Changes in cardiac metabolism: a critical step from stable angina to ischaemic cardiomyopathy

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Cardiac work requires a high rate of adenosine triphosphate (ATP) breakdown. ATP is resynthesized in the mitochondria with energy from the combustion of fatty acids, glucose and lactate. Fatty acids are the main fuel for the heart, supplying 60–90% of the energy, with the balance (10–40%) from pyruvate oxidation (formed from glycolysis and lactate). Fatty acid oxidation inhibits pyruvate oxidation in the mitochondria. During myocardial ischaemia, oxygen consumption and ATP production is reduced, causing accelerated glycolysis and lactate production; the pH falls and cell function is impaired. Paradoxically, with a partial reduction in coronary flow, the myocardium continues to derive most of its energy from the oxidation of fatty acids despite a high rate of lactate production; this fatty acid oxidation during ischaemia inhibits pyruvate oxidation, and drives pyruvate conversion to lactate. Partial inhibition of fatty acid oxidation in ischaemic myocardium, such as with the long-chain 3-ketoacyl thiolase inhibitor trimetazidine, reduces lactate production and H+ accumulation during ischaemia, and results in clinical benefit in patients with angina pectoris.

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Introduction

The pump function of cardiac muscle is supported by high rates of myocardial blood flow, oxygen consumption, and combustion of fat and carbohydrates (glucose and lactate). Myocardial ischaemia occurs when there is a deficit between the normal rate of oxygen delivery to the myocardium required for a given heart rate, afterload and inotropic state, and the actual rate of oxygen delivery to the myocardium. The primary effect of ischaemia is mitochondrial metabolic dysfunction caused by reduced aerobic formation of adenosine triphosphate (ATP); this triggers accelerated anaerobic glycolysis and disruption of normal cardiac cell function

Traditional therapies for ischaemia are aimed at restoring the balance between oxygen delivery and ATP formation, and the myocardial demand for ATP. This is achieved either by increasing blood flow to the myocardium via coronary vasodilatation, or by reducing the oxygen requirement of the ischaemic tissue through decreasing heart rate, arterial blood pressure and cardiac contractility. These haemodynamic approaches to the treatment of ischaemic heart disease have proven relatively effective at reducing the symptoms of angina and improving exercise time. Nevertheless, many patients with coronary artery disease continue to have severe angina despite maximally tolerated traditional therapy or following revascularization procedures. Such patients would benefit from additional pharmacotherapy that would reduce the symptoms of ischaemia without further suppressing cardiac contractility, heart rate, or arterial blood pressure.

An alternative or adjunctive treatment for myocardial ischaemia is to reduce the production and release of angina-producing stimuli, and lessen the ischaemic burden of the patient by optimizing energy metabolism in the ischaemic myocardium. This approach differs from traditional therapies (e.g. beta-adrenergic receptor antagonists, calcium channel blockers, or long-acting nitrates) in that there are no direct effects on coronary blood flow, heart rate, or afterload. Rather, these agents alter the metabolism of the ischaemic tissue so that there is less accumulation of lactate, and a lesser fall in intracellular pH and ATP. The present brief review presents the biochemical and physiological rationale for this pharmacological approach to treatment of chronic stable angina.

Metabolism in healthy myocardium

Before considering myocardial metabolism during ischaemia, it is important to have an understanding of metabolism in the normal healthy heart.
Cardiac function is maintained by the synthesis and breakdown of adenosine triphosphate

Under conditions of normal coronary blood flow, ATP is broken down by myosin ATPase, releasing energy that fuels tension development and systolic work (Fig. 1). ATP breakdown is also employed by the sarcoplasmic reticulum Ca\(^{2+}\)-ATPase to remove Ca\(^{2+}\) from the cytosol at the end of systole and allow for diastolic relaxation. Approximately two-thirds of the ATP used by the heart goes to contractile shortening, and the remaining one-third is used for the sarcoplasmic reticulum Ca\(^{2+}\)-ATPase and other ion pumps\(^{[1,2]}\). ATP is constantly resynthesized from adenosine diphosphate and inorganic phosphate in the mitochondria by oxidative phosphorylation. In the healthy heart the processes of ATP synthesis and breakdown are exquisitely matched such that there is never a significant fall in ATP concentration, even with large increases in cardiac power output\(^{[3]}\).

