

Dietary fuels and metabolic consequences are context specific

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Rationale: Cardiac metabolism is thought to be altered in insulin resistance and type 2 diabetes (T2D). Our understanding of the regulation of cardiac substrate metabolism and insulin sensitivity has largely been derived from *ex vivo* preparations which are not subject to the same metabolic regulation as in the intact heart *in vivo*. Studies are therefore required to examine *in vivo* cardiac glucose metabolism under physiologically relevant conditions.

Objective: To determine the temporal pattern of the development of cardiac insulin resistance and to compare with dynamic approaches to interrogate cardiac glucose and intermediary metabolism *in vivo*.

Methods and results: Studies were conducted to determine the evolution of cardiac insulin resistance in C57Bl/6 mice fed a high-fat diet (HFD) for between 1 and 16 weeks. Dynamic *in vivo* cardiac glucose metabolism was determined following oral administration of [U-13C] glucose. Hearts were collected after 15 and 60 min and flux profiling was determined by measuring 13C mass isotopomers in glycolytic and tricarboxylic acid (TCA) cycle intermediates. Cardiac insulin resistance, determined by euglycaemic-hyperinsulinaemic clamp, was evident after 3 weeks of HFD. Despite the presence of insulin resistance, *in vivo* cardiac glucose metabolism following oral glucose administration was not compromised in HFD mice. This contrasts our findings in skeletal muscle, where TCA cycle activity during the oral glucose tolerance test was reduced in mice fed a HFD. However, similar to that seen in skeletal muscle, glucose derived pyruvate entry into the TCA cycle in the heart, irrespective of diet, was almost exclusively *via* pyruvate dehydrogenase, with pyruvate carboxylase mediated anaplerosis being negligible after oral glucose administration.

Conclusions: Under experimental conditions which closely mimic the postprandial state, the insulin resistant mouse heart retains the ability to stimulate glucose metabolism.