Cardiac Energetic Impairment in Heart Disease and the Potential Role of Metabolic Modulators

A Review for Clinicians

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Abstract—Cardiac energetic impairment is a frequent finding in patients with both inherited and acquired diseases of heart muscle. In this review the mechanisms of energy generation in the healthy heart and their disturbances in heart muscle diseases are described. Therapeutic agents targeted at correcting cardiac energetic impairment are discussed.

The heart consumes vast amounts of energy, and cardiac energetic impairment is a characteristic feature of several inherited and acquired diseases of heart muscle. In the fasting state, the heart typically generates $\approx 70\%$ of its energy from $\beta$-oxidation of fatty acids, 10% to 30% from oxidation of glucose, and the remainder from ketones, lactate, and amino acids. However, it is a metabolic omnivore, changing its substrate utilization according to metabolic demand, oxygen, and substrate availability, and this flexibility seems crucial for the maintenance of normal cardiac function. Acute adaptations (eg, to increased workload) occur via altered activity of metabolic enzymes. Chronic adaptations also occur in both health and disease related to altered gene expression and will be discussed in this review. Before proceeding to disturbances of these processes in cardiac disease and to the pharmacological modulation of cardiac metabolism, substrate metabolism and energy generation will be briefly reviewed.

Glycolysis and Carbohydrate oxidation

After uptake into the cytosol via insulin-dependent (glucose transporter 4 [GLUT 4]) and -independent (GLUT 1) transporters, glucose is converted via a series of 10 intermediate steps in the cytosol (glycolysis) to pyruvate which is actively transported into the mitochondria (Figure 1). The pyruvate dehydrogenase (PDH) enzyme complex in the mitochondrial matrix catalyses the conversion of pyruvate to acetyl coenzyme A (CoA). PDH is a rate-limiting step in carbohydrate oxidation, being negatively regulated by kinase and positively regulated by phosphatase enzymes and subject to both positive (upstream, by pyruvate) and negative (downstream, by acetyl-CoA/CoA, ATP/ADP, and nicotinamide adenine dinucleotide (NAD)/NAD+ ratios) allosteric regulation.

Hypoxia inhibits PDH via hypoxia-inducible factor stabilization, therefore pyruvate is converted to lactate by the enzyme lactate dehydrogenase, but this only generates 2 molecules (net) of ATP per molecule of glucose metabolized. Hypoxia also has more generalized effects on cardiac metabolism such as including inhibiting PDH, increased peroxisome proliferator–activated receptor-γ (PPAR-γ) coactivator 1α expression, modulating the enzyme activities of Krebs cycle, increasing the proteasomal degradation of PPAR-α and retinoid X receptor-α (RXRα) and controlling the mitochondrial permeability transition pore opening (Figure 1). Under aerobic conditions, acetyl CoA generated from pyruvate or from $\beta$-oxidation of fatty acids (see below) enters the tricarboxylic acid (TCA) cycle in the mitochondrial matrix. One unit of acetyl CoA and 2 U of water generate 3 U of nicotinamide adenine dinucleotide from NAD+, which acts as an electron donor to complex I of the electron transport chain (see below). The oxidation of succinate to fumarate by succinate dehydrogenase (which is also complex II of the electron transport chain) also donates electrons to the electron transport chain.

Fatty Acid Oxidation

The heart is able to metabolize fatty acids circulating in the bloodstream or derived from the breakdown of intracellular triacylglyceride stores. Several mechanisms are involved in the uptake of long-chain fatty acids into the myocyte, including the breakdown of triglycerides by lipoprotein lipase, fatty acid translocase (CD36), plasmalemmal fatty acid–binding protein, and fatty acid transport protein 1 (Figure 1). Within the cardiac myocyte, long-chain fatty acids are converted to long-chain fatty acyl CoA by the enzyme fatty acid acyl CoA synthase, but unlike short chain fatty acids require a specific transport system (the carnitine shuttle) to enter the mitochondria. On the outer mitochondrial membrane, the enzyme carnitine palmitoyltransferase type 1 (CPT-1) catalyzes the addition of a carnitine group to the long-chain fatty acid acyl CoA which crosses to the opposite side of the mitochondrial membrane in exchange for CoA, where the enzyme CPT-2 cleaves the carnitine off. CPT-1 is the rate-limiting step in long-chain fatty acid metabolism and is potently inhibited by malonyl CoA produced from acetyl CoA by the
actions of the biotin-dependent enzyme acetyl CoA carboxylase located in the endoplasmic reticulum.4 Another enzyme, malonyl CoA decarboxylase (MCD) catalyzes the reverse reaction. Direct pharmacological inhibitors of the CPT enzymes and of MCD (thereby indirectly inhibiting CPT-1) exist and will be discussed.

