OF HEART FAILURE

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2. Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
3. Mayo Clinic, Rochester, MN, USA

Background: Our preclinical animal and preliminary clinical data indicate that sex differences exist for a number of sera biomarkers of heart failure in myocarditis and acute dilated cardiomyopathy (DCM) patients. We have found that sex differences exist for sST2, vitamin D, vitamin D binding protein and interleukin-1 receptor antagonist, for example, that correlate to markers of heart failure like low ejection fraction and New York Heart Association (NYHA) class in a sex-specific manner.

Objectives/Methods: In this study we examined whether sex differences existed in 1) sera biomarkers that predict poor cardiac function/heart failure and 2) whether sera biomarkers correlated to % ejection fraction, NYHA class, BNP/NT-proBNP and/or CRP by sex and age (i.e., menopause status in women using age 50 as a cut off) in men and women with myocarditis or acute DCM. We also examined these parameters in a mouse model of coxsackievirus-induced myocarditis/DCM.

Results: We have found that sex differences exist for all heart failure biomarkers that we have examined so far in the mouse model and in patients. For sST2, only men drove the association of sST2 and NYHA class, with women’s levels of sST2 below those of men. A similar result was observed in the mouse model with higher levels of sST2 correlating to low ejection fraction in mice with myocarditis. Interestingly, sera sST2 levels were increased past age 50 in both men and women. In contrast, circulating vitamin D levels display sex differences but an inverse relationship exists for vitamin D compared to % ejection fraction or NYHA class in men and women or male and female mice with myocarditis.

Conclusions: These findings highlight the critical importance of examining biomarkers of heart failure in the context of sex and age as we adopt a more personalized medicine approach to healthcare.
DIFFERENTIAL ROLES OF MITOPHAGY IN THE HEART UNDER FASTING AND DIABETIC CONDITIONS
New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY, USA

Mitochondria not only provide energy for cardiac contraction but also regulate the survival and death of cardiomyocytes. A pool of healthy mitochondria is maintained by several coordinated quality control mechanisms including mitophagy, a process that degrades dysfunctional mitochondria through the autophagy-lysosome pathway. Mitophagy is cardioprotective under certain conditions but may become detrimental when over-activated. In this study, we investigated the functional significance of mitophagy in the heart under either fasting or diabetic conditions. We used a novel mitophagy reporter transgenic mouse line to determine cardiac mitophagy flux in the presence and absence of lysosome inhibitors. A 24-hour fasting increased mitophagy flux in the heart, which was accompanied by increased LC3-II protein levels in the mitochondrial fractions, suggesting that 24-hour fasting enhanced mitophagy. Surprisingly, the 48-hour starvation did not further increase mitophagy. Instead, it reduced it as compared to 24-hour fasting and normal feeding. In addition, mitophagy flux was diminished in the type 1 diabetic mouse heart, which was associated with increased mitochondrial fragmentation. Overexpression of the E3 ligase Parkin, a positive regulator of mitophagy, restored mitophagy but impaired cardiac function after 48-hour fasting, suggesting that reduced mitophagy is an adaptive response essential for maintaining cardiac function during starvation. In contrast, Parkin overexpression increased mitophagy flux in the diabetic heart and attenuated diabetic cardiac injury, demonstrating a protective role of mitophagy in the diabetic heart. Collectively, these results suggest that mitophagy could be either protective or detrimental to the heart, and the functional role of cardiac mitophagy in different contexts must be individually determined.
IMPROVEMENTS IN BIVENTRICULAR CARDIAC MECHANICS NOTED IN PATIENTS WITH AL AMYLOIDOSIS AFTER STEM CELL TRANSPLANTATION

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Objectives: 1) Utilize strain imaging to assess the degree of cardiac organ response in patients with primary amyloidosis (AL) treated with autologous-hematopoietic stem cell transplantation (auto-HCT). 2) Determine if strain patterns correlate with serum biomarkers. 3) Assess whether strain patterns predict clinical improvement.

Background: AL amyloidosis is characterized by extracellular deposition of insoluble protein fibrils often with multisystem organ involvement. 2D-echo and strain imaging offer non-invasive modalities for identifying early cardiac changes in patients with AL amyloidosis, especially in those with renal dysfunction in whom serum biomarkers may be less reliable.

Methods: Seven patients with AL amyloidosis treated with a Melphalan based myeloablative regimen and Auto-HCT were evaluated retrospectively. 2D-echo was obtained up to 36-days before and within 14-months after treatment. Strain imaging was performed using EchoInsight. NYHA functional classification and Mayo staging were determined for each patient. Statistical analysis was performed using SPSS.

Results: Median follow-up from transplant was 47.4 months with one death at 20.4 months. Mean NYHA classification decreased from 2.3 to 1.9 after transplant. Longitudinal, radial and circumferential left ventricular strain (LV) were evaluated, but only the global longitudinal strain (GLS) showed an improvement (baseline -14.69%; follow-up -16.84%; mean absolute improvement 2.15%; p < 0.05). Right Ventricular Free-Wall Strain (RVFWS) showed a mean absolute improvement of 6.2% (p < 0.05) in patients with stable NYHA classification. There was no difference in left ventricular ejection fraction (LVEF) before and after treatment.

Conclusions: This study demonstrates a clinically meaningful improvement in cardiac mechanics one year after Auto-HCT, which may prove useful in assessing cardiac organ response in AL patients with renal dysfunction when serum biomarkers are less reliable. We also show evidence that changes in left ventricular GLS may occur independent of pre-transplant Mayo stage and that improvements in RVFWS may predict clinical improvement while LVEF may not track with clinical changes.
OBJECTIVE: Assess in-hospital mortality among patients with Takotsubo Cardiomyopathy and psychiatric diagnoses.

BACKGROUND: Takotsubo Cardiomyopathy (TCM) is characterized by reversible wall motion abnormalities without corresponding coronary disease, often in response to medical illness or stress. Studies examining in-hospital mortality among psychiatric patients are scarce.

METHODS: This is a retrospective chart review of 61 patients diagnosed with TCM at the University of Arizona between 2010-2015 with negative cardiac angiography and/or resolution of wall motion abnormality without coronary intervention. In-hospital mortality in patients with psychiatric diagnoses was compared to patients without psychiatric conditions. Age, gender, troponin, brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF) impairment <30%, and illness severity (a composite of intubation, pressor therapy, and/or electrical defibrillation/cardioversion) were also compared.

RESULTS: Using Pearson's chi-squared analysis and unpaired t-testing, patients with psychiatric conditions have a significantly higher in-hospital mortality rate than those without psychiatric conditions (12% vs 0%, p =0.03). Severity of illness, LVEF impairment, BNP, troponin, age and gender do not significantly differ (Table 1).

CONCLUSION: Underlying psychiatric disorders are associated with higher in-hospital mortality independent of illness severity, LVEF, cardiac biomarkers, age and gender. Further research is needed to evaluate the increased mortality of TCM patients with psychiatric comorbidity.

Table 1. Comparison between Takotsubo Cardiomyopathy patients with and without prior psychiatric diagnoses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with prior psych diagnosis (n=25)</th>
<th>Patients without prior psych diagnosis (n=36)</th>
<th>Difference with p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>63.4 +/- 17.1</td>
<td>65.0 +/- 12.6</td>
<td>1.6 p = 0.6753</td>
</tr>
<tr>
<td>Female Gender</td>
<td>22 (88%)</td>
<td>26 (72.3%)</td>
<td>15.7% p = 0.1438</td>
</tr>
<tr>
<td>Mean Peak Troponin (ng/mL)</td>
<td>2.44 +/- 2.65</td>
<td>2.15 +/- 2.55</td>
<td>0.29 p = 0.6688</td>
</tr>
<tr>
<td>Mean BNP (pg/mL)</td>
<td>924.2 +/- 1118.9</td>
<td>1345.2 +/- 2177.1</td>
<td>421 p = 0.3785</td>
</tr>
<tr>
<td>Left Ventricular Impairment (EF &lt;30%)</td>
<td>6 (24%)</td>
<td>8 (22%)</td>
<td>2% p = 0.8559</td>
</tr>
<tr>
<td>Severe Illness</td>
<td>8 (32%)</td>
<td>14 (38.8%)</td>
<td>6.8% p = 0.5894</td>
</tr>
<tr>
<td>- Defib/Cardioversion</td>
<td>4 (16%)</td>
<td>2 (5.6%)</td>
<td>10.4% p = 0.1839</td>
</tr>
<tr>
<td>- Shock (pressors used)</td>
<td>5 (20%)</td>
<td>11 (30.6%)</td>
<td>10.6% p = 0.3588</td>
</tr>
<tr>
<td>- Intubation</td>
<td>5 (20%)</td>
<td>11 (30.6%)</td>
<td>10.6% p = 0.3588</td>
</tr>
<tr>
<td>In-hospital Mortality</td>
<td>3 (12%)</td>
<td>0 (0%)</td>
<td>12% p = 0.0345</td>
</tr>
</tbody>
</table>
NUTRACEUTICALS IN THE PREVENTION AND TREATMENT OF Atherosclerosis

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Objectives: To investigate the effects of nutraceuticals on key processes associated with atherosclerosis in vitro and in vivo.

Background: Atherosclerosis is an inflammatory disease of the vasculature in which macrophages play key roles at all stages and represent promising therapeutic targets. Unfortunately, current therapies against atherosclerosis are not fully effective and associated with other issues such as adverse side effects. In addition, there have been many failures on pharmaceutical agents identified from drug discovery programs. Nutraceuticals represent promising alternatives in the prevention and treatment of atherosclerosis but requires a thorough understanding of their actions together with the underlying mechanisms. The purpose of this study was to address this with emphasis on key macrophage processes associated with atherosclerosis.

Methods: A combination of macrophage cell lines and primary cultures were used with gene expression analysed by atherosclerosis profiler arrays and real time quantitative PCR. Foam cell formation was investigated by following the uptake of fluorescently labeled modified LDL, intracellular lipid profiling and cholesterol efflux assays. Inflammasome activation was evaluated by following the release of interleukin (IL)-1beta using an ELISA and ROS production using a kit from Abcam. The effects in vivo were analysed in C57BL/6 mice fed a high fat diet.

Results: The studies focused on polyphenols, flavanols and omega-6 polyunsaturated fatty acids. These either inhibited or had no effect on several key macrophage processes associated with atherosclerosis such as pro-inflammatory gene expression, the uptake of modified LDL, macropinocytosis, ROS production and the activation of the inflammasome. In addition, where analysed, the nutraceutical inhibited several atherosclerosis-associated markers in mice fed a high fat diet. The mechanisms underlying such actions will be presented.

Conclusions: The studies provide new insights into the beneficial actions of nutraceuticals in atherosclerosis.
ATHEROSCLEROSIS: FROM BASIC MECHANISMS TO NOVEL OPPORTUNITIES FOR DIAGNOSIS, PROGNOSIS AND TREATMENT

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THE SPASMGENIC ACTION OF THE PROTEASOME INHIBITOR CARFILZOMIB ON ARTERIAL AND VENOUS CONDUITS FROM PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFT SURGERY IS ACCENTUATED BY PREEXISTING TYPE II DIABETES
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Carfilzomib (CFZ) is a proteasome inhibitor recently approved in the US for the treatment of relapsed/refractory multiple myeloma. Its most severe side effects include sudden death, pulmonary hypertension, heart failure and myocardial ischemia. Angina of unknown mechanism was also reported. We previously shown that CFZ exerts powerful spasmogenic effects in isolated rabbit aortic strips. Of note, CFZ is not contraindicated in patients with recent myocardial infarction/unstable angina who were excluded from the phase II safety trials based on which CFZ approval was granted.

Aim of study: To investigate the effects of CFZ on vascular tone and reactivity of left internal thoracic artery (LITA) and saphenous vein (SV) specimens harvested during elective coronary artery bypass grafting (CABG).

Methods and Results: Of the 185 consecutive patients enrolled, 86 had type 2 diabetes (DMP) and 99 did not (NDMP). Specimens were spirally cut into vascular strips, subsequently immersed in an isolated organ bath. CFZ (10^-9-10^-7 mol/L) induced a dose-dependent increase in vessel tension, which was more pronounced in DMP (p<0.05). Nitroglycerin (NTG) and nifedipine (NFP) lessened, though not abolished, CFZ-induced vasoconstriction, with percentages of inhibition peaking at 62.2% and 49.4%, respectively, at their highest concentration (10^-5 M). Pretreatment with CFZ amplified the spasmogenic effects of different agents, including KCl, noradrenaline (NA) and angiotensin 2 (A2), as well as curbed the vasodilatory response of NTG and NFP on the plateau of contraction induced by KCl, NA and A2 (p<0.01). Both effects were significantly more pronounced in DMP (p<0.05). Finally, the endothelium-dependent vasodilation induced by acetylcholine was dramatically reduced in all conduits pretreated with CFZ, especially in SV grafts from DMP (p<0.01).

Conclusions: CFZ exerts substantial spasmogenic effects on vascular tone and reactivity of arterial and venous conduits. Vasoreactivity to CFZ is increased in DMP possibly due to preexisting endothelial dysfunction. Further studies are warranted to establish the clinical safety of CFZ in patients with known CAD and/or history of coronary spasm.
EPIDEMIC REGULATION OF ACUTE CORONARY SYNDROMES
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Background: Long noncoding RNAs (lncRNA) are long transcripts of more than 200 nt of length not encoding for proteins. LncRNAs represent a novel source of molecules with regulatory function at transcriptional and epigenetic level, but only few information are available on their role in cardiology. As different mechanisms and prognosis have been described between type 2 Diabetic (T2DM) vs Not Diabetics patients with NSTEMI (ND-NSTEMI). We sought to assess whether LncRNA are involved in the different phenotypes in NSTEMI patients with and without diabetes.

Material and Methods: Platelet RNA from 3pts with NSTEMI without diabetes, 3 NSTEMI T2DM and 3 controls (CTRL) were isolated for lncRNA and mRNA microarray study (ARRAYSTAR Inc USA); according with literature, we considered a p<0.001 and a fold induction >3.5 as a significant sign of up or down-regulation.

Results: Global transcriptomic analyses detected 20,642 lncRNA and 18,949 mRNA in our three cohort of patients. In particular we found significant dysregulation in: a) 14 lncRNA in ND-NSTEMI vs CTRL (9 up-regulated, 5 dysregulated), b) 16 lncRNA, (6 up-regulated, 10 down-regulated) in NSTEMI T2DM vs CTRL and c) 356 lncRNA, (168 up-regulated, 188 down-regulated) in ND-NSTEMI vs NSTEMI T2DM. Moreover, using the same definition of dysregulation, we found 8 mRNA, (4 up-regulated and 4 down-regulated), significantly dys-regulated in NSTEMI vs CTRL, 16 mRNA, (10 up-regulated, 6 down-regulated), in NSTEMI T2DM vs CTRL and 109 mRNA, (51 up-regulated, 58 down-regulated), in NSTEMI vs NSTEMI T2DM. Dys-regulated transcripts were involved in calcium signalling pathway, fibrinolysis and platelet activation.

Conclusion: Our study demonstrates the presence of an important dys-regulation at epigenetic level between patients with NSTEMI and CTRL, suggesting that LncRNA are pivotal player in NSTEMI; surprisingly, the larger differences were found between NSTEMI pts with and without diabetes, suggesting an important epigenetic effect in NSTEMI with T2DM.
LOW SERUM LEVELS OF SOLUBLE RECEPTOR FOR ADVANCED GLYcation END PRODUCTS IS NOT AN UNIVERSAL BIOMARKER FOR CARDIOVASCULAR DISEASE

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Interaction of advanced glycation end products (AGEs) are heterogeneous group of irreversible adducts formed from non-enzymatic glycation of proteins, nucleic acid, and lipids with reducing sugars. Interaction of AGEs with its cell-bound receptor RAGE (receptor for AGEs) increases the expression of inflammatory mediators and generation of oxygen radicals and activates nuclear factor kappa-B which have adverse effects. Circulating soluble receptor for AGEs (sRAGE) acts as decoy for RAGE by binding with RAGE ligands, AGEs, and has protective effects against delirious effects of interaction of AGEs with RAGE. Serum levels sRAGE are low in patients with coronary artery disease, heart failure, essential hypertension, hypercholesterolemia and Alzheimer’s disease. Based on these findings, low levels of serum has been suggested to be a biomarker of the disease. However, we and others have shown that serum levels of sRAGE are high in diabetes and chronic kidney disease. Hence low levels sRAGE as a disease biomarker would not apply for these two conditions. Considering these observations, and involvement of AGEs, sRAGE and RAGE in AGE-RAGE–mediated disease, I proposed that the ratio of AGEs/sRAGE should be considered as universal biomarker/risk marker of the disease. We have demonstrated that the serum levels of both AGEs and sRAGE are elevated in diabetes and chronic kidney disease, the increase being more in AGEs than sRAGE. In patients with end stage renal disease, we have reported that the levels of AGES and sRAGE were respectively 6.77 times and 2.45 times higher than in healthy control subjects. We also reported that the ratio of AGES/sRAGE are elevated in patients with coronary artery disease. In conclusion, the elevated ratio of AGES/sRAGE, but not the low serum levels of sRAGE, is a universal biomarker for disease states.
Atherosclerosis in the carotid artery is a common cause of stroke in North America. For those with a prior transient ischemic attack (TIA) or minor stroke, data from 20 years ago indicates a high 90 day risk of recurrence of 12-20%. However, recent registry data (2009-2011) which includes patients on contemporary treatment for atherosclerosis shows a 12 month recurrence rate of <7%. Medical therapy has improved, with compelling data for patients with symptomatic carotid disease: aspirin + clopidogrel therapy reduces recurrence and is superior to aspirin alone if started within 24 hours of symptom onset, with no increase in risk of hemorrhage. To compare the safety and efficacy of carotid artery endarterectomy (CEA) with carotid artery stenting (CAS) in patients with both symptomatic and asymptomatic carotid stenosis, the CREST trial was undertaken at 108 US and 9 Canadian sites. The primary endpoint (up to 4 years) was any stroke, MI or death within the periprocedural period and ipsilateral stroke thereafter. Both procedures, in expert hands, were relatively safe with similar net outcome. The effects were durable over 10 year follow-up. A major question remains regarding optimal management of patients with asymptomatic carotid disease. With the marked improvement in the medical management of atherosclerosis, in asymptomatic patients is there a difference in outcome for intense medical management vs. CEA, or intense medical management vs. CAS? The CREST 2 Trial was launched to answer this question. An important secondary outcome measure is cognitive function at four years. The trial is ongoing with projected enrollment completion in 2020. At this point, intensive medical management is appropriate for all patients with symptomatic or asymptomatic carotid disease, there are good carotid intervention options for symptomatic disease and the relative value of mechanical interventions in asymptomatic disease will be known soon.
Accumulating evidence has demonstrated that aerobic exercise not only reduces risk factors associated with cardiovascular diseases but also confers direct robust cardiovascular protection in animal models and has been associated with improved survival following a heart attack in humans. The mechanisms of actions underlying exercise-elicited cardiovascular benefits are currently a focus of interesting. Exosomes are endogenous small (30-100 nm) vesicles secreted by multiple cell types into the blood, where they can transmit signals throughout the body. Recently, a wealth of evidence indicate that exosomes can mediate autocrine, paracrine, and endocrine functions via transmitting a variety of signaling molecules in their payload including proteins, mRNAs, and non-coding RNAs (such as microRNAs) to target cells. In this way, exosomes emerge as novel elements of intercellular communication and mediate therapeutic effects of stem cells in the cardiovascular system. However, the role of exercise-derived circulating exosomes in cardioprotection against MI/R injury has not been explored.

We recently found that exercise-derived circulating exosomes isolated from the serum were powerfully cardioprotective in both in vitro and in vivo models of myocardial ischemia/reperfusion (MI/R). miRNA array revealed that miR-G were markedly increased in exercise-derived circulating exosomes in both human and rats. More importantly, administration of miR-G significantly attenuated cardiomyocyte apoptosis and enhanced myocardial survival signal (p-Akt) via targeting phosphatase ppmlf in MI/R rats, whereas inhibition of cardiac miR-G in vivo attenuated swim exercise-induced cardioprotective effects.

