Editorial

Mitochondrial dysfunction in heart failure: potential for therapeutic interventions?

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Cardiac work is supported by a high rate of ATP hydrolysis, matched by ATP production through mitochondrial oxidative phosphorylation (Fig. 1). Low ATP content in cardiac tissue was observed in patients with chronic heart failure despite the absence of myocardial ischaemia [1]. Mitochondrial function in cardiac tissue from the failing heart demonstrated that the capacity of the mitochondria for oxygen consumption and oxidative phosphorylation are significantly reduced compared to the normal heart [2]. Furthermore, morphological examination of the failing heart by electron microscopy revealed that the mitochondria are disrupted and damaged [3]. The paper by Jarreta et al. in this issue of Cardiovascular Research shows in both idiopathic dilated cardiomyopathy (IDC) and heart failure patients with a history of ischaemic coronary disease (IC) that the activity of complex III of the electron transport chain is reduced, without changes in the activities of complexes I, II or IV, or in the mitochondrial marker enzyme citrate synthase [4]. Evidence for a causal link between impaired mitochondrial metabolic function and cardiac failure was found in several cases of inherited cardiomyopathies [5], presenting as classic IDC. Surprisingly little is known about the molecular aspects of mitochondrial pathology in the failing heart. While point mutations in key mitochondrial enzymes could significantly impair the ability of the mitochondria to generate ATP, Jarreta et al. [4] found only neutral polymorphisms in the mitochondrial cytochrome b gene, suggesting that the complex III defect is not a primary mitochondrial disease.

A myriad of good questions is raised by the work of Jarreta et al. [4]. Are there functional consequences of the complex III defect? Is a 35% reduction in activity enough to result in a decrease in the rate of oxidative phosphorylation and a meaningful drop in the ATP content? Of interest, cardiomyopathy is not a presentation in patients with a congenital complex III defect [6]. The molecular cause of this decrease in complex III activity in heart failure is not known. Complex III contains 11 subunits, and the only one that is encoded on mitochondrial DNA, cytochrome b, has been shown by Jarreta et al. [4] to be normal. The status of the other subunits needs to be determined before the molecular mechanism(s) can be fully understood. Additionally, the mitochondria in the heart exist as two populations (interfibrillar and subsarcolemmal) which respond differently to inherited card-

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Fig. 1. Schematic depiction of myocardial energy metabolism. Abbreviations: PDH, pyruvate dehydrogenase; I, II, III, IV and V, complexes I through V; CAC, citric acid cycle; SR, sarcoplasmic reticulum.

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diomyopathy [7], ischaemic injury [8], and aging [9]. Is there a selective decrease in complex III in only one population? Also, is there a greater production of free radicals due to the decreased complex III activity?

In addition to defects in the electron transport chain, the failing heart has important, clinically relevant mitochondrial abnormalities in the metabolism of carbon substrates for the generation of reducing equivalents (NADH and FADH$_2$) (Fig. 1). The oxidation of fatty acids normally supplies approximately two thirds of the energy for oxidative phosphorylation [10]. Heart failure patients may have impaired oxidation of glucose and lactate and enhanced fatty acid oxidation that contributes to contractile dysfunction [11]. Thus pharmacotherapies aimed at increasing myocardial oxidation of pyruvate (derived from glucose and lactate) (Fig. 1) could be beneficial for the failing heart [12]. In line with this, pharmacological activation of pyruvate dehydrogenase (the key site regulating the oxidation of carbohydrate) results in a significant improvement in left ventricular function without an increase in myocardial oxygen consumption [13]. The enhanced pyruvate oxidation lowers lactate accumulation and efflux from the cell, and helps maintain myocyte pH and ion homeostasis [10]. This would allow more efficient use of ATP for contractile work by myosin ATPases, and for relaxation by the Ca$^{2+}$ ATPase on the sarcoplasmic reticulum, and a greater rate of left ventricular power for a given rate of myocardial oxygen consumption. Pyruvate oxidation also can be increased by partially inhibiting fatty acid oxidation, which removes product inhibition on pyruvate dehydrogenase [10]. The partial fatty acid oxidation inhibitors trimetazidine and ranolazine have been used successfully for the treatment of stable angina [10], without eliciting any of the classic anti-ischaemic effects of traditional therapies (e.g. decrease heart rate, coronary vasodilation, decreased arterial blood pressure). This approach remains to be tested in heart failure patients.

A switch to greater carbohydrate oxidation and less fatty acid oxidation is observed with chronic treatment with the beta-adrenergic receptor antagonist metoprolol, and is associated with improvement in left ventricular function [14]. This may be due to down-regulation of carnitine palmitoyl transferase-I (a key enzyme regulating fatty acid β-oxidation in the mitochondria), as observed with long-term treatment with metoprolol in dogs with progressive heart failure [15]. In addition, progression of heart failure following a myocardial infarction in the rat is prevented with ACE inhibitors, as is the fall in state III respiration in isolated cardiac mitochondria [16]. Perhaps the suppression of heart failure induced neural–hormonal activation prevents the decline in complex III activity observed by Jarreta et al. [4].

Clearly the failing heart has mitochondrial abnormalities that impair the ability of the tissue to synthesize ATP. Future work will attempt to identify the causes of these abnormalities, and determine the role they play in the progression of heart failure. Congestive heart failure is a malignant disease and drugs that can stop the progression of the disease are sorely needed. Therapies aimed at preserving mitochondrial function and optimizing substrate metabolism appear to be worthwhile pursuits in the effort to stop the progression of heart failure.

References