In the mitochondrial matrix, the long-chain acyl CoA fatty acids undergo β-oxidation, comprising a recurring series of 4 reactions culminating in the release of acetyl CoA. Flavin adenine dinucleotide is converted to flavin adenine dinucleotide H2 and NAD into nicotinamide adenine dinucleotide during each of these cycles, producing reducing equivalents for the electron transport chain. Acetyl CoA enters the TCA cycle. There are pharmacological inhibitors of fatty acid β-oxidation enzymes, and these will be discussed.

Among several ligands, PPARs form heterodimers with retinoid X receptors and bind to promoter regions of a large number of genes involved in metabolism, especially those involved in fatty acid metabolism, and the PPAR-α/RXR heterodimerization is regulated by cytosolic free fatty acid. The activity of the PPAR-γ/RXR complex is also increased by the transcriptional coactivator peroxisome proliferator–activated receptor γ coactivator 1α which plays a central role in the control of energy metabolism, increasing the expression of genes involved in fatty acid metabolism, and of GLUT 4 and inducing mitochondrial biogenesis. Several factors upregulate PPAR-γ coactivator 1α expression, including reactive oxidant species (ROS) cAMP response element-binding proteins, and the metabolic sensors AMP kinase and sirtuin 1. Sirtuin 1, in particular, controls key aspects of fat and glucose metabolism with its ability to influence several transcription factors involved in cardiac energy turnover.

**Generation of ATP via the Electron Transport Chain**

At the inner mitochondrial membrane, a series of redox reactions occur (Figure 1) in which electrons are donated to and then transferred from one complex to another. The final electron acceptor complex (cytochrome C oxidase, complex IV) donates the electrons to oxygen, which combines with hydrogen to form water. The energy derived by these electron
transfers is used to pump protons from the matrix into the intermembrane space, generating an electrochemical gradient across the inner mitochondrial membrane. Complex V contains an ion channel component (Fo) through which protons flow back into the mitochondrial matrix, releasing energy that drives the phosphorylation of ADP to ATP by the F1 component of the complex.

In health, minor electron leakage (<1%) may occur during these electron transfers (particularly at complexes I and III), resulting in the generation of superoxide but in disease states may be greater, contributing substantially to increased oxidative stress. Theoretically, 38 molecules of ATP can be generated by the complete oxidation of 1 molecule of glucose through the above processes (2 each from glycolysis and the TCA cycle and 34 from the electron transport chain); however, in practice, the net yield is somewhat less, in part because of some degree of uncoupling of the electron transport chain. Uncoupling proteins are expressed in the inner mitochondrial membrane in several tissues. In the heart muscle, uncoupling protein 3 (and to a lesser extent, uncoupling protein 2) is expressed, and this is increased by the PPAR-α/RXR heterodimer when plasma free fatty acids are elevated. When activated (principally by ROS and by lipid peroxides), these cause a modest degree of proton leak across the mitochondrial membrane, and in doing so can reduce superoxide production at complex I of the respiratory chain, thereby protecting mitochondrial DNA from oxidative damage. Acute elevation of plasma free fatty acids markedly reduces myocardial mechanical efficiency, likely by increasing mitochondrial uncoupling. Mitochondrial uncoupling may also occur via the adenine nucleotide translocase and the mitochondrial ATP-dependent potassium channel.