Our findings reveal a novel cardioprotective mechanism through which exercise protects the heart against MI/R injury by delivering the endogenous protective signal, miR-G, via circulating exosomes.
ATHEROSCLEROSIS: FROM BASIC MECHANISMS TO NOVEL OPPORTUNITIES FOR DIAGNOSIS, PROGNOSIS AND TREATMENT

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TARGETED THERAPEUTIC STRATEGY IN HIGH-RISK PLAQUE

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Atherosclerotic plaque is a chronic inflammatory disorder with lipid accumulation within arterial walls. In particular, macrophages mediated plaque progression and rupture. While PPAR gamma agonist is known to have pleiotropic effects on atherogenesis, its clinical application has been limited due to undesirable systemic effects, including edema, weight gain, and congestive heart failure. Recently, we newly developed macrophage mannose receptor (MMR)-targeted biocompatible nanocarrier, and loaded lobeglitazone in it (MMR-Lobe), which is able to specifically activate PPAR gamma pathway within the inflamed high-risk plaques. Using in vivo serial optical imaging of carotid artery, MMR-Lobe markedly reduced both plaque burden and inflammation in atherogenic mice without undesirable systemic effects. Comprehensive analysis of en face aorta by ex vivo imaging and immunostainings well corroborated the in vivo findings. Mechanistically, by in vitro assays, MMR-Lobe has a high affinity to macrophage foam cells, and it promotes cholesterol efflux via LXR alpha, ABCA1, ABCG1 dependent pathway, and inhibits inflammatory activity. This novel targetable PPAR gamma activation in macrophages could be a promising therapeutic strategy for high-risk plaques.
IMPACT OF REACTIVE OXYGEN SPECIES ON CORONARY ATHEROSCLEROSIS

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Background: Coronary arterial remodeling, which is a response to the growth of atherosclerotic plaques, is associated with plaque vulnerability. Oxidative stress induced by reactive oxygen species (ROS) via NAD(P)H oxidase in the vasculature also plays a crucial role in the pathogenesis of atherosclerosis-based cardiovascular disease. In this study, the relationship between coronary arterial remodeling and ROS generation was examined by comparing pre-interventional intravascular ultrasound (IVUS) findings of atherosclerotic lesions to the histochemical findings of corresponding specimens obtained by directional coronary atherectomy (DCA).

Methods and Results: Pre-DCA IVUS images of 49 patients were analyzed. The remodeling index was calculated by dividing the target-lesion external elastic membrane cross-sectional area (EEM-CSA) by the reference-segment EEM-CSA. Expansive remodeling was defined as a remodeling index of greater than 1.0. ROS generation and NAD(P)H oxidase p22phox expression in DCA specimens were evaluated using the dihydroethidium staining method and immunohistochemistry as the ratio of the positive area to the total surface area in each specimen, respectively. ROS generation and p22phox expression were significantly greater in lesions with expansive remodeling than in lesions without remodeling (0.18 ± 0.12 vs 0.03 ± 0.02, p<0.0001, 0.10 ± 0.08 vs 0.04 ± 0.05, p=0.0039, respectively). Both ROS generation and p22phox expression significantly correlated with the IVUS-derived remodeling index (r=0.77, p<0.0001, r=0.53, p<0.0001, respectively).

Conclusions: Simultaneous examination with IVUS and immunohistochemistry analyses suggests that NAD(P)H oxidase-derived ROS is related to the coronary arterial remodeling process associated with plaque vulnerability.
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IMMUNOLOGICAL CONCEPTS DRIVING ATHEROSCLEROTIC PLAQUE REGRESSION

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Atherosclerosis is characterized by the accumulation of lipids, cells and fibers in the arterial wall. Atherosclerotic plaques form in regions of low blood flow, whereas vessels exposed to high shear stress remain lesion-free. We created a surgical mouse model, arteriovenous fistula (AVF), which increases blood flow in the brachiocephalic artery (BCA) specifically, without altering serum lipid levels. LDLR KO mice were placed on a high-fat diet (HFD). Control mice were sacrificed at week 12. Sham and AVF surgery was performed at week 12 and mice were kept on a HFD for a further 1-4 weeks.

We found that high blood flow is beneficial and leads to a significant ~50% regression of BCA plaque size in AVF mice compared with Controls, by week 4. We performed flow cytometry to characterize the different cell populations within Sham and AVF plaques. At day 7 after surgery, there was no difference in macrophage (F4/80+) or dendritic cell (CD11c+) content between Sham and AVF. However, we found a significant, 4-fold increase in the total number of CD45-CCR7+/PDGFRα+ cells in the BCA plaques of AVF mice vs Shams (p<0.01). No such change was observed in the aortic sinus plaques of AVF or Shams. CCR7 was previously found to be overexpressed in regressing plaques upon an abrupt lowering of plasma lipids, but in CD45+ cells. In our model, plasma lipids remained high and CCR7+ cells instead expressed PDGFRα, a perivascular and multi-lineage differentiation marker. This cell population also expressed mesenchymal stem cell markers (CD90, CD44, CD34) and CD68.

Our data point to an unexpected increase in the CD45-/CCR7+/PDGFRα+ cell population in the early plaque regression process. They suggest that mesenchymal-type cells may promote regression in plaques exposed to high blood flow.
ATHEROSCLEROSIS: FROM BASIC MECHANISMS TO NOVEL OPPORTUNITIES FOR DIAGNOSIS, PROGNOSIS AND TREATMENT

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CHITOTRIOSIDASE AS A NON-LIPID MARKER OF ATEROSCLEROSIS AND PROGNOSTIC FACTOR IN CARDIOVASCULAR EVENTS
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Objectives. The search of new serum non-lipid markers of atherosclerosis and predictors of cardiovascular events is important in contemporary society. The aim: to evaluate the activity of serum chitotriosidase (CHIT1) and compare it with inflammatory (hs-CRP) and common lipid markers in patients with atherosclerosis.

Background. Chitinases are enzymes – effectors in both innate and acquired immunity. Recently enhanced expression and activity of CHIT1 in humans was suggested as a possible marker of atherosclerosis. In clinical proteomics, CHIT1 was included in the list of 177 biomarkers associated with the development of CVD.

Methods. 107 persons, male were enrolled: 1) group of low ischemic heart disease (IHD) risk, 25 donors (aged 31.4±6.5); 2) high IHD risk, 50 patients with hypertension, aged 56.8±2.9; 3) 32 patients with IHD (56.5±6.9) undergoing coronary bypass surgery (1 month, 1, 2 and 3 years after surgery, treated or non-treated by simvastatin, 20-40 mg/kg), Novosibirsk Regional Cardiovascular Unit. Patients with diabetes mellitus, kidney insufficiency were excluded from this study. Serum chitotriosidase activity was determined by fluorescent method against 4-methylumbelliferyl-beta-D-N-N’-N’’-triacetylchitotrioside as a substrate (Guo et al., 1995).

Results. Serum CHIT1 activity (an enzyme released from the activated macrophages) was significantly increased in aged persons (p<0.01) as well as hs-CRP concentration (correlated with serum cholesterol and triglyceride levels). Baseline level of CHIT1 increased in patients of high risk of IHD (before operation, p<0.01 and 3-8 hrs after cardiosurgery, p<0.001). Simvastatin treatment (1 month, 1, 2 and 3 years after cardiosurgery) significantly decreased serum CRP-hs, total cholesterol and non-HDL-cholesterol. However, simvastatin treatment of these patients had no effect on CHIT1 activity steady significantly increased at all periods studied (1, 2 and 3 years after surgery).

Conclusion. CHIT1 has been suggested to represent a new, independent non-lipid biomarker for the development of atherosclerosis.
ATHEROSONEROSIS: FROM BASIC MECHANISMS TO NOVEL OPPORTUNITIES FOR DIAGNOSIS, PROGNOSIS AND TREATMENT

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NEW INSIGHTS INTO MYOCARDIAL ISCHEMIA/REPERFUSION INJURY --- HOW TO DAMP-EN A RAGE-ING HEART
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Background: Mechanisms underlying ischemia/reperfusion injury have been extensively investigated. However, treatments to reduce myocardial IRI have largely failed in the clinical application. Revisiting the mechanisms underlying IRI may provide new insights that may translate into more effective treatment regimens in the fight IRI.

Methods and Results: Using an in vivo mouse model of IRI, we have shown that myocardial infarction during reperfusion will not occur in mice unless the duration of ischemia is greater than 20 minutes. Mice subject to 40-min of myocardial ischemia, infarct size (IS) was 55% of risk region at 60-min after reperfusion. Inhibition of cell-free DNA (cfDNA) or HMGB1 upon reperfusion suffices to reduce IS to 30-33% of risk region. However, no further reduction in IS could be realized if both cfDNA and HMGB1 were inhibited at the same time. We found that after 40 min of ischemia, the myocardium released both HMGB1 and cfDNA into blood stream upon reperfusion. Perfusate from ischemic hearts had higher HMGB1 and cfDNA levels than blood sampled prior to reperfusion. Injection of perfusate from 40'/0' (I/R) hearts or plasma from 40'/5' mice to mice with 20'/60' IRI upon reperfusion significantly increased IS. Depleting either cfDNA or HMGB1 in those same 40'/5' plasma samples abolished the infarct exacerbation found in mice with 20'/60' IRI. Furthermore, the infarct exacerbating effect of the plasma from 40'/5' mice disappeared in splenectomized mice or RAGE KO mice.

Conclusions: Myocardium rendered necrotic by ischemia releases HMGB1 and cfDNA during reperfusion. The combination of these two Damage-Associated Molecular Pattern molecules are necessary to activate splenic leukocytes via RAGE to exacerbate myocardial infarction during reperfusion. This inter-organ signaling axis creates a feed-forward amplification loop that exacerbates reperfusion injury, such that little further myocardial injury will result from reperfusion, provided that there is no injury to cardiomyocytes during ischemia.
EFFECT OF BASELINE REGIONAL WALL MOTION ABNORMALITIES ON CORONARY FRACTIONAL FLOW RESERVE

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Background: Fractional flow reserve (FFR), the hyperemic ratio of distal (Pd) to proximal (Pa) coronary pressure, is used to identify the need for coronary revascularization. Regional wall motion abnormalities at rest (RWMA) may affect the FFR measurements.

Study Design: A retrospective cross sectional study was performed including all patients who underwent cardiac catheterization with FFR study for the needs of revascularization and had echocardiographic assessment for underlying RWMA during January 2010 to January 2016. Data on various hemodynamic and non-hemodynamic variables (explained below) that could possibly affect FFR was obtained. Simple and two-sample t-tests were used to perform the analyses. Cut off of less than 0.8 was used to define significant FFR value.

Results: Study population included 189 patients with mean age of 64(11) years. Baseline characteristics with 26 percent females, angiographic mean stenosis severity of 60 percent (13), LVEDP 16mmHg(7), MAP 101mmHg(14), HR 74bpm(16), spO2 96 percent(2.3), Lesion site [proximal 75(40 percent), mid 81(43 percent), distal 12(6 percent), branch vessel 21(11 percent)], diabetic 36 percent, renal disease 8.5 percent, PVD 10 percent, hypertension 85 percent, hyperlipidemia 100 percent, smoker 25 percent, preserved versus reduced LVEF of 94 percent versus 6 percent respectively (cut off of 40), with 81.5 percent had underlying angina symptoms. Adenosine was used in 167 (88 percent) cases where as Nipride was used in rest of the cases. RWMA was noted in 56 (30 percent) of the cases compared to normal wall motion in rest of 133 (70 percent) cases, in the area of distribution of the vessels underwent FFR study. 21 (37 percent) cases in the RWMA group whereas 50 (37 percent) cases in normal wall motion group had abnormal FFR. No difference in FFR trends were noted in patients with underlying RWMA compared to normal wall motion [0.83(0.75, 0.91)] versus [0.82(0.74, 0.90)] respectively with p value of 0.58.

Conclusion: In this study population, baseline regional wall motion abnormalities were not associated with significant FFR values compared to normal wall motion in the territorial distribution of vessel undergoing FFR study.
META-ANALYSIS COMPARING BIORESORBABLE VS. DRUG-ELUTING STENTS

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Background: Some concerns have been raised about the occurrence of acute, late or very late stent thrombosis with drug eluting stents (DES) [1]. To address this bioresorbable stents (BRS) have been introduced; however, there are few studies comparing the efficacy of BRS vs. DES.

Objectives: The aim of this meta-analysis was to compare the effects of BRS vs. DES on a range of clinical outcomes.

Methods: To identify potential randomised clinical trials systematic searches were carried out in EMBASE, PubMed, Web of Science and the Cochrane Central Registry of Controlled Trials (CENTRAL) (until 24/02/2017) searching for “bioresorbable” and “drug eluting stent”. This was followed by a meta-analysis investigating device success (no use of an unassigned device), mortality, target lesion revascularisation (TLR), incidence of myocardial infarction (MI), target lesion failure (TLF), target vessel revascularisation (TVR), early thrombosis (equal to or less than 30 days), late thrombosis (>30 days), in segment late lumen loss (change in minimal lumen diameter post-procedure to 6-13 months) and minimum luminal diameter post-procedure (MLDPP) (in device).

Results: Seven studies involving 4914 participants were identified. There were no significant differences in the incidences of early thrombosis (odds ratio (OR) 1.67 [95% confidence interval (CI) 0.79-3.54, p=0.18]), late thrombosis (OR 1.11 [95% CI 0.51-2.42, p=0.8]), mortality, MI, TLR, TLF, and TVR for BRS vs. DES. Device success (OR 0.16 [95% CI 0.08-0.31, p<0.00001]) and MLDPP (in device) (mean difference (MD) -0.11mm [95% CI -0.14-0.07, p<0.00001]) were significantly lower and in segment late lumen loss (MD 0.04mm [95% CI 0.00-0.07, p=0.04) was significantly higher for BRS.

Conclusions: BRS use did not reduce the incidence of thrombosis or revascularisation and was associated with lower device success, higher in segment late lumen loss and lower MLDPP (in device). Reference Brie D et al (2016) Int J Cardiol. 215, 47-59.
ADVANCES IN INTERVENTIONAL CARDIOLOGY

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ROUTINE ANGIOGRAPHIC FOLLOW-UP VERSUS ROUTINE CLINICAL FOLLOW-UP AFTER PCI: META-ANALYSIS OF RANDOMIZED CONTROLLED CLINICAL TRIALS
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Objective: Purpose of this meta-analysis was to evaluate clinical impact of routine coronary angiography follow-up (AF) versus routine clinical follow-up (CF) after PCI.

Background: In several previous studies, routine AF after percutaneous coronary intervention (PCI) increased the rate of coronary revascularization, but did not improve clinical outcomes. Based on these study results, the current clinical guidelines in the United States have already disregarded routine Coronary AF, even after PCI for left main coronary artery disease, whereas the current clinical guidelines in Europe regarded routine AF after high-risk PCI as Class IIB.

Methods: We conducted a meta-analysis of published randomized controlled clinical trials that compared routine angiographic follow-up (AF group) versus clinical follow-up (CF group) after PCI. We identified five RCT. Observational studies and registries were not included.

Results: There was no difference in death (odds ratio 0.86, 95% CI: 0.55-1.34) Figure 1 and MI (odds ratio 0.78, CI: 0.52-1.16) between two groups Figure 2. However, there was significantly increased target lesion revascularization in AF group (odds ratio 1.62 95% CI: 1.32-1.98) as compared to CF group Figure 3.

Conclusion: No clinical benefits are observed with coronary angiography follow up. However, TLR rates are significantly increased within coronary angiography group after PCI.

Figure 1-Death

Figure 2-MI

Figure 3-TLR
PERCUTANEOUS CORONARY INTERVENTION OUTCOMES IN PATIENTS WITH PRE-PROCEDURAL THROMBOCYTOPENIA
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Background: Previous studies reveal approximately 2% risk of bleeding in patients undergoing PCI. We aimed to compare clinical outcomes in patients with pre-procedural thrombocytopenia undergoing PCI.

Methods: A retrospective chart review of patients undergoing PCI at our center between 2010 and 2015 was conducted. A total of 146 patients with pre-procedural thrombocytopenia (platelet count < 150,000/L) were included. Patients were divided into two groups based on platelet counts: Group A <100K/L (n=54) & Group B 100K/L-150K/L (n=92). End points were cardiovascular mortality, bleeding outcomes and length of ICU/hospital stay. Bleeding outcomes were classified according to GUSTO criteria 1) severe bleeding resulting in hemodynamic compromise, 2) moderate bleeding requiring transfusion 3) mild resulting in neither.

Results: Commonest causes of thrombocytopenia included history of Liver disease, Hematologic Malignancies, and Chemotherapy. Bleeding events following PCI were noted in 17 patients (11.6%) with a total of 4 major, 9 minor and 5 minimal bleeding events, with almost equal predisposition in both groups (group A= 9, group B= 8). Bleeding sources included Upper GI bleed (n=4), Lower GI Bleed (n=4), and Hematomas (n=7). Almost all the hematomas were related to access site (n=6). MACEs were noted in 3 patients (group A= 1, group B= 2) including 1 patient dying of Cardiac arrest. Drug eluting stents (DES) were placed in 126 patients (86.3%). There were no episodes of major bleeding in patients who received BMS compared to 4 events in the DES group. No significant difference in overall bleeding events (p=0.15), length of ICU stay (p=0.804) or hospital stay (p=0.318) was observed between the two thrombocytopenic groups.

Conclusion: This study suggests there is a 1 in 10 risk of bleeding after PCI in patients with thrombocytopenia, although mortality outcomes remain favorable. Thrombocytopenia should be considered an important addition to future PCI risk prediction models.
USE OF CHEST X-RAY TO PREDICT PRESENCE OF TORTUOUS RIGHT BRACHIOCEPHALIC ARTERY PRIOR TO RIGHT RADIAL ACCESS FOR CARDIAC CATHETERIZATION PROCEDURES; A RETROSPECTIVE STUDY

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Background: Cardiac catheterization is one of the most widely used diagnostic and therapeutic modality in modern cardiology. Over the past decade, there has been a paradigm shift towards transradial approach as the preferred access site. Ease of performance, lower bleeding risk, patient’s comfort, early ambulation, and reduced post procedural monitoring make it superior to femoral artery access. A subset of patients have a tortuous right brachiocephalic (innominate) artery, making catheter manipulation difficult. We hypothesized that those patients may be identified by certain measurable parameters of their bony thorax, identified by certain measurements on chest radiographs.

Methods: We reviewed chest x-ray films of 56 patients that had undergone radial cardiac catheterization in our lab. We prospectively identified 23 patients with a tortuous innominate artery identified by fluoroscopy (cohort group), and 33 patients without tortuosity (control group). Chest radiograph measurements were obtained and analyzed for statistical significance between cohort and control groups using t-test and p-value models.

Results: Among all measurements obtained, Vertebrocarinal Distance (VCD), identified as thoracic distance from the T1 spinous process to the carina, measured on chest radiograph, is the most statistically significant value, with mean VCD of 9.7 cm in in male cohort group, compared to 12.1 cm in male control group (P value of <0.001), and mean VCD of 9.0 cm in female cohort group, compared to 10.9 cm in female control group (P value of <0.001). VCD index for height, the area of rectangle formed between VCD and thoracic diameter at carinal level, was also statistically significant.

Conclusion: Short distance between the spinous process of T1 vertebral body and the inferior edge of carinal bifurcation measured on chest X-ray is a strong predictor of tortuous right innominate artery, and may be helpful in decision regarding access site choice prior to start of cardiac catheterization.
SHOULD WE STILL DOUBT TRANSRADIAL ACCESS IN STEMI?

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Introduction: Primary coronary angioplasty (PPCI) is the best reperfusion therapy in ST elevated myocardial infarction (STEMI). Transradial access has shown lower mortality in this scenario. Other benefits, such as same day or early discharge, have been described.

Objective: To compare clinical and procedural results of PPCI by transradial vs femoral access.

Methods: From 2000 to December 2016, 472 consecutive PPCI where done in patients with STEMI. Class D of KK classification and STEMI as an epiphenomenone were excluded. Final population: 426 patients. Group A transradial access (n=150) and Group B femoral access (n=276). Baseline characteristics were group A and B respectively, n(%): mean age 57±8.9 vs 58.8±12; male 134(89)vs236(86); diabetics 24(16)vs51(18); smoking 112(75)vs192(70); BMI 25±4.1vs24±3.5 p<0.05; EF 57±14.9 vs 54.8±14.5; Killip class II/III 17(11) vs 58(21) p<0.05; LAD 67(45) vs 119(43); multivessel disease 67(45) vs 143(52); same session multivessel treatment 29(19) vs 33(12) p<0.05; initial TIMI 0 88(59) vs 159(58); bifurcation treated 4(3) vs 10(4); 7/8Fr 12(8)vs21(8); thromboaspiration 18(12) vs 24(9); IIbIIIa 18(12) vs 55(20); mm of stent 42.3±27.8 vs 33.7±20.8 p<0.05; contrast used ml 197.2±67.6 vs 229.4±83.3 p<0.05; fluoro min 13.3±9.5 vs 15±11.1; door to balloon time min 92±48 vs 111±60 p<0.05.

Results: Results were group A and B respectively n(%): Final TIMI 3 146(97) vs 253(92) p<0.05; final blush 3 144(96) vs 244(88) p<0.05; early coronary occlusion 3(2) vs 5(2); vascular access complication 4(3) vs 4(1); cardiovascular in hospital mortality 2(1) vs 4(1); hospitalization days 3.8±3.3 vs 5.3±6.9 p<0.05; discharge at 48 hs 49(33) vs 39(14) p<0.05.

Conclusion: Transradial PPCI allows the treatment of similar anatomical situations and the use of dedicated devices in STEMI when compared to femoral access. It did also allowed the use of guiding catheter larger than 6 Fr, less contrast use, without increasing both fluoroscopy time nor door to balloon time. Additional benefits such as less hospital stay was observed in transradial access.
Background: Current guidelines recommend that Door to balloon time (DTB) should not be more than 90 minutes for ST-Elevation Myocardial Infarction (STEMI) patients. Adoption of this as a quality measure has improved mortality and reduced myocardial death. Median DTB times fell from 96 minutes in 2005, to 64 minutes in 2010. However, despite efforts to further reduce DTB below current recommendations, evidence is lacking that this has reduced mortality.

