REVIEW ARTICLE

MECHANISMS OF DISEASE

The Failing Heart — An Engine Out of Fuel

Stefan Neubauer, M.D., F.R.C.P.

From the Department of Cardiovascular Medicine, University of Oxford and John Radcliffe Hospital, Oxford, United Kingdom. Address reprint requests to Dr. Neubauer at the Department of Cardiovascular Medicine, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom, or at stefan.neubauer@cardiov.ox.ac.uk.

N Engl J Med 2007;356:1140-51.

Heart failure is an enormous medical and societal burden.[1,2] It is a common disease: more than 2% of the U.S. population, or almost 5 million people, are affected, and 30 to 40% of patients die from heart failure within 1 year after receiving the diagnosis.[3] Heart failure can be disabling, and it can severely reduce a patient's quality of life. It consumes approximately 2% of the National Health Service budget in the United Kingdom, and in the United States, the total annual cost of treatment for heart failure is approximately $28 billion. Moreover, the financial burden of heart failure will increase in coming decades because of the aging population and the improved treatments of its causes.

Over the past 20 years, there has been considerable progress in the treatment of chronic heart failure with angiotensin-converting–enzyme (ACE) inhibitors,[4,5] aldosterone antagonists,[6] beta-receptor blockers,[7,8] and resynchronization therapy.[9,10] Even with the very best of modern therapy, however, heart failure is still associated with an annual mortality rate of 10%.[10] The search for better treatments is one of the major challenges in cardiology.

Chronic heart failure is multifactorial. There are many reasons why a human heart can fail,[11] but the available evidence suggests that the failing heart is an engine out of fuel — that is, altered energetics play an important role in the mechanisms of heart failure. For this reason, the modulation of cardiac metabolism has promise as a new approach to the treatment of heart failure.

This review describes cardiac energy metabolism, appraises the methods used for its assessment, evaluates the role of impaired energy metabolism in heart failure, and gives options for metabolic therapy.

THE ENERGY-STARVATION HYPOTHESIS

The concept that the failing heart is an energy-starved engine that has run out of fuel is decades old. It was proposed in 1939 by Herrmann and Decherd,[12] who, in their article entitled "The Chemical Nature of Heart Failure," described a significantly reduced creatine content in failing myocardium. Over the next 20 years, the energy-depletion hypothesis was pursued by various groups,[13-15] and today, energy metabolism in the heart — myocardial energetics — is a topic of considerable interest.[16-24] A major reason for the attention to this topic is that any energy-sparing treatment for heart failure such as beta-receptor blockers,[7,8] ACE inhibitors,[4,5] or angiotensin II blockers[25,26] improves the prognosis. The failing heart has been compared to a weak and tired horse, and if this horse is nourished properly, it can recover and work in the long term, albeit at a reduced level.[27]

CARDIAC ENERGY METABOLISM

Deprivation of cardiac energy has a major role in heart failure.[18] The heart consumes more energy than any other organ. It cycles about 6 kg of ATP every day —

20 to 30 times its own weight. Each day, it beats about 100,000 times and pumps approximately 10 tons of blood through the body. To acquire the energy that is necessary to carry out its function, the heart converts chemical energy stored in fatty acids and glucose into the mechanical energy of the actin–myosin interaction of myofibrils. Failure to produce an adequate amount of energy causes mechanical failure of the heart.

COMPONENTS OF CARDIAC ENERGY METABOLISM

Cardiac energy metabolism is complex (Fig. 1). The metabolic machinery has three main components. The first is substrate utilization — the use of fuel that comes from food. This process entails the cellular uptake of mainly free fatty acids and glucose, the breakdown of these components by beta-oxidation and glycolysis, and the entry of the resulting intermediary metabolites into the Krebs cycle. The second component is oxidative phosphorylation — the production of energy by the mitochondrial respiratory chain. The phosphorylation of ADP by this mechanism produces the high-energy phosphate compound ATP, which is the direct source of energy for all energy-consuming reactions in the heart. The third component is ATP transfer and utilization — the transport of energy to and its consumption by the heart's motor, the myofibrils. This process entails an energy-transfer mechanism termed the creatine kinase energy shuttle.[28-30]

THE CREATINE KINASE SYSTEM

In the third component of cardiac energy metabolism, ATP transfer and utilization, mitochondrial creatine kinase catalyzes the transfer of the high-energy phosphate bond in ATP to creatine to form phosphocreatine and ADP. Phosphocreatine, a smaller molecule than ATP, rapidly diffuses from the mitochondria to the myofibrils, where myofibrillar creatine kinase catalyzes the reformation of ATP from phosphocreatine. The free creatine, formed by the removal of phosphate from phosphocreatine, diffuses back to the mitochondria.