Randle described the regulation of fatty acid and carbohydrate metabolism, a phenomenon known as the Randle Cycle, whereby increased fatty acid utilization results in increased acetyl CoA production, thereby inhibiting PDH activity, and increases cytoplasmic citrate, which in turn inhibits glycolysis. Conversely, when carbohydrate metabolism is increased, citrate from the TCA cycle is exported to the cytoplasm where it is converted to acetyl CoA and then to malonyl CoA with consequent inhibition of CPT-1 activity, thereby reducing fatty acid metabolism.

**Energy Sensing**

An exquisite system of energy sensing exists in the heart to match energy production to energy demand. This is beyond the scope of this review, but central to this is the AMP kinase enzyme.

**Energy Transfer**

ATP is generated in the mitochondria but is mainly consumed elsewhere principally by sarcomeric proteins and ion channels. The predominant mechanism of energy transfer is the creatine kinase (CK) system. Mitochondrial CK generates phosphocreatine via the phosphorylation of creatine. Phosphocreatine is transported to cellular sites of energy consumption, where a reversal of this reaction by the cytosolic isoform of CK releases ATP. In heart muscle disease, there is typically a disproportionate reduction in phosphocreatine versus ATP concentrations in cardiac muscle. Local energy availability is determined by the ratio ATP/(ADP+Pi) (the phosphorylation potential), thus in heart failure even though ATP concentrations may only be slightly reduced, the presence of an elevated ADP concentration may significantly reduce free energy. Additional energy transport systems include the adenylate kinase and glycolytic systems. These play only minor roles in energy transfer in health.

**Energy Impairment in Heart Muscle Diseases**

Cardiac energetic impairment plays an important and probably causal role in experimental models of heart failure. Reduced cardiac phosphocreatine/ATP ratio has been demonstrated using 31P magnetic resonance spectroscopy in patients with systolic heart failure irrespective of pathogenesis and in 1 study was a powerful predictor of subsequent mortality. Cardiac phosphocreatine/ATP ratio was also markedly reduced in patients with heart failure with normal left ventricular (LV) ejection fraction, in hypertrophic cardiomyopathy and other heart muscle diseases including Fabry disease and Friedreich ataxia, and in aortic stenosis, reversed after aortic valve replacement. CK flux (a measure of CK activity) is reduced by ~50% in patients with heart failure.

**Mechanisms Responsible for Cardiac Energetic Impairment in Heart Muscle Diseases**

Abnormalities occur at multiple points in the cascade of energy generation, transfer, and utilization in heart failure. These will be reviewed below.

**Reduced Energy Production**

Epicardial coronary artery disease and microvascular disease including capillary rarefaction may limit oxygen and substrate delivery to the myocardium in some patients with heart failure and cardiomyopathy. Inconsistent changes have been reported in the relative contributions of glucose versus fatty acid utilization in both experimental and human heart failure, causing much debate, but in truth, despite the ready availability of both major substrates, the capacity to use both major fuel sources is reduced. The inconsistencies are likely to relate to differences in pathogenesis and stage of the heart failure and of techniques used to assess substrate utilization. In experimental models of LV hypertrophy and in the rapid pacing-induced heart failure model, there is reversion to a fetal genotype, with reduced expression of genes encoding enzymes involved in fatty acid metabolism (including CPT and β-oxidation enzymes) in association with downregulation of the PPAR-α/RXR pathway and of PPAR-γ coactivator 1α expression. In most experimental models of LV hypertrophy and heart failure, glucose uptake and glycolysis are either maintained or enhanced, because of increased GLUT 1 expression despite the frequent occurrence of insulin resistance (and thereby accordingly reduced GLUT 4 expression) but carbohydrate oxidation is not increased in parallel, attributable to reduced activity of PDH. The evidence in clinical heart failure is somewhat conflicting. Insulin resistance is commonly present in patients with heart failure, resulting in elevated plasma free fatty acids, downregulation of the GLUT 4 transporter, and reduced PDH activity. The consensus is that
downregulation of fatty acid oxidation may be a relatively late feature. Explanted hearts of patients undergoing cardiac transplantation had reduced expression of enzymes associated with fatty acid oxidation compared with tissue from donor hearts. Successful treatment of patients with heart failure with LV assist devices increased CD36 and CPT-1 mRNA expression, reduced cardiac ceramide and diacylglycerol levels and systemic insulin resistance, and increased cardiac insulin signaling. Cross heart sampling studies with stable isotope infusion have reported divergent results about fatty acid versus glucose uptake as have positron emission tomography studies. Positron emission tomography measures glucose uptake but not carbohydrate oxidation.