Objective: Our aim was to show that there is little additional benefit of reducing DTB any further and in fact, this may lead to worse outcomes. Instead we sought alternative areas where reduction in total ischemic time (TIT) may reduce mortality.

Methods: We performed a thorough literature search, reviewing data on reduction of DTB below 90 minutes; we compared the benefits of further reduction of DTB with its associated risks, whilst proffering suggestions to reducing total ischemic time hence mortality outside of the DTB.

Results: Studies confirm reduced mortality benefit of lowering DTB time to within 90 minutes in STEMI patients. However, strict efforts to lower DTB time more than 90 minutes (60 or even 30 minutes), may lead to increased incidence of false activation of the cardiac catheterization lab, incorrect diagnosis with adverse events and missing pathology due to starting with culprit lesion catheterization.

Conclusions: Incredible progress has been made in the coordination of care and mortality reduction as a result of emphasis on improving door-to-balloon time, however further reduction does not seem to be of benefit. Reduction in TIT by: patient education in recognizing ischemic symptoms and call for help, reduced patient transfer times, and faster STEMI diagnosis time may play a greater role in mortality reduction.
Intramural hematoma (IH) is a potentially thrombogenic lesion caused by spontaneous coronary artery dissection. In an acute coronary syndrome, an IH may be difficult to distinguish from plaque rupture during coronary angiography. In the absence of ongoing ischemia, conservative management has been advocated for the treatment of IH. This case explores the difficulties and potential complications associated with both an invasive or conservative management strategy.

Our case involves a 65 year-old female who experienced three ST elevation myocardial infarctions (STEMI) over a 3-week period. She presented with an inferior STEMI with successful deployment of a drug eluting stent (DES) to the mid RCA. Post deployment angiogram showed luminal protrusion suspicious for an IH. Conservative management was elected. Seven days later she presented with cardiogenic shock and inferior STEMI; angiography revealed luminal occlusion at the level of the prior IH. Intravascular ultrasound confirmed the presence of IH. A DES was deployed across the obstruction and another IH was noted at the proximal stent margin. Admission was complicated by an intracranial hemorrhage (ICH); antiplatelet therapy was held. On day 14, she endured a third inferior STEMI attributed to subacute stent thrombosis. IIB/IIIA inhibitors were contraindicated due to her ICH. Thrombosis was lessened by dottering the lesion, but dynamic thrombus formation was seen so an ad hoc “stent cleaning” technique with inflated balloon was needed to alleviate recurrent thrombus (referred to as the “chimney sweep” technique).

This patient exemplifies the difficulties with IH management and limitations in preventing dissection extension or hematoma enlargement. The original hematoma observed following stent placement resulted in subsequent vessel narrowing and thrombosis leading to two subsequent STEMIs. The “chimney sweep technique” achieved successful 12 month outcomes without stent thrombosis. We suggest this technique as a bail out therapy for subacute in-stent thrombosis in the appropriate clinical setting.
SUBCLAVIAN ARTERY STENOSIS WITH INTERNAL MAMMARY ARTERY OCCLUSION AND MULTI-VESSEL OSTIAL STENOSIS

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Background: Subclavian artery stenosis with left internal mammary artery (LIMA) occlusion and multi-vessel ostial coronary artery disease (CAD) is uncommon and challenging to manage. Although there is benefit in coronary artery bypass grafting (CABG), our patient was determined to be at prohibitive risk and therefore underwent percutaneous coronary intervention (PCI) with drug-eluting stents.

Case Presentation: A 73-year-old female presented to clinic with symptoms of angina, shortness of breath, and weakness. Her past medical history includes peripheral vascular disease with left subclavian artery stenosis status-post stenting with LIMA occlusion, CAD, hypertension, obstructive sleep apnea, chronic obstructive pulmonary disease, diabetes mellitus type II, and chronic kidney disease. Left heart catheterization showed absent left main coronary artery, 90% ostial lesion of the left anterior descending artery (LAD), 80% ostial lesion of the left circumflex artery (LCX) and 70% ostial lesion of the right coronary artery (RCA). She was referred for CABG however was felt to be at prohibitive risk for surgery considering the absence of a patent LIMA, and severe calcification of her aortic root. Therefore, she was recommended and underwent successful PCI with drug-eluting stents; one in the ostium of her LAD, one in the ostium of her LCX, and three in her RCA. Following intervention she did not have recurrence of angina, however continued to feel weak and fatigued.

Discussion: This case represents a challenge in clinical decision making. In a patient with CAD with multi-vessel ostial stenoses, CABG is recommended and has mortality benefit and reduced revascularization. However, our patient has symptomatic left subclavian stenosis artery status-post stenting and re-stenosis with LIMA occlusion. Therefore, she underwent PCI with multiple drug-eluting stents instead of CABG. This case highlights the importance of clinical judgement to individualize management strategies and maximize patient outcomes.
HEART FAILURE: PREDICTORS, NEW TREATMENT OPTIONS AND OUTCOME

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CLINICAL AND ECHOCARDIOGRAPHIC PREDICTORS OF ARRHYTHMIAS DETECTED WITH 24-HOUR HOLTER ELECTROCARDIOGRAPHY AMONG HYPERTENSIVE HEART FAILURE PATIENTS IN NIGERIA

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Background: Hypertensive heart failure (HHF) is the commonest form of heart failure (HF) in Nigeria. There is paucity of data in Nigeria, on 24-hour Holter electrocardiography (24-HHECG) and important predictors of arrhythmias among HHF patients.

Objectives: To determine the 24-HHECG characteristics among HHF patients. To determine the clinical and echocardiographic predictors of arrhythmias detected using 24-HHECG among HHF patients.

Methods: One-hundred HHF patients as well as fifty age and sex matched apparently healthy controls, were prospectively recruited over a period of one year. They all had baseline laboratory tests, echocardiography and 24-HHECG. Results: HHF patients had significantly higher counts of premature ventricular contractions (PVCs) than the controls (p ≤0.001). Ventricular tachycardia (VT) was recorded in 29% of HHF patients as compared to controls who had no VT on 24-HHECG. The standard deviation of all normal to normal sinus RR intervals over 24 hours (SDNN) was abnormally reduced among HHF patients when compared with controls (p = 0.046). There was positive correlation between AF and the following parameters; PVCs (r = 0.229, p = 0.015), New York Heart Association (NYHA) (r = 0.196, p = 0.033) and VT (r = 0.223, p = 0.018).

Following multiple linear regression, left ventricular ejection fraction (LVEF) (p ≤0.001) and serum urea (p = 0.037) were predictors of PVCs among HHF patients. Serum creatinine (p ≤0.001), elevated systolic blood pressure (SBP) (p = 0.005) and PVCs (p ≤0.001) were important predictors of VT among HHF patients.

Conclusion: Renal dysfunction and reduced LVEF were important predictors of ventricular arrhythmias. High counts of PVCs and elevated SBP were predictive of the occurrence of VT among HHF patients. NYHA class and ventricular arrhythmias have a significant positive correlation with AF. SDNN is reduced in HHF patients.
HEART FAILURE: PREDICTORS, NEW TREATMENT OPTIONS AND OUTCOME

ANEMIA-RELATED HIGH OUTPUT HEART FAILURE IN SICKLE CELL DISEASE (SCD)—DOES IT EXIST?

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Objective: To see if anemic hydroxyurea-naïve Sickle-cell disease (SCD) patients have heart failure (HF)

Background: Existing literatures suggests that SCD patients can develop anemia-related high output HF in addition to transmural infarction which leads to left ventricular dysfunction.

Method: This is a cross sectional study of 208 hydroxyurea-naïve consecutive anemic SCD patients, aged 10-52 years at steady state and 94 healthy non-matched controls in Nigeria. SCD patients had electrophoretic and or liquid chromatography documentation of major sickling phenotypes. Control group had non-sickling phenotypes. Cardiac measurements were performed with Transthoracic ECHO according to American Society of Echocardiography guidelines.

Results: Pulmonary arterial systolic pressure (PASP) was indirectly obtained from Right ventricular systolic pressure calculated by: 4 multiplied by square of Tricuspid regurgitant velocity (TRV). SCD patients had significantly higher mean±SD values for TRV than did the controls (2.1±0.6 vs. 1.8±0.5;P=0.001). 25% of SCD patients had elevated PASP as defined by jet velocity ≥2.5 m/s(estimated systolic PASP ≥30 mm Hg) compared to 7% of controls (P<0.001). In 4%, jet velocities was ≥3.0 (estimated PASP≥41) compared to 0% controls. SCD patients, unlike controls, had significantly higher left ventricular dimensions but no qualitative evidence of systolic dysfunction, (i.e ejection fraction (EF) ≤0.5. Also, the patients had higher ratio of early to late ventricular filling velocities (E/A). Within the SCD group, there was no clear pattern of worsening diastolic function with increased TRV. E/A had a significant positive relationship with TRV in bivariate analysis (R=0.20; P=0.013).

Conclusions: We were unable to demonstrate the existence of anemia-related HF in SCD patients. On the contrary, biventricular function is preserved with no evidence of left ventricular dysfunction. Compared to USA cohort a high TRV does not appear to be a risk factor for mortality in the African cohort based on a seven year follow up study.
A SPECIALTY SPECIFIC CARDIOLOGY CARE TEAM MODEL IN A PATIENT-CENTERED MEDICAL HOME SETTING IMPROVES EFFICIENCY, ACCESS, QUALITY AND PRODUCTIVITY IN A MULTI-SPECIALTY INTEGRATED HEALTHCARE DELIVERY SYSTEM

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Objective: There has not been a gold standard specialty care team model in a Patient-Centered Medical Home setting for a structured to maximize efficiency, quality and access to care. A pilot study was conducted with a comprehensive care-team implementation around a specialist to improve quality of patient care, physician productivity and patient access.

Methods: The study was a retrospective analysis of two cardiologists’ practices located in Long Island and Queens. Cardiologists were compared during two time periods: July to September 2015 (prior to care team implementation) and July to September 2016 (post care-team implementation). Cardiology service line staff trained the care-team extenders (medical assistants and a clinical procedure coordinator) and key performance indicators (press ganey, new consult to follow-up ratio, no-show rate, work RVU and third next available appointment) were assessed prior to and after implementation.

Results: New consult to follow-up ratio increased by an overall 15%. Provider one and two had annualized WRVU increased by 1062.8 (13%) and 1674 (15%) respectively. The third next available appointment decreased from 24 to 4 (RRR 83%) and 37 to 20 (RRR 46%) respectively. Provider one performed 174 visits prior to and 351 visits post care-team (102% increase). Provider two performed 280 visits prior to and 364 patients post care-team (30% increase).

Conclusions: In a Multi-specialty Integrated Healthcare delivery model in a PCMH setting, implementation of a specialty specific cardiology care-team support structure improves efficiency, access, quality and productivity. The key performance indicator for procedural and clinical volume was higher with a care-team with respect to an increase in wRVU’s and an increase in visit volume. Patient access was improved by an increase in new consults and a reduction in third next available appointments while maintaining industry standard press ganey scores. This model reflects an improvement in quantity and quality of healthcare for an Accountable Care Organization.
EFFECT OF BETA-BLOCKER THERAPY ON READMISSIONS AND MORTALITY IN HEART FAILURE PATIENTS WITH ONGOING COCAINE USE

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Background: Beta blockers are first line agents for reduction of symptoms, hospitalization and mortality in heart failure patients with reduced ejection fraction (HFrEF). However, the safety and efficacy of continuous beta-blocker therapy (BBT) in patients who actively use cocaine remain controversial and available literature is limited. We aimed to evaluate the effect of BBT on readmissions and mortality in HFrEF patients with ongoing cocaine use.

Methods: We conducted a retrospective chart review of patients with a new diagnosis of HFrEF between 2011 and 2014 based on ICD9-CM codes. We included patients aged 18 and older who tested positive for cocaine on a urine toxicology test obtained at the time of index admission. Patients were followed for 1 year. We assessed for Beta-blocker prescription rate at the time of discharge from the index admission. A multivariate logistic regression was used to assess the effect of BBT on the 30-day all-cause and heart failure related readmissions. The 1-year mortality rate was also reported.

Results: In our study population N= 268 and mean age [in yrs] = 54 (std=6.9), the beta-blocker prescription rate is 86.2%. The 30-day readmission rate for BBT vs no BBT groups were 20% vs 41% (OR 0.17, 95% CI= 0.05-0.56, P=0.004) for heart-failure related readmissions and 25% vs 46% (OR 0.19, 95% CI= 0.06-0.64, P=0.007) for all-cause readmissions. The 1-year mortality rates for BBT vs no BBT groups were 5% vs 8% (OR 0.88, 95% CI= 0.17-7.19, P=0.91).

Conclusion: Physicians continue to prescribe outpatient Beta-blocker for most HFrEF patients regardless of cocaine-use status. BBT reduces readmission rate but not 1-year mortality in HFrEF patients with ongoing cocaine use. Large observational studies are needed to further elucidate the efficacy and safety of continuous BBT in this population.
EFFECTIVENESS OF IMPLEMENTATION INTERVENTIONS IN IMPROVING PHYSICIAN ADHERENCE TO GUIDELINE RECOMMENDATIONS IN HEART FAILURE: A SYSTEMATIC REVIEW

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Background: The uptake of guideline recommendations that improve heart failure (HF) outcomes remains suboptimal. We reviewed implementation interventions that improve physician adherence to these recommendations, and identified contextual factors associated with implementation success.

Methods: We searched databases from January 1990 - February 2015 for studies testing interventions to improve uptake of Class I HF guidelines. We used the EPOC and Process Redesign frameworks for data extraction. Primary outcomes included: proportion of eligible patients offered guideline-recommended pharmacotherapy, self-care education, left ventricular function assessment, and/or device consideration. We reported clinical outcomes when available.

Results: We included 35 studies, including 9 randomized controlled trials (RCTs). Provider-level interventions (N=13 studies) included: audit and feedback, reminders, and education. Organization-level interventions (N=15) included: medical records systems changes, multidisciplinary teams, and clinical pathways. System-level interventions (N=3) included: provider/institutional financial incentives. Four studies assessed multi-level interventions. We could not perform meta-analyses due to statistical/conceptual heterogeneity. Twenty-nine studies reported significant improvements in at least 1 primary outcome. Clinical pathways, multidisciplinary teams, and multifaceted interventions were most consistently successful in increasing physician uptake of guidelines, while audit and feedback alone was largely ineffective. Among RCTs, pharmacist and nurse-led interventions improved target dose prescriptions. Eleven studies reported clinical outcomes; significant improvements were reported in 3, including a clinical pathway, a multidisciplinary team, and a multifaceted intervention. Baseline assessment of barriers, staff training, iterative intervention development, leadership commitment, and policy/financial incentives were associated with intervention effectiveness. Most studies (N=18) had medium risk of bias; 8 RCTs had low risk of bias.

Conclusion: Our study is limited by the quality and heterogeneity of the primary studies. Clinical pathways, multidisciplinary teams, and multifaceted interventions appear to be most consistent in increasing guideline uptake. Our work highlights the need for improved research methodology to reliably assess the effectiveness of implementation interventions.
Introduction: Danon disease is a rare X-linked dominant disorder caused by mutations in the lysosome-associated membrane protein 2 (LAMP2) gene. It is manifested by skeletal myopathy, intellectual disability, and cardiomyopathy. Although females are less severely affected than males, cardiac disease is still a significant concern.

Case Presentation: A 19 year old female was incidentally found to be in atrial flutter when she presented to her primary care provider with streptococcal pharyngitis. She had no prior history of arrhythmias or syncopal/near-syncopal spells; family history was significant only for epilepsy (mother) and diabetes (father). Transthoracic echocardiogram showed concentric left ventricular (LV) wall thickness with no dynamic LV outflow tract obstruction. A catheter ablation of the cavotricuspid isthmus (CTI) was attempted but her atrial flutter recurred after a month. She underwent a cardiac magnetic resonance imaging study which showed near-circumferential delayed enhancement of the mid-myocardium, suggestive of an infiltrative cardiomyopathy or lysosomal storage disease. Laboratory evaluation was negative for monoclonal protein elevation or deficiencies in alpha-galactosidase and acid alpha-glucosidase. She then underwent an electrophysiology study where repeat CTI ablation was successfully performed; no supraventricular or ventricular arrhythmias were induced. A concomitant right ventricular biopsy was performed as well. Implantable cardioverter defibrillator placement was deferred due to the lack of induced ventricular arrhythmias and sudden cardiac death history. Histopathology showed vacuolization of myocytes with glycogen abundance consistent with Danon disease. Subsequent genetic testing revealed a likely pathogenic variant in the LAMP2 gene (c.887 T>C; p.Leu296Pro); her mother was not a carrier. She did well initially but developed atrial flutter recurrence two years later requiring a third ablation.

Conclusion: Females with Danon disease are at risk for cardiomyopathy and arrhythmias (atrial, ventricular, and accessory pathway). Extensive evaluation including imaging and electrophysiologic testing should be performed in order to delineate appropriate management strategies for these patients.
HEART FAILURE: PREDICTORS, NEW TREATMENT OPTIONS AND OUTCOME

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CANCER AND TAKOTSUBO CARDIOMYOPATHY – IS THERE A CONNECTION?
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Introduction: Takotsubo Cardiomyopathy (TCM) is a rare form of cardiomyopathy triggered by stress. The mechanism of transient left ventricular (LV) dysfunction is unknown but catecholamine-induced damage is a proposed theory. We present a case of a patient with TCM that lead to the diagnosis of a lung malignancy.

Case: 58-year-old male with history of essential hypertension and coronary artery disease (CAD) with a left anterior descending coronary artery (LAD) stent in 2012, presented to the hospital with sudden onset 4-hour evolution of precordial chest pain associated with shortness of breath. He was tachycardic, normotensive, and hypoxic. Electrocardiogram showed ST segment elevation in leads V2-V5. Troponin I was negative. Cardiac catheterization showed LV apical hypokinesis consistent with TCM. Echocardiogram showed LV ejection fraction of 30% with severe septal and apical hypokinesis. Chest radiography revealed a left upper lobe lung mass. Computed tomographic imaging showed a large left upper lobe lung mass with extensive satellite nodularity and possible hepatic, adrenal and bone metastatic foci. The patient developed hypoxemic respiratory failure and required mechanical ventilation. Bronchoscopy revealed poorly differentiated adenocarcinoma.

Discussion: Takotsubo cardiomyopathy has been described in cancer patients undergoing malignancy treatment. In TCM patients, prevalence of cancer has been reported as 4-29%, exceeding the expected prevalence of cancer in age-matched populations. A majority (77.5%) of the cardiomyopathy cases were triggered by a stressful situation either surgery or chemotherapy. A retrospective study of a pool of cancer patients with TCM found that 12.5% had diagnosis of lung cancer. In the International Takotsubo Registry, malignancy was found to be the trigger in 0.5% of the TCM patients. Our case depicts a phenomenon in which the undiagnosed lung malignancy manifested as TCM without any other identifiable stressor. Malignancies may be a state of chronic inflammation and can increase adrenoreceptor sensitivity leading to TCM.
CHRONIC KIDNEY DISEASE AMONG PATIENTS WITH MULTIPLE CHRONIC CONDITIONS

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Introduction: Chronic kidney disease (CKD) increases cardiovascular risk from 10 to 30 times, with arterial hypertension (AH) and diabetes mellitus (DM) being its major causes in Brazil and worldwide, respectively.

Objectives: To evaluate the profile of chronic renal disease among a population with multiple chronic conditions (MCC).

Methods: Cross-sectional observational study evaluating medical records of a secondary public service for hypertensive and diabetic patients with high cardiovascular risk between 11/2016 and 01/2017. We defined CKD, glomerular filtration rate (GFR) <60 ml/min, high LDL cholesterol >100 mg/dL, high blood glucose >100 mg/dL. Results: In a population of 1646 users, the prevalence of CKD was 22.1%. Among these, GFR was 41.9±13.6 ml/min and were characterized by a higher pulse pressure (p <0.050), triglyceride levels (p <0.050), previous cancer (p <0.004), systolic heart failure (p <0.001), high LDL-cholesterol (p <0.057), simvastatin use (p <0.05), and lower fasting blood glucose values (p <0.02). These patients showed a greater tendency for asymptomatic peripheral vascular disease (p <0.080).

Conclusion: The CKD was found to be prevalent among the MCC population and significantly associated with other comorbidities that should be systematically screened in a population of similar profile. In spite of the greater use of statins, the users still showed with lipid profile outside the recommended goal.
FULMINANT MYOCARDITIS CAUSED BY INFLUENZA A/H3

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Background. Fulminant myocarditis has been rarely reported in association with A/H3 influenza. We report comprehensive clinical and echo (TTE) findings in a 38 year old man with no past medical history and no prior influenza vaccination.

