229 **THE IMPAIRMENT OF INNATE CARDIOPROTECTIVE SIGNALING IN THE AGED, DIABETIC RAT HEART**

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Introduction Aging and type 2 diabetes represent two interacting risk factors for ischaemic heart disease (IHD). Some contradictory clinical data suggest the diabetic heart to be less vulnerable to infarction; however patients still experienced worse clinical outcomes. This led us to hypothesize that the diabetic heart, may develop smaller infarcts but could be more susceptible to ischaemic damage i.e. the threshold at which infarct size translates into worse clinical outcomes is lower for diabetic patients. To verify this, we employed a type 2 diabetic rat model at different ages and investigated the susceptibility of the heart to varied durations of ischaemia- reperfusion injury(IRI) and the ability to condition against this lethal event using ischaemic preconditioning (IPC). Impaired phosphorylation of pro-survival Akt, a known mediator in the cardioprotective effect of preconditioning, has been

suggested to be involved in insulin resistance. Therefore, we assessed whether Akt activation was impaired in these aging diabetic animals and if the changes we found had any detrimental effects on some downstream cardioprotective targets.

Methods Hearts from diabetic Goto-Kakizaki (GK) rats, aged 3–18 months were assigned to one of the following experimental groups: a) Langendorff isolated heart perfusions, subjected to 20min (sublethal ischaemia) or 35 min (lethal ischaemia) followed by 60 min reperfusion; some hearts were pretreated prior to lethal ischemia with 3 cycles of 5 min ischaemia, (ischaemic preconditioning, IPC, a well-known cardioprotective maneuver); the end point was to compare the size of the infarct amongst groups; b) Western blot analysis (for prosurvival Akt, PGC-1α, a regulator of mitochondrial biogenesis, and catalase, an endogenous antioxidant); and c) measurements of the intracellular ROS/H_2O_2 content, at baseline.

Results The aged GK heart demonstrated an increased susceptibility to sub-lethal ischaemia with infarct sizes of 38.6%±3.1 (3 months) and 55.5%±3.3 (18 months) and to lethal ischaemia with infarct sizes of 45.5%±3.1 (3 months) and 62.1%±6.0 (18 months). With IPC there was a 63% decrease in infarct size at 3months and no protection seen at 18 months. The 18 month GK heart also demonstrated a decreased rate pressure product output compared to the 3month group (34623±4312.4 *vs.* 54437.4 ±6937.4, mmHg/sec). Surprisingly, an age-related **increase** in phosphorylated Akt was seen, with no subsequent increase in activation following an IPC stimulus. Furthermore, a decrease in basal PGC-1α and catalase expression and increased H_2O_2 and ROS levels were also observed in the 18 month GK heart.

Conclusions Overall our data seem to indicate that chronic activation of Akt occurs in aging diabetic hearts which could lead to alterations in downstream signaling, rendering the heart more susceptible to IRI and less amenable to IPC. This may occur via a down regulation of factors essential for maintaining mitochondrial function and antioxidant defense.