Creatine is produced by the liver and kidneys and transported to the heart, where it is taken up by a specific plasma-membrane creatine transporter[31] against a 50-fold concentration gradient. Creatine kinase catalyzes the phosphorylation of about two thirds of the total creatine pool in the heart to phosphocreatine, and the other one third remains as free creatine. A small amount of creatine is constantly lost from the heart by passive diffusion across the sarcolemma.[32] An important function of the creatine kinase system is to act as an energy buffer. When the energy demand outstrips the energy supply, the phosphocreatine level falls, keeping ATP at a normal level, but the free ADP level rises.[29] The increased level of free ADP inhibits the function of many intracellular enzymes, causing failure of the heart's contraction mechanism. Thus, a metabolic derangement in the cardiac myocyte can occur when phosphocreatine levels fall and free ADP levels rise, even if ATP levels remain unchanged.

ASSESSMENT OF CARDIAC ENERGY METABOLISM

The various components of energy metabolism in the heart can be measured with the use of standard methods in myocardial specimens obtained during a biopsy or at the time of transplantation or in cardiac tissue from animals. The analysis of ATP and phosphocreatine in tissue samples is problematic, however, because of the instability of these molecules.[29] For this reason, the principal method for measuring ATP and phosphocreatine is phosphorus-31 magnetic resonance (^{31}P-MR) spectroscopy.[33-36] This method can be used with high-field magnets of up to 12.0 Tesla (a measure of magnetic field strength) in rodents and with standard clinical magnetic resonance imaging (MRI) systems (usually 1.5 Tesla) in humans. As shown in Figure 2A, ^{31}P-MR spectra yield peaks for phosphocreatine and the three phosphorus atoms of ATP (γ-ATP, α-ATP, and β-ATP) that are proportional to the concentrations of these metabolites. The MRI system can obtain cine images of the heart at the same time for quantification of cardiac function. The most powerful method for assessing energy metabolism in heart failure entails the in vivo assessment of turnover rates of glucose and fatty acids[38-41] and rates of oxidative phosphorylation[42] and ATP transfer.[34,36] An important methodologic consideration is intracellular compartmentalization.[43] Whether a cardiac myocyte functions normally cannot be determined by measuring the average cellular level of ATP, phosphocreatine, or ADP, but instead is determined by their concentrations in the perimyofibrillar space and near the sarcoplasmic reticulum and sarcolemmal ion pumps. No method is currently available to make such measurements; therefore, they have to be extrapolated from global measurements.