In summary, in most experimental models, hypertrophied and failing hearts have a reduced capacity to metabolize both major fuel sources (carbohydrate and fatty acids). The data in clinical heart failure are less consistent, but at least in severe heart failure, the same changes are evident.

**Increased Mitochondrial ROS and Its Consequences for Energy Production**

In heart failure, mitochondrial ROS production is increased in part attributable to post-translational modification of complex 1 and probably complex III. Deleterious consequences include mitochondrial DNA damage, post-translational modification of mitochondrial proteins including enzymes, activation of mitogen activated protein kinases (resulting in hypertrophy and fibrosis), and increased activity of mitochondrial uncoupling proteins. Increased mitochondrial ROS production during ischemia and reperfusion plays a central role in the opening of the mitochondrial permeability transition pore shortly after reperfusion; this causes release of proapoptotic factors including cytochrome C into the cytosol and acutely dissipates the electrochemical gradient across the inner mitochondrial membrane causing loss of ATP production and leading to ischemia–reperfusion injury.

**Disturbed Energy Transfer**

There is a substantial impairment of the CK system in heart failure manifest as a reduction (by ≈50%) in CK flux (measured using 31P magnetic resonance spectroscopy). Myocyte creatine uptake is impaired because of reduced expression of its transporter, expression of CK is reduced, and activity of the myofibrillar isoform of CK is reduced because of increased cytosolic oxidative stress. Reduced CK activity results in a marked reduction in phosphorylation potential at the sites of energy utilization even if ATP concentrations are only modestly reduced, because of a rise in ADP levels. However, the mitochondrial CK knockout mouse does not develop a cardiac phenotype potentially attributable to compensatory increase in cytosolic CK and an increase in mitochondrial volume.

**Energy Wastage**

Cardiac cavity dilation (often with wall thinning) increases wall tension and energy demand, further compounded by mechanical dyssynchrony especially but not exclusively in those with left bundle branch block. Partial correction of this mechanical dyssynchrony by cardiac resynchronization therapy increased cardiac mechanical efficiency. Disturbed calcium handling is typically present in heart failure (in part related to impaired cellular energetics) and leads to increased cytosolic calcium concentrations which may in turn increase energy expenditure via cellular ATPases and mitochondrial dehydrogenases. In hypertrophic cardiomyopathy, mutations of genes encoding sarcomere proteins increase cross-bridge turnover and actin-activated ATPase activity with increased energy utilization. Cardiac energetic impairment precedes development of LV hypertrophy and may be the stimulus for hypertrophy. The associated microvascular disease results in myocardial ischemia that may also potentially compromise energy production, particularly on exercise. Other mechanisms of energy wastage are shown in Figure 2.

**Therapeutic Metabolic Modulating Agents**

Several pharmacological agents are available or are in development for cardiac disorders which act at least in part through metabolic mechanisms. Most of these inhibit fatty acid metabolism and, via the reciprocal allosteric activation of PDH described earlier, increase carbohydrate oxidation, thereby reducing the oxygen cost of ATP generation (Figure 3). Theoretically, carbohydrate utilization requires ≈12% less oxygen per unit of ATP production versus fatty acid utilization, but high circulating levels of fatty acids (commonly seen in heart failure) may cause a much more substantial oxygen wasting effect, probably in part via increased mitochondrial uncoupling.

** Provision of Metabolic Substrates or Modification of Substrate Utilization**

**Pyruvate**

Intracoronary pyruvate infusion in patients with chronic heart failure increased cardiac output and reduced pulmonary capillary wedge pressure.

