**RISK FACTORS FOR NON-PLATELET THROMBOXANE GENERATION**

**J.J. Rade1**, N. Kakouros1, S.M. Nazarian2, P.B. Stadler1, T.J. Kickler2

1. University of Massachusetts Medical School, Worcester, MA, USA

2. Johns Hopkins School of Medicine

*Background*- Persistent thromboxane generation while on aspirin therapy is associated with an increased risk of cardiovascular events. The Reduction in Graft Occlusion Rates (RIGOR) study found that aspirin-insensitive TXA2 generation, indicated by elevated urine 11-dehydroTXB2 (UTXB2) 6 months after coronary artery bypass (CABG) surgery, was a potent risk factor for vein graft thrombosis and originated predominantly from non-platelet sources. Our goal was to identify risks factors for non-platelet TXA2 generation.

*Methods and Results*- Multivariable modeling was performed using clinical and laboratory variables obtained from 260 RIGOR subjects with verified aspirin-mediated inhibition of platelet TXA2 generation. The strongest variable associated with UTXB2 6 months after surgery, accounting for 47.2% of the modeled effect, was urine 8-isoPGF2á (U8-isoPGF2á), an arachidonic acid metabolite generated non-enzymatically by oxidative stress (standardized coefficient 0.442, P<0.001). Age, gender, race, lipid therapy, creatinine, left ventricular ejection fraction and aspirin dose were also significantly associated with UTXB2 (P<0.03), though only accounted for 4.8 to 10.2% of the modeled effect. U8-isoPGF2á correlated with risk of vein graft occlusion (OR 1.67, p=0.001) though was not independent of UTXB2. In vitro studies revealed that endothelial cells generate TXA2 in response to oxidative stress and direct exposure to 8-isoPGF2á.

*Conclusions*- Oxidative stress-induced formation of 8-isoPGF2á is strongly associated with non-platelet thromboxane formation and early vein graft thrombosis after CABG surgery. The endothelium is potentially an important source of oxidative stress-induced thromboxane generation. These findings suggest therapies that reduce oxidative stress could be useful in reducing cardiovascular risks associated with aspirin-insensitive thromboxane generation.