

Metabolic remodelling in heart failure revisited

Miranda Nabben, Joost J. F. P. Luiken and Jan F. C. Glatz

The Review by Edoardo Bertero and Christoph Maack (Metabolic remodelling in heart failure. *Nat. Rev. Cardiol.* **15**, 457–470; 2018)¹ addresses the changes in cardiac energy metabolism that occur during the development of heart failure (HF). The authors convincingly argue that alterations of intermediate substrate metabolism and oxidative stress, rather than an ATP deficit per se, account for maladaptive remodelling and dysfunction. Despite the comprehensive discussion of this topic, some aspects need further clarification or elaboration.

HF is a clinical syndrome characterized by a myocardial abnormality causing systolic and/or diastolic ventricular dysfunction². The main examples, as discussed in the Review¹, are pressure overload-induced HF, ischaemic HF, and diabetes-induced HF (diabetic cardiomyopathy). From a metabolic perspective, these forms of HF differ markedly in that in both pressure overload-induced HF and ischaemic HF, substrate preference shifts towards increased glucose utilization, whereas in diabetic cardiomyopathy, fatty acids become the preferred substrate^{3,4}. In the Review, HF is considered to be caused by pressure overload or ischaemia, whereas diabetic cardiomyopathy is discussed separately, which is confusing. For example, the statement that “The failing heart is characterized by an increase in glucose uptake and glycolytic rates” (page 461)¹ is valid for pressure overload-induced HF and ischaemic HF, not diabetes-induced HF.

Toxic intracellular accumulation of lipid species (lipotoxicity) is mentioned as a contributing cause of HF. However, the contribution of lipotoxicity to the progression of HF is well-known in diabetic HF but has not been established for pressure overload-induced HF³. The same applies for the role of decreased insulin sensitivity in developing HF⁴. Moreover, lipotoxicity and insulin resistance are unlikely to be general features of the pressure-overloaded heart.

With respect to targeting substrate metabolism as a treatment option for HF, the hypothesis is discussed that inhibition of fatty acid oxidation might be beneficial because it would induce a shift towards increased utilization of glucose, which has

higher oxygen efficiency than fatty acids. Such intervention is helpful in ischaemic HF but not in pressure overload-induced HF^{5,6} and certainly not in diabetic HF because that would lead to a further mismatch between fatty acid uptake and oxidation, resulting in increased intracellular accumulation of toxic lipid species^{5,7}.

The interplay between the intracellular utilization of glucose and of fatty acids for oxidative energy provision (the Randle cycle) is adequately described, but the Review does not mention that a major rate-governing kinetic step in overall myocellular glucose utilization is cardiac glucose uptake⁸, and that in fatty acid utilization it is the fatty acid uptake process (that is, trans-sarcolemmal transport)⁹. Specifically, the relative presence of glucose transporters (GLUT1 and GLUT4) and fatty acid transporters (mainly SR-B2, also known as CD36) in the sarcolemma determines the myocardial utilization of glucose and fatty acids, respectively, and, as a corollary, controls cardiac substrate preference. Therefore, increased sarcolemmal CD36 has been found to be an important early hallmark of the development of diabetic HF⁹. Furthermore, selectively manipulating the recruitment to the sarcolemma of either GLUT4 or CD36 has been reported in experimental animal studies as a suitable approach to rebalance cardiac

substrate utilization and improve cardiac contractile function¹⁰.

Finally, besides discerning between forms of HF, distinction should also be made between stages of HF development because the type and degree of metabolic adaptation of the heart change during the course of HF progression⁷. Monitoring the cardiac metabolic state is, therefore, not only of interest for early identification of changes in substrate preference but also to predict and assess the effectiveness of treatment.

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<https://doi.org/10.1038/s41569-018-0115-8>

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Competing interests

The authors declare no competing interests.

Reply to ‘Metabolic remodelling in heart failure revisited’

Edoardo Bertero and Christoph Maack

We thank Nabben and colleagues for their constructive Correspondence (Metabolic remodelling in heart failure revisited. *Nat. Rev. Cardiol.* <https://doi.org/10.1038/s41569-018-0115-8>; 2018)¹ on our Review (Metabolic remodelling in heart failure. *Nat. Rev. Cardiol.* **15**, 457–470; 2018)². We agree with their comments and acknowledge that most of these critical

points result from the necessity of giving readers a comprehensive overview of a broad area of cardiovascular research within the limited space of a Review article. Here are our responses to their comments.

We decided to discuss diabetic cardiomyopathy separately from pressure overload-induced and ischaemic heart failure (HF) because they differ