CARDIAC METABOLISM

Ketone bodies for the starving heart

The heart is an organ with high energy demands and metabolic flexibility, thus allowing for various energy substrates for ATP production under different physiological conditions. Zhang et al., Fernandez-Caggiano et al. and McCommis et al. converge on the mitochondrial pyruvate transporter as a key metabolic hub for the maintenance of cardiac metabolism and a critical determinant of cardiac metabolic plasticity during heart failure.

P. Christian Schulze and Jasmine M. F. Wu

Cardiac metabolism relies on the oxidation of fatty acids as the primary source for ATP production. Whereas glucose and glycolysis contribute substrates to approximately 30% of basal cardiac metabolism, other alternative substrates, including amino acids, lactate and ketone bodies, contribute only modest amounts to basal ATP production in the healthy heart in adults.

Enhanced cellular metabolism of glucose in the absence of oxygen was initially described in yeast by Louis Pasteur in 1861 and was later linked to anaerobic glycolysis and named the 'Pasteur effect'[1]. Otto Warburg's subsequent findings that tumour cells produce large amounts of lactate through anaerobic glycolysis were termed the 'Warburg effect', a phenomenon that he incorrectly described as not only a metabolic characteristic but the primary reason for, and driver of, tumourigenesis[2]. More recent data have linked the Warburg effect in tumour cells to an increased need for biomass synthesis and maintenance of cell viability, thereby ushering in a new age of metabolic modulators as novel tumour treatments[3,4].

Changes in cardiac metabolism during episodes of ischaemia are primarily caused by a lack of oxygen, thus resulting in impaired oxidative metabolism and in mitochondrial dysfunction, and leading to enhanced cardiac glucose utilization through anaerobic glycolysis, pyruvate accumulation and lactate production. However, similar effects on gene expression and enzyme activity have been found in failing myocardium even in the absence of hypoperfusion and hypoxemia (ischaemia). These changes have been linked to increased myocardial-wall stress[5], activation of a foetal gene expression program[6] and lipotoxic accumulation of intermediates of fatty acid metabolism[7,8], among other factors. Given the lower efficiency of ATP production per mole of glucose in anaerobic glycolysis than in full aerobic oxidation, the apparent paradox of an anaerobic glycolytic cardiac metabolic state with resulting energy deficiency in the setting of sufficient oxygen and substrate supply has not been fully explained to date.

A functional mitochondrial pyruvate carrier (MPC), composed of MPC1 and MPC2, is critical for cellular homeostasis, because it is required for pyruvate import into mitochondria, thereby supplying substrates through acetyl-CoA for the tricarboxylic acid (TCA) cycle[9]. MPC biochemical function was initially described in 1971 (ref. [10]) and was followed by reports of diminished MPC activity in cancer cells with an associated decrease in pyruvate oxidation[11]. MPC loss of function in neoplastic cells promotes cancer growth, thus suggesting that impaired MPC activity at least partially accounts for the Warburg effect and its influence on cancer cell metabolism[12]. Furthermore, mitochondrial pyruvate uptake through the MPC is needed for efficient hepatic gluconeogenesis and the regulation of blood glucose levels[13].

In this issue of *Nature Metabolism*, the intersecting investigations of three independent groups converge on the dysregulation of MPC in the failing heart as a metabolic hub for uncoupling glycolysis and glucose oxidation in heart failure[14–16]. In examining the failing human myocardium, Fernandez-Caggiano et al.[15] observed decreased myocardial levels of MPC1, an effect that was recapitulated in animal models of cardiac hypertrophy, and failure via angiotensin II infusion or transverse aortic constriction (TAC). Cardiac-specific genetic deletion of either MPC1 or MPC2 resulted in cardiac hypertrophy, failure and premature death, as well as impaired cardiac mitochondrial pyruvate utilization. After overexpression of MPC1, thereby driving MPC formation and activity in the heart, Fernandez-Caggiano et al. observed improved cardiac function and diminished hypertrophy after TAC, thus indicating that pyruvate transport into the mitochondria is a critical hub for maintaining cardiac metabolism and function during cardiac insult and maladaptation.

Using a mouse model of cardiac genetic deletion of MPC1, Zhang et al.[14] independently observed the development of cardiac hypertrophy, heart failure and premature death. Their metabolomic phenotyping of MPC1-deficient failing hearts revealed a signature of glucose overreliance and decreased carbon flux into mitochondrial TCA-cycle intermediates, with an accumulation of anabolic metabolites including pyruvate, lactate, amino acids and pentose-phosphate-pathway intermediates, along with increased glycogen formation. In an effort to rewire cardiac metabolism by circumventing glycolysis and mitochondrial pyruvate import, Zhang et al. fed either a ketogenic or a high-fat diet to mice with failing hearts due to MPC1 deletion and observed that both diets reversed cardiac remodelling. These benefits, however, were no panacea, because a ketogenic diet when administered concurrently with injury did not reverse the outcomes after TAC; only pretreatment with 3 weeks of ketogenic diet feeding before TAC was protective.

