GAP JUNCTION MODULATION PREVENTS ENDOTHELIAL DYSFUNCTION INDUCED BY ISCHEMIA-REPERFUSION INJURY IN MAN

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Authors: Christian M. Pedersen, Ninian Lang, Gareth D. Barnes, Michael R. Schmidt, Hans Erik Botker, Rajesh K. Kharbanda, Nick L. Cruden, David E. Newby, University of Edinburgh, Centre for Cardiovascular Science, Edinburgh, United Kingdom, Aarhus University Hospital Skejby, Aarhus, Denmark

Background: Ischemia-reperfusion (IR) injury impairs endothelial function through a mechanism that may involve intercellular gap junctions. Rotigaptide (ZP-123) is an anti-arrhythmic drug promoting intercellular coupling by increasing gap junction conductance. We tested the hypothesis that rotigaptide protects the forearm arterial circulation from IR-induced endothelial dysfunction.

Methods: Healthy male subjects (n=11) attended twice for a double blind randomized crossover study. IR injury (upper arm cuff inflated to 200 mmHg for 20 min) was induced on both occasions. Using bilateral forearm venous occlusion plethysmography, blood flow was measured during intra-brachial infusion of acetylcholine (ACh; 5-20 μg/min) before and after IR injury during intra-brachial infusion of rotigaptide/matched placebo.

Results: Resting blood flow remained unchanged throughout (P=NS). ACh caused arterial vasodilatation (P<0.01) that was unaffected by rotigaptide (P=NS). IR injury caused substantial impairment of ACh-induced vasodilatation during placebo (P=0.007), but not rotigaptide (P=NS), infusion (Figure).

Conclusion: IR injury-related endothelial vasomotor dysfunction is reversed by rotigaptide. This is the first clinical study to demonstrate protection afforded by enhanced gap junction communication during IR injury. The potential therapeutic benefits of gap junction modulation now need to be assessed in patients with cardiovascular disease.