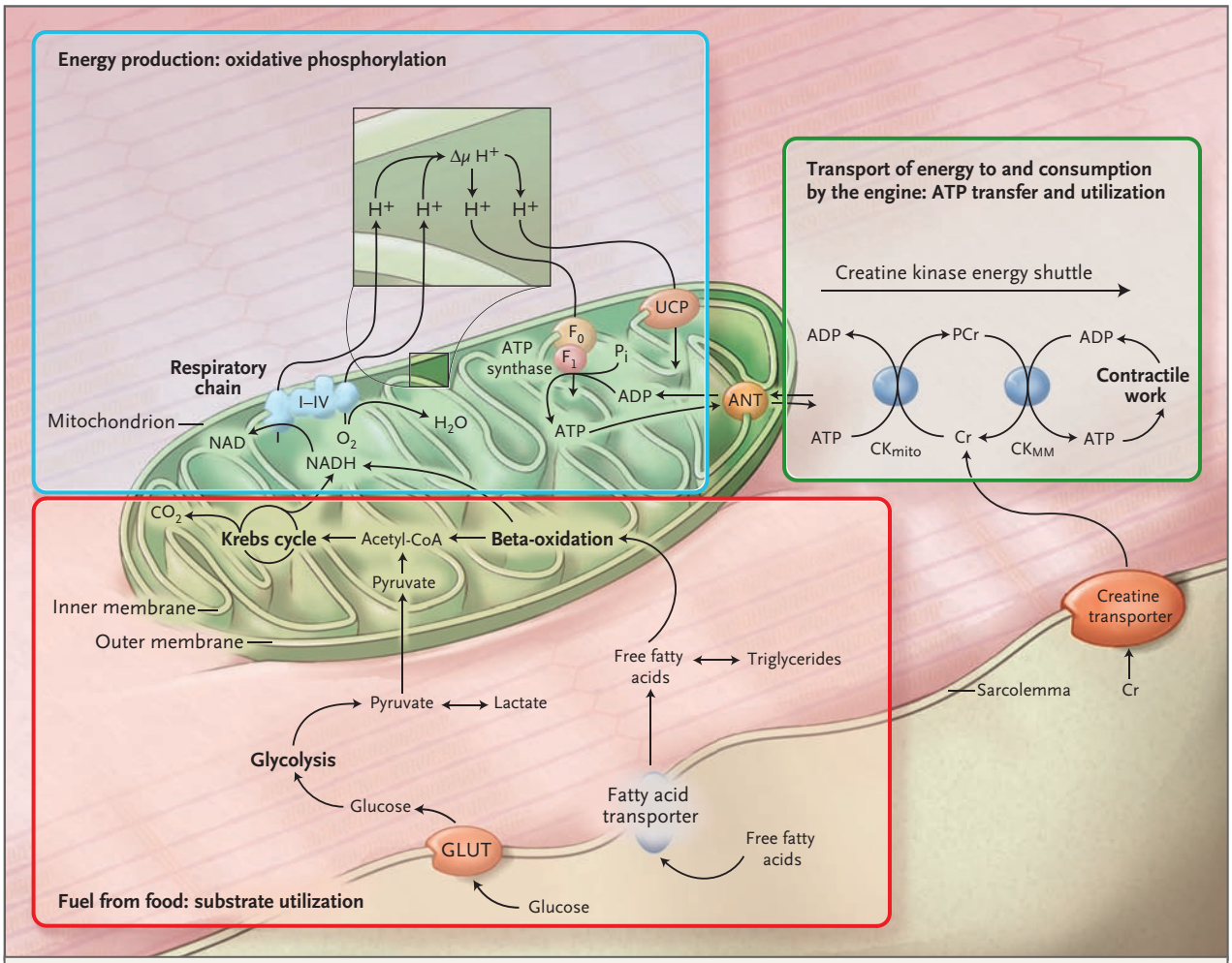

Figure 1. Cardiac Energy Metabolism.

Energy metabolism in the heart has three components. The first is substrate utilization (outlined in red), the cellular uptake of substrates and their breakdown by beta-oxidation and glycolysis; these processes result in the formation of acetyl coenzyme A (CoA), which is fed into the Krebs cycle and produces NADH and carbon dioxide (CO_2). The second component is oxidative phosphorylation (outlined in blue), the production of energy. Respiratory-chain complexes I through IV transfer electrons from NADH to oxygen, thereby creating a proton electrochemical gradient ($\Delta\mu\ H^+$) across the inner mitochondrial membrane as well as NAD and water. This gradient drives the F_1, F_0 ATP synthase, which produces ATP by phosphorylating ADP. Uncoupling proteins (UCPs) cause mitochondria to produce heat rather than ATP. The third component is energy transfer and utilization (outlined in green), the transport of energy to and consumption by myofibrillar ATPase and other ATP-consuming reactions, such as sarcolemmal and sarcoplasmic reticulum ion pumps. ATP transfer is achieved by the creatine kinase energy shuttle. Creatine, which is not produced in the heart, is taken up by the creatine transporter. GLUT denotes glucose transporter, P_i inorganic phosphate, ANT adenine nucleotide translocase, PCr phosphocreatine, Cr free creatine, CK_{mito} mitochondrial creatine kinase isoenzyme, and CK_{MM} myofibrillar creatine kinase isoenzyme.