Case. Patient was admitted with 5 days of progressive dyspnea and fatigue associated with low grade fever, rhinorrhea, myalgia and cough. Examination: blood pressure 100/70 mmHg; heart rate regular at 125 bpm; O2 saturation 98% (2 L/min nasal cannula); respiratory rate 32 bpm; diaphoretic using accessory respiratory muscles; coarse breath sounds and normal heart sounds on auscultation. Labs: WBC count 36,000 with 86% PMNs; mild transaminitis; elevated creatinine kinase and creatinine; negative rapid influenza A and B test. Chest X ray: mild pulmonary congestion. ECG: sinus tachycardia, low voltage and non specific ST-T wave abnormalities. Serial cardiac troponin I: steady mild elevation around 0.4 ng/mL. Patient was initially treated for sepsis from an unknown source with Ceftriaxone and Vancomycin. TTE on Day 2 showed moderately reduced left ventricle (LV) systolic function, moderate diffuse hypokinesis and thickening as well as hyper-reflectivity of LV walls due to myocardial edema/inflammation. A small pericardial effusion was also noted (Panel A top row). These findings were consistent with myopericarditis. Patient developed persistent fevers and refractory hypoxemia requiring intubation and mechanical ventilation. Hemodynamic compromise led to initiation of pressers. A nasopharyngeal PCR was positive for influenza A/H3. Respiratory viral panel and blood cultures were otherwise negative. He was started on Oseltamivir. His condition gradually improved and he was successfully extubated (day 5). A TTE (day 7) showed marked improvement of LV systolic function and longitudinal strain with resolution of myocardial edema (Panel B bottom row).

Conclusion. We hereby report a unique case of fulminant myocarditis caused by influenza A/H3 with rapid recovery demonstrated clinically and by TTE.
NEW CONCEPTS IN THE PATHOGENESIS, DETECTION AND TREATMENT OF CARDIOVASCULAR DISEASES

OXIDIZED LDL INDUCED DENDRITIC CELL MATURATION AND T CELL ACTIVATION --- A NOVEL IMMUNOLOGICAL ROLE OF PCSK9

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**Background:** Dendritic cells (DCs) and activated T cells are common co-localized in atherosclerotic plaques. Proprotein convertase subtilisin kexin 9 (PCSK9) targets the LDL-receptor (LDLR) for degradation, and results in increased LDL-levels. We here study immune effects of PCSK9 on OxLDL induced DC maturation and T cell activation.

**Methods and Results:** T cells were isolated from peripheral blood of healthy individuals, or from carotid specimens of patients undergoing carotid endarterectomy. Human peripheral blood monocytes were differentiated into DCs. Naïve T cells were co-cultured with pretreated DCs. The effects of PCSK9 and its inhibition by silencing were studied. OxLDL induced PCSK9 in DCs, an effect not affected by statins. OxLDL promoted DC maturation with increased expression of CD80, CD83, CD86 and HLA-DR. T cells exposed to OxLDL-treated DCs proliferated and produced IFN-γ and IL-17, thus with polarization to Th1 and/or Th17 subsets. Silencing of PCSK9 reversed the OxLDL effects on DCs and T cells. DC maturation was repressed and the production of TNF-α, IL-1β, and IL-6 was limited, while TGF-β and IL-10 secretion were increased. Th1 and/or Th17 polarization was inhibited, while T regulatory cells were induced with IL-10 production. OxLDL induced miRNA let-7c, miR-27a, miR-27b, miR-185. Silencing PCSK9 repressed miR-27a and to a lesser extent let-7c. Further, PCSK9 silence enhanced the BLIMP1 and SOCS1 expression induced by OxLDL. Experiments on T cells from carotid atherosclerotic plaques or healthy individuals showed similar results.

**Conclusions:** We demonstrate for the first time immunological effects of PCSK9 in relation to activation and maturation of DCs and plaque T cells induced by OxLDL, a central player in atherosclerosis. This may directly influence atherosclerosis and cardiovascular disease, independent of LDL-lowering.
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SEX DIFFERENCES IN THE EFFECT OF VITAMIN D ON INFLAMMATORY HEART DISEASE: PROTECTIVE IN WOMEN BUT DAMAGING IN MEN
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An estimated 1 billion people worldwide have deficient or insufficient levels of vitamin D (VitD), while roughly 25% of individuals in the US are reported to have inadequate VitD levels. Considerable evidence indicates that VitD deficiency is associated with an increased risk of cardiovascular disease (CVD), yet it remains unclear whether low VitD is simply a biomarker of CVD or has a true pathologic role. Myocarditis, an inflammatory heart disease, appears as lymphocytic myocarditis (LM) or giant cell myocarditis (GCM), yet the role of VitD deficiency in the pathogenesis of disease is unknown. We found that 75% of GCM patients had deficient or inadequate levels of VitD (<19ng/mL) whereas only 20% of LM patients had low levels. Following therapy, VitD levels in women but not men with GCM significantly improved (p=0.04). Myocarditis patients are at risk of heart failure, which is reflected by a low ejection fraction (EF). In GCM patients, low EF correlated with low VitD levels in both men and women (r² = 0.42). In contrast, poor EF and low VitD was only correlated in women with LM (r²=0.54), but surprisingly men had an opposite correlation- high VitD correlated with low EF (r²=0.81). When we used examined the role of VitD using VitD receptor (VDR) deficient mice in a model of LM, we found that VDR decreased myocarditis in females (p=0.007) but increased inflammation in males (p=0.006). Comparison of microarray data during myocarditis in mice to known VitD response element genes revealed that genes associated with proinflammatory (e.g. caspase-1, p=7.0x10^-5) and profibrotic (e.g. TGF-beta, p=8.6x10^-6) immune responses were significantly upregulated in the heart of males, providing a mechanism to explain how VDR increases disease in males. These findings in the mouse model confirm that sex differences exist in the function of VitD/VDR in men and women with LM.
NEW CONCEPTS IN THE PATHOGENESIS, DETECTION AND TREATMENT OF CARDIOVASCULAR DISEASES

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SERUM LEVEL OF DHA IS INDEPENDENTLY ASSOCIATED WITH CORONARY ARTERY DISEASE IN CHINESE ELDERLY POPULATION

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Background: Recent studies were failed to demonstrate that n-3 polyunsaturated fatty acids (n-3PUFAs) supplement reduced cardiovascular events, which contradicted previous evidence. In addition, there is little clinical evidence of n-3PUFAs in Chinese population.

Objective: To investigate the relationship between serum levels of n-3PUFAs and coronary artery disease (CAD), and explore the clinical related factors of n-3PUFAs in Chinese elderly.

Methods: 460 patients (age 69.07 ±12.03) with multiple cardiovascular risk factors or clinical diagnosed CAD were enrolled in this study. Serum levels of n-3PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), were measured by liquid chromatography mass spectrometry and clinical information was collected.

Results: Serum levels of n-3PUFAs, both EPA and DHA, were significantly lower in patients with CAD than those without CAD (median EPA: 326.5 vs. 412.0 ng/mL, p=0.002; median DHA: 1159.9 vs. 1645.3 ng/mL, p=0.013). Multivariate logistic regression analysis showed that high DHA level was independent protective factor for CAD (OR:0.52, 95% CI: 0.31~0.88, P=0.014). Serum levels of n-3PUFAs were associated with alcohol (95% CI: -398.54 ~ -13.18, P=0.036), proton pump inhibitors (95% CI: -2164.65 ~ -130.81, P=0.027), body mass index (95% CI: -301.54 ~ -29.67, P=0.017) and albumin (95% CI: 16.11 ~ 195.97, P=0.021).

Conclusions: Serum DHA is a protective factor for CAD. The clinical related factors of n-3PUFAs include alcohol and proton pump inhibitors.
NEW CONCEPTS IN THE PATHOGENESIS, DETECTION AND TREATMENT OF CARDIOVASCULAR DISEASES

EFFICACY OF CANRENONE ADDED ON TOP OF MAXIMUM TOLERATED DOSE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS/ANGIOTENSIN II TYPE 1 RECEPTOR BLOCKERS PLUS HYDROCHLOROTHIAZIDE AS ASSESSED BY 24-H AMBULATORY BLOOD PRESSURE MONITORING IN UNCONTROLLED HYPERTENSIVE PATIENTS

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Background: The aim of this study was to assess the effect of the addition of canrenone, an aldosterone receptor antagonist, on ambulatory BP in uncontrolled hypertensive patients already treated at the highest tolerated dose of angiotensin converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor (AT1R) antagonists plus hydrochlorothiazide (HCT).

Methods: Ambulatory BP monitoring was performed at baseline and after 3 months of combination therapy in 158 outpatients with stage 1-2 hypertension who were randomized to add canrenone 50 or canrenone 100 on the preexisting therapy with ACE inhibitors or AT1R antagonists plus HCT. 24h systolic and diastolic BP were considered normalized when the values were <130mmHg and < 80mmHg, respectively.

Results: The addition of canrenone reduced 24h, daytime and nighttime systolic and diastolic BP in both treatment arms (p<0.001); as for pulse pressures, 24h (p<0.001), daytime (p<0.001) and nighttime values (p<0.001 for the 50 mg treatment group and p<0.01 for 100 mg group) were also reduced. The degree of reduction was: delta 24 systolic BP; 50 mg/day: -13.5±11.2, 100 mg/day: -16.1±13.5 mmHg (p=ns for 50mg vs. 100mg); delta 24h diastolic BP: 50 mg/day: -8±8; 100 mg/day: -11.2±8.3 (p<0.05 between the two dosages). 67.5% and 74% of patients normalized 24h systolic and diastolic BP (p<0.05), respectively, in the 50 mg arm and 61.6% and 68.5% of patients normalized BPs (p<0.05) in the 100 mg arm (p=ns for 50mg vs 100mg). The % of patients whose nocturnal fall was >10% with respect to diurnal values did not change during combination therapy.

Conclusions: Canrenone added to ACE inhibitors or AT1R antagonists in a clinical setting of stage 1 or 2 hypertension was efficacious as assessed by 24h ambulatory BP and safe.
RANOLAZINE AFTER NOVEL TREATMENT FOR ERBB2 POSITIVE BREAST CANCER (TDM1) PREVENTS CARDIOTOXICITY IN VITRO AND IN VIVO

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Background: Ado trastuzumab emtansine (TDM1) is a novel antibody–drug used in metastatic ErbB2 positive breast cancer patients. We aim to elucidate whether Ranolazine (R), administered after TDM1 treatment, blunts or not cardiotoxicity in vivo and in vitro.

Methods: In vitro, human fetal cardiomyocytes (HFC) were treated with TDM1 for 3 days and then treated in the absence or presence of R for 3 days. Cell viability was assessed by cell counting and MTT assay. To evaluate cardiac function in vivo, C57/BL6 mice, 2-4 months old, were daily treated with TDM1 (44.4 mg/kg/day). At day 0 and after 7 days, fractional shortening (FS) and ejection fraction (EF) were measured, by M/B mode echocardiography, and radial and longitudinal strain (RS and LS) were evaluated using 2D speckle-stracking. These measurements were repeated after 5 days of R treatment (305 mg/Kg/day), started at the end of TDM1 treatment.

Results: R reduces TDM1 toxicity in HFC, as evidenced by the higher percentage of viable cells treated with TDM1+ R with respect to the cells treated with TDM1 alone (p < 0.01). After 7 days with TDM1 administration, FS decreased to 53.6±0.9% versus 61.0±0.8% (sham), (p < 0.01), and EF decreased to 85.5±3.5% versus 91.0±0.8% (sham), (p < 0.01). Moreover, RS decreased to 20.92±3.2% versus 42.2±10.1% (sham) (p < 0.01), and LS decreased to -15.5±2.8% versus -23.6±6.7% (sham), (p < 0.01). In mice treated with TDM1+R, the indices of cardiac function partially recovered: FS 58±2.4% (p < 0.05), EF 88.8±1.7%, (p < 0.05), RS (35.7±8.2%, p > 0.05), whereas the alteration of LS persists even after treatment with R (-17.3±3.7%, p > 0.05)

Conclusions: We show that in vivo R post-treatment reduces cardiotoxic effects due to TDM1, as demonstrated by the recovery of FS, EF and RS values.
NEW CONCEPTS IN THE PATHOGENESIS, DETECTION AND TREATMENT OF CARDIOVASCULAR DISEASES

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TISSUE-ENGINEERED HEART VALVES WITH THE AUTOASSEMBLY METHOD

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Introduction: Present valve prostheses available for children are unadapted: non-growing, rapidly calcifying, requiring anticoagulotherapy, etc. We hypothesize that an in vitro fabricated tissue-engineered heart valve can circumvent these drawbacks. The autoassembly method was chosen to avoid exogenous material. We first demonstrated its potential with fibroblasts sheets assembled on an Edwards Lifesciences® metallic support. The metal restraining growth, we thereby used an origami approach with fusion steps. Next, we adapted the simpler tubular approach with a novel precontraction phase. Unfortunately, it presented insufficient suture retention. Our actual objective is to improve valve fabrication by seeding cells directly on a machined, tridimensional valve template, offering a one-piece valve sutured on all its circumference. The first step allowed us to assess its feasibility, we set to try it out in vitro.

Methods: We propose seeding fibroblasts on the template surface, treated for cell adherence, followed by 6 weeks of maturation in a serum-free media (SFM) and 1 week of contraction to predetermined dimensions, allowing for leaflet coaptation. Finally, the valve can be placed in our bioreactor and compared with static tissue to evaluate dynamic conditioning influence on mechanical properties and histological anisotropy.

Results: Tridimensional culture tested on templates with a simpler geometry resulted in tissues easy to manipulate. Plasma treatment modified polycarbonate surface chemistry with a cell adhesion similar to commercial culture plates. Machining leaved grooves, raising the ultimate tensile strength (UTS) by 2.1 parallel to them. SFM reduced contraction percentage (50%), increased thickness (162 µm) and UTS (0.41 MPa), to values like those of radial pulmonary valves (0.29 MPa). However, the assay applying the method developed to valve culture failed.

Conclusion: Our main hypothesis for this failure is the inadequate gas exchange into the valve container, limiting matrix production and cell survival. Even though this method still needs improvements, preliminary results confirm its feasibility and leave us expecting promising results.
NEW CONCEPTS IN THE PATHOGENESIS, DETECTION AND TREATMENT OF CARDIOVASCULAR DISEASES

CYSTATIN C IN ACUTE LIPEMIA IN MICE PRETREATED BY ATORVASTATIN OR/AND FENOFIBRATE
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Objectives: The aim: to study the hypolipidemic effects of statin or/and fenofibrate in acute lipemia and evaluate serum cystatin C level as one of the sensitive marker of early cardio-renal pathology.

Background: Statins are well-known hypolipidaemic drugs; however, their use can be associated with severe adverse side effects. Fibrates lower blood TG levels by reducing the liver production of VLDL (the TG-carrying particles) and by speeding up the removal of TG from the blood.

Methods: Acute lipemia in CBA/Lac mice was induced by the single administration of poloxamer 407 (P-407, 250 mg/kg); atorvastatin (70 mg/kg, Torvacard, Zentiva, Slovakia) or/and Tricor (50 mg/kg, Abbott, France) were administered per os 24 h before P-407. Serum lipids were measured using Biochemical Analyzer Beckman Coulter (USA); cystatin C concentration by Cystatin C mouse ELISA kit (BioVendor, Czechia).

Results: In intact mice atorvastatin decreased serum LDL (p<0.05) and TG (p<0.05); tricor decreased TG (p<0.02). Acute lipemia was characterized by significant elevation of all atherogenic lipids and decreased HDL-cholesterol (p<0.001). Atorvastatin pretreatment in mice with lipemia decreased atherogenic lipids (p<0.01) but not to the level of intact mice, increasing HDL (p<0.001). Tricor pretreatment in lipemia decreased serum cholesterol (p<0.05) and TG (p<0.01) (all data were higher than in intact mice) with increase of ALT activity. Serum Cystatin C concentration increased in intact mice with atorvastatin (p<0.001) or tricor (p<0.001) administration as well as in P-407 group (p<0.05). Pretreatment by atorvastatin in mice with lipemia decreased cystatin C to the normal level, while tricor did not change elevated cystatin C level (vs P-407); combined atorvastatin + tricor pretreatment increased cystatin C concentration (p<0.05 vs P-407).

Conclusion: High doses of atorvastatin or trikor increased Cystatin C concentration in intact mice and in acute lipemia pretreated by combination of atorvastatin + tricor, efficiently preventing hyperlipidaemia.
Transapical aortic valve implantation utilizing the J-valve in patients with aortic regurgitation: a one-year results of the multi-centre study

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Objectives: Transapical transcatheter aortic valve implantation (TA-TAVI) has shown promising results in screened patients with high-risk profile. In this study, we present the first multi-centre outcome of a new second-generation TA-TAVI system, the J-Valve™ system, in patients with aortic regurgitation (AR).

Methods: This prospective study, was conducted at three largest cardiac centres in China, enrolled 43 patients (mean age 73.8 ± 5.7), the preoperative EuroSCORE II score was 11.01.0%. Clinical and echocardiographic evaluations were performed at baseline, post-procedure, discharge and 30 days, and also at 6 and 12 months. The primary endpoint was a combined efficacy endpoint after 1 year, which included all-cause mortality after more than 30 days and failure of current therapy for AR requiring hospitalization for symptoms of valve-related cardiac decompensation or prosthetic heart valve dysfunction. Secondary endpoints were major stroke, and life-threatening, disabling, or major bleeding during follow up.

Results: TA-TAVI with the J-Valve™ device was successful in 40/42 patients (procedural success rate 95.2%). The overall mortality at 30 days and 12 months was 2.3% and 2.5% respectively. Conversion to surgery was necessary in one patient (2.5%). Pacemaker implantation for new onset conduction disorders was necessary in two patients (5.0%). All patients with completed follow up (n=38) reported improvements in at least one of the NYHA classes. None of the patients had severe post-procedural aortic regurgitation (>2+). The combined ratio of successful implantation without adverse events in our cohort was 88.1%.

Conclusions: Transapical J-Valve™ implantation was safe and effective in the treatment of AI patients at high risk for surgery. Satisfactory hemodynamic performance during the one year follow-up was demonstrated with low peri- and post-operative complications.
SUCCESSFUL PERCUTANEOUS MITRAL VALVE REPAIR IN SETTING OF PRIOR ANNULOPLASTY

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Background: We describe a unique case of a patient with a prior mitral valve annuloplasty who underwent percutaneous mitral valve repair. This is only the second reported case in literature.

Case: 63-year-old man with a history of hypertension, hyperlipidemia, and surgical mitral valve repair for degenerative valve disease presented with worsening exertional dyspnea. He had a history of minimally invasive annuloplasty with a semi-rigid Edward Physio 2 (size 32 mm) ring approximately 5 years ago. Examination: Alert and fully oriented. Precordium: S1, S2. Grade III holosystolic murmur best heard at the apex. Lungs: scattered rales at both lung bases. 3D transesophageal echocardiogram revealed severe eccentric mitral regurgitation with flail motion of the posterior leaflet due to rupture of tertiary chordae (Figure A). Annular ring prosthesis appeared stable without para-prosthetic leak. Mean gradient across the mitral valve was 4 mmHg. Left ventricle was mildly dilated with an ejection fraction of 60%. Using a transfemoral transseptal approach, a MitraClip device was deployed at A-2-P-2 segment under transesophageal echocardiography and fluoroscopy guidance (Figures B and C). This implantation led to an acute decrease in mitral regurgitation to trace (Figure D). There was relief of symptoms and percutaneous mitral valve repair obviated the need for repeat surgical repair.

Discussion: This case demonstrates that percutaneous mitral valve repair is a viable treatment option in cases with prior surgical mitral valve repair and elevated surgical risk. Patients with prior surgical mitral valve annuloplasty were excluded from the original trials. Percutaneous repair in this patient provided him with an option of obviating or delaying surgery as a definitive treatment option.
RHEUMATIC MITRAL STENOSIS: WHO NEEDS INTERVENTION?
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Rheumatic mitral valve stenosis continues to be a challenge in Egypt. Most of our patients are symptomatic females even with a mild-moderate degree of mitral valve stenosis. The trend in our country is more towards managing these patients conservatively with medical treatment till they develop a more severe degree of stenosis. Purpose: is to determine the role of exercise echocardiography in the management of disproportionately symptomatic patients with mild-moderate mitral stenosis (MS).

Methods: 35 patients with pure rheumatic non-tight MS were divided according to their resting echocardiography into two groups. Group one: 18 patients with MVA (1.1-1.49 cm²), group two: 17 patients with MVA (1.5-1.99 cm²). All patients with pure MS were studied by Doppler echocardiography, both during rest and immediately post a symptom-limited exercise test. Mean trans-mitral gradient (MPG) and the estimated pulmonary artery systolic pressure (EPASP) were documented. Results: Sixteen patients in group one (88.9%) and 10 patients (58.8%) in group two developed an increase; either in the MPG of more than 10 mmHg or in the EPASP more than 60 mmHg, denoting a more severe degree of MS. It is worth mentioning that when group 2 were subdivided, those having MVA between 1.5-1.7 cm² developed an increase in the MPG and EPASP of 87.5% and 75% respectively. P < .001 and P < .001, respectively). According to these results, the treatment strategy in group one pushed for mitral valve intervention and in those with a MVA between 1.5-1.7 cm², the treatment strategy was worth revision.