**d-Ribose**

D-ribose is an aldose monosaccharide that can be metabolized via the pentose phosphate pathway in the cytosol to form

**Mechanisms of energy impairment in cardiac diseases**

1. Altered energy sensing
2. Altered substrate uptake (e.g., insulin resistance)
3. Decreased ability to metabolise substrates (PDH block, down regulation of FA oxidation enzymes (‘fetal gene expression’); PGC-1α)
4. Reduced activity of individual ETC complexes (including ROS related damage) or of their functional organisation in to respirasomes
5. Increased activity of UCPs and ANT (ROS)
6. Impaired energy transfer (decreased creatine transporters, decreased CK activity – probably ROS related
7. Energy wasting (e.g., mechanical dyssynchrony)

Figure 2. Mechanisms of energy impairment in cardiac diseases. ANT indicates adenine nucleotide translocator; CK, creatine kinase; ETC, electron transport chain; FA, fatty acids; PDH, pyruvate dehydrogenase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator; ROS, reactive oxygen species; and UCPs, uncoupling proteins.
reducing equivalents in the form of nicotinamide adenine dinucleotide phosphate and also generates purines and pyrimidines. In experimental models of cardiac ischemia, d-ribose supplementation accelerates recovery of cardiac high-energy phosphates and functional recovery after relief of ischemia. In a mouse post–myocardial infarction model of heart failure, ribose supplementation did not preserve high-energy phosphates or cardiac function. Small observational studies have suggested improvements in symptoms and ventilatory efficiency with d-ribose supplementation in patients with heart failure.

Fumarate
Conversion of the TCA cycle intermediate fumarate to oxaloacetate is via the enzyme fumarate hydratase. The cardiac-specific fumarate hydratase knockout mouse does not exhibit LV dysfunction until later in life because of anaplerotic replenishment of the TCA cycle by the amino acids aspartate and glutamate. However, young mice were resistant to cardiac ischemia–reperfusion injury. This was attributable to elevation of fumarate, and the protection could be recapitulated by fumarate supplementation, with clinical potential. Fumarate potently activated the redox-sensitive transcription factor nuclear respiratory factor 2 with associated upregulation of genes encoding antioxidant enzymes and resultant cytoprotective effects.

Direct Pharmacological Activation of PDH–Sodium Dichloroacetate
This agent activates PDH by inhibiting the kinase. Dichloroacetate has been shown to be cardioprotective in a rat heart failure model, thereby improving cardiac function and survival by decreasing oxidative stress and by activation of pentose phosphate pathway. A 30-minute infusion of sodium dichloroacetate in patients with heart failure increased LV stroke work while reducing myocardial oxygen consumption, indicating a substantial increase in mechanical efficiency and is a proof of concept for metabolic modulation therapy.

CPT-1 Inhibitors
Perhexiline (Reversible CPT-1 Inhibitor)
Perhexiline was an effective antianginal agent used in the early 1980s, but was voluntarily withdrawn by the manufacturers because of reports of liver toxicity and peripheral neuropathy. Subsequent studies demonstrated that perhexiline reversibly inhibited CPT-1 and -2 in the liver and cardiac mitochondria and that the toxicity was attributable to phospholipid accumulation in liver and peripheral nerves related to chronic exposure to high plasma levels of the drug related in large part to polymorphic variation in the activity of the Cytochrome P450 2D enzyme predominantly responsible for its metabolism and preventable by monitoring of plasma levels with appropriate dose titration.
In a randomized placebo-controlled trial in 56 patients with chronic heart failure, perhexiline increased exercise capacity, LV ejection fraction, and quality of life. In another randomized, controlled trial in 46 patients with symptomatic hypertrophic cardiomyopathy, perhexiline increased exercise capacity and this could be explained by an increase in cardiac energetic status (phosphocreatine/ATP ratio) leading to augmented LV diastolic filling on exercise. A randomized, double-blind, placebo-controlled trial is underway to investigate the role of perhexiline in normal LV ejection fraction (NCT00839228).

In another recent study, perhexiline did not reduce the incidence of low cardiac output syndrome in patients undergoing coronary artery bypass grafting.

Perhexiline also reduces generation of superoxide by NADPH oxidase enzymes, reduces expression of thioredoxin-interacting protein, an inhibitor of thioredoxin (a potent intracellular antioxidant) and of glycolysis, and inhibits mammalian target of rapamycin C1 (potentially leading to improved cell survival via increased autophagy). In a metabolic and proteomic study, perhexiline not only caused the known shift from fatty acid β-oxidation to glucose oxidation (via CPT-1 and -2 inhibition), but also induced a complex rebalancing of carbon and nucleotide phosphate fluxes via augmented lactate and amino acid uptake. The proteomic data showed PDH activation.