Fatty acids are the predominant fuel for the heart

Fatty acids supply approximately 60–90% of the energy used to synthesize ATP in the healthy human heart (Fig. 1)\(^{[1–7]}\). The rate of fatty acid uptake by the heart is primarily determined by the concentration of fatty acids in the plasma\(^{[6]}\), which varies widely between 0·1 and approximately 1·5 mmol·l\(^{-1}\). Plasma fatty acids come from the breakdown of triglyceride in fat cells, and the broad range in plasma concentration is due to the hormonal control of hormone-sensitive lipase by insulin and noradrenaline (norepinephrine) in this tissue. Insulin suppresses fatty acid levels, and thus fatty acid levels are low when insulin levels are high after a meal. On the other hand, noradrenaline increases fatty acid release from fat cells so that fatty acid levels are elevated under times of stress, such as physical exercise, fasting, or myocardial ischaemia. Diabetic patients (both types 1 and 2) have high fatty acid levels because of low insulin levels and/or resistance to the normal insulin-induced suppression of fatty acid release from fat cells. Thus, during times of stress, when catecholamines are high and insulin is low, the heart is faced with a high plasma free fatty acid concentration, and fatty acid oxidation by the heart is high.

Fatty acids are oxidized in the mitochondria, where they release energy in the form of reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide (FADH\(_2\)) for the electron transport chain and the subsequent formation of ATP by oxidative phosphorylation (Fig. 2)\(^{[8]}\). On entering the cell, fatty acids are esterified to fatty acyl-coenzyme A (CoA), which makes the fatty acid more water-soluble. In order to cross the inner mitochondrial membrane, the fatty acid must be converted to fatty acylcarnitine by the enzyme carnitine palmitoyl transferase\(^{[8]}\). Once in the mitochondrion the fatty acid undergoes beta-oxidation, a process that repeatedly cleaves off two carbon acetyl-CoA units, generating NADH and FADH\(_2\) in the process. The acetyl-CoA is further oxidized to CO\(_2\) in the citric acid cycle. The rate of fatty acid beta-oxidation is primarily regulated by the concentration of free fatty acids in the plasma, the activity of the carnitine transferase/translocase system on the mitochondrial membranes, and the activity of a series of enzymes that catalyze the multiple steps of fatty acid beta-oxidation (Fig. 2)\(^{[8]}\).

Glucose and lactate metabolism

Glucose and lactate supply between approximately 10% and 40% of the energy requirement of the heart (Fig. 1)\(^{[1,2,4,5,7]}\). Glucose is taken up by the myocardium and is either stored as glycogen, or broken down by glycolysis to pyruvate in the cytosol of the cell (Fig. 2). Lactate is extracted from the blood, converted to pyruvate in the cytosol, and further oxidized to acetyl-CoA in the mitochondrial matrix. In the normal healthy human heart, pyruvate is derived in approximately equal proportions from glycolysis and lactate uptake\(^{[4,5,7]}\). Pyruvate is oxidized to acetyl-CoA in the mitochondria by the enzyme pyruvate dehydrogenase (PDH; Fig. 3). The rate of flux of pyruvate to acetyl-CoA is determined by the amount of active enzyme present in the tissue and the concentration of the substrates (CoA, nicotinamide adenine dinucleotide [NAD\(^{+}\) and pyruvate), and the products (acetyl-CoA and NADH)\(^{[2,9]}\).

Fatty acid oxidation inhibits glucose and lactate oxidation

Oxidation of glucose and lactate is strongly inhibited by high rates of fatty acid oxidation in the heart\(^{[1,2,5,7,10,11]}\). Lowering plasma fatty acid concentration by pharmacological means (e.g. with niacin\(^{[12,13]}\), or directly inhibiting fatty acid
oxidation in the mitochondria (e.g., with a carnitine palmitoyltransferase I inhibitor[14,15] or with the 3-ketoacyl thiolase [3-KAT] inhibitor trimetazidine[16]) will result in an increase in the rates of glucose and/or lactate uptake and oxidation. The molecular site of fatty acid inhibition of pyruvate oxidation (and thus glucose and lactate oxidation) is at the level of PDH. PDH and beta-oxidation of fatty acids yield the common products acetyl-CoA and NADH. Flux of pyruvate to acetyl-CoA is inhibited by acetyl-CoA and NADH, and thus high rates of fatty acid oxidation result in elevated NADH : NAD+ and acetyl-CoA : free CoA ratios, which strongly inhibit flux through PDH (Fig. 3)[2,9]. The amount of active enzyme is also under acute allosteric control by PDH kinase, which phosphorylates and inhibits PDH[2,9–11]. The activity of PDH kinase is stimulated by increases in the NADH : NAD+ and acetyl-CoA : free CoA ratios, and thus high rates of fatty acid oxidation stimulate PDH kinase and inhibit the rate of glucose and lactate oxidation by the heart. Studies conducted in humans and large animals have demonstrated that pharmacological inhibition of the rate of fatty acid oxidation by the heart accelerates the flux of pyruvate through PDH, and the uptake and oxidation of glucose and lactate by the heart[2,12,13,15].