Conclusion: This study showed that exercise echo can have an important role in the clinical decision-making of challenging patients with MV disease. Exercise echocardiography had an additional value to the treatment strategy in 75% of the patients with a MVA less than 1.7 cm²/BSA.
DIVERSE LAYOUT OF MULTI-HOLE SECUNDUM ATRIAL SEPTAL DEFECT AND DEVICE OCCLUSION USING DIFFERENT PERATRIAL TECHNIQUES

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Objectives: This study sought to analyze the safety, efficacy, and mid to long term follow up results of peratrial device closure of multi-hole secundum Atrial Septal Defects (MASDs) using different methods.

Methods. One hundred and six patients underwent peratrial device closure of MASDs through right parasternal incision. Patients were categorized into 4 types according to MASDs layout: Type A showing layout of large (more than 15mm)-moderate (equal & more than 5-less & equal 15), large-small (less than 5mm), moderate-moderate, moderate-small or small-small, with or without accompanying small hole near either or both defects and inter-defects distance less than 7mm. Type B, similar layout as Type A with inter-defects distance more than 7mm. Type C presenting as moderate-moderate, small-small and a small defect middling both, inter-defects distance more than 7mm. Type D seen as more than 5 small defects, may contain a moderate hole in a cribriform formation. The method used is from previous reports. Five patients underwent new inter defects septal puncture technique to occlude MASDs. Follow up was done at discharge (3-5Days), 1, 3, 6, 12 months and yearly thereafter.

Results. The procedure was successful in all patients. The maximum diameter of MASD was 14 plusminus 7mm (range 3-26mm). The size of devices was 20 plusminus 8mm (6-36mm). Single device deployment was done in 89 patients, and residual shunt immediately after device deployment were higher in these patients. Which gradually disappeared on follow-up. Simultaneous double device deployment was done in 17 patients. Procedure completion rate was 100%. Complete occlusion rate for 106 patients at discharge was 63%, and rose to 81% at 12 months follow up. There were no other late complications.

Conclusions. Our series of patients showed that peratrial device closure of MASD is safe and effective technique. Use of double device deployment was related to better results. It is advantageous by being minimally invasive, cost effective, and easiest maneuverability for MASD occlusion
INTRODUCTION: Mitral valve aneurysm (MVA) is a rare entity usually complicating infective endocarditis. We present a rare case of perforated posterior mitral leaflet (PML) MVA with severe mitral regurgitation (MR) but compensated heart failure.

CASE PRESENTATION: A 61-year-old female with history of tonsillar cancer on chemotherapy was admitted with pneumonia and new neurological deficits. Blood cultures grew Staphylococcal epidermidis. Echocardiography demonstrated a pedunculated, mobile PML vegetation with moderate to severe MR. Transesophageal echocardiography (TEE) confirmed a large (3.5 x 1.2 cm²), flail mass prolapsing into the left atrium (LA), with perforated PML causing moderate to severe MR. Patient tolerated mild dyspnea for almost 16 months. Follow-up TEE was negative for vegetation, but revealed PML perforation with severe MR into a 1.8 x 1.7 cm² aneurysm projecting into the LA. This aneurysm had a perforation as well with flow into the LA cavity.

DISCUSSION: MVA results from degeneration of the leaflets, most commonly in the setting of infection either primary or extension from adjacent infected aortic valve along the intervalvular fibrosa. Also, mechanical stress from aortic regurgitation has been proposed to cause weakness of mitral leaflets forming aneurysm. Anterior mitral leaflet MVA are more common, and are associated with juxtaposed infected aortic valves. PML aneurysms are extremely rare, and usually cause MR from ruptured aneurysm, flail leaflet from ruptured chordae, or poor leaflet coaptation. Partial PML involvement results in mild regurgitation, whereas ruptured aneurysm and complete leaflet involvement causes severe regurgitation with decompensated heart failure.

CONCLUSION: Perforated PML MVA has rarely been reported. This case was unique such that the flow through the perforated PML entered the aneurysm first before exiting into the LA. This self-containment of blood in the aneurysm prevented florid MR and decompensated heart failure. This anatomy was therefore referred to as “a heart inside the heart”.

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PULMONARY VEIN STENOSIS TREATED WITH PERCUTANEOUS STENT FOLLOWING SINGLE LUNG TRANSPLANTATION
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Pulmonary vein stenosis (PVS) after lung transplantation is a rare but potentially fatal complication requiring swift identification and treatment. Clinically, PVS is challenging to diagnose as it presents similarly to other post-transplantation complications. Although there are no clear guidelines on its management, rapid identification of vascular complications can prevent the need for retransplantation or revision. We describe a 60 year old Middle Eastern woman who underwent single lung transplantation for usual interstitial pneumonitis (UIP) which was complicated by pulmonary vein stenosis.

Our patient presented for lung transplantation evaluation for idiopathic pulmonary fibrosis secondary to UIP. She underwent transplantation without cardiopulmonary bypass and had an uncomplicated postoperative course. About one year later, she was admitted for acute hypoxemic respiratory failure initially attributed to pneumonia and graft rejection. An extensive workup to investigate this sudden decompensation identified shunting of blood with 54% perfusion to the native lung and 46% to the transplanted left lung. Computed tomography revealed stenosis of the left common pulmonary vein with greater than 50% stenosis at the anastamotic site, the junction of the left pulmonary vein and left atrium. In an effort to preserve the allograft, the patient underwent successful percutaneous balloon angioplasty and stenting of the left common pulmonary vein. Intracardiac echocardiography and intravascular ultrasound (IVUS) were used in the procedure. Angiography revealed near occlusive stenosis at the ostium of the left pulmonary vein and a gradient of 12-16mmHg between the left pulmonary vein and left atrium. IVUS aided in visualization of the lesion and positioning of the stent. A 10x29mm balloon expandable stent was placed in the left common pulmonary vein. Post dilation, the stenosis was reduced to less than 10% and the gradient was 3-4mmHg. The procedure was well tolerated, oxygen requirements were reduced and patient was treated with antiplatelet therapy.

Figure 1.a Percutaneous balloon angioplasty and b. Stenting of the left common pulmonary vein
THE ASSOCIATION BETWEEN BICUSPID AORTIC VALVE PHENOTYPE, AORTIC VALVE LESION TYPE AND AORTIC CONFIGURATION

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Objectives: The aim of this study was to investigate the association between bicuspid aortic valve phenotype, aortic valve lesion type and aortic configuration.

Background: Patients with bicuspid aortic valve (BAV) present with various phenotypes of valve, different aortic valve lesion type and the aortic root (AoR) dilatation and/or the ascending aorta (AAo) dilatation.

Methods: We retrospectively review 345 patients of BAV with thoracic aortic imaging either CTA or MRA, who underwent the surgery of aortic root and/or ascending aorta from February 2010 to February 2017, including: normal valve function (n=75), valve stenosis (n=151) and valve insufficient (n=119). BAV phenotypes was identified during operation under direct vision, according to the number and spatial orientation of the raphes. Aortic dilatation configuration was classified as three types by using 3-dimensional reconstruction.

Results: Associations between BAV phenotype and aortic configuration were weak (p=0.313). Aortic configuration associated with aortic lesion type in patients with BAV (p<0.001). AoR dilatation alone only occurred in the patients with aortic valve insufficient (12, 3.5%). AAo+AoR dilatation was significantly more frequent occurring in the patients with valve insufficient (81.5%, p<0.001). There is no significant association between AAo dilatation and valve lesion type (p=0.777).

Conclusions: Associations between BAV phenotype and aortic configuration were weak. Aortic configuration associate with the aortic valve lesion type in patients with BAV. The significant association between AoR and aortic valve insufficient emerged, which may indicate that the dilatation of AoR is the initial factor of aortopathy in patients of BAV with valve insufficient.
VALVULAR AND STRUCTURAL HEART DISEASE: MECHANISMS AND TREATMENT OPTIONS

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RHEUMATIC HEART DISEASE IN SICKLE CELL DISEASE IN SUB-SAHARAN AFRICA

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Objective: To demonstrate incidence of Rheumatic Heart disease (RHD) in Sickle cell disease (SCD) patients.

Background: RHD remains a major public health and clinical concern in Sub-Saharan Africa with about 50% of the world RHD burden. RHD incidence in general population varies from 5-36% with higher incidence in rural areas (where there is limited access to antibiotics and delay in diagnosis of rheumatic fever). This is unlike SCD population where there is paucity of data.

Method: Cross-sectional study of 208 hydroxyurea-naive consecutive SCD patients aged 10-52 years at steady state and 94 healthy non-matched controls were studied in Rural sites of a Teaching hospital in Nigeria. SCD patients were required to have electrophoretic and or liquid chromatography documentation of major sickling phenotypes. Control group was required to have non-sickling phenotype. Cardiac measurements were performed with transthoracic echo (TTE) for ventricular functions according to American Society of Echocardiography guidelines.

Results: The only valvular disease identified is tricuspid regurgitation in SCD patients who have significantly higher mean±SD values for TRV than controls (2.1±0.6 vs. 1.8±0.5; P=0.001). 0% of SCD patient has any features suggestive of RHD. This was similar in the control. However, the SCD cohorts were mostly of low socioeconomic status with less than 5% likelihood of life-time transfusion and less than 20% life-time access to doctors. This’ unlike control which was largely hospital workers and medical students who mostly have basic understanding and access to medical care.

Conclusion: Although the frequency with which RHD and SCD coexist is unknown, it would have been expected that the frequency would have been at least similar to the general population. We propose that as is the case with sickle cell and malaria infection, balanced genetic polymorphism or some other genetic basis leading to evolution of the sickle cell trait may provide some degree of protection to RHD in SCD patients. More research is needed on this.
DIABETES AND HYPERTENSION ARE INDEPENDENT RISK FACTORS FOR THE PRESENCE OF AORTIC VALVE DISEASE

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Background: Recent study find that combining many atherosclerotic risk factors correlates with the occurrence of aortic stenosis. The goal of this study was to evaluated any associations between diabetes, hypertension and hyperlipidemia with the occurrence of aortic valve disease using a very large data base.

Method: Using ICD-9 coding for aortic valve disease, hypertension, diabetes and hyperlipidemia, we evaluate any association between aortic valve diseases with these risk factors utilizing the large database of national inpatient sample (NIS).

Results: We used a total of 1,491,273 patients who had a diagnosis of aortic valve disease from 1988 to 2007. In univariate analysis, diabetes, hypertension and hyperlipidemia correlated with the occurrence of aortic valve disease. Aortic valve disease occurred in 20.6% of diabetes patients vs 13.5% of non-diabetes patients, OR 1.6, CI 1.6-1.7. Aortic valve disease occurred in 38.9% of patients with hypertension VS 29.7% without hypertension. OR 1.5, CI 1.48-1.53. Aortic valve disease occurred in 15.6% of patients with history of hyperlipidemia vs 14.2% without it. OR 1.12, CI 1.09-1.15. All p values < 0.001. After adjusting for sex, age and race, only hypertension and diabetes remained independently associated with the aortic valve disease.

Conclusion: traditional risk factor for atherosclerosis also appear to be associated with the occurrence of aortic valve disease. The cause of these associations are not known warranting further investigations.
MOLECULAR AND CELLULAR CARDIOLOGY, BASIC RESEARCH

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SILENCING OF CSF1R AND CSF1 IN MYELOID CELLS AMELIORATES EXPERIMENTAL AUTOIMMUNE MYOCARDITIS

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Background: Myocarditis is characterized by the infiltration of leukocytes into heart tissue and subsequent impairment of heart function. High leukocyte numbers in the inflamed heart correlate with poor prognosis. Monocytes are the predominant leukocytes at the site of inflammation and are thought to mediate further tissue damage. They develop from hematopoietic stem cells in a Colony Stimulating Factor (CSF1) dependent manner via several defined progenitor stages.

Objectives: We here sought to modulate the inflammatory response in murine experimental autoimmune myocarditis (EAM) through inhibition of monocyte development by silencing CSF1 and its receptor CD115.

Methods and Results: EAM was induced by injection of myosin-peptide in male BALB/C mice at the age of 8 weeks. Silencing of CSF1 and respectively its receptor CD115 by nanoparticle-encapsulated siRNA (siCSF1 and siCD115) started 14 days after induction of EAM. Injection of nanoparticles containing siRNA against Luciferase (siLuc) served as a control. FACS analysis revealed reduced monocyte-infiltration into heart tissue in animals receiving siCSF1 or siCD115-nanoparticle therapy compared to the control group. Echocardiographic evaluation of heart function showed that siCSF1 and siCD115 nanoparticle therapy improve left ventricular ejection fraction compared to the control group. In addition, histological analysis of hearts demonstrated reduced fibrosis in both siCSF1 and siCD115 treated animals 60 days after induction of EAM.

Conclusion: We here show that in vivo silencing of CSF1 and CD115 effectively reduce the monocytic response in hearts of animals during acute autoimmune myocarditis thereby limiting tissue damage and preserving heart function.
ADIPOCYTE CELL SHEETS REDUCE MACROPHAGE PHENOTYPE 1 CELLS' INFILTRATION DURING THE REMODELING PROCESS OF XENogeneIC SCAFFOLDS IN VIVO

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Background: Surgical therapy of cardiovascular diseases frequently requires replacement of diseased tissues with prosthetic devices or grafts. Calcification is the main reason for the degeneration of implanted grafts. However, some factors reduce stenosis and attenuate calcification of implanted grafts.

Objective: In this study, we used an autologous induced adipocyte cell sheet (IACS) as a drug delivery system to determine whether its secretion ability has a beneficial effect on the remodeling process of grafts in a rat subcutaneous model.

Method: IACSs were generated from rat adipose tissue-derived cells that secreted abundant adiponectin (APN), hepatocyte growth factor, and vascular endothelial growth factor in vitro. Two types of grafts were used in the rat subcutaneous model: decellularized and IACS-wrapped decellularized porcine vascular grafts. The inflammation and calcification of grafts were tested by pathology and immunohistochemistry methods.

Results: Transplanted IACSs secreted APN into the decellularized porcine vascular graft in rats at 4 weeks. After explanting from the rat subcutaneous model at 1, 2, 4 and 8 weeks, immunofluorescence staining showed that IACS wrapped grafts had a dominant M2 phenotype of macrophages (p < 0.001) at all-time points and showed constructive remodeling and less calcification at 8 weeks. The decellularized graft showed a predominately CCR7+ cell response (M1 phenotype) (p < 0.001) and was characterized by chronic inflammation and severe calcification at 8 weeks.

Conclusion: Transplantation of IACSs with a biological scaffold had a profound influence on the macrophage phenotype and downstream remodeling processes. The method might reduce inflammatory reactions during remodeling of xenogeneic scaffolds and result in less calcification.
SPI-B PLAYS A PROTECTIVE ROLE IN PRESSURE OVERLOAD-INDUCED HEART FAILURE THROUGH ATTENUATION OF CARDIAC INFLAMMATION

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Chronic hypertension can initiate the development of cardiac hypertrophy, ultimately resulting in congestive heart failure. It is widely accepted that inflammation with migration of bone marrow-derived cells into the heart is involved in the pathogenesis of pressure overload-induced cardiac hypertrophy and fibrosis. Spi-B, a member of Ets transcription factor family, is thought to be involved in immunomodulation. To investigate the pathophysiological roles of Spi-B in pressure overload-induced cardiac hypertrophy and heart failure in mice, male Balb/c (WT) and SpiB deficient (Spi-B-KO) mice were subjected to transverse aortic constriction (TAC). Cardiac hypertrophy, fibrosis, cardiac function by echocardiography and expression of cardiac remodeling-related molecules, inflammatory cytokines and chemokines were examined. Three weeks after TAC, Spi-B-KO mice exhibited more significant loss of cardiac function with severer cardiac hypertrophy and fibrosis, compared with WT mice, indicating that Spi-B played protective roles in TAC-induced cardiac hypertrophy, fibrosis and heart failure. Consistently, the intracardiac expression of col1a1 and col3a1 was more significantly increased throughout the experimental period, whereas that was transiently increased at 3 days after TAC in WT mice. Intracardiac gene expression for inflammatory cytokines and chemokines was also augmented and sustained in Spi-B-KO mice, compared with WT ones. In addition to the above differences between WT and Spi-B-KO mice, intracardiac gene expression for the matricellular protein such as osteopontin, tenascin, peristatin and versican was much higher in Spi-B KO mice. These observations suggested that Spi-B plays protective roles in the pathogenesis of pressure overload-induced heart failure through negative regulation of immune-responses to cardiac mechanical stress.
HUMAN CARDIOMYOCYTES EXPRESS KLOTHO WHICH DECREASES IN PATIENTS WITH HIGH CARDIOVASCULAR RISK

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Background: Klotho proteins (α and β) are membrane-based circulating proteins that regulate cell metabolism, as well as the lifespan, modulating activity of Fibroblast Growth Factors (FGFs) and other molecules. It was demonstrated that higher plasma circulating Klotho levels reduce cardiovascular risk, suggesting Klotho has a protective role in cardiovascular diseases. So far, it is known that klotho has been identified in various organs, but it is unknown whether cardiomyocytes also express Klotho and related FGF21 and FGF23 proteins, and whether high cardiovascular risk (HCVr) could affect their cardiac expression, as well as that of molecules involved in endoplasmic reticulum stress (GRP78), oxidative stress (SOD1), inflammation (NF-kB and iNOS), apoptosis (Bax and Bcl2) and fibrosis (TGF-β1 and Sirius-red).

Methods: We selected 20 patients (56.0±1.5y.o.) with high estimated 10-year atherosclerotic cardiovascular risk (>5%<7.5%) and 10 age-matched control subjects (55.3±2.2y.o.) with low estimated 10-year low risk (<5%), who underwent cardiac surgery for reasons different from coronary artery by-pass. All subjects had normal ejection fraction, without myocardial hypertrophy and previous myocardial infarct, h/o severe arrhythmia and/or concomitant diseases. In myocardial biopsies harvested from the right atrium prior to administration of cardioplegic solution, we evaluated by histochemistry and immunohistochemistry the expression of Klotho, FGF-21 and FGF-23 (receptors whose activity requires Klotho as co-receptor), as well as whether HCVr influenced the magnitude of the above molecules, of stress- and apoptosis-related factors, and fibrosis markers.

Results: Only cardiomyocytes from HCVr patients showed lower Klotho and higher FGF-21 and -23 immunostaining. Furthermore, HCVr was also accompanied by strong reduction in Bcl2 staining, as well as increased expression of Bax, stress-related markers (GRP78, SOD1, NF-kB, iNOS) and fibrosis.

Conclusions: Here, for the first time we showed that human cardiomyocytes express Klotho proteins. Their expression, as well as that of antiapoptotic markers is significantly down-regulated in HCVr patients, who, conversely, exhibited dramatic up-regulation of well-known stress-related molecules. Further translational are necessary to better characterize the pathophysiological role played by Klotho, as well as its practical utility in clinical practice.
RESTORATION OF AUTOPHAGY ACTIVITY IN HIGH GLUCOSE INDUCED CARDIOMYOCYTE BY MESENCHYMAL STEM CELL THERAPY

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Autophagy was inhibited in STZ-induced diabetic cardiomyocyte in response to hyperglycemia. So far, autophagy regulation in hyperglycemic cardiomyocyte remained unclear. Mesenchymal stem cells (MSCs) were known to regulate autophagy activity in several tissues such as kidney, liver and lung. Interestingly, the impact of MSC therapy to autophagy activity of diabetic cardiomyopathy is still unknown. In our study, high glucose (33mM) induced neonatal cardiomyocytes (NCM) and STZ-induced Type 1 DM (T1DM) cardiac tissues were used to investigate the activity of apoptosis, survival, and autophagy. Results indicated that HG and STZ-T1DM up-regulated mitochondrial dependent apoptosis pathway. Consistently, survival activity was downregulated. Autophagy activity of T1DM hearts was evaluated at 24 weeks after STZ-induction by protein levels of Beclin1, LC3-II, LAMP2. The formation of autophagosome and autolysophagosome were inhibited in T1DM heart. Following MSC therapy, autophagy activity and survival pathway were surprisingly improved in T1DM hearts. The autophagy pathway (Beclin1, Atg7, LC3II and LAMP2) and the survival pathway (p-IGF1R, p-Akt and Bcl2) were all up-regulated among MSC therapy. In consistent with above, apoptosis pathway was inhibited in T1DM hearts coupling with MSC transplantation. To conclude, these findings demonstrated that hyperglycemia inhibited autophagy in vitro and in vivo. MSC therapy not only restored activity of autophagy but also up-regulated survival pathway and inhibited apoptosis in T1DM hearts.
MICRORNA-210 MEDIATES PKC delta-DEPENDENT UPREGULATION OF JNK TO CAUSE CARDIAC MITOCHONDRIAL DAMAGE AND APOPTOSIS FOLLOWING ADVANCED GLYCATION END-PRODUCTS EXPOSURE

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Backgrounds: Hyperglycemia results in the formation of advanced glycation endproducts (AGEs), which can induce reactive oxygen species (ROS) production leading to diabetic cardiomyopathy. Our previous study showed that AGE induced ROS-dependent apoptosis is mediated via the protein kinase C (PKC) delta-enhanced mitochondrial damage in cardiomyocytes. MicroRNA-210, a regulator of mitogen-activated protein kinase-JNK (JNK), which is a downstream of PKC delta has been reported to play a role to mediate mitochondrial function. Therefore, we hypothesized that miR-210 mediates PKC delta-dependent upregulation of JNK to cause cardiac mitochondrial damage and apoptosis following AGE exposure.