Independently expanding on these findings, McCommis et al.[16] observed similar remodelling of cardiac metabolism and output in mice with cardiac-specific MPC2 deletion, and were also able to rescue the function of MPC2-deficient failing hearts with a ketogenic diet. A metabolomic assessment of acylcarnitine species in mice fed either normal chow or a ketogenic diet revealed a critical build-up of medium-chain and long-chain acylcarnitine species in the hearts of mice fed the chow rather than the ketogenic diet. In testing diets with various fat contents, McCommis et al. found that the effects of cardiac MPC deficiency were prevented or even reversed by high-fat feeding compared with low-fat or medium-chain-triglyceride feeding. Beyond the ketogenic diet, short-term

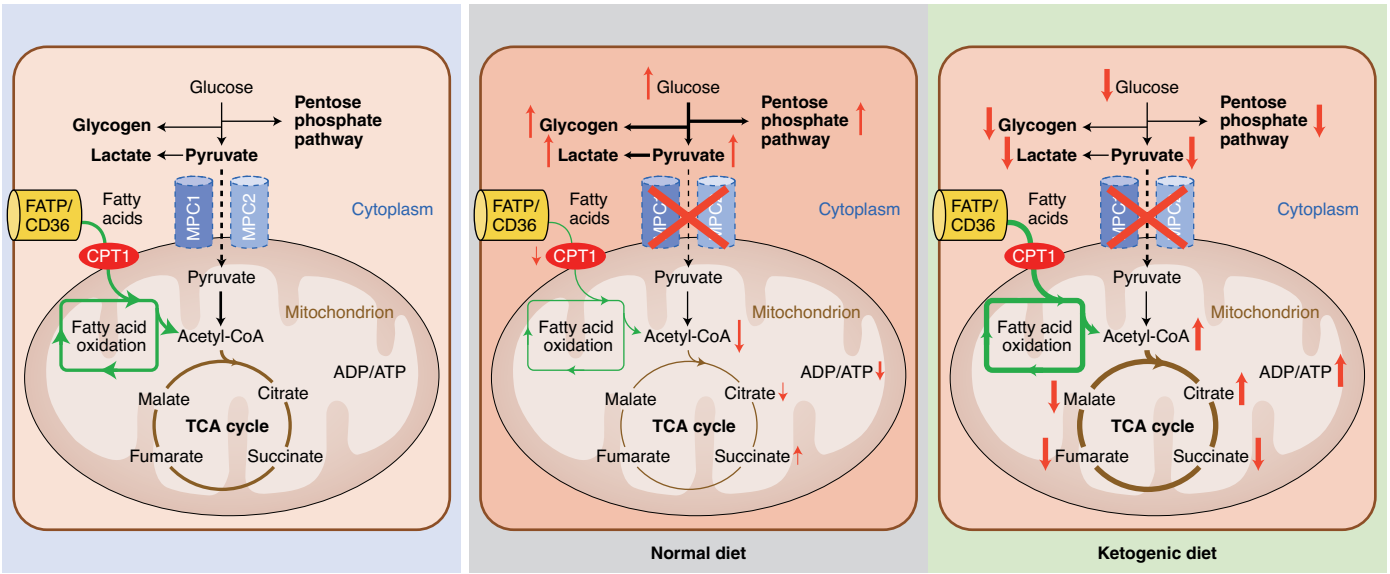

Fig. 1 | Cardiac intermediary metabolism in normal and failing myocardium, and the role of the ketogenic diet in correcting substrate metabolism in heart failure. Cardiac metabolism relies on oxidation of fatty acids as the primary source for ATP production (~70% of ATP production), whereas glucose and glycolysis contribute substrates to approximately 30% of basal cardiac metabolism (left). In heart failure, fatty acid oxidation is impaired, and increased glycolysis cannot compensate for decreased glucose oxidation. MPC suppression decreases pyruvate flux from glycolysis into mitochondria even under normoxic conditions, thus leading to accumulation of lactate, pyruvate and pentose-phosphate-pathway intermediates, as well as impaired overall TCA-cycle flux with decreased ATP synthesis (middle). A ketogenic diet enhances fatty acid oxidation rates and TCA-cycle flux, thus resulting in increased ATP synthesis along with rescued levels of glycolytic intermediates, lactate and glycogen (right). FATP/CD36, fatty acid transport protein; CPT1, carnitine palmitoyltransferase I.

starvation with ketosis and, to a lesser extent, direct ketone-body supplementation (β-hydroxybutyrate injection or ketone ester supplementation) also prevented cardiac remodelling. Detailed transcriptional, proteomic and metabolomic analyses suggested that enhanced fatty acid oxidation, rather than primary metabolism of ketone bodies, was responsible for these effects.