CPT-1–inhibiting properties have also been reported with the β-blockers Carvedilol and Metoprolol, potentially accounting in part for the beneficial effects of these agents in heart failure.

**Oxfenicine and Etomoxir (Irreversible Inhibitors of CPT-1)**

Oxfenicine is an irreversible CPT-1 inhibitor (Figure 3) that has cardiac anti-ischemic properties and slows the development of heart failure in a canine rapid pacing heart failure model. It causes cardiac hypertrophy in some animal models, with lipid accumulation in kidney, liver, and cardiomyocytes if given in higher doses for prolonged periods.

Etomoxir was originally developed as an oral hypoglycemic agent and is also an irreversible CPT-1 inhibitor. It prevented the development of contractile dysfunction in the rat aortic banding model in one study but failed to do so in another. An open label study of etomoxir in 10 patients with chronic heart failure reported improved LV ejection fraction and exercise hemodynamics, but a randomized controlled trial was terminated early by the Drug Safety Monitoring Committee because 4 patients in the etomoxir group developed substantial increases in liver transaminases.

**MCD Inhibitors**

MCD inhibitors increase malonyl CoA levels, thereby inhibiting CPT-1 activity (Figure 3). Isolated hearts from MDC−/− mice retain normal cardiac function and metabolism under aerobic conditions, but have improved contractile recovery following ischemia–reperfusion, associated with reduced fatty acid oxidation and increased glucose oxidation. In an in vivo pig model of demand-induced ischemia, an MCD inhibitor increased myocardial malonyl CoA levels, reduced fatty acid oxidation, increased glucose oxidation, reduced lactate accumulation, and increased cardiac work. Furthermore, in a rat global ischemia–reperfusion model, treatment with an MCD inhibitor increased glucose oxidation and maintained cardiac function during recovery.

**Partial Inhibitors of Fatty Acid β-Oxidation**

In a working rat heart model trimetazidine inhibited the β-oxidation enzyme long-chain 3 ketoacyl CoA thiolase, associated with reduced fatty acid uptake and increased glucose oxidation attributable to increased PDH activity. However, in a positron emission tomography study in patients with dilated cardiomyopathy, little effect was observed on cardiac fatty acid uptake from the bloodstream, but there was a significant reduction in fatty acid utilization from intracellular stores. In a rabbit model of heart failure, an enhanced electron leak (site of ROS production) at complex II was attenuated and the activity of complex I was increased by trimetazidine. Trimetazidine is an effective anti-ischemic agent in angina patients and reduces intracoronary platelet aggregation. Trimetazidine therapy improved cardiac energetic status in patients with LV systolic dysfunction attributable to dilated cardiomyopathy as assessed by the phosphocreatine/ATP ratio using 31P magnetic resonance spectroscopy. Two recent meta-analyses support its effectiveness in chronic heart failure as add-on to contemporary medical management showing improved symptomatic status (New York Heart Association class), cardiac function (LV ejection fraction) and reduced rehospitalization because of heart failure. There was a borderline significant reduction in mortality. A study currently underway is investigating the role of trimetazidine in nonobstructive hypertrophic cardiomyopathy (NCT01696370). It has been shown to reduce cardiac ischemia–reperfusion injury in patients undergoing coronary artery bypass grafting.

Ranolazine is an effective antianginal (as monotherapy or add-on). It is a partial inhibitor of fatty acid β-oxidation, but there is controversy about the role of this mechanism in vivo at therapeutic plasma concentrations. More recently, it has been shown to inhibit the late inward sodium channel, thereby reducing intracellular calcium (via the sodium-calcium exchange channel) and reducing LV diastolic wall tension.

**Agents That Reduce Insulin Resistance**

The thiazolidinediones are PPAR-γ agonists that are effective insulin sensitizers. However, despite the theoretical benefits of increasing insulin sensitivity, they cause fluid retention and (probably thereby) increase heart failure symptoms and hospitalization attributable to heart failure. Metformin acts at least in part by activation of 5′-AMP–activated protein kinase, the master energy sensor. Recent observational data in a large primary care database suggest that it may reduce all-cause mortality in patients with HF.