Methods & Results: Cardiac miR-210 and mitochondria function were downregulated following AGE exposure. Furthermore, JNK was upregulated and involved in AGE-induced mitochondrial damage. Interestingly, the result of luciferase activity of the miR-210 mimic treatment was significantly lower than control and was reversed following the inhibitor treatment, indicating JNK is a target of miR210. Moreover, JNK activation induced by AGEs was reduced by the treatment of miR-210 mimic and reversed by the treatment of miR-210 inhibitor, indicating the regulation function of miR-210 for JNK activation following AGE exposure. Additionally, the JNK-dependent mitochondrial dysfunction was reversed following the treatment of miR210 mimic, and miR210 inhibitor showed no effect on JNK-induced mitochondrial dysfunction in AGE-exposed cardiomyocytes.

Conclusion: PKC delta enhanced JNK-dependent mitochondrial damage is mediated through the reduction of miR210 in cardiomyocytes following AGE exposure.
P21-ACTIVATED KINASE 1 IS NECESSARY FOR AN EFFICIENT AUTOPHAGY

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Doxorubicin (DOX) is an extensively used chemotherapeutic agent that can produce fatal cardiotoxicity. Due to this limitation, it is important to identify methods to protect patients from DOX-induced cardiomyopathy without affecting its anti-tumor effects. We previously reported that DOX upregulates autophagy, which contributes to DOX cardiotoxicity. P21-activated kinase 1 (PAK1) has been shown to regulate cardiac contractility and to protect cardiomyocytes from DOX-induced cell death. In this study, we explored the roles of PAK1 in the basal autophagy and DOX-induced autophagy. H9c2 cardiac myoblasts were sequentially treated with siRNA targeting PAK1 and DOX. The results indicated that PAK1 knockdown reduced autophagy under the basal and DOX treated condition as shown by the reduced levels of autophagy marker protein LC3-II and fewer numbers of autophagosomes and autolysosomes. Collectively, these results suggest that PAK1 is required for autophagy in cardiomyocytes.
ANTIOXIDANT EFFECT OF ELTACIN IN THERAPY OF PATIENTS WITH ISCHEMIC HEART DISEASE

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2. Hospital 60, Moscow, Russia
3. Research Institute of Cytochemistry and Molecular Pharmacology, Moscow, Russia

Objectives: Oxidative stress significantly contributes to the development and/or progression of cardiovascular diseases such as atherosclerosis, ischemia-reperfusion injury, chronic ischemic heart disease. The aim of this investigation was to determine the effect of eltacin contained amino acids (glutamate, cysteine, glycine) on cellular antioxidant defense in old patients with angina pectoris.

Methods: The use of eltacin (220 mg x 3 times per day) in addition with traditional therapy (β-adrenoblockers, aspirin, Ca-antagonists, nitrates, diuretics) of aging patients (69 ± 2.7 years old) with angina pectoris functional class II-III was estimated. Before and 21 days after the therapy ECG-monitoring, EchoCG data were examined. Activities of antioxidant enzymes, reduced (GSH) and oxidized (GSSG) glutathione maintenance in erythrocytes, malonyldialdehyde (MDA) level in plasma have been tested.

Results: The use of eltacin in therapy of patients resulted in an increase of glutathione (GSH) maintenance, GSH/GSSG ratio and activity of GSH-related enzymes (glutathione peroxidase, glutathione transferase) as well as glutaredoxin and thioredoxin, Cu,Zn-superoxide dismutase, catalase in erythrocytes up to control values depressed until the treatment. The increase of antioxidant state of erythrocytes was accompanied by the decrease of lipid peroxidation and depression of ROS production. Extent of the development of antioxidant response was time-related and correlated with positive alteration of patient states: a rise of exercise tolerance, reduction of myocardial power consumption, antiarrhythmical effect.

Conclusions: It may be concluded that eltacin has ability to reduce oxidative stress by increasing antioxidant defense that give it perspective for the use in therapy of ischemic heart disease.
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RELATION BETWEEN SECONDHAND SMOKE EXPOSURE AND CARDIOVASCULAR RISK FACTORS IN NEVER SMOKERS
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2. Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea
3. Hanil General Hospital, Seoul, Korea

Objective: Secondhand smoke exposure (SHSE) in non-smokers has been associated with premature cardiovascular mortality and ischemic heart disease. We conducted a cross-sectional, population-based study evaluating the relationship between SHSE, measured by subjective and objective methods, and conventional cardiovascular risks such as blood pressure and lipid profiles.

Methods: We extracted information on 7,376 healthy adults who had never smoked, for whom there were available urine cotinine levels, from the Korea National Health and Nutrition Examination Survey 2008–2011. SHSE was defined using self-report questionnaires and urine cotinine levels. The main outcomes included systolic and diastolic blood pressure and serum lipid profiles.

Results: The mean age of the study population was 45.4 years and 77.8% were female. Self-reported SHSE had no significant association with study outcomes except for diastolic blood pressure and serum triglyceride levels, which had marginally positive relationships (p=0.078 and 0.070, respectively). Unadjusted models found no significant relationship between urine cotinine levels and any study outcomes. Triglyceride level was inversely associated with urine cotinine after multivariable adjustment (p=0.015); there were no significant relationships between other outcomes.

Conclusions: Although SHSE is associated with increased risk of cardiovascular mortality and morbidity, we did not find any significant relationship between SHSE and blood pressure or lipid levels in this cross-sectional study. Using objective measurements of urine cotinine did not alter this relationship. Further long-term prospective studies are needed to evaluate the effect of SHSE as a cardiovascular risk factor.
NONALCOHOLIC STEATOHEPATITIS DOES NOT INCREASE THE RISK OF ADVERSE CARDIAC OUTCOMES FOLLOWING LIVER TRANSPLANTATION

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2. Golden Heart Medical, Rosemead, CA, USA

Background: It is unclear if nonalcoholic steatohepatitis (NASH) is a risk factor for adverse cardiovascular outcomes after liver transplantation (LT).

Objective: To compare NASH with other cirrhosis etiologies in 1) the prevalence of coronary artery calcium (CAC), and 2) adverse outcomes following LT.

Methods: We retrospectively identified 358 consecutive patients who underwent LT at a tertiary university hospital center between 2010 and 2015. Thirty-nine patients were diagnosed with NASH, with the remainder (319) diagnosed with alternate cirrhosis etiologies. All patients received chest CT scans during their pre-operative evaluation. Major adverse cardiovascular events (MACE) were evaluated during the index hospitalization. Student’s T-test was performed for continuous variables, Chi-Square test for categorical variables, with p<0.05 considered significant.

Results: NASH patients were more likely to be female (62%) and older (57.6 y), with a high prevalence of CAD risk factors including HTN, DM, hyperlipidemia, and obesity (Table). There was no significant difference between groups for presence of CAC (p=0.57). There was no significant difference between groups for inpatient MACE (p=0.71), cardiac mortality (p=0.34), or all-cause mortality on longterm follow-up.

Conclusions: In this single center, retrospective study, NASH cirrhosis was not associated with increased prevalence of CAC or worse post-operative outcomes.

Table:

<table>
<thead>
<tr>
<th></th>
<th>Other Cirrhosis (N=319)</th>
<th>NASH (N=39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>113(35.4)</td>
<td>24(61.5)</td>
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<tr>
<td>Age</td>
<td>52.8±10.3</td>
<td>57.6±9.7</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI</td>
<td>26.7±5.7</td>
<td>33.8±7.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82(25.7)</td>
<td>22(56.4)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Hyperlipidemia</td>
<td>16(5.0)</td>
<td>7(18.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>67(21.0)</td>
<td>20(51.3)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Prior Substance Abuse History</td>
<td>76(23.8)</td>
<td>3(7.7)</td>
<td>0.02</td>
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<tr>
<td>Family History of CAD</td>
<td>31(9.7)</td>
<td>13(33.3)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Calcification in coronary arteries</td>
<td>124(38.9)</td>
<td>17(43.6)</td>
<td>0.57</td>
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</tbody>
</table>

Complications

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<tr>
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<th>Other Cirrhosis (N=319)</th>
<th>NASH (N=39)</th>
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<tbody>
<tr>
<td>Post-op MACE</td>
<td>19(6.0)</td>
<td>1(2.6)</td>
<td>0.71</td>
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<tr>
<td>Emergent coronary revascularization</td>
<td>1(0.3)</td>
<td>0(0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Post-op arrhythmias</td>
<td>39(12.2)</td>
<td>5(12.8)</td>
<td>0.92</td>
</tr>
<tr>
<td>Peri-operative infection</td>
<td>129(40.4)</td>
<td>16(41.0)</td>
<td>0.99</td>
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</table>

Long term Mortality Outcomes

<table>
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<tr>
<th></th>
<th>Other Cirrhosis (N=319)</th>
<th>NASH (N=39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>9(2.8)</td>
<td>2(5.1)</td>
<td>0.34</td>
</tr>
<tr>
<td>Non-cardiac death</td>
<td>26(8.2)</td>
<td>3(7.7)</td>
<td>1.0</td>
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THE EFFECT OF GINGER SUPPLEMENTATION ON THE LIPID PROFILES, BLOOD GLUCOSE, QUALITY OF LIFE AND FUNCTIONAL CAPACITY IN PATIENTS WITH CORONARY ARTERY DISEASES

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Background: Cardiovascular disease remains the main cause of mortality in the world. Ginger supplementation is a traditional herbal treatment for coronary artery diseases (CAD) and may contain compounds that are useful for heart and blood vessels. The aim of this study was to determine the effect of ginger supplementation on clinical outcomes and quality of life for atherosclerosis coronary disease.

Materials and Methods: This study was a placebo-controlled triple blind clinical trial involving 72 patients with CAD not candidate for revascularization for 2 months from October to December 2015. Cholesterol, blood glucose, triglyceride and VLDL, HDL, LDL was measured at the beginning and after two months. Ginger powder and placebo were given 1600 mg per day. Quality of life questionaries’ SF36 and symptom limited exercise test were done before and after the intervention. Test variables using Paired T-Test, Student T-Test, Wilcoxon and Mann-Whitney were compared and P ≤ 0.05 was considered significant.

Results: In the experimental group weight, FBS, TG, VLDL compared to the control group (placebo) decreased statistically significant (P ≤ 0.05). In Ginger consumer groups peak of exercise test and duration (METS) increased statistically significant (P ≤ 0.05). Total score for quality of life as well as chest pain score improved in the intervention group was more effective than placebo (P ≤ 0.05).

Conclusion: This study showed that taking ginger supplement for 2 months in patients with coronary artery disease is valuable for reducing blood lipid, reducing mean fasting blood sugar, improve performance and quality of life and chest pain, and it that taking this supplement.
THE STUDY OF CHANGES OF MOLECULAR BIOMARKERS DURING DEVELOPMENT OF OBESITY USING NUTRIGENOMIC TOOLS

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Background: Obesity and its related complications have emerged as global health problems. However, the mechanisms of the delayed pathological alterations during the development of diet-induced obesity (DIO) are not fully understood.

Objective: The aim of this study was to establish the time-course of changes in hepatic and adipocyte morphology, and the global transcriptional landscape in liver and visceral WAT during the development of DIO.

Methods: Male C57BL/6 J mice were fed a high-fat diet (HFD) or normal diet (ND) and sacrificed at 8 time-points over 24 weeks.

Results: HFD-fed mice developed early clinical indicators of obesity-related co-morbidities including fatty liver, insulin resistance, hyperglycemia and hypercholesterolemia. Excessive fat accumulation was evident in liver and visceral WAT deposits (Epidydimal, Perirenal, Retroperitoneum, Mesentery) after 2–4 weeks. Plasma adipokines, leptin, resistin and adipisin, increased early and time-dependently, while adiponectin decreased late after 20 weeks. Time-course microarrays revealed the genes associated with immune responses were upregulated with an oscillating expression pattern between weeks 2 and 8, relatively downregulated between weeks 12 and 16, and eventually upregulated after week 20 in the liver of the mice fed HFD. The genes associated with immune responses were also upregulated at late stage, in the eWAT of the mice fed HFD. These results suggested that a critical transition occurred in the immune system-related transcriptomes of the liver and eWAT around week 16 of the DIO development, and this may be associated with the delayed pathological alterations such as insulin resistance, glucose intolerance and an elevated atherogenic index after week 16. Maff seemed to be a key transcription factor for the immune system-related critical transition that occurred at week 16.

Conclusion: New therapeutic approaches targeting liver and visceral adipose tissue genes altered by HFD feeding may help ameliorate the deleterious effects of diet-induced obesity.
LIPIDS, OBESITY, METABOLIC SYNDROME AND DIABETES

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ACUTE EFFECTS OF EXERCISE ON POST-PRANDIAL ACTIVITY OF DIPEPTIDYL PEPTIDASE-4 IN TYPE 2 DIABETES MELLITUS

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2. Laboratory of Molecular and Cellular Physiology, Federal University of Espirito Santo, Vitoria, ES, Brazil

The post-prandial “hyperglycemic spikes” may be relevant to the pathophysiology of diabetic complications and cardiovascular disease. Because glucagon-like peptide-1 (GLP1) remains active under hyperglycemic conditions in type 2 diabetes (DM2), dipeptidyl peptidase-4 (DPP4) has gained considerable interest as a therapeutic target, and a variety of DPP4-inhibitors that prolong the insulinotropic effect of GLP1 are now in clinical use as antidiabetic drugs. Substantial DPP4 activity is found in plasma and may be altered in inflammatory diseases. However, there are a lack of evidences regarding the effect of feed and exercise on DPP4 activity in DM2. The aim was to evaluate post-prandial DPP4 activity and the effect of a single bout of aerobic exercise on the postprandial DPP4 activity. Six subjects with DM2 (5 female, age 57.5 ± 9.5 years, BMI 26.9 ± 4.9 kg/m², HbA1c 6.8 ± 0.2%) performed 40 min of treadmill exercise (5/6 km/h; DM2-EXE) or control intervention (DM2-CON) in a random crossover design at 9:00am. A standard mixed breakfast and meal at 8:00am and 12:00pm were done. Plasma DPP-4 activity was evaluated before breakfast, 15 min after exercise or control intervention and 60 min after lunch. No differences (p>0.05) were found between DM2-EXE (0.031 ± 0.004 FU/min) and DM2-CON (0.033 ± 0.006 FU/min) interventions on DPP-4 activity before breakfast. No changes (p>0.05) were observed on DPP-4 activity after DM2-EXE (+0.1 ± 13.9%) and DM2-CON (-8.2 ± 15.4%) interventions. However, 1-h after lunch, reduced DPP-4 activity was observed (p<0.05) only for DM2-CON intervention (DM2-CON, -9.6 ± 8.7%; DM2-EXE -1.2 ± 10.5%). Aerobic exercise had no effect on DPP4 activity immediately after exercise. Postprandial reduction of DPP4 activity which is seen in DM2-CON intervention is absent with aerobic exercise. It may be taken as an index of indirect incretin gut response failure that is attenuated with aerobic exercise.
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strict control of diabetes mellitus may not prevent arteriosclerosis

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¹. Toho University Sakura Medical Center, Tokyo, Japan

Strict control of diabetes mellitus (DM) has been reported to fail in prevention of cardiovascular events. However, there have been few reports on association between progression of carotid arteriosclerosis and control level of DM.

Methods: The 41 patients on strict control (SC) (mean age 61.32 years old) and 46 patients on standard or no control (NC) were studied (mean age 63.29 years old). HbA1c of SC group was maintained under 6.9%, and that of NC group was maintained over 7%. Plaque score (PS) was calculated by ultrasonography. Changes of PS were evaluated for 5.31 years. Cardio-ankle vascular index (CAVI) was also evaluated.

Results: In most of patients, systolic blood pressure was maintained under 140 mmHg, and LDL cholesterol level was kept under 140 mg/dl. Number of arteriosclerosis risk factor in patients on SC was similar to that in those on NC. Mean PS was 3.82 in SC group and 3.42 in NC group. PS increased from 3.82±2.29 to 4.46±2.32 in SC (mean±SD) and from 3.42±1.98 to 4.95±2.36 in SG (P<0.05 each). CAVI did not change significantly (mean 8.92 to 9.01).

Conclusions: Strict control of DM may not prevent progression of carotid arteriosclerosis. Stability of CAVI cannot be associated with prevention of arteriosclerosis.
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CTRP1 INHIBITS HYPERGLYCEMIA IN DIO MODEL

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Complement-C1q/tumor necrosis factor related protein 1 (CTRP1) is a 35-kDa glycoprotein that is secreted from various tissues. Although CTRP1 is highly increased in patients with type II diabetes and obesity, the metabolic roles of CTRP1 remain largely unknown. To unveil the physiological roles of CTRP1 in vivo, CTRP1 transgenic (TG) mice were challenged by a high-fat diet (HFD) and a high-sucrose drink (HS). Homeostatic model assessment-estimated insulin resistance values were decreased in HFD- or HS-fed CTRP1 TG mice compared with wild-type control mice. In this context, CTRP1 stimulated glucose uptake through the glucose transporter GLUT4 translocation to the plasma membrane and also increased glucose consumption by stimulating glycolysis. To analyze the roles of CTRP1 in lipid metabolism, acetyl-CoA carboxylation (ACC) and hormone-sensitive lipase levels were determined in CTRP1 TG mice, and the effect of CTRP1 on fatty acid oxidation was assessed in C2C12 myotubes. CTRP1 was found to inhibit ACC by phosphorylation and to stimulate fatty acid oxidation in C2C12 myotubes. Taken together, CTRP1 performs active catabolic roles in vivo. Therefore, CTRP1 seems to perform a defensive function against nutritional challenges.
Heart rate variability (HRV) provides valuable information in various clinical settings. Limited information exists on changes in cardiac autonomic modulation in extremely obese patients (BMI>40).

The aim of this study was to investigate the influence of extreme (morbid) obesity and concomitant diseases on cardiovascular autonomic function. Participants of this study are 40 women and 40 men in mean age 47.9 years old diagnosed with morbid obesity (mean BMI =47.49) and hospitalized to further bariatric treatment. In 42 patients diagnosed with hypertension (treated with beta blockers and ACE inhibitors along with well controlled blood pressure), type 2 diabetes (treatment with the oral drugs) also occurred. Furthermore, 46 patients were diagnosed with depression. None of the participants used antidepressants or sedative agents. Total of 80 healthy (40 women and 40 men) in mean age 42.7 years old and with mean BMI= 24.6 were formed in group of controls. All of patients had 24-hour ECG monitoring with Holter method in order to evaluate the autonomic activity with time and frequency domain analysis (heart rate variability - HRV).

Results: Obese group showed a significant reduction of parasympathetic activity and a significant increase in sympathetic activity. No significant differences in cardiac autonomic modulation were noted between the Hypertensive-Diabetic patients and those, only with morbid obesity. However, in studied group, obese patients with depression had lower time and frequency domain parameters (p<0.05) except SDNN, SDANN and LF/HF ratio in contrast to obese non-depressive individuals. Additional load of diabetes and hypertension in depressed patients did not affect the cardiac autonomic modulation differences. Further prospective study can be undertaken within the same subjects to evaluate the effect of weight loss on the cardiac autonomic activity.

Conclusions:
1. Extreme obesity altered cardiac autonomic activity independently of hypertension and diabetes.
2. Depression associated with morbid obesity intensified HRV reduction.
LIPIDS, OBESITY, METABOLIC SYNDROME AND DIABETES

CORRELATION OF LIPID PROFILE AND LIPOPROTEIN RATIOS WITH ANGIOGRAPHICALLY SIGNIFICANT CORONARY ARTERY DISEASE: A RETROSPECTIVE DESCRIPTIVE STUDY

F.J. Navarro, R.E. Ramboyong
The Medical City, Pasig City, Philippines

Background: Lipid profile determination aids in cardiovascular risk assessment. The exclusive use of low-density lipoprotein (LDL) cholesterol as a risk marker has been contested by epidemiologists and clinicians.

Objective: This study aims to determine the association of lipid profile and lipoprotein ratios with the presence of angiographically significant coronary artery disease (CAD).

Methodology: This is an observational, retrospective cohort study conducted on all patients who underwent coronary angiography and requested with lipid profile from July 2015 to June 2016. Their corresponding lipid profile components: Total Cholesterol (TC), High density lipoprotein (HDL), LDL, Triglycerides (TRIG) and lipoprotein ratios: TC/HDL, LDL/HDL and TRIG/HDL were analyzed. Statistical analyses of the data were conducted using Independent Samples t Test, Area under the Curve (AUC) and Analysis of Variance (ANOVA). Logistic regression analysis determined the association between the lipid profile and lipoprotein ratios with the presence of CAD.

