**Modulation of Gap Junctional Coupling as an Anti-Arrhythmic Strategy to Prevent Reperfusion Ventricular Arrhythmias**

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Background: Heterogeneities and abrupt changes in gap junctional coupling and action potentials during early reperfusion are thought to contribute to reperfusion arrhythmogenesis. We tested the hypothesis that modulating gap junctional coupling can reduce the incidence of reperfusion arrhythmias, and used optical mapping to assess the mechanisms of any anti-arrhythmic effect.

Methods: Using a Langendorff apparatus, rat hearts were perfused with 50nM AAP10 to increase coupling (n=10), 30μM carbenoxolone (CBX) to reduce coupling (n=13) or control (n=10). Hearts were then subjected to left anterior descending artery ischaemia for 8 minutes and reperfused. A further 18 hearts were loaded with a voltage-sensitive dye (RH237), perfused with an excitation-contraction uncoupler (blebbistatin), and AAP10, CBX or control (n=6 each), then subjected to ischaemia and reperfusion as above whilst transmembrane voltage transients were recorded.

Results: Both AAP10 and CBX reduced reperfusion VF incidence (AAP10 50%, CBX 77%, Control 90%; P<0.05). AAP10 reduced action potential duration dispersion in ischaemic myocardium (AAP10 2.3±0.8ms; CBX 5.1±1.2ms; Control 4.9±2.0ms, P<0.05). AAP10 also improved conduction across the ischaemic anterior left ventricle (LV) (Activation time: AAP10 15.3±1.3ms; CBX 25.7±2.2ms; Control 23.2±2.0ms, P<0.05) prior to reperfusion. CBX prolonged this activation time post-reperfusion (AAP10 10.3±0.8ms; CBX 15.8±2.8ms; Control 9.5±1.2ms), thus resulting in smaller changes in conduction velocities pre- and post-reperfusion.

Conclusion: Both increasing and reducing gap junctional coupling reduced the rate and delayed the onset of reperfusion VF. The anti-arrhythmic effect of increasing gap junctional coupling may be mediated by its effects of reducing of action potential heterogeneity and improving conduction during reperfusion. Further uncoupling may be protective via attenuation of the abrupt changes in coupling and conduction that occur at reperfusion.