DERANGEMENT OF ENERGY METABOLISM IN HEART FAILURE

The changes in cardiac energy metabolism in heart failure are shown in Figure 3, which summarizes the findings in animal models[19,44-57] and clinical studies of heart failure.[58-68] Changes occur in all three components of cardiac energy metabolism: substrate utilization, oxidative phosphorylation, and high-energy phosphate metabolism.

SUBSTRATE UTILIZATION

Substrate utilization can become limiting for cardiac function in heart failure as a result of reduced substrate uptake, oxidation, or both. This may also occur as a result of the change in the relative

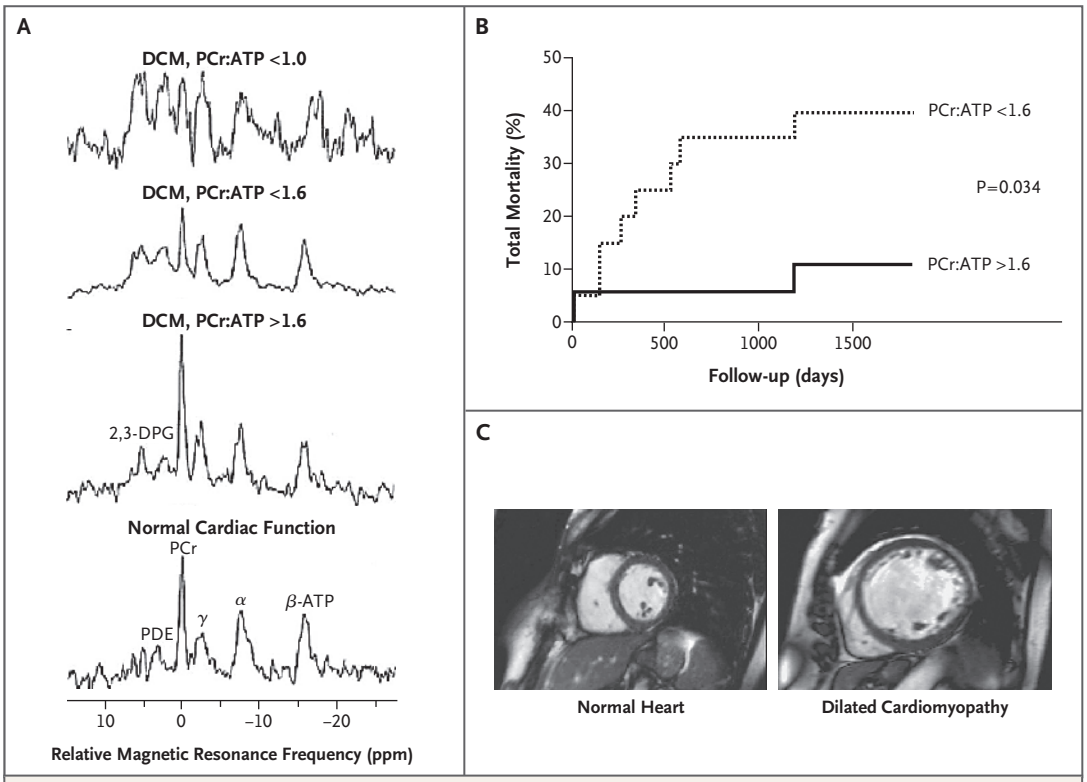

Figure 2. The Phosphocreatine:ATP Ratio in Heart Failure.

Panel A shows cardiac ^{31}P-MR spectra in (from bottom to top) a healthy subject, a patient with dilated cardiomyopathy (DCM) and a normal phosphocreatine (PCr):ATP ratio (>1.6; 1.6 was the median of the ratio), a patient with DCM and a reduced PCr:ATP ratio (<1.6), and a patient with DCM and a severely reduced PCr:ATP ratio (<1.0). The patient with the severely reduced ratio died 7 days after undergoing magnetic resonance examination. 2,3-DPG denotes 2,3-diphosphoglycerate, PDE phosphodiesters, and γ, α, and β phosphorus atoms of ATP. Panel B shows a Kaplan–Meier life-table analysis of mortality in two groups of patients with DCM: one with a higher PCr:ATP ratio and one with a lower ratio. Patients with an initially low ratio had an increased mortality over the study period (average follow-up, 2.5 years). Data are from Neubauer et al.[37] Panel C shows short-axis cine MRI scans of a normal heart and the severely dilated heart of a patient with DCM.