Energy metabolism during ischaemia

Accelerated glycolysis, lactate production and a fall in pH

The primary result of ischaemia is mitochondrial metabolic dysfunction caused by reduced oxygen delivery to the tissue, resulting in a decrease in ATP formation by oxidative phosphorylation (Fig. 4)[1,2,17]. The reduction in aerobic ATP formation stimulates glycolysis, and an increase in myocardial glucose uptake and glycogen breakdown occurs[1,2]. Unlike under conditions of normal blood flow, however, during ischaemia pyruvate produced by glycolysis is not so readily oxidized in the mitochondria, and there is a high rate of conversion of pyruvate to lactate in the cytosol, and a rise in tissue lactate content. Instead of the normal uptake of lactate from the blood, the ischaemic myocardium switches to production of lactate. Cell homeostatis is dramatically disrupted; there is accumulation of lactate and H+, a fall in intracellular pH, and a reduction in contractile work (Fig. 4). Thus, during ischaemia there is accelerated glycolysis and pyruvate formation concurrent with impaired pyruvate oxidation in the mitochondria, which results in lactate accumulation in the tissue.

The ischaemia-induced fall in intracellular pH has several negative effects on the ability of cardiac muscle to maintain Ca2+ homeostatis and use the energy released from the breakdown of ATP to perform contractile work. First, the amount of ATP required by the sarcoplasmic Ca2+ pump is greater when pH is decreased[18]. Second, the Ca2+ concentration for a given amount of force generation is greater at a lower pH, and thus a higher cytosolic Ca2+ concentration is required during systole to produce a given amount of mechanical power[18]. Thus, at low pH, for a given rate of ATP synthesis, more of the energy released from ATP breakdown contributes to the ‘chemical work’ of regulating Ca2+ content in the cytosol, and less to contractile work. In addition, the efflux of H+ from the cardiomyocyte...
Cardiac energy metabolism during ischaemia of moderate severity (approximately 40% of normal blood flow). The up and down arrows indicate the changes compared with normal aerobic conditions. Relative to aerobic conditions, ischaemia results in an increase in glycolysis without an increase in the rate of pyruvate oxidation, thus causing lactate to accumulate in the cell. Despite accelerated glycolysis and lactate production, the relatively high rate of residual oxygen consumption is fuelled primarily by the oxidation of fatty acids. ADP=adenosine diphosphate; ATP=adenosine triphosphate; Pi=inorganic phosphate.

that occurs in exchange for Na+ leads to a greater Na+-Ca2+ exchange across the cell membrane, and further wasting of ATP in order to maintain Ca2+ homeostasis[19].

Fatty acids are the main fuel for the mitochondria during partial ischaemia

During moderate myocardial ischaemia, the residual oxygen consumption is largely supported by the oxidation of fatty acids (Fig. 4)[2,8,17,20]. In fact, the relative contribution of fatty acids to the energy requirement of the myocardium is not significantly affected by ischaemia of moderate severity[2,17,20]. Studies conducted in large animal models show that reductions in coronary blood flow of 30–60% do not affect the relative contribution of fatty acids to mitochondrial oxygen consumption, despite a dramatic switch to lactate production. In studies conducted in swine and dogs using isotopically labelled glucose and fatty acid tracers, there was a continued high rate of fatty acid oxidation with an increase in the relative contribution of glucose to mitochondrial oxidative metabolism when coronary blood flow was reduced by 30–60%[2,17,20]. Even though there was a switch from lactate uptake to lactate production and a decrease in myocardial ATP content during ischaemia, fatty acid continued to be the predominant fuel for the heart. It is important to note that patients undergoing myocardial ischaemia have very high plasma free fatty acid concentrations (>1·0 mmol·l−1) because of activation of the peripheral sympathetic nervous system[21], which would fuel a high relative contribution of fatty acid to myocardial substrate oxidation.

