

Metabolic arithmetic: do two wrongs make a right?

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This editorial refers to ‘Diabetic db/db mice do not develop heart failure upon pressure overload: A longitudinal *in vivo* PET, MRI, and MRS study on cardiac metabolic, structural, and functional adaptations’ by D. Abdurrachim et al., pp. 1147–1159.

The healthy adult heart has metabolic flexibility, that is, an ability to utilise a wide variety of fuel substrates dependent on availability. For example, a distinct preference for free fatty acids under the normal fasting state, but with periods of insulin-stimulated glucose utilisation in response to feeding. It has long been established that substrate preference and utilisation is altered under pathological conditions and this may be adaptive or maladaptive depending on circumstance and duration.¹ Unsurprisingly, the diabetic heart has impaired glucose uptake and is dependent on fatty acid oxidation (FAO), whereas pressure-overload hypertrophy is associated with a switch towards glucose utilisation and impaired FAO.² However, little is known concerning how these common co-morbidities interact metabolically and the downstream consequences for *in vivo* cardiac function.

The study by Abdurrachim and colleagues addresses this question using a deceptively simple longitudinal design, which belies the combination of multiple, highly sophisticated, imaging modalities.³ They use the murine db/db model of type-2 diabetes and subject diabetic and non-diabetic controls to transverse aortic constriction (TAC), a commonly used model of pressure-overload cardiac hypertrophy and failure. *In vivo* assessment was undertaken at baseline and repeated at early and late time-points up to week 12 post-surgery, utilising, magnetic resonance imaging (MRI) for cardiac function and structure; ¹H magnetic resonance spectroscopy (MRS) for lipid (triglyceride) and creatine levels; ³¹P-MRS for cardiac energetic status (Phosphocreatine/ATP ratio); and glucose uptake via ¹⁸F-fluorodeoxyglucose positron emission tomography (PET). This is a highly ambitious design and no trivial undertaking, it is a major strength that the evolution of disease is followed serially detailing the relationship between metabolic changes and *in vivo* function. The use of non-invasive *in vivo* techniques to assess metabolism, as opposed to isolated perfused hearts, is also to be applauded, since the findings reflect the full diabetic milieu.⁴ However, the ambitious study design also gives rise to limitations. In order to access hardware, the study was necessarily split between two institutions. Furthermore, diabetic animals in the PET arm of the study did not tolerate repeated fasting and general anaesthetics, resulting in the final time-point being under-powered.

So what is the take home message? As expected, the non-diabetic controls develop overt hypertrophy and contractile dysfunction, commensurate with increased glucose uptake and associated with reductions in energy status (PCr/ATP) and *ex vivo* mitochondrial FAO capacity. In contrast, the diabetic hearts were relatively protected following TAC, they developed less severe hypertrophy and only mild dysfunction, which was associated with near normalisation of glucose uptake, energy status, and mitochondrial FAO. Put simplistically, the metabolic remodelling in the diabetic mice appears to effectively cancel out the opposing remodelling that occurs in cardiac hypertrophy and failure (*Figure 1*).