contributions of fatty acids (60 to 90%) and glucose (10 to 40%) to ATP synthesis. Studies of substrate utilization in heart failure have yielded conflicting results, but most indicate that fatty acid utilization, which is unchanged or slightly increased in early heart failure,[19,44] is substantially decreased in advanced heart failure.[45] Changes in glucose utilization are also inconsistent, but many studies show that it is increased early in heart failure.[46,47] In advanced heart failure, insulin resistance develops in the myocardium, and most studies have shown a decline in glucose utilization.[58-60] However, the interpretation of these results is complicated by the substantial increases in the concentrations of plasma free fatty acids, glucose, and insulin that are common in heart failure. These increases make it difficult to separate the changes in the metabolic pathway capacities that are inherent in the heart muscle from the indirect changes in the myocardium that are due to the altered metabolic milieu.[19]

OXIDATIVE PHOSPHORYLATION

Impaired oxidative phosphorylation can reduce cardiac function by providing an insufficient supply of ATP to cardiac myocytes. In heart failure, cardiac mitochondria have structural abnormalities and are probably increased in number.[49] The activity of electron transport–chain complexes and ATP synthase capacity are reduced[50,61,69]; the regulation of oxidative phosphorylation by the phosphate acceptors ADP, AMP, and creatine is impaired[41]; and the levels of uncoupling proteins (which cause mitochondria to produce heat rather

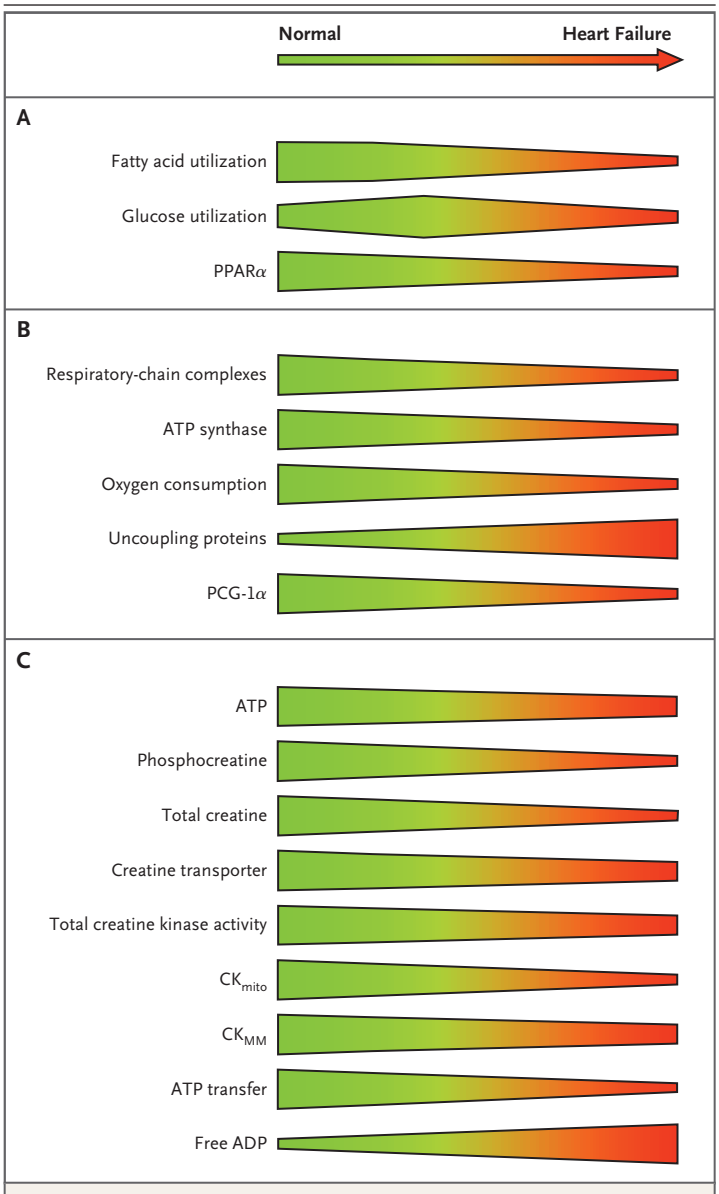

Figure 3. Changes in Cardiac Energy Metabolism in Heart Failure.

