Fuelled by obesity, hypertension, diabetes, and an aging population, heart failure (HF) is increasingly common in the Western population. Its pathophysiology reflects the complex and multifactorial background, and involvement of neurohormones, cytokines and oxidative stress in an interrelated network of pathways and players. Linking gene expression to loss of function in HF has helped to unravel many of these players, such as the central role of tumor necrosis factor-α (TNF-α) in HF. However, a compensatory, nuclear peroxisome proliferator activated receptor (PPAR)-α-mediated adaptive response promotes greater expression of free fatty acids (FFA)-metabolising enzymes, and reliance on FFA as the major fuel, leading to reduced glycolysis, glucose and lactate oxidation, also described as the Randle hypothesis [1]. In the presence of sustained stress, metabolic maladaptation is characterised by decreased expression of PPAR-α, downregulation of genes controlling the oxidation of FFA, reactivation of a foetal gene program and increased glucose oxidation [2]. In addition, whilst a healthy heart features oxidation of FFA as predominant source of fuel for contraction in the steady state, it is the metabolic flexibility of switching between various substrates in response to changes in workload that provides the most hybrid-fuel efficiency at the given physiological demand. In HF, impaired capacity of FFA oxidation couples with inadequate compensatory increase in glucose oxidation. When the failing heart faces an increased FFA load (as in diabetes or obesity), intramyocardial lipid accumulation occurs. In the absence of significant coronary artery disease, it seems paradoxical that the heart “fails in the midst of plenty” [1]; both FFA and glucose are the main providers of energy for the beating heart. However, energy transfer becomes impaired at the level of intermediary metabolism, phenotypically revealed by a decline in the phosphocreatine [PCr]/adenosine triphosphate [ATP] ratio [3]. [PCr]/[ATP] ratios correlate with the severity of HF and importantly, are a prognostic indicator of mortality in patients. These clinical observations have led to the formulation of the “energy starvation hypothesis” stating that the failing heart is unable to meet the haemodynamic requirements of the body because there is not enough chemical energy available [4].

Given that the myocardial creatine kinase system plays a pivotal role in the buffering and transfer of high energy phosphates from the sites of energy production to the sites of utilisation, this led to the simplistic concept that elevating cardiac creatine levels may prevent the progression of the disease. Creatine, however, is not synthesised in the heart but is taken up by cardiomyocytes against a concentration gradient via the Na+–creatine cotransporter (creatine transporter, CrT). External creatine supplementation failed to improve the myocardial creatine (and PCr) content due to a downregulation of the CrT in response to high extracellular creatine [5]. Thus, other models were sought for to investigate whether increasing CrT expression would provide a metabolic strategy for treatment of HF [6].

In this issue of the Journal of Molecular and Cellular Cardiology, Philips et al. [7] expanded on their previous study [8], reporting that overexpression of the CrT in 24– to 37-week-old mice (CrT-OE mice) led to supranormal myocardial creatine and phosphocreatine concentrations. Unexpectedly, chronically increased myocardial creatine levels in the CrT-OE model were not beneficial, but induced progressive cardiac hypertrophy and HF. The present study now provides elegant links between the cardiometabolic and pathophysiological features of LV remodelling, in a multimodal bio-signature, combing the proteomic/metabolomic readout with cardiovascular imaging in a longitudinal fashion. These investigators observed and contrasted cardiometabolic features of the CrT-OE model with wild-type littermate controls. In this transgenic HF model with overexpression of the CrT in 24– to 37-week-old mice (CrT-OE mice), a comprehensive bio-signature of multifaceted cardiovascular disease processes is followed by a decline in the phosphocreatine [PCr]/adenosine triphosphate [ATP] ratio [3]. [PCr]/[ATP] ratios correlate with the severity of HF and importantly, are a prognostic indicator of mortality in patients. These clinical observations have led to the formulation of the “energy starvation hypothesis” stating that the failing heart is unable to meet the haemodynamic requirements of the body because there is not enough chemical energy available [4]. Given that the myocardial creatine kinase system plays a pivotal role in the buffering and transfer of high energy phosphates from the sites of energy production to the sites of utilisation, this led to the simplistic concept that elevating cardiac creatine levels may

