**DIURNAL RHYTHMS AND THE PATHOGENESIS OF CARDIOVASCULAR DISEASE**

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Cardiovascular physiology such as heart rate and blood pressure and the incidence of adverse cardiac events exhibit diurnal variation. Shift workers have an increased risk of myocardial infarction and sudden death. We are the first to actually demonstrate that disturbed diurnal rhythms can cause cardiovascular disease. Earlier we had discovered diurnal changes in gene expression in over 13% of genes expressed in the heart and aorta of normal mice; about 1% exhibited strict clock-like cosinar cycling; another 1% showed abrupt and remarkable, sustained increases or decreases in expression with onset at the light:dark interface. Using a murine model of pressure overload (transverse aortic constriction - TAC) in a rhythm disruptive 10hr light/10 hour dark environment, we demonstrated disorganized rhythms in gene expression, exacerbated hypertension, disproportionate perivascular and myocardial fibrosis but only minimal myocyte hypertrophy relative to TAC under a normal diurnal cycle. Phenotypic and molecular rescue only occurred when a normal cycle was restored. We also examined cardiovascular integrity using a natural genetic model of circadian clock disruption; the +/tau hamster exhibits 22h cyclic behaviour patterns. In our 24 hour world +/tau hamsters exhibit fragmentation of diurnal activity and die prematurely; pathology demonstrates severe dilated cardiomyopathy. Under 22h diurnal cycles appropriate for their genotype, hamster behavior, tissue structure and life expectancy are normal.

In conclusion: synchrony of external and internal diurnal rhythms is critical for maintaining the integrity of cardiovascular tissues. Diurnal variation in gene expression (and the corresponding proteome) should be an essential consideration in any search for biomarkers.