In patients with heart failure, changes in substrate utilization (Panel A) include initial up-regulation and subsequent reduction of glucose utilization and a decrease in fatty acid utilization, in part mediated by down-regulation of peroxisome proliferator–activated receptor α (PPARα). Oxidative phosphorylation changes (Panel B) are characterized by decreased energy production, with reductions in oxygen consumption and respiratory-chain and ATP synthase activity, in part mediated by down-regulation of PPARα coactivator 1α (PCG-1α). Changes in high-energy phosphate metabolism (Panel C) include a severely impaired creatine kinase energy-transfer mechanism, increased free ADP levels, and, in advanced heart failure, reduced ATP content. Free ADP is calculated from the creatine kinase equilibrium assumption: $ADP = ([ATP] \times [creatine]) \div ([phosphocreatine] \times [H^+] \times K_{eq})$, where H^+ is the intracellular hydrogen ion concentration and K_{eq} is the equilibrium constant of the creatine kinase reaction. CK_{mito} denotes mitochondrial creatine kinase isoenzyme, and CK_{MM} myofibrillar creatine kinase isoenzyme.

than ATP) may be increased.[70] These changes result in a substantial reduction of oxygen consumption and energy production in the failing myocardium.

HIGH-ENERGY PHOSPHATE METABOLISM

Impaired ATP transfer and utilization may limit contractile function by means of a decrease in the average ATP concentration, a reduction in the ATP transfer capacity through creatine kinase so that insufficient high-energy phosphate bonds are transported from the mitochondria to the myofibrils, or an increase in the concentration of free ADP.

Myocardial ATP levels remain normal (at approximately 10 mmol per liter) until the advanced stages of heart failure, when they decrease by no more than 30 to 40%.[65,66,71] The average ATP levels remain far above those required for ATP-consuming reactions such as myosin–ATPase, and do not limit contractile function in heart failure. However, both phosphocreatine and total creatine levels decrease at earlier stages and to a greater extent (by 30 to 70%).[66,67] Down-regulation of the creatine transporter function contributes to the reduced total creatine, and thus phosphocreatine, levels in heart failure.[72,73]

There are profound changes in the creatine kinase system in heart failure.[67,74-78] Mitochondrial creatine kinase activity may be reduced to as little as 20% of normal activity, and myofibrillar creatine kinase activity can decrease by up to 50% as compared with normal values. The losses of high-energy phosphates and creatine kinase activity cause a severe decline in ATP transfer[53,54,79,80] — that is, a decrease in energy flux within the cell — and thus a reduction in energy delivery to the myofibrils by up to 71%.[81] This metabolic abnormality may contribute to contractile dysfunction and particularly to the loss of inotropic reserve that is characteristic of the myocardium in heart failure.

When the failing heart is stimulated with catecholamines, thereby causing high-workload conditions, the free ADP concentration increases to a value that is approximately twice that in normal myocardium.[82] The increase of free ADP in the relevant microcompartments (the perimyofibrillar microcompartment and the microcompartments near the sarcoplasmic reticulum and sarcolemmal ion pumps) during high-workload conditions limits the contractile reserve of the fail-

ing heart, and this reduction in inotropic reserve is manifested clinically as dyspnea on exertion.

Most of the evidence concerning the derangement of myocardial energetics in heart failure in humans is based on studies with ^{31}P-MR spectroscopy. This method can be used to determine the ratio of phosphocreatine to ATP, which is a powerful index of the energetic state of the heart. The creatine kinase reaction equilibrium favors ATP synthesis over phosphocreatine synthesis by a factor of approximately 100. Therefore, whenever the demand for ATP outstrips ATP synthesis, phosphocreatine levels decline first, and ATP decreases only when phosphocreatine is substantially depleted. In chronic heart failure, however, a second mechanism comes into play: the total creatine level falls, and this reduction further decreases the phosphocreatine:ATP ratio[62,63,68] (Fig. 2). Myocardial phosphocreatine:ATP ratios are reduced in heart failure, and they correlate with New York Heart Association classes[63] and with indexes of systolic[83] and diastolic[84] function. One study of 39 patients with dilated cardiomyopathy indicated that the phosphocreatine:ATP ratio may be a stronger predictor of both total mortality and mortality attributable to cardiovascular disease than functional or clinical indexes[37] (Fig. 2B), but this finding requires confirmation in larger clinical trials.