Results: Three hundred thirty (330) patients were investigated, 73% (242) had significant CAD findings. Analysis by logistic regression showed that a higher HDL value indicates a low probability of significant CAD by coronary angiography with a regression coefficient of -0.023. A TC/HDL value of greater than 4.24 is the optimal threshold in predicting an angiographically significant CAD with a sensitivity of 62% and specificity of 50%; for LDL/HDL a value greater than 2.74 has a sensitivity of 61% and specificity of 50% and for TRIG/HDL a value greater than 2.84 has a sensitivity of 60.7% and specificity of 50%.

Conclusion: Lipoprotein ratios including: TC/HDL, TRIG/HDL and LDL/HDL can potentially be used in predicting angiographically significant CAD.
DIFFERENTIAL GENDER BASED DIAGNOSTIC TESTING AND PREVALENCE OF CARDIOVASCULAR DISEASE, A COHORT ANALYSIS OF VETERANS ADMINISTRATION REGISTRY DATA

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2. Captain James A Lovell Federal Health Care Center, North Chicago, IL, USA

Background: Cardiovascular disease remains the leading cause of mortality in women with 421,918 deaths in 2007 in the United States and women tend to have higher mortality following myocardial infarction and a higher incidence of subsequent heart failure (HF).

Objectives: We looked at the comparative prevalence of cardiovascular conditions and utilization of diagnostic testing in male and female veterans.

Methods: Data for this report were derived from centralized Veterans Health Administration (VHA) administrative files (The Monthly Enrollment File and the Outpatient Encounter File from the VHA’s National Patient Care Database) for the financial year 2010. Gender based comparison of the prevalence of cardiovascular condition was made between three cohorts based on age. Age-adjusted odds ratios and 95 percent confidence intervals were determined using logistic regression.

Results: Women had higher rates than men in all age groups for chest pain/angina (odds ratio 1.00 (0.99-1.02) p value less than 0.05). Coronary artery disease (CAD) (odds ratio 0.30 (0.29-0.30) p value less than 0.05) and HF (odds ratio 0.56 (0.54-0.58) p value less than 0.05) are less likely to be diagnosed in women than men of the same age. Across all age groups, the most common cardiovascular procedures in outpatients with chest pain/angina were for electrocardiogram, echocardiogram, nuclear stress test and non-imaging (exercise) stress test for both men and women. Although the rates of procedures were similar for men and women across all age groups, women were less likely to receive electrocardiograms (56.05 percent vs 59.74 percent) or stress tests (27.69 percent vs 32.37 percent) in all age groups in their workup for chest pain/angina.

Conclusions: Gender based disparities in rates of diagnostic procedures for chest pain/angina evaluation exist and may be a factor in fewer women being diagnosed with CAD and HF.
Objective: To identify predictors that allow for early detection of cardiovascular disease in African American women

Background: Cardiovascular (CV) mortality is high in African Americans in the United States. Cardiovascular disease (CVD) remains the leading cause of death in African American females. We hypothesize that certain cardiovascular risk factors are predictors of abnormal peripheral vascular compliance. We aim to identify determinants of abnormal vascular compliance by assessing the association between known CVD risk factors and the extent of vascular compliance

Methods: This cross-sectional study utilized survey responses and results from a noninvasive screening tool. The study included only African American women. Traditional CV risk factors were independent variables (history of hypertension, high serum lipids, family or personal history of CVD). The instrument employed biomarkers that detect blood vessel elasticity. Outcome measures included small and large vessel compliance. Both survey responses and screening results were obtained from 70 consecutive participants. We conducted a univariate and bivariate descriptive analysis. A Chi-square or Fishers exact test was used to determine the significance as appropriate. We adjusted for potential confounders in our multivariable analysis. SAS 9.4 software was used for all the data analyses.

Results: Our study indicates that personal history of cardiovascular disease is strongly associated with abnormal small vessel compliance (Pvalue - 0.01). Family history of cardiovascular disease is strongly associated with abnormal large artery compliance (Pvalue - 0.02). History of cardiovascular disease in both parents is associated with abnormal large artery compliance (Pvalue - 0.04). Interestingly, Living Situation (Living alone) was associated with abnormal large artery compliance (Pvalue - 0.03).

Conclusion: Family and personal history of CVD, and living alone have strong associations with abnormal vascular compliance. Cardiovascular mortality is high in Black and African American females. Identifying predictors of abnormal vascular compliance can allow for early disease detection and intervention.
HEART DISEASE IN WOMEN

INITIAL EVALUATION OF THE MULTIMORBIDITIES AND THE FEMININE UNIVERSE: TO KNOW TO BETTER CARE
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Introduction: The female universe presents several characteristics, which become more exuberant after climacteric. The prevalence of multiple chronic conditions (MCC) has increased and the evaluation of these conditions according to gender has its relevance, especially in the decision to better manage these conditions.

Objectives: To evaluate the biopsychosocial profile of women with MCC in outpatient follow-up.

Methods: Cross-sectional observational study, evaluating medical records of a secondary public service to assist hypertensive and diabetic population, between 11/2016 to 01/2017. We have declared atherosclerotic disease (DAD), the one with atherosclerotic lesions independent of the affected vascular bed; DRC, glomerular filtration rate (GFR) <60 ml / min.

Results: 1646 records of the service were evaluated, corresponding to 67.8% of the sample. Compared with males, women presented with lower age range (p< 0.001) and schooling (p< 0.028), higher prevalence of family history of cardiovascular diseases (p< 0.023), sedentary lifestyle (p< 0.001), hypertension (p< 0.001), type 2 diabetes mellitus (p< 0.001), hypothyroidism (p< 0.001), osteoarthrosis (p< 0.003), depression (p< 0.001); while they presented lower prevalence of tobacco use (p< 0.001) and alcohol (p< 0.001).

Conclusion: The female gender presents peculiar characteristics to the screening, diagnosis and handling of multi-morbidities that should be carried out in a systematic way in favor of a better care of this population.
ACUTE CORONARY SYNDROMES, INTERVENTIONAL THERAPIES

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EFFECT OF BASELINE SYMPTOMS OF ANGINA ON CORONARY FRACTIONAL FLOW RESERVE
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Background: Fractional flow reserve (FFR), the hyperemic ratio of distal (Pd) to proximal (Pa) coronary pressure, is used to identify the need for coronary revascularization. Baseline symptoms of angina may affect the FFR measurements.

Study Design: A retrospective cross sectional study was performed including all patients who underwent cardiac catheterization with FFR study for the needs of revascularization and had echocardiographic assessment for underlying RWMA during January 2010 to January 2016. Data on various hemodynamic and non-hemodynamic variables that could possibly affect FFR (explained below) was obtained. Simple and two-sample t-tests were used to perform the analyses. Cut off of less than 0.8 was used to define significant FFR value.

Results: Study population included 189 patients with mean age of 64(11) years. Baseline characteristics with 26 percent females, angiographic mean stenosis severity of 60 percent(13), LVEDP 16mmHg(7), MAP 101mmHg(14), HR 74 bpm(16), spO2 96 percent(2.3), Lesion site [proximal 75 (40 percent), mid 81(43 percent), distal 12(6 percent), branch vessel 21(11 percent)], diabetic 36 percent, renal disease 8.5 percent, PVD 10 percent, hypertension 85 percent, hyperlipidemia 100 percent, smoker 25 percent, preserved versus reduced LVEF of 94 percent versus 6 percent respectively(cut off of 40), with 56 (30 percent) had RWMA at baseline. Adenosine was used in 167 (88 percent) cases where as Nipride was used in rest of the cases. Before undergoing FFR study, symptoms of angina were present in 154(81.5 percent) of cases compared to 35 (18.5 percent) without angina symptoms. No difference in FFR trends were noted in patients with baseline angina symptoms [0.82(0.73, 0.91)]versus[0.84(0.76, 0.92)] respectively with p value of 0.18.

Conclusion: In this study population, baseline symptoms of angina were not associated with significant FFR values compared to no baseline angina, in the territorial distribution of vessel undergoing FFR study.
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PROCEDURAL EFFICACY OF FEMORAL VS RADIAL IN PERCUTANEOUS CORONARY INTERVENTIONS IN PATIENTS PRESENTING WITH STEMI
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Background: Radial access in cardiac catheterization has increased in the last few decades. We report an analysis of procedural efficacy in patients presenting with ST-elevation myocardial infarction (STEMI).

Methods: Data from 533 consecutive patients presenting with STEMI were collected from University of South Dakota, at Sanford Heart Hospital from 2011 to 2015. Data was analyzed to evaluate procedural efficacy as determined by fluoroscopy time and contrast use.

Results: Femoral access represented 34% (181/533), and radial access represented 66% (352/533). Crossover from radial to femoral access represented 23% of initial radial access. Radial access showed trend towards increased contrast use (p = 0.0735) and increased fluoroscopy time (p = 0.165). Crossover from radial to femoral access were associated with increased fluoroscopy time (p = 0.178) and contrast use (p = 0.337) when compared to initial femoral access. Crossover from radial to femoral had similar fluoroscopy time (p = 0.710) and contrast use (p = 0.730) compared to initial radial access.

Conclusions: In patients presenting with STEMI, initial radial access appears to be non-inferior to initial femoral access with respect to procedural efficacy, although radial access showed a trend towards increased fluoroscopy time and contrast use. Crossover from radial to femoral access showed trend towards decrease procedural efficacy when compared to initial femoral access, but showed similar efficacy when compared to initial radial access.
IMPACT OF HYPERURICEMIA ON THE CLINICAL OUTCOME AFTER PERCUTANEOUS CORONARY INTERVENTION FOR IN-STENT RESTENOSIS

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Background: There have been limited data on the impact of hyperuricemia on long-term clinical outcome after percutaneous coronary intervention (PCI) for in-stent restenosis (ISR).

Methods: From January 2009 to July 2015, 317 patients who underwent repeat PCI for ISR were divided into the normal serum uric acid (UA) level group and the higher serum UA level group. Higher UA group included the patients with hyperuricemia more than 6.8 mg/dL or the patients took anti-hyperuricemic medication.

Results: During a median follow-up period of 1088 days, the cumulative incidence rates of major adverse event (MAE), a composite of all-cause death, non-fatal myocardial infarction and any revascularization, was similar between two groups (Higher UA 36.4% vs Normal UA 29.9%, p=0.389; log-rank p=0.367). Follow-up angiographic outcome showed the similar late lumen loss (0.8 ± 0.9 mm vs 0.8 ± 1.1 mm, p=0.895) and binary restenosis rate (28.1% vs 34.7%, p=0.622). Multivariate Cox regression analysis indicated not uric acid level but higher low-density lipoprotein cholesterol (LDL-C) level and lower left ventricular ejection fraction (LVEF) as the independent risk predictors for MAE (LDL-C, HR 1.011, 95% CI 1.003 - 1.019, p=0.006; LVEF, HR 0.972, 95%CI 0.948 - 0.996, p=0.022).

Conclusion: Hyperuricemia was not associated with poor clinical outcome after repeat PCI for ISR lesion.
Background: Spontaneous coronary artery dissection (SCAD) is an uncommon cause of coronary artery disease.

Aim: The aim of the study is to analyze the clinical profile, angiographic profile, in hospital outcomes, management and follow up of patients with angiographic SCAD

Method: This is a retrospective, single center study. We retrospectively reviewed medical records and coronary angiograms of patients admitted to our institute from Jan 2010 TO Dec 2011. Out of 19,676 diagnostic coronary angiograms, 64 patients had SCAD and were included in the study.

Results: A total of 64 cases of SCAD were identified. The patients comprised of 60 (93.8%) males and 4 (6.3%) females with an age range of 25 to 70 years. The incidence of SCAD was 0.32%. In this series risk factors for SCAD were smoking (50%), diabetes (29.7%) and hypertension (27.9%). Majority had single vessel involvement 55 patients (85.9%). Left anterior descending artery was involved in 45.3% patients followed by right coronary 37.3% and circumflex artery 9.3%. Twelve patients (18.8%) had received fibrinolytic therapy prior to angiogram and there was no mortality in this group. All the patients were managed conservatively and there was no in hospital mortality. The mortality at 1 year follow up was 6.2%.

Conclusion: SCAD occurs in 0.32% of patients undergoing coronary angiogram for evaluation of coronary artery disease. Majority of SCAD occurs in men. The left coronary artery is most commonly. Most of the patients with SCAD have good prognosis following optimal medical therapy. The mortality rate was 6.25% at 1 year.
SPONTANEOUS CORONARY ARTERY DISSECTION FOLLOWED BY IATROGENIC FEMORAL ARTERY DISSECTION IN A PATIENT WITH EHLERS-DANLOS SYNDROME

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Background: Spontaneous coronary artery dissection (SCAD) is a rare, sometimes fatal condition, with 80% of cases affecting young women without coronary risk factors. Revascularization is challenging and is recommended for patients with favorable anatomy.

Case: 45 years old female with history of Ehlers-Danlos Syndrome type 4 presented with sudden onset substernal chest pain, radiating down to her left arm associated with dyspnea and dizziness. Initial ECG showed no abnormality except sinus bradycardia. Troponins were elevated to 0.12, and ECG showed new T-wave inversion in V1-V3. CT angiogram ruled out pulmonary embolism, coronary artery and aortic dissection. Echo showed ejection fraction of 65% with basal inferior and infero-septal hypokinesis. Cardiac catheterization via right femoral artery revealed dissection of the Right Coronary Artery (RCA). Considering patient’s history of Ehlers-Danlos Syndrome, it was decided to manage patient conservatively, however, due to persistent symptoms of chest pain, catheterization was repeated. Attempt to place a stent in RCA failed. She was discharged on dual anti-platelets and was enrolled in cardiac rehabilitation. After a week, she developed paraesthesias and claudication of right lower extremity during exercise. An ultrasound demonstrated a dissection and a 6 cm nonocclusive thrombus within the proximal right common femoral artery and distal right external iliac artery with significant impingement of false lumen on the true lumen (true lumen size of 0.2cm). Patient was managed conservatively with a structured exercise program, right foot care by avoiding extremes of temperature and using appropriate footwear to prevent pressure sores or ulcerations. Aspirin, beta-blockers, nitrates and cardiac rehabilitation were continued.

Conclusion: CT angiogram may miss a coronary artery dissection. Coronary angiogram is the gold standard to diagnose SCAD. One must think of SCAD in patients with history of Ehlers-Danlos syndrome that presents with chest pain, and should watch for the peri-procedural complications.
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COULD RELYING TOO MUCH ON RADIAL APPROACH RISK LOSING THE TRADITIONAL FEMORAL SKILLS?

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Objectives: This study was conducted to assess the perceived comfort level of cardiology fellows with radial catheterizations and predict the practice patterns in the US in the near future.

Background: The adoption of transradial catheterization has been relatively slow in the United States. Level of fellowship training, academic affiliation, and clinical scenarios (elective vs. urgent), seems to be variables that determine comfort level of pursuing transradial vs. transfemoral cardiac catheterization.

Methods: A 21-question online survey on cardiology fellows’ preferred cardiac catheterization access site was conducted between April and June 2015. Data on access preference and perceived competency was analyzed based on the fellow’s level of training and type of training program (University vs Community).

Results: A total of 101 responses were received out of a total of 250 invitations; 85 (85%) of these respondents completed all questions. Data was collected from fellows of several programs nationwide. Of the 85 respondents with complete data, 22%, 29% and 19% were 1st, 2nd and 3rd year cardiology fellows respectively. Most respondents (82%) were from University based programs, 46.3% considered that their programs provided a balance of both radial and femoral training. Irrespective of the training year, most fellows seemed to prefer radial over femoral access. Senior fellows appeared to be equally comfortable with a femoral access approach (P=0.03). There was no difference by training site (University vs. Community programs) (P=0.921).

Conclusions: In 2015, US cardiology fellows appear to prefer radial over femoral access for cardiac catheterizations. Although it is good to see the shift towards better radial access skills; we need to stress the importance of the femoral skills that will be necessary to keep in the armamentarium of interventional cardiologists.
RADIAL ARTERY OCCLUSION AFTER CARDIAC CATHETERIZATION: SIGNIFICANCE, RISK FACTORS AND MANAGEMENT
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Objective: To provide a concise review of the significance of radial artery occlusion (RAO) after transradial (TR) coronary angiography and to highlight methods to identify high risk groups, prevention tactics, and therapeutic options for this rare but potentially devastating complication.

Background: TR cannulation is poised to supplant transfemoral (TF) cannulation as the access site of choice in coronary angiography, catheterization, and percutaneous coronary intervention procedures worldwide. With lower incidence of vascular complications, improved patient satisfaction, preference among general and interventional cardiology fellows, the use of TR access and its complications are expected to rise in the foreseeable future. RAO is an often underreported and overlooked complication that can present as critical limb ischemia up to four months post procedure. Currently, rates as low as 0.8% to as high as 30% have been identified and thus our aim is to create awareness, provide preventative measures and management options of this complication.

Discussion: Prevention of RAO begins with identifying subsets of patients that are considered higher risk as they would benefit from additional monitoring prior to, during and after TR access. Pre-procedure radial artery patency evaluation via the Allen’s tests can assist in identifying patients who are unsuitable for TR access. Intraoperatively, the use of the Seldinger technique, smaller sheath size, adequate prophylactic anticoagulation, and intra-arterial vasodilator prior to sheath removal have all shown to be beneficial in reducing ROA. The duration of treatment with anticoagulation for non-surgical patients in those whom ROA occurs is unknown, however it is reasonable to use direct acting oral anticoagulants for three months.

Conclusion: As the use of TR access continues to increase, practitioners must be vigilant in reducing the risks for RAO. This can be achieved by identifying high risk patients, performing pre-procedural patency evaluation, maintaining appropriate anticoagulation in the intraoperative setting and assuring post procedural hemostasis.
Improvement of Cardiac Sympathetic Nervous Activity After TAVR Evaluated by Using 123I-MIBG SPECT

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Background: Whether patients with aortic stenosis (AS) have increased sympathetic nervous activity (SNA) remains to be established, and the effects of transcatheter aortic valve replacement (TAVR) on the sympathetic nervous system are also unknown. We sought to investigate the early therapeutic effects of TAVR on cardiac SNA in patients with severe AS.

Objective: To evaluate cardiac SNA, 123I-metaiodobenzylguanidine single photon emission–computed tomography (123I-MIBG SPECT) was performed.

Methods: We studied 8 patients with severe symptomatic AS (84.6 ± 4.4 years old, 3 males, aortic valve area 0.60 ± 0.14 cm²) treated by TAVR (7 transfemoral approaches, 1 transapical). All patients underwent 123I-MIBG SPECT at baseline and 2 weeks after TAVR.

Results: In 123I-MIBG SPECT imaging, washout rate was significantly improved from 27.93 ± 7.44 to 23.50 ± 6.52; P = 0.027). By contrast, the early and delayed heart/mediastinum ratio (HMR) did not change. (early HMR 2.51 ± 0.44 to 2.51 ± 0.40; P = 0.500, delayed HMR 2.21 ± 0.44 to 2.51 ± 0.40; P = 0.500).

Conclusions: 123I-MIBG washout ratio was significantly decreased after TAVR. These results suggest that TAVR can improve sympathetic turnover. We reported, for the first time, by using nuclear cardiology that patients with AS had improved SNA after TAVR. This study provides evidence of a new beneficial effect of TAVR with regard to normalization of sympathetic nervous system hyperactivity.
TRICUSPID VALVE REPAIR VERSUS REPLACEMENT FOR VERY SEVERE FUNCTIONAL TRICUSPID REGURGITATION

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Background: The optimal decision regarding whether to repair or replace the tricuspid valve (TV) remains controversial in patients with very severe functional tricuspid regurgitation (TR).

Objectives: We sought to compare clinical outcomes of TV repair versus replacement for very severe TR associated with severe TV tethering.

Methods: We included 96 consecutive patients (20 men, 58±11 years of age) who had both severe tethering of TV and very severe functional TR, and consequently underwent TV surgery during left-sided valve surgery. TV repair was performed on 79 patients (repair group), whereas 17 patients underwent TV replacement (replacement group). The primary end-point of the study was defined as the composite of operative mortality, cardiac death, repeat TV surgery and hospitalization due to congestive heart failure during follow-up.

Results: The two groups had similar baseline clinical, echocardiographic and operative characteristics, but operative mortality was significantly higher in the replacement group than in the repair group (P=0.008). During a median follow-up of 87 months, 19 (24%) patients in the repair group and 8 (47%) in the replacement group attained the composite end point, and the estimated 10-year event-free survival rate was significantly higher in the repair group (75 ± 6%) than in the replacement group (43 ± 2%) (P = 0.019). TV replacement was independently associated with end points in the Cox proportional hazards analysis after adjustment with propensity score (hazard ratio, 4.033; 95% CI, 1.470 to 11.071; P=0.007).

