Myocardial energy metabolism in dilated cardiomyopathy

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Abstract

Dilated cardiomyopathy can be broadly defined as heart failure with an enlarged left ventricular chamber, but with no evidence of ischemic heart disease or myocardial infarction. Recent studies from patients and animal models show that dilated cardiomyopathy results in a decrease in myocardial content of adenosine-5′-triphosphate (ATP) and phosphocreatine and a decrease in the capacity for mitochondrial oxidative metabolism and aerobic ATP production. There is a switch in the source of fuel, with a decrease in the rate of myocardial fatty acid oxidation and greater glucose oxidation. Pharmacologically preventing the decrease in fatty acid oxidation with a peroxisome proliferator-activated receptor-α agonist does not appear to be beneficial. On the other hand, treatment with partial inhibitors of myocardial fatty acid oxidation has favorable effects on cardiac energy metabolism, contractile function, and structure.

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Introduction

Cardiac power generation requires a high rate of conversion of chemical energy from bloodborne substrates (fatty acids, glucose, and lactate) to contractile power (*Figure 1*). Inability to meet the energy requirement results in heart failure, which is most clearly manifest by an inability to perform physical exercise. Most forms of heart failure are associated with a history of cardiac ischemia, myocardial infarction, hypertension, and/or left ventricular (LV) hypertrophy, with either a normal or decreased ejection fraction. Heart failure can also present with a dilated LV and low ejection fraction, but without the classic history of ischemia, infarction, or hypertension. This condition is broadly referred to as dilated cardiomyopathy (or ''idiopathic dilated cardiomyopathy''); it has no clear cause, yet a poor prognosis similar to other forms of heart failure. Dilated cardiomyopathy can be caused by inherited metabolic defects, specifically those in mitochondrial oxidative metabolism, or may be acquired, such as with chronic tachycardia, pregnancy, exposure to toxins, alcoholism, or diabetes. Several adaptations in myocardial substrate metabolism have been described in response to dilated cardiomyopathy. This brief overview will highlight recent findings related to myocardial energy metabolism in dilated cardiomyopathy.

Cardiac energy metabolism in dilated cardiomyopathy

The energy for cardiac mechanical work and relaxation comes from adenosine-5′-triphosphate (ATP), which is broken down to adenosine diphosphate (ADP) and inorganic phosphate to fuel contraction, and Ca^{2+} uptake into the sarcoplasmic reticulum to initiate diastolic relaxation (*Figure 1*). Oxidative phosphorylation rapidly resynthesizes ATP in the

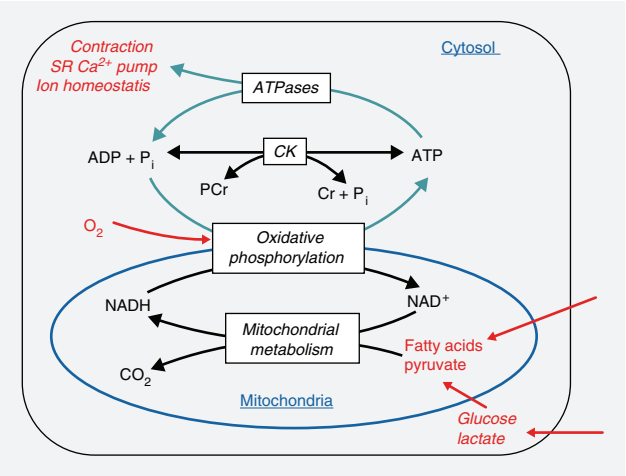

Figure 1. Schematic depiction of cardiac energy metabolism. Adenosine-5′-triphosphate (ATP) is broken down in the cytosole to fuel the contractile work of systole, Ca^{2+} uptake into the sarcoplasmic reticulum, which ends systole and initiates relaxation and diastolic filling, and for ion pumps on the sarcolemma. ATP is resynthesized in the mitochondria by oxidative phosphorylation, which is fueled by electrons that are transferred to NADH with the metabolism of fatty acid and pyruvate in the mitochondrial matrix (ADP adenosine diphosphate, CK creatine kinase, Cr creatine, PCr phosphocreatine, NADH nicotinamide adenine dinucleotide).