Hypertrophic cardiomyopathy is an exemplar of myocardial energy depletion.[85] In patients with hypertrophic cardiomyopathy, the cardiac phosphocreatine:ATP ratio is reduced through a range of specific mutations that affect the sarcomere, whether or not left ventricular hypertrophy is present.[86] Because the abnormalities in energetics are an early and integral part of the primary heart muscle disease, one can infer that the compromise of myocardial energetics has a causal role in hypertrophic cardiomyopathy.

MOLECULAR REGULATORS OF ENERGY METABOLISM

The energy demands of the heart vary widely during cardiac development and with physiologic or abnormal stress. Energy production must be closely coupled with energy demand, but the heart has little capacity for substrate storage. However, there are mechanisms that induce the expression of genes that encode the molecular regulators of energy metabolism.[87]

NUCLEAR-RECEPTOR TRANSCRIPTION FACTORS

Several nuclear-receptor transcription factors are activated by lipid metabolites in a manner analogous to the activation of nuclear receptors by steroid hormones. These transcription factors rapidly couple gene expression with a changing substrate milieu, and they typically require coactivator proteins for their action. Among these transcription factors, the most widely studied are the nuclear receptors of the peroxisome proliferator–activated receptor (PPAR) family, which comprises three isoforms: PPARα, PPARβ, and PPARγ. All three affect cardiac lipid metabolism, but the primary regulator appears to be PPARα, which controls the expression of enzymes directly involved in fatty acid oxidation. In cardiac hypertrophy in both animal models[88] and humans,[89,90] the expression of PPARα is decreased in proportion to the depression of fatty acid utilization. For this reason, the down-regulation of PPARα is thought to be the main mechanism underlying the switch in substrate utilization from fatty acids to glucose. This switch is typical of the hypertrophied heart.

A nuclear-receptor coactivator, PPARγ coactivator-1 (also known as PCG-1α), is a master regulator of metabolic function in mitochondria. It activates multiple genes that are responsible for fatty acid uptake and oxidation and for oxidative phosphorylation.[87] These genes include *PPARα* and *PPARβ* and nuclear respiratory factors 1 and 2. Experimental studies suggest that the inhibition of PCG-1α,[91,92] probably as a direct consequence of high plasma catecholamine levels,[93] leads to down-regulation of mitochondrial gene expression.[20] In this way, it contributes to the impairment of oxidative phosphorylation in the failing heart. The development of heart failure is accelerated by PCG-1α deficiency,[93] suggesting that this coactivator may have a cardioprotective function.

Despite these advances, more work is needed to fully understand which changes in metabolic signaling are adaptive, maladaptive, or both (depending on the stage of heart failure). Furthermore, the molecular regulators of changes in creatine transport and creatine kinase expression in heart failure are unknown.

GENE-KNOCKOUT MODELS AND LOSS-OF-FUNCTION MUTATIONS

The causal role of altered energetics in heart failure has been controversial for decades, and this

controversy remains unsettled. A promising way to obtain definitive answers is through studies of genetically manipulated mice with selective knockout (loss of function) of genetic components of the metabolic machinery or of single-gene inborn errors of metabolism in humans. Table 1 lists the genetic abnormalities that have been studied in mouse models[94-103] and humans,[104-108] along with the corresponding metabolic and functional cardiac phenotypes. The deletion of a variety of genes that encode specific metabolic components related to substrate utilization, oxidative phosphorylation, and high-energy phosphates causes a loss of contractile reserve, overt heart failure, cardiac hypertrophy, tachyarrhythmias, or bradyarrhythmias. These genetic studies show that a fully integrated metabolic machine is important for normal cardiac function and that selective ablation of components of energy metabolism can cause early or advanced heart failure.