High rates of fatty acid oxidation inhibit pyruvate oxidation during ischaemia

The impaired pyruvate oxidation during ischaemia of moderate severity is due to the rise in mitochondrial NADH secondary to the fall in oxygen consumption and to the high rates of fatty acid oxidation. During moderate ischaemia, there is a build-up of NADH and a rise in the NADH : NAD+ ratio in the mitochondria, which feedback and inhibit flux through PDH via product inhibition (Fig. 5). The build-up of NADH during ischaemia is the result of the decrease in oxygen consumption and electron transport chain flux, resulting in a back-up of NADH oxidation and a fall in NAD+ content. Studies conducted in pigs and dogs showed that ischaemia does not decrease the degree of direct PDH inhibition by phosphorylation[2,22,23], suggesting that the impairment in the in vivo rate of pyruvate oxidation during ischaemia is not due to deactivation of the enzyme, but rather to product inhibition by an increase in the NADH : NAD+ ratio.

Optimization of energy metabolism during ischaemia

Myocardial ischaemia is treated with drugs that are aimed at restoring normal metabolism by the following mechanisms: delivering more oxygen to the tissue via coronary vasodilatation; decreasing the demand for mitochondrial oxygen consumption by reducing arterial blood pressure, contractility and heart rate; or optimizing myocardial metabolism by decreasing fatty acid oxidation and stimulating pyruvate oxidation in the mitochondria (e.g. by the use of glucose–insulin–potassium therapy for acute myocardial infarction, or trimetazidine for stable angina)[1,2].

Metabolic agents that suppress fatty acid oxidation and increase the oxidation of pyruvate by PDH in the mitochondria will reduce the ischaemia-induced disruption in cardiac metabolism[2]. In other words, inhibiting cardiac fatty acid oxidation and increasing the oxidation of pyruvate results in less lactate production and less of a fall in cell pH, with clinical benefit to the ischaemic patient[2,24–27]. This direct metabolic approach is optimally suited to conditions in which there is sufficient residual oxygen delivery to the myocardium to support pyruvate oxidation in the mitochondria. In other words, it is important that there be a sufficient rate of acetyl-CoA oxidation and oxygen consumption so that increasing the rate of pyruvate oxidation has a meaningful effect on the rate of lactate production. Metabolic interventions clearly work well with demand-induced ischaemia (e.g. exercise-induced angina), as has been observed in several positive trials with the 3-KAT inhibitors trimetazidine and ranolazine, which partly reduce fatty acid oxidation[25–27]. Those agents show clear clinical benefit, as reflected in improved exercise duration, without eliciting any direct effects on heart rate or blood pressure.

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oxidized nicotinamide adenine dinucleotide (NAD+) due to accelerated glycolysis and lactate production in the cytosol. In the mitochondria there is a rise in the ratio of lactate production during ischaemia. There is a fall in ATP content, high rates of glycolysis, pyruvate formation and ATP production. This leads to a fall in ATP content, high rates of glycolysis, pyruvate formation and lactate accumulation, and a fall in intracellular pH. The high rate of lactate production during ischaemia, pyruvate oxidation is inhibited by fatty acid oxidation, which contributes to the accelerated lactate production, intracellular acidosis and general disruption to cell homeostasis. Ischaemia-induced dysfunction can be minimized by metabolic agents that partly inhibit fatty acid oxidation, and increase the combustion of glucose and lactate.

Conclusion

Myocardial ischaemia of moderate severity dramatically alters fuel metabolism, reducing the rate of oxygen consumption and ATP production. This leads to a fall in ATP content, high rates of glycolysis, pyruvate formation and lactate accumulation, and a fall in intracellular pH. The myocardium continues to derive most of its energy (50–70%) from the oxidation of fatty acids. Despite the high rate of lactate production during ischaemia, pyruvate oxidation is inhibited by fatty acid oxidation, which contributes to the accelerated lactate production, intracellular acidosis and general disruption to cell homeostasis. Ischaemia-induced dysfunction can be minimized by metabolic agents that partly inhibit fatty acid oxidation, and increase the combustion of glucose and lactate.

References
