O167

Remote ischemic preconditioning reduces infarct size, procoagulant platelet formation and protects against platelet mitochondrial membrane loss

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Remote ischemic preconditioning (RIPC), consisting of brief cycles of non-harmful ischemia to a peripheral limb, protects the myocardium during acute myocardial infarction (MI). The mechanism remains unclear. We hypothesize that RIPC attenuates procoagulant platelet formation via protection against platelet mitochondrial membrane depolarisation.

Aim: To investigate the effect of RIPC on procoagulant platelet formation in human stable coronary artery disease (CAD) and a rat model of MI.

Method: Human subjects with angiogram-proven stable CAD were exposed to RIPC (3x5min cycles, 200mmHg using sphygmomanometer on arm). Rats were subjected to RIPC (3x5min limb ischaemia) or no RIPC followed by MI induction by ligation of their left coronary artery. Blood was collected from all subjects pre- and post-RIPC, and from rats 24h post-infarct. Procoagulant platelets were measured by combined uptake of GSAO/CD62P, and platelet mitochondrial membrane potential ($\Delta\Psi m$) was measured using the TMRE flow cytometry assay. MI area was measured by histology.

Results: Human CAD patients had increased procoagulant platelet formation ($p<0.05$) and increased loss of TMRE+ platelets ($p<0.01$) in response to agonist stimulation compared with healthy controls. RIPC was associated with a reduction in procoagulant platelets and a corresponding reduction of TMRE loss ($p<0.01$) in these patients. RIPC prior to MI in rats significantly reduced infarct size in the animals ($p<0.0001$) and resulted in protection against procoagulant platelet formation ($p<0.05$). 90% of animals without RIPC demonstrated a reduction in TMRE+ platelets with agonist stimulation post-MI. With RIPC, ~60% of rats demonstrated an increase in TMRE+ platelets post-MI (chi-squared $p<0.05$).

Conclusion: MI and CAD are associated with increased procoagulant platelet formation. RIPC protects against this phenomena if given prior to MI in a rat model, or given during steady state in human subjects with stable CAD. The platelet effect suggest a mechanistic link to the protective effect of RIPC in cardiovascular diseases.