Fuelled by obesity, hypertension, diabetes, and an aging population, heart failure (HF) is increasingly common in the Western population. Its pathophysiology reflects the complex and multifactorial background, and involvement of neurohormones, cytokines and oxidative stress in an interrelated network of pathways and players. Linking gene expression to loss of function in HF has helped to unravel many of these players, such as the central role of tumor necrosis factor-α (TNF-α) in HF. However, a compensatory, nuclear peroxisome proliferator activated receptor (PPAR)-α-mediated adaptive response promotes greater expression of free fatty acids (FFA)-metabolising enzymes, and reliance on FFA as the major fuel, leading to reduced glycolysis, glucose and lactate oxidation, also described as the Randle hypothesis [1]. In the presence of sustained stress, metabolic maladaptation is characterised by decreased expression of PPAR-α, downregulation of genes controlling the oxidation of FFA, reactivation of a foetal gene program and increased glucose oxidation [2]. In addition, whilst a healthy heart features oxidation of FFA as predominant source of fuel for contraction in the steady state, it is the metabolic flexibility of switching between various substrates in response to changes in workload that provides the most hybrid-fuel efficiency at the given physiological demand. In HF, impaired capacity of FFA oxidation couples with inadequate compensatory increase in glucose oxidation. When the failing heart faces an increased FFA load (as in diabetes or obesity), intramyocardial lipid accumulation occurs. In the absence of significant coronary artery disease, it seems paradoxical that the heart “fails in the midst of plenty” [1]; both FFA and glucose are the main providers of energy for the beating heart. However, energy transfer becomes impaired at the level of intermediary metabolism, phenotypically revealed by a decline in the phosphocreatine [PCr]/adenosine triphosphate [ATP] ratio [3]. [PCr]/[ATP] ratios correlate with the severity of HF and importantly, are a prognostic indicator of mortality in patients. These clinical observations have led to the formulation of the “energy starvation hypothesis” stating that the failing heart is unable to meet the haemodynamic requirements of the body because there is not enough chemical energy available [4]. Given that the myocardial creatine kinase system plays a pivotal role in the buffering and transfer of high energy phosphates from the sites of energy production to the sites of utilisation, this led to the simplistic concept that elevating cardiac creatine levels may
not always their consequence [14]. Transgenic animals undeniably play a central role in revealing potential mechanisms that operate in vivo. Whether these models appropriately substitute for the ‘descriptive and holistic approach’ of model systems and whether the experimental nature of inducing disease-like syndromes in non-human species allows a straightforward translation onto the human phenotype, remains hotly debated [14,15]. Clearly, a genetic manipulation leads to a significant misbalance in the biological network of interrelated pathways as a whole: rather than resulting in a single gene-molecule effect, the readouts reveal complex changes. Yet, there is still a general lack of control for compensatory off-target effects. Instead, the phenotype is directly attributed to the primary genetic perturbation. In combination with a systems biology approach, transgenic animal models could reveal more profound insights into disease mechanisms.

The use of CrT-OE mice in the present study of cardiac metabolism by H1-MRS illustrates this point. Whilst H1-MRS enables the detection of total creatine, it is the 31P-MRS that allows detection of cardiac energetic metabolites, such as PCr, ATP, inorganic phosphate and intracellular pH [16]. Transgenic models of low creatine (guanidinoacetate-N-methyltransferase-knockout mice, GAMT−/−) [17] and high cardiac creatine levels (CrT-OE mice) [8] both produce HF-like phenotypes, with left ventricular dysfunction and remodelling, and cardiometabolic impairment. Yet, they produce differential [PCr]/[ATP] MRS readouts; whilst the former clearly features reduced activity of these metabolites, in CrT-OE mice, the levels of these two metabolites are increased. In CrT-OE mice, the metabolic impairment stems from increased free ADP concentrations, which may in turn, result in a reduction in the available free energy of ATP hydrolysis, and potentially directly contribute to contractile dysfunction. Thus, the use of MRS in this transgenic model may have potentially ‘phenotyped’ homeostatic perturbation related to this particular transgenic mouse, and contributed less to a better understanding into the role of energy metabolism in human HF [15]. Nonetheless, if increased free creatine results in decreased glycolytic capacity, this is a truly novel mechanism. Future studies are required to establish the time course of PCr/total creatine abnormalities in order to define the relation between left ventricular dysfunction and creatine metabolism. Similarly, isolated perturbation of enolases, but not other glycolytic enzymes is not a strong argument for impaired glycolysis in the present context of HF. Alternative explanations for the modest drop in lactate are more lactate efflux from the heart or less lactate production, i.e. the flux through the glycolytic pathway is similar but more pyruvate is oxidised in mitochondria.

The advent of -omics technologies increases our recognition that genetic manipulations frequently lead to alterations of seemingly unrelated biochemical pathways. The study of Phillips et al. highlights the importance of analysing compensatory changes in transgenic animal models, in particular the effects on metabolism [18], before interpreting cardiovascular phenotypes, and demonstrates that such a comprehensive approach can reveal new aspects of cardiovascular pathophysiology with potential therapeutic implications.

Acknowledgements

Dr. M. Mayr is a Senior Research Fellow of the British Heart Foundation.
References


Valentina O. Puntmann
Cardiovascular Section,
Division of Investigative Sciences,
Imperial College London, UK

Manuel Mayr
King’s BHF Centre, King’s College, T25 Coldharbour Lane, London SE5 9NU, UK
E-mail address: manuel.mayr@kcl.ac.uk.

Corresponding author. Tel.: +44 0 20 7848 5238; fax: +44 0 20 7848 5296.

20 November 2009