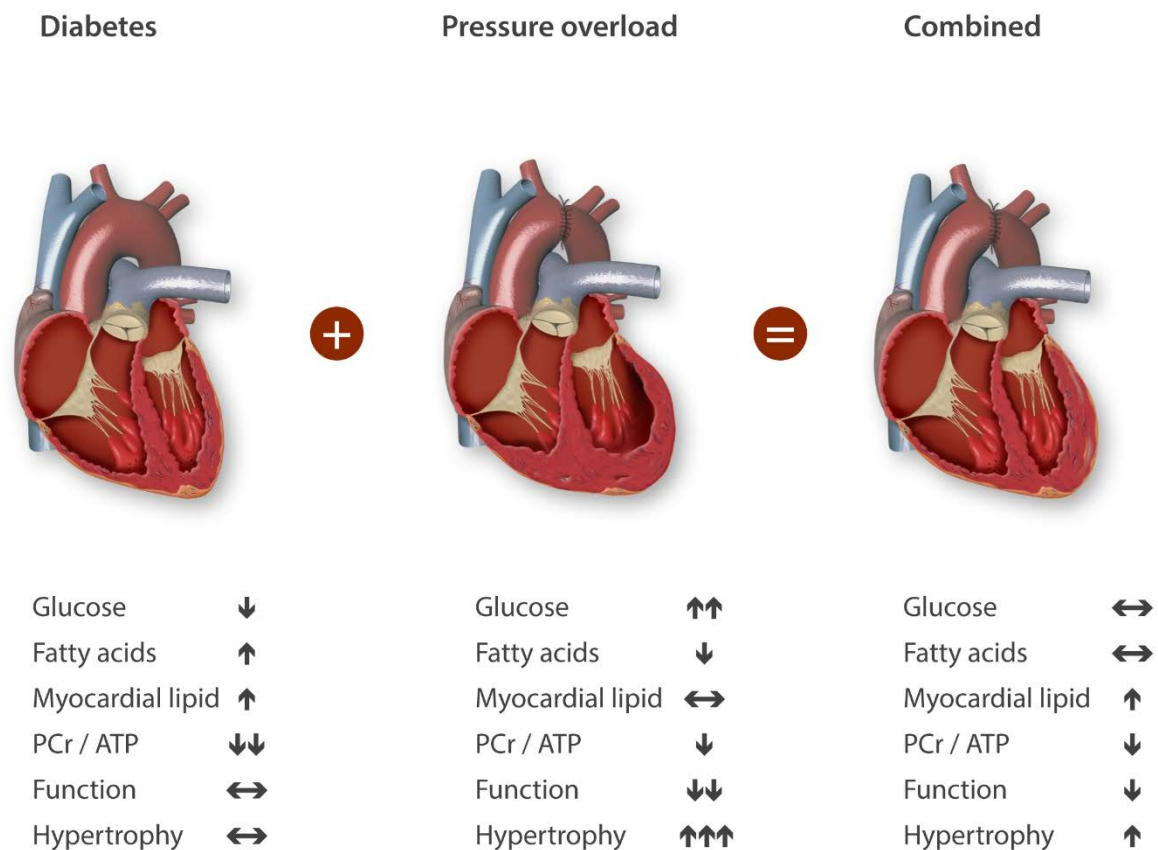


Figure 1 Schematic summary of directional changes in diabetic and pressure-overload hearts relative to normal conditions.

There is some precedent in the literature. Other studies have used high-fat feeding to induce obesity and insulin-resistance before inducing heart failure and are in broad agreement. For example, cardiac function was not exacerbated post-TAC in mice,⁵ and in rats post myocardial infarction, *in vivo* function was preserved and glucose utilisation reduced.⁶ Cardiac-specific knockout of acetyl-CoA carboxylase 2 (ACC2) also favours FAO and these mice were protected against pathological hypertrophy,⁷ in this context, it is notable that diabetic mice in the current study had higher expression of inactive phosphorylated ACC2. However, similar patterns of substrate preference are observed in GLUT1 knockout mice and do not confer a protective effect, which may reflect differences in adaptive responses or chronic metabolic signalling (see ⁸ for a review of genetically altered mouse models).

So how translatable is this concept – should we expect all diabetic hearts to be protected? It is unlikely to be that simple, the db/db mouse has a spontaneous mutation in the leptin receptor and therefore exhibits hyperleptinaemia, but with impaired leptin signalling. Consequently they lack the normal satiety signal and are hyperphagic, extremely obese, with severe hyperglycaemia despite elevated insulin levels. They also exhibit profound dyslipidaemia, in particular, high plasma triglycerides, fatty acids and cholesterol.^{9,10} In contrast, leptin receptor mutations are a vanishingly rare cause of human obesity. Nevertheless, obese individuals do exhibit hyperleptinaemia and this correlates with tissue leptin resistance, which may affect some tissues more than others.¹¹ Therefore, db/db mice recapitulate many aspects of type-2 diabetes in the context of obesity, but the chronology of contributing factors may differ and they exhibit whole-body leptin resistance.

General extrapolation to the diabetic heart will therefore depend on the relative contributions of insulin versus leptin resistance. Leptin acts centrally, but also targets peripheral tissues, such as the heart, where it has complex and often paradoxical effects (see ¹¹ for review). Defective leptin signalling (e.g. due to cardiac leptin resistance) is expected to be pro-hypertrophic, pro-apoptotic and to promote a mismatch between fatty acid uptake and FAO that results in excess lipid accumulation with the potential for lipotoxicity.^{10,11} For example, Abdurrachim *et al.* show elevated myocardial triglyceride levels in the db/db mice, but these were not modified by pressure overload,³ presumably because the defect in leptin signalling is driving this phenotype.

Other factors urge cautious interpretation. Diabetic patients are at much greater risk of developing heart failure,¹² and diabetic mice in the current study had increased mortality during acute stressors, e.g. TAC surgery and PET scans. Nevertheless, these findings may provide insight into the obesity paradox, whereby obese patients are at greater risk of developing heart failure, but have better outcomes compared to their lean contemporaries.¹³

A more generalised interpretation, regardless of the relevance to other diabetic models, is that this study supports current thinking concerning metabolic therapy for heart failure. Early approaches advocated major shifts towards either glucose or FA metabolism, but it was soon apparent that too much of any one substrate could be detrimental, leading to a consensus that the best strategy is to maintain metabolic flexibility.¹⁴ By implication, successful metabolic therapy should provide a nudge in whichever direction is necessary to maintain the heart as an omnivore. The metabolic interplay of complex co-morbidities (e.g. diabetes and hypertrophy) suggests a role for individualised metabolic profiling to guide precision medicine.

An interesting aside is the apparent disconnect between energetic status and cardiac function. The diabetic mice started with normal function despite low PCr/ATP, while by the end, function had deteriorated and PCr/ATP improved. In the non-diabetic mice, cardiac dysfunction preceded the drop in PCr/ATP by 11 weeks. This supports the somewhat controversial view that impaired energetics represents a biomarker for the failing heart, but is not necessarily a causative force driving dysfunction.¹⁵

Abdurrachim and colleagues have given us a fascinating and multi-faceted study that should stimulate further mechanistic research. The authors implicate reduced phosphorylation of protein kinase D-1 in the diabetic mice as a potential mechanism for protection, but other signalling pathways are also likely to be altered, e.g. differences in glucose uptake having knock-on effects on redox homeostasis via the pentose phosphate pathway and on protein O-GlcNacylation.⁸ Ultimately, mechanistic insight may suggest therapeutic approaches that mimic the positive aspects of the diabetic heart, in which case, two wrongs really will make a right.

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