Efficacy of remote ischaemic preconditioning in diabetic rats

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Purpose: The diabetic myocardium paradoxically displays not only greater resistance to ischaemia/reperfusion injury (IRI) but also decreased sensitivity to cytoprotection by either pharmacological or ischaemic conditioning. Remote ischaemic preconditioning (RIPC), through induction of transient non-injurious ischaemia in a distant organ or tissue, triggers significant protection against myocardial IRI in healthy subjects, but its efficacy in the diabetic is unknown.

Methods: Diabetic status of lean Goto Kakizaki (GK) rats was confirmed by measurement of fasting blood glucose (FBG) and comparison to age-matched Wistar rats. 48h later, sedation with pentobarbitone (45mg/kg ip) anaesthesia and surgical isolation of the right femoral neurovascular bundle was undertaken in the GKs. RIPC was induced by a robust 3-cycle 5min femoral arterial occlusion / 5 min reperfusion protocol; sham controls were left unoccluded. After 40min, hearts were harvested and perfused in Langendorff mode for 10min prior to 35min normothermic regional ischaemia by left anterior descending artery ligation followed by 1h reperfusion. Area at risk (AAR) and infarct size (IS) were determined by Evans' blue and triphenyltetrazolium chloride staining, respectively.

Results: Diabetes was confirmed in the GK rats with significantly higher glucose levels than age-matched Wistars (FBG 11.7 ± 0.6 vs 7.9 ± 0.3mmol/L; p < 0.0001). Despite this, the robust 3-cycle RIPC regimen was found to significantly attenuate IS/AAR in the GK hearts compared to controls (18.4 ± 3.3% vs 30.5 ± 3.6%; p=0.03). Interestingly, RIPC induced coronary hyperaemia in GK hearts (16.0 ± 0.7 vs 13.3 ± 0.7ml/min; p=0.02) which was abrogated by the administration of the broad-spectrum nitric oxide synthase inhibitor, L-NAME (100 mmol/L).

Conclusions: We demonstrate for the first time that it is possible to trigger RIPC and significantly attenuate myocardial infarction in a diabetic rat, using a robust 3-cycle remote limb ischaemia model. RIPC also induces a coronary hyperaemia that appears mediated, at least in part, by nitric oxide. These encouraging data have implications for the design of future clinical RIPC trials from which diabetic patients should not be excluded.