There is increasing use in diabetics of glucagon-like peptide 1 agonists and of dipeptidyl peptidase IV inhibitors that increase endogenous levels of GLP-1 by reducing its breakdown. In addition to its insulin-sensitizing actions, GLP-1 stimulates insulin release and has other pleiotropic actions via its receptor, which is widely expressed, including in the heart.
Recombinant GLP-1 increased myocardial glucose uptake and improved LV performance in conscious dogs with pacing-induced dilated cardiomyopathy. In a small pilot crossover study, the intravenous GLP-1 analog (exenatide) increased cardiac index and reduced pulmonary capillary wedge pressure in type 2 diabetic patients with heart failure and reduced ischemia–reperfusion injury in patients with ST-segment–elevation myocardial infarction.

Therapies That May Improve Function of the Respiratory Chain

Coenzyme Q10 is a carrier or shuttle that transfers an electron from complex I to complex III in the electron transport chain. It also acts as an antioxidant. Plasma and cardiac tissue levels are reduced in heart failure. In addition to its role in energy transfer, it also acts as an antioxidant. Several small studies in heart failure showed conflicting results, but recently a placebo-controlled trial in 420 patients with New York Heart Association class III and IV heart failure (SYMBIO Q) reported a reduction in the primary end point of major cardiac events at 2 years, and additionally improved New York Heart Association class, and reduced both heart failure hospitalizations and cardiovascular mortality.

Therapies That May Be Effective via Enhanced Energy Transfer

Carnitine Supplementation

Carnitine is derived from dietary sources and may also be synthesized endogenously. In addition to its key role in long-chain fatty acid uptake into the mitochondria (the Carnitine shuttle), it also modulates glycolysis and TCA cycle activity. Myocardial carnitine levels are low in heart failure. Several studies of carnitine supplementation have been reported in heart failure, some with methodological flaws and with variable results.

Creatine

Cardiac and skeletal muscle creatine content are reduced in heart failure, but this is largely attributable to reduced expression of its transporter. Supplementation has been assessed in several small studies. Acute infusion of creatine increases LV ejection fraction. Chronic oral creatine supplementation does not improve cardiac function, but improves skeletal muscle strength and endurance.

Therapies That May Be Effective via Unknown Mechanisms

Allopurinol

The xanthine oxidase inhibitor allopurinol has been shown to increase the treadmill time to onset of chest pain and ST-segment depression in patients with angina. Improved metabolic efficiency may contribute to this effect. Indeed, in a previous study in patients with heart failure, intracoronary allopurinol decreased myocardial oxygen consumption, despite preservation of its stroke work and unchanged workload. In a recent placebo-controlled study in patients with heart failure of non-ischemic pathogenesis, intravenous allopurinol increased CK flux as assessed by 31P magnetic resonance spectroscopy.

Xanthine oxidase enzyme expression is increased in explanted hearts from patients with end-stage heart failure. It seems likely that the increase in CK flux observed is a consequence of reduced ROS generation as a result of inhibition of xanthine oxidase. A randomized controlled trial of oxypurinol (the active metabolite of allopurinol) in patients with heart failure (oxypurinol compared with placebo for Class III–IV NYHA congestive heart failure) was negative. However, the dose used (600 mg) was low, being bioequivalent to ≈80 mg allopurinol, which is ≈5-fold lower than the effective dose of the latter. These were studies with small numbers and provide incentive in investigating allopurinol further in large randomized placebo-controlled trials.

Conclusions

Cardiac energy metabolism is a tightly regulated process. With the growing understanding of the complex maladaptations of disease that occur in the energy generation, energy transfer, and utilization, several therapeutic targets have emerged. Consequently, several metabolic modulators have been developed in the recent years with some showing promising results in small studies. More large randomized controlled trials are needed to establish these therapies in various cardiac diseases.

Acknowledgments

We dedicate this review to the memory of Professor William Stanley.

Disclosures

Dr Frenneaux is inventor on method of use patents for perhexiline in heart muscle diseases. The other authors report no conflicts.

References


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