THE CARDIOPROTECTIVE EFFICACY OF DRUGS TARGETING ADRENERGIC RECEPTOR PATHWAYS WHEN ADDED PRIOR TO CARDIOPLEGIC ISCHAEMIC ARREST

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Pre-conditioning of perfused heart with drugs targeting α and β adrenergic receptors has been shown to be cardioprotective against global ischaemic and reperfusion injury. These drugs include Isoprenaline (β-receptor agonist), A61603 (α1A-receptor agonist) and the cAMP permeable analogue 8-Br-cAMP-AM (8-Br). All these interventions produce an inotropic response in the heart which may underly the mechanism of protection that involves glycogen store depletion and inhibition of the mitochondrial permeability transition pore. However, whether these interventions are also efficacious when used during cardioplegic arrest is not presently known. This study aims to address this issue. Adult male Wistar rat hearts were arrested with cardioplegia and subjected to 45-minutes ischemia followed by 2 hours reperfusion on a Langendorff setup. Hearts were pre-treated with either isoprenaline (100nM), 8-Br (10uM), or A61603 (10nM). To assess cardioprotection, haemodynamic function, lactate dehydrogenase (LDH) release and infarct size were measured. Onset of ischemic contracture occurred earlier following isoprenaline and 8-Br treatment compared to cardioplegia alone. Pre-conditioning with 8-Br improved functional recovery and reduced LDH release and infarct size. Isoprenaline also exhibited some protection against IRI with a reduction in infarct size. Treatment with A61603 did not provide any protection for the heart. This work shows that activation of α1A-receptor is only protective when used during normothermic ischaemia but not when used in conjunction with cardioplegia. It also suggests that cAMP analogues confer strong protection when used during cardioplegic arrest and provide an excellent tool for intervention given the known changes in β-adrenergic receptors sensitivity in disease states.