Conclusions: Compared with TV repair, replacement was associated with higher operative mortality and worse long-term clinical outcomes in patients with very severe functional TR. Repair should be the preferred surgical option even for severe TR associated with more advanced tethering and right ventricular dilatation.
THE INTEGRATED VALUE OF SST2 AND GLOBAL LONGITUDINAL STRAIN IN THE EARLY STRATIFICATION OF PATIENTS WITH SEVERE AORTIC VALVE STENOSIS: A TRANSLATIONAL IMAGING APPROACH

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Background. Aortic valve stenosis (AVS) is associated with significant left ventricular hypertrophy and myocardial fibrosis (MF). Left ventricular (LV) global longitudinal strain (GLS) is a better indicator of systolic dysfunction than ejection fraction (EF). ST2 is a member of the interleukin (IL)-1 receptor family and a modulator of hypertrophic and fibrotic responses.

Methods. Twenty-two patients with severe AVS and preserved EF underwent surgical aortic valve replacement. They performed laboratory analysis, including serum ST-2 (sST2), echocardiography (including GLS), left heart catheterization and inter-ventricular septum biopsy to assess MF (%). sST2 assay and echocardiography were performed on 10 controls for comparison.

Results. Compared to controls, patients showed higher sST2 levels (p<0.0001). sST2 showed correlation with Age (r=0.58; p=0.0004), E/e’average (r=0.58; p=0.0007), GLS (r=0.61; p=0.0002), LAVi (r=0.51; p=0.003), LVMi (r=-0.43; p=0.01), sPAP (r=0.36; p=0.04) and SVi (r=-0.47; p<0.005). At multivariate analysis, GLS was the only predictor of sST2 (Multiple R2=0.35; p=0.0004). No correlation was found between MF and sST2.

Conclusions. Patients with severe AVS present elevated sST2 levels, reflecting a significant systolic and diastolic impairment. LV GLS resulted the only independent predictor of sST2 levels.
INTRACARDIAC ECHOCARDIOGRAPHY GUIDANCE DURING ANTEGRADE BALLOON AORTIC VALVULOPLASTY FOR SEVERE AORTIC STENOSIS

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Background: The use of balloon aortic valvuloplasty (BAV) is increasing in the current transcatheter aortic valve replacement era. The recent development of the real time phased-array intracardiac echocardiogram (ICE) imaging could play a critical role in monitoring therapeutic effects of balloon inflations or in diagnosing potential complications in their early stages.

Methods: In this study, 11 severe aortic valve stenosis (AS) patients who underwent ICE-guided BAV were retrospectively compared with 12 AS patients in whom the conventional technique was used. ICE guided BAV was obtained in all cases starting April 2015 (ICE group) while conventional technique without ICE guidance (non-ICE group) was used in cases prior to this date. All BAV procedures were performed by a transvenous transseptal (antegrade) approach to access the aortic valve.

Results: The mean age were not found to be statistically significant between the groups (83.4±1.5 vs. 84.2±1.4, p=0.68). Technical success was achieved in all patients. Mean transaortic valve pressure gradient improved from 55.1 ± 18.9 mmHg to 37.0 ± 14.4 mmHg (P<0.01) and aortic valve area increased from 0.63 ± 0.18 cm² to 0.85 ± 0.19 cm² (P<0.01). There was no statistically significant difference between ICE group and non-ICE group. One patient died from a cardiovascular cause within 30 days of BAV procedure and 1 patient developed tamponade in non-ICE group. The rates of patients with worsening aortic valve regurgitation were higher in the non-ICE group than in the ICE group after the procedure. Average procedure time was found to be significantly shorter in the ICE group than in the non-ICE group (93±14 minutes vs. 101±15 minutes, P = 0.011).

Conclusion: ICE is now employed to provide real-time imaging of relevant intracardiac structures for BAV procedures. The use of ICE during BAV procedures facilitates procedural efficacy and identifies and potentially reduces complications.
AORTIC VALVE AND ROOT PROPORTIONS - DETAILED OBSERVATIONS
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Background: Calcific aortic stenosis is the most common lesion requiring valve replacement. Transcutaneous procedures (TAVR) are rapidly increasing. Yet we lack detailed information on aortic valve and root anatomy. This study used gated cardiac CT to measure size and proportions of the valve leaflets, sinuses of Valsalva, and ascending aorta.

Methods: 150 gated cardiac CT scans were performed for a variety of clinical indications. The following were measured: area of each cusp (short axis plane), height of each sinus (from leaflet base to sinotubular junction), width of each sinus (from central coaptation point to outer sinus edge), annular perimeter, perimeter at mid-sinus level, and perimeter at the sinotubular junction.

Results: The right cusp (RCC) was largest, the left (LCC) smallest, and the non- (NCC) intermediate. Each cusp was larger in men than women, even after indexing for BSA (chart). By contrast, sinus width and height did not differ between the sexes. No significant differences were noted between races.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P value</th>
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<tbody>
<tr>
<td>RCC (mm²)</td>
<td>142±38</td>
<td>117±32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LCC (mm²)</td>
<td>124±29</td>
<td>109±29</td>
<td>0.004</td>
</tr>
<tr>
<td>NCC (mm²)</td>
<td>130±33</td>
<td>116±33</td>
<td>0.02</td>
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Interestingly, the ratio of sinus height (average): annular radius was 1.69±0.18, very close to the “golden ratio” of 1.62 found throughout the natural world. Annular perimeter did not vary by age. However, perimeter at the mid-sinus level and at the sinotubular junction were increased at older ages though the association was weak (p=0.01, r squared=0.05 and p=0.002, r squared=0.07).

Conclusions: The aortic valve cusps are of unequal size; this may have to do with surrounding structures (e.g. interannular fibrosa and atrial septum). Cusps are smaller in women than men, even after indexing to BSA. The proportion of sinus height: annular radius approximates the “golden ratio” which may help foster vortex formation.
Introduction: Intravenous (IV) drug use is commonly associated with right sided infective endocarditis (IE) and can lead to infection by unusual pathogens. A 65 year old male with recurrent blood cultures positive for Serratia marcescens developed endocarditis with Candida parapsilosis. His past medical history included cocaine and heroin use. Echocardiography before surgery found a 2 x 3 cm vegetation at the tricuspid valve.

Case: A 65 year old African American male was repeatedly admitted to a local hospital for sepsis with Serratia marcescens. Initial echocardiography showed mild tricuspid valve regurgitation with focal tricuspid valve leaflet thickening, and transesophageal echo found no evidence of vegetations. He was not compliant with antibiotics and was repeatedly re-admitted with blood cultures positive for Serratia. Echocardiography 46 days after his initial echo showed a 1.5 x 1.8 cm vegetation at the tricuspid septal leaflet and severe tricuspid regurgitation. Bilateral airspace densities suspicious for septic emboli were seen on chest computed tomography. He was diagnosed with IE, discharged to an extended care facility, and later returned to the hospital with blood cultures positive for Candida parapsilosis. Echocardiography before surgery found a 2 x 3 cm mobile vegetation at the anterior tricuspid valve leaflet. He underwent valve replacement, and blood cultures post-surgery were negative.

Discussion: Candida is involved in 2-4% of endocarditis cases with risk factors including IV drug use and prior bacterial endocarditis. The IDSA recommends treatment with amphotericin B or a high-dose echinocandin for native valve Candida endocarditis along with valve replacement and antifungal treatment for at least 6 weeks post-surgery. Even with treatment, the general in-hospital mortality rate of IE is estimated at 15-20%. Patients with IV drug use are frequently re-admitted and at risk for recurrent IE. Surgical management can be a difficult decision when patients are not interested in drug abstinence.
BIOPROSTHETIC VALVE THROMBOSIS: MYTH OR MYSTERY?

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Background: The risk of bioprosthetic valve (BPV) thrombosis is considered to be very low. It is commonly recognized late or overlooked altogether due to lack of awareness of its existence among clinicians.

Case: A 61-year-old man presented with right-sided hemiparesis and aphasia. CT angiogram showed an occlusion of the M1 segment of the left middle cerebral artery, which was treated with mechanical thrombectomy. About one year before, he underwent 3-vessel CABG and mitral valve replacement with a BPV. He completed recommended anticoagulation with a vitamin-k antagonist (VKA) for 3 months. A routine transthoracic echocardiography ordered as a part of the stroke pathway showed a small, mobile mass attached to the BPV. This was further evaluated with transesophageal echocardiography (TEE), which showed a highly mobile, 1.2 cm X 1.2 cm echodense mass attached to the leaflets of the BPV without significant mitral regurgitation. The mean gradient across the mitral valve was 9 mmHg.

Clinical Decision Making: The differential diagnoses for this echodense mass on the BPV were infective endocarditis (IE) and BPVT. IE was ruled out by multiple negative blood cultures and lack of clinical symptoms and signs. He was then started on anticoagulation with the presumed diagnosis of stroke secondary to embolization from the BPVT. He made a steady neurological recovery and is due to have a follow-up TEE to evaluate for resolution of the thrombus.

Conclusion: BPV thrombosis may be more common than previously reported, as illustrated in our case, and it can be effectively treated with VKA. Hence, it is critical to recognize this clinical entity to avoid surgery, which may be the treatment of choice for other differential diagnosis, such as IE.
CARDIOMYOPATHY AND HEART FAILURE: DIAGNOSIS AND MANAGEMENT

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CHRONIC TOTAL OCCLUSION REVASCULARIZATION IN PATIENTS PRESENTING FOR HEART TRANSPLANTATION
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Background: Recommendations for revascularization of chronic total occlusions (CTOs) have not been well established. Revascularization of an ischemic territory in patients with angina is well validated and practiced. Recent study has shown percutaneous coronary intervention (PCI) on CTOs (CTO-PCI) in patients with evidence of viability to improve left ventricular ejection fraction (LVEF). There is limited data to support CTO revascularization carte-blanche in patients with heart failure with reduced ejection fraction (HFrEF). In addition, the role of myocardial viability studies in these patients has also not been well established and debatable at best.

Methods: We present a series of 4 patients who were deemed to be end stage secondary HF secondary to ischemic cardiomyopathy, referred to our center for advanced heart failure therapies (AHFT) including orthotopic heart transplantation (OHT) and Left ventricular assist devices (LVADs). These patients had a mean ejection fraction (EF) of 30%. They all underwent viability testing and then were referred for revascularization on finding of viable myocardium. Three of the patient had disease of the left anterior descending artery and one of the patients had disease of the left circumflex artery. All four patients underwent CTO-PCI and subsequently were able to be optimized on heart failure medications. They all showed clinical improvement and the need for advanced therapies was delayed sine die.

Conclusion: AHFT including OHT and LVADs are expensive and are not benign by any measure. They should be reserved as a last resort after all therapies have been exhausted. Our series shows that patients with CTOs demonstrating myocardial viability should be evaluated for revascularization prior to initiation AHFTs. Larger studies on a bigger magnitude are needed in this area to better validate this practice.
AMLODIPINE OVERDOSE INDUCED NONCARDIOGENIC PULMONARY EDEMA

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Introduction: Amlodipine overdose can be life threatening. We describe a case of Amlodipine overdose in a patient with subsequent development of Non Cardiogenic Pulmonary edema.

Case: 30 year old male with PMH of schizophrenia, Depression, and HTN presented with dizziness and SOB after he intentionally ingested 20 tablets of 10 mg amlodipine. He was hypotensive on initial presentation and responded well to IV fluids. Physical exam was significant for mild distress and slight tremors with flat affect without JVD, crackles or wheezing. However, within 24 hours he developed hypoxemia and pulmonary edema. Patient had received 5 liters of fluid on floors. Echocardiogram showed normal Left ventricular function with an EF 60-65%. Patient was transferred to ICU for close management with IV diuresis and placed on BiPAP.

Discussion: Pulmonary edema secondary to CCB overdose is likely due to capillary transudation due to selective pre-capillary vasodilatation, which causes an increase in Transcapillary hydrostatic pressure leading to interstitial edema. At high doses, the rate of CCB clearance decreases, prolonging the half-life. Despite hypotension, these patients may maintain a surprisingly clear mental status, possibly due to the Neuro-protective effects of CCBs. Precipitous decline in mental status secondary to hypotension or development of Acute respiratory failure secondary to pulmonary edema might need intubation. Management guidelines are not very clear as the available literature is only from case reports and from animal studies with current recommendation mainly focusing on resuscitative efforts with Crystalloids.

Conclusion: Amlodipine overdose can lead to life threatening non-cardiogenic pulmonary edema. The management is challenging due to the long elimination half-life of amlodipine and delayed onset of side effects. Aggressive pulmonary toilet and intensive care monitoring with use of BIPAP was key in delaying impending respiratory demise. Cautious fluid resuscitation is also key as these patients tolerate low BP well. CCB: Calcium Channel Blocker
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CARDIOMYOPATHY AND HEART FAILURE: DIAGNOSIS AND MANAGEMENT

THE EFFECT OF PARATHYROID HORMONE (PTH) LEVEL ON SHORT TERM CLINICAL OUTCOME OF PATIENTS WITH CHRONIC SYSTOLIC HEART FAILURE; A DESCRIPTIVE PROSPECTIVE STUDY

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Background: Chronic systolic heart failure (CHF) is the most common cause of hospitalization in patients over 65 years. CHF is a clinical disorder caused by abnormalities in the structure or function of the heart that occurred due to inherited or acquired changes, causing the clinical signs. So, the aim of this study was to investigate the effect of parathyroid hormone (PTH) in short term clinical outcome (6 months) of patients with chronic systolic heart failure.

Materials and Methods: In this descriptive prospective study, a total of 202 patients were enrolled according to inclusion and exclusion criteria in cardiovascular wards of Imam Khomeini University Hospital, year 2015-2016. Of these, 126 patients (62.3%) were male and 76 patients (37.6%) were female. Patients diagnosed with CHF according to Framingham criteria and placed in systolic HF subgroup (ejection fraction less than or equal to 40%) and were followed up for adverse clinical outcomes (responding to treatment, number of hospitalization, need for pacemaker, sudden death and mortality) during 6 months. PTH level was assessed by ECL methods. Statistical analysis was performed by chi-square test, correlation test, T-test, logistic regression analysis and ROC curve by SPSS version20.

Results: The chance of short term adverse clinical outcome in group who had PTH> 39 pg/ml were 5/85 times more than those with PTH<39 pg/ml. Also, higher NYHA class was associated with increased level of PTH (P value <0.001).

Conclusion: According to this study, it was found that the higher level of PTH is associated with severity of heart failure and the its short-term adverse clinical outcomes.
Sequential Cardiomyopathies: Resolution of One Cardiomyopathy Incites Another
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Introduction: The relationship between untreated thyroid disorders and cardiovascular dysfunction is well-established. Ordinarily cases follow a predictable pattern where cardiac function improves with the correction of circulating thyroid hormone levels and remains stable on continued medical therapy. We present a rare case demonstrating treatment of a previous hypothyroid cardiomyopathy that subsequently led to the development of a second, hypertrophic cardiomyopathy.

Case: 76-year-old female with known coronary artery disease status-post multi-vessel stenting and prior history of hypothyroid cardiomyopathy which was successfully treated (EF 55 percent) presented years later with progressive dyspnea and NYHA Class III angina. Echocardiography and heart catheterization revealed a hypertrophic cardiomyopathy with a hyperdynamic LV systolic function (EF >70 percent), severe left ventricular outflow (LVOT) obstruction (greater than 50 mmHg), a mitral valve with systolic anterior motion (SAM) and severe eccentric mitral insufficiency. The patient underwent a ventricular septal myectomy and mitral valve replacement.

Discussion: Cardiomyopathies are precipitated by a variety of causes; therefore, identifying the specific etiology is crucial and allows for prompt treatment. In this case, early thyroid hormone replacement led to the complete reversal of the prior dilated cardiomyopathy. However, once a euthyroid state was achieved, it is plausible a genomic predisposition activated a late-onset hypertrophic cardiomyopathy. Symptomatic patients with evidence of severe LVOT obstruction are typically treated with septal myectomy or alcohol septal ablation. In our case, the myectomy and mitral valve replacement resolved the patient’s symptoms and led to the recovery of previously lost cardiac function. Even after resolution, continued cardiology follow-up and interval imaging studies are essential as subsequent cardiomyopathies can develop. Our case also underscores the need for genomic research of predisposing genetic factors underlying cardiomyopathy patients.
DIFFERENT PROGNOSTIC FACTORS ACCORDING TO LEFT VENTRICULAR SYSTOLIC FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Background: Initial left ventricular (LV) systolic function is a main determinant of clinical outcomes in patients with acute myocardial infarction (AMI). This study was performed to investigate whether AMI patients have different prognostic factors according to their baseline LV systolic function.

Methods and Results: A total of 12988 patients with AMI from a nationwide database were analyzed. Major adverse cardiovascular events (MACE) within 12 months of AMI, including death, nonfatal myocardial infarction (MI), and revascularization, were assessed. Patients were stratified into 2 groups according to LV ejection fraction (LVEF): those with LVEF<40% and LVEF≥40%. Prognostic factors for MACE were identified in each group. Patients with LVEF<40% (n=1962, 15.1%) were older and had more unfavorable cardiovascular risk factors than those with LVEF≥40% had (n=11026, 84.9%). The rate of MACE was higher in patients with LVEF<40% than in those with LVEF≥40% (26.8% vs 11.4%, P<0.001). Independent predictors of 12-month MACE in patients with LVEF≥40% were history of MI, high Killip stage, three-vessel disease, and lower renal function, which are already known as risk factors. However, diabetes mellitus (hazard ratio [HR], 1.54; 95% confidence interval [CI], 1.12-2.11; P=0.008), and the use of rennin-angiotensin system (RAS) blockers (HR, 0.67; 95% CI, 0.47-0.97; P=0.034) were independent factors for 12-month MACE in patients with LVEF<40%.

Conclusions: Prognostic factors determining 12-month MACE after AMI are different according to LVEF. Management following AMI should be tailored according to their LV systolic function.
A PHOTOVOICE EXPLORATION OF SELF-CARE EMPOWERMENT IN SINGAPOREAN PATIENTS LIVING WITH CHRONIC HEART FAILURE

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Aim of the study: The study aimed to explore the perceptions of empowerment to self-care in patients with chronic heart failure (CHF).

Background: CHF is the most common cardiovascular reason for hospitalization mostly due to inadequate and unsustained self-care, which is influenced by empowerment.

Methodology: This study adopted a descriptive qualitative design using Photovoice to elicit and document patients’ perceptions on empowerment to self-care. A purposive sample of 16 participants were asked to take photos of images that represented their perceptions. These photos were used to focus the subsequent unstructured audiotaped face-to-face interview sessions, which were transcribed verbatim and analysed using thematic analysis. The study was conducted at a Cardiology inpatient ward and outpatient clinic at one public hospital in Singapore.

Findings: Five themes emerged namely (1) accepting life; (2) appreciating life; (3) maintaining meaning in life; (4) establishing a new normal life, and (5) maintaining a photo diary. These were supplemented with fourteen subthemes and participants’ quotes. Participants described going through four phases of empowerment to self-care as conceptualised in the first four themes and sustained self-care using a photo diary.

Conclusion: This study uncovered that empowerment is a volatile concept that is sustained and maintained through active and passive processes. As an active process, empowerment was illustrated by the conversion of powerlessness to powerfulness within the patient. As a passive process, empowerment was illustrated by the transfer of power from healthcare providers to the patients through interventions based on the identified influencing factors of self-care. Empowerment in this study focused on the conversion of powerlessness to powerfulness within the patient, which itself is an active empowering process that increases self-confidence and self-efficacy. With this scaffold, passive empowerment can then be effectively conducted with the transfer of power from healthcare providers to the patients using the aforementioned external factors.
CHANGES IN WEIGHT AND SERUM BNP LEVEL ARE CORRELATED IN PATIENTS WITH ACUTE HEART FAILURE UNDERGOING ULTRAFILTRATION THERAPY
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Background: Change in weight is commonly used in clinical practice to monitor decongestive therapy in patients with acute decompensated heart failure (ADHF). Ultrafiltration (UF) has emerged as an efficacious therapeutic strategy in this setting but there is a paucity of data on appropriate methods for objective monitoring of decongestion by this therapy. We previously reported on the strong correlation between weight loss and fluid removal in these patients. In this study, we sought to determine whether changes in serum B-type natriuretic peptide (BNP) can be helpful in this setting.

Methods: Available data from clinical trials of UF in ADHF performed between January 2000 and December 2016 were included in the analysis. These studies evaluated decongestion both through weight change and BNP or N-Terminal BNP (NT-proBNP). Pertinent data were extracted and using Spearman’s rank correlation analysis, the degree of dependence and correlation between these two variables was determined.

Results: A total of 442 patients from 6 studies (4 randomized controlled trials) were included. The mean age was 68 years. Two studies reported NT-proBNP while the other 4 measures BNP before and after ultrafiltration therapy. Weight loss ranged from 4.7 to 10.7 Kg (mean 6.3 ± 2 Kg) and reduction in BNP levels ranged from 211 to 3266 pg/ml (mean 1212 ± 1621 pg/ml). There was a strong correlation between weight loss and changes in natriuretic peptide levels (r = 0.89, p = 0.02).

Conclusion: Currently available evidence suggests that there is a strong correlation between weight loss and changes in serum natriuretic peptides in patients with ADHF who undergo UF therapy. Therefore, both markers may reliably be used to monitor the degree of decongestion in these patients. Future studies are needed to clarify whether prospective use of these parameters could help improve the outcomes in ADHF by guiding UF therapy.