mitochondria. This process is fueled by electrons generated by metabolism of carbon substrates, namely fatty acids and pyruvate, in the mitochondrial matrix, which passes electrons to nicotinamide adenine dinucleotide (NADH) and the electron transport chain. Here oxygen is consumed and oxidative phosphorylation resynthesizes ATP (*Figure 1*). Normally the healthy myocardium sets the blood flow, oxygen delivery, mitochondrial metabolism, NADH formation, and ATP synthesis to match need for ATP breakdown. When there is a brief mismatch (i.e., during the transition from rest to exercise), the breakdown of phosphocreatine (PCr) by creatine kinase (CK) can rapidly synthesize ATP (*Figure 1*). Hence ATP content stays relatively constant even with abrupt increases in LV power output.

Long-chain fatty acids (primarily oleate, palmitate, and linoleate) are a healthy human heart's main fuels, supplying approximately 50% to 80% of the energy requirement under post-absorptive conditions. The balance is from pyruvate oxidation, which is derived in roughly equal proportions from glucose and lactate. Under normal conditions the myocardium has tremendous metabolic flexibility, and is able to generate a maximal rate of oxygen consumption, ATP formation, and cardiac power using either fatty acids or carbohydrates as the sole substrate [1].

Patients with advanced dilated cardiomyopathy have poor systolic and diastolic function, and switch the fuel for cardiac metabolism away from fatty acid oxidation toward greater glucose oxidation [2,3]. This is illustrated in *Figure 2*, which shows a reduction in myocardial free fatty acid oxidation, and greater glucose uptake by the myocardium in patients with dilated cardiomyopathy. Substrate metabolism was assessed directly using ^{3}H-oleate to measure fatty acid oxidation, and arterial and coronary sinus catheterization to assess transmyocardial substrate uptake. Similar results were found using noninvasive positron emission tomography [3], and also in the canine tachycardia model of dilated cardiomyopathy [4–6]. Moreover, the decline in fatty acid oxidation was inversely related to the extent of LV dilation (*Figure 3*). When the hearts of patients with dilated cardiomyopathy were stressed by an acute bout of atrial pacing at 130 beats/min (*Figure 2*), there was not the normal increase in myocardial glucose uptake seen in the controls, suggesting that there is a loss of ''metabolic flexibility'' in these patients.

There is growing evidence to suggest that defective mitochondrial ATP generation contributes to cardiac

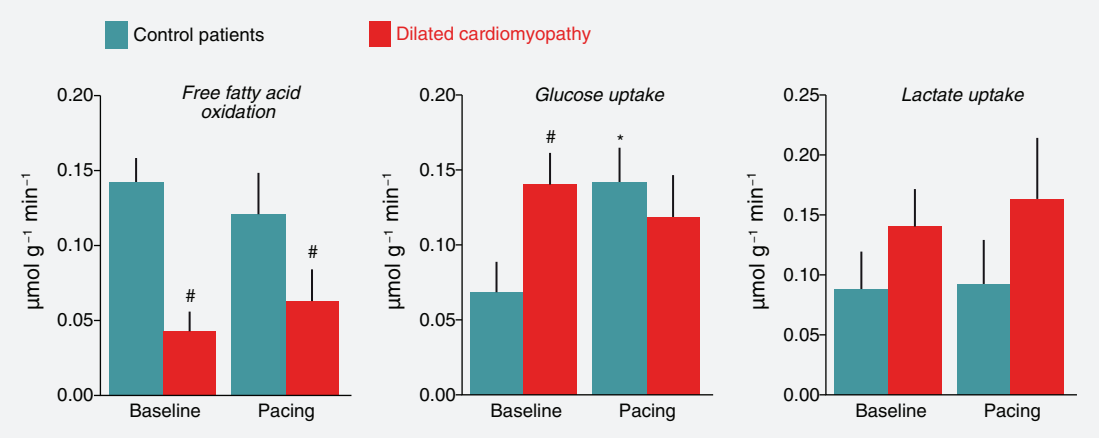

Figure 2. Myocardial substrate metabolism in control patients and patients with dilated cardiomyopathy. Figure drawn from data presented in Neglia et al (2007). Am J Physiol Heart Circ Physiol 293:H3270–H3278 [2].