Altogether, these studies reveal a central role of mitochondrial pyruvate utilization in regulating basal cardiac metabolism and function, and highlight the potential role of dietary interventions in enhancing fatty acid metabolism to reverse cardiac dysfunction and remodelling.

Ketone bodies (β-hydroxybutyrate, acetoacetate and acetone) are produced in hepatic mitochondria from fatty acid–derived acetyl-CoA. Under conditions in which carbohydrates are limited, such as starvation or a low-carbohydrate diet, ketone bodies serve as an alternative energy source. In oxidative tissues, such as the heart, brain and muscles, ketone bodies are oxidized, thus producing acetyl-CoA as a substrate for the TCA cycle[17,18].

Whereas ketone oxidation only modestly contributes to energy production under basal metabolic conditions, several recent studies have suggested that ketone-body metabolism significantly affects the failing heart. In line with the findings of the current studies, a high-fat diet has been shown to attenuate cardiac remodelling in animals with hypertensive disease or pressure-overload-induced heart damage[19,20]. After pressure overload, animals with impaired ketone oxidation show poorer pathological remodelling and cardiac performance[21,22]. In contrast, ameliorated pressure-overload-induced damage is observed in animals with elevated ketone metabolism after overexpression of ketone-oxidation genes[23]. Collectively, these studies support a cardioprotective role of ketone bodies under conditions of myocardial stress and provide a foundation for the dietary interventions used by Fernandez-Caggiano et al., Zhang et al. and McCommis et al.

Increased glycolysis in the presence of insufficient glucose oxidation cannot compensate for the decreased energy supply after heart injury and in the chronically failing myocardium[24]. MPC suppression, the crucial regulator of pyruvate flux from glycolysis into mitochondria, could explain the preference of the failing myocardium for anaerobic glycolysis even under normoxic conditions (the Warburg effect in the failing heart). Peripheral lipolysis is increased in heart failure, owing to chronic catecholamine stimulation, thus resulting in high circulating free fatty acids[7,25]. Fatty acid oxidation in heart failure is impaired partly because of decreased mitochondrial carnitine-shuttle-mediated uptake, which in turn leads to increased circulating levels of acylcarnitines and decreased fatty acid β-oxidation.

Ketone-body availability and utilization increase in heart failure, and maintenance of ketone metabolism appears to be protective in hypertrophic and failing hearts[21–23,26]. Therefore, ketone bodies may serve as a cardioprotective alternative energy supply. However, whereas ketones can be readily oxidized, and high levels of ketones increase TCA-cycle flux and intermediates, ketone-body supplementation is insufficient to increase the impaired efficiency of energy metabolism in the failing heart[27,28]. According to this trio of studies, a chronic ketogenic environment, rather than an acute increase in ketosis, appears to exert beneficial effects in the failing myocardium, owing to increased fatty acid oxidation, but still impairs cardiac efficiency. This disruption in cardiac metabolism might be explained by impaired glucose oxidation because of decreased MPC levels restricting the flux of pyruvate into mitochondria. Studies examining the effects of ketogenic therapies in people with heart failure are currently limited, but the observed increase

in intermediates of ketone-body metabolism in patients treated with sodium-dependent glucose cotransporter-2 inhibitors is intriguing[29,30].

Although the findings in these three studies have advanced understanding of the contribution of the MPC to cardiac metabolism in the failing myocardium, several questions remain to be answered. How MPC levels are regulated in both healthy and failing hearts, and whether transcriptional, translational or post-translational regulation dictates the decreased levels or function of this complex in the failing myocardium remain unclear. In addition, the mechanistic contribution of the MPC complex to activation of the foetal gene expression program remains to be explored. Metabolically, the specifics of how ketone-body metabolism enhances fatty acid oxidation are also unclear; a replenishment of TCA-cycle intermediates (for example, oxaloacetate) from ketones might be hypothesized to lead to increased TCA-cycle flux, with associated increased fatty acid uptake to mitochondria through activation of carnitine palmitoyltransferase I. Here, the specific levels and regulatory functions of malonyl-CoA and citrate may provide a mechanistic connection.

The current findings suggest a role for specific ketogenic diets as a supportive, non-pharmacologic treatment in people with heart failure. The known energy deficiency of the failing myocardium might be speculated to be modifiable through substrate selectivity and therapeutic metabolic modulation. A better understanding of the interplay between the metabolism of ketone bodies and fatty acids under chronic ketogenic conditions may help to identify specific targets for direct augmentation of fatty acid oxidation and sustainable energy supply in the failing heart (Fig. 1). ❐

P. Christian Schulze ✉ and Jasmine M. F. Wu

Department of Internal Medicine I (Cardiology, Angiology and Intensive Medical Care), University Hospital Jena, Friedrich-Schiller-University Jena, Jena, Germany.

✉*e-mail: christian.schulze@med.uni-jena.de*

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Competing interests

The authors declare no competing interests.