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IMPAIRED METABOLIC AND FUNCTIONAL ADAPTATION TO HYPOXIA IN THE TYPE 2 DIABETIC HEART

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Aims Cardiovascular disease is the leading cause of mortality in people with type 2 diabetes. Following a myocardial infarction, the heart must adapt to the decreased oxygen availability by switching to more oxygen-efficient metabolism. We hypothesise that adaptation to hypoxia is impaired in type 2 diabetes.

Methods Type 2 diabetes was induced in rats by high fat feeding combined with a low dose of streptozotocin (25mg/kg i.p). Following induction of diabetes, control and diabetic rats were housed in a hypoxia chamber for three week at 11% oxygen, to study chronic adaptation to hypoxia. Subsequently, hearts were isolated and perfused for measurement of substrate metabolism, or mitochondria were isolated and respiration was measured. In a separate study, hearts from normoxic diabetic and control rats were perfused *ex vivo* with hypoxic buffer, to study the acute response to hypoxia.

Results Under normoxic conditions, diabetic hearts had a 30% decrease in glycolysis, a 14% decrease in pyruvate oxidation and a 34% increase in fatty acid oxidation, compared with normoxic control rats. When control rats were housed in hypoxia they adapted their cardiac metabolism to be more oxygen efficient, by increasing anaerobic glycolysis by 18%, increasing glycogen reserves by 24%, decreasing fatty acid oxidation by 18% and decreasing mitochondrial respiration by 26%. In contrast, when diabetic rats were housed in hypoxia they were unable to adapt metabolism to the same extent, being significantly different to hypoxic control rats. Glycolytic rates and glycogen content was significantly lower in hypoxic diabetic hearts compared with hypoxic controls, similarly fatty acid oxidation rates and mitochondrial oxygen consumption were both significantly higher in hypoxic diabetic hearts compared with hypoxic control hearts. Metabolic rates and mitochondrial oxygen consumption from hypoxic diabetic rat hearts were comparable to those in normoxic control hearts.

Normoxic control and diabetic rat hearts were perfused with hypoxic buffer to study the functional and metabolic response to acute hypoxia. During acute hypoxia, diabetic hearts had 58% lower heart rates and 68% higher end-diastolic pressures compared to control hearts, associated with 55% lower rate of hypoxia-induced glycolysis. During the subsequent reoxygenation period, diabetic hearts had a 34% decrease in recovery of cardiac function compared with control hearts.

Conclusions Adaptation to chronic hypoxia is limited in type 2 diabetic rat hearts, with anaerobic metabolism lower and oxidative metabolism higher than control heart. This increased dependence on oxidative metabolism under oxygen-limited conditions was associated with contractile dysfunction in the diabetic heart. This may contribute to the decreased recovery of the diabetic heart following a myocardial infarction.