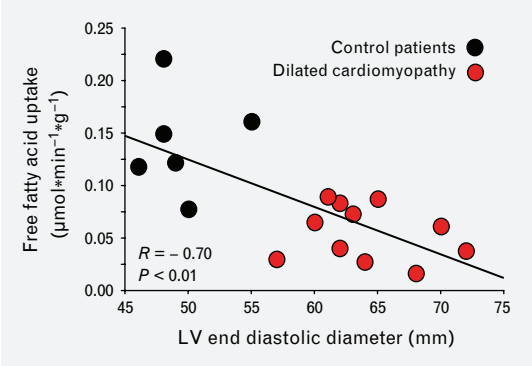

Figure 3. Myocardial fatty acid uptake plotted as a function of left ventricular end diastolic diameter. Figure drawn from data presented in Neglia et al (2007). Am J Physiol Heart Circ Physiol 293:H3270–H3278 [2].

dysfunction in patients with dilated cardiomyopathy. In the canine model, there is a decrease in myocardial ATP, PCr and creatine (Cr) during the progression to severe dilated end-stage heart failure [7]. Many studies found that heart failure results in a decrease in the capacity for mitochondrial ATP generation at the level of oxidative phosphorylation, particularly seen in a decline in the electron transport chain's integrative function [1,8,9]. Unfortunately, it is very difficult to assess mitochondrial function in samples from normal humans and patients with dilated cardiomyopathy, thus we do not have a clear understanding of the precise molecular mechanisms responsible for the decrease is ATP and impaired oxidative phosphorylation in this condition.

At present, it is not clear whether these alterations are the cause or consequence of dilated cardiomyopathy. Clearly there are relatively rare inherited defects in mitochondrial metabolism that present as dilated cardiomyopathy [10], however this does not explain the vast majority of cases. In general, it appears that the mitochondrial defects and the switch in substrate metabolism are acquired over the course of the disorder's development and progression. While it is clear that it is important to maintain mitochondrial ATPgenerating capacity in dilated cardiomyopathy, it is less clear if it is important to maintain the normal high rate of fatty acid oxidation. Maintaining myocardial fatty acid oxidation over the progression of tachycardia-induced dilated cardiomyopathy using fenofibrate, an agonist for peroxisome proliferator-activated receptor-α, did not improve cardiac function or slow the progression of heart failure [11]. On the other hand, treatment with oxfenicine, an inhibitor of myocardial fatty acid oxidation at the level of carnitine palmitoyl transferase I, prevented LV dilation and delayed decompensated heart failure in this model [12]. This approach has not been evaluated specifically in patients with dilated cardiomyopathy, but small clinical studies in heart-failure patients have shown promising results with the partial fatty acid oxidation inhibitors perhexiline [13] or trimetazidine [14–17]. These finding suggest that the decline in fatty acid oxidation in dilated cardiomyopathy is not detrimental, and inhibition of fatty acid oxidation has potential as a therapy for this condition.

In summary, dilated cardiomyopathy results in a decreased capacity for mitochondrial oxidative metabolism and aerobic ATP production, and a decrease in the rate of myocardial fatty acid oxidation and increased glucose oxidation. Pharmacologically preventing the decrease in fatty acid oxidation with peroxisome proliferator-activated receptor-α agonist does not appear to be beneficial, but treatment with partial inhibitors of myocardial fatty acid oxidation has favorable effects on cardiac energy metabolism, contractile function, and structure. ■

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