The strength of these genetic studies, however, is also their weakness, because chronic heart failure is multifactorial and entails many mechanisms other than those controlled by the single gene under study. Furthermore, we do not understand how a gene encoding a highly conserved protein with a central role in cardiac energetics can be deleted and yet not result in overt heart failure (Table 1). Whether and to what extent adaptations occur in response to the deletion of an essential metabolic component are unknown.

IMPLICATIONS FOR THE TREATMENT OF HEART FAILURE

ACE inhibitors, diuretics, and beta-blockers may have indirect metabolic effects on the heart,[39,63,109] but they do not directly affect energy metabolism. Could energy metabolism be a specific target for therapy in patients with heart failure?

MODULATION OF SUBSTRATE UTILIZATION

A promising strategy for metabolic intervention in heart failure is to modulate substrate utilization. In a study of eight patients with heart failure, intracoronary infusion of pyruvate improved cardiac function in the short term,[110] and in a dog model of heart failure, an increase in glucose utilization by glucagon-like peptide 1 improved left ventricular function.[111] In addition, in a mouse model of heart failure, transgenic overexpression of glucose transporter 1 prevented the development of left ventricular dysfunction.[112]

Direct manipulation of substrate utilization is feasible with the use of partial inhibitors of fatty acid oxidation or carnitine palmitoyl transferase 1 inhibitors. These compounds have complex types of action,[19,21,23] but they all partially inhibit fatty acid utilization and promote glucose utilization. Whether the suppression of fatty acid oxidation is beneficial or detrimental in heart failure is highly controversial, and the cause or stage of heart failure may dictate the outcome of this kind of treatment. Regardless of the theoretical arguments, a number of recent proof-of-principle clinical studies have suggested that partial inhibition of fatty acid oxidation is promising. For example, treatment with trimetazidine, an inhibitor of fatty acid oxidation, improved left ventricular function over a period of 6 months in elderly patients[113]; an 18-month study confirmed this finding in patients with heart failure due to a previous myocardial infarction.[114] Small, single-center, and thus far unconfirmed studies have shown that in patients with heart failure of ischemic or nonischemic origin, 2 months of treatment with the fatty acid oxidation inhibitor perhexiline[115] or 3 months of treatment with the carnitine palmitoyl transferase 1 inhibitor etoxomir[116] improved the left ventricular ejection fraction. The results of these small studies have to be interpreted cautiously. Some were not conducted under randomized, blinded, or placebo-controlled conditions, and others included patients with angina, which may in part explain the beneficial effect of inhibiting fatty acid oxidation. Nevertheless, they provide support for the results of studies of the effects of such inhibitors in animal models of heart failure.[117,118]

The effects of PPAR activators on cardiac substrate utilization are complex. They include direct up-regulation of fatty acid oxidation and its indirect down-regulation through reduced plasma lipid levels. The findings that heart failure develops in mice that overexpress PPARα[119] and that PPAR activators may have beneficial,[120] adverse,[121] or no[122] effects in animal models of heart failure indicate that the actions of these compounds in the failing heart need to be better understood before larger clinical trials can be considered.

MODULATION OF OXIDATIVE PHOSPHORYLATION

A second strategy to metabolic therapy in heart failure is direct stimulation of oxidative phosphorylation. Currently, however, there are no effective stimulators of oxidative phosphorylation. Even so,

Table 1. Mouse Gene-Knockout Models and Human Inborn Errors of Metabolism and Their Cardiac Phenotypes.*

Genetic Abnormality	Metabolic Abnormality	Cardiac Phenotype
Mouse gene-knockout models		
Long-chain and very-long-chain acyl–CoA dehydrogenase	Inhibition of very-long-chain and long-chain fatty acid beta-oxidation	Very-long-chain acyl–CoA dehydrogenase: ventricular tachycardia, severe bradycardia[94] Long-chain acyl–CoA dehydrogenase: cardiomyopathy, sudden death[95]
PPARα	Substrate utilization switch from fatty acids to glucose and lactate	Reduced contractile reserve and depletion of cardiac energy stores during inotropic challenge[96]
Glucose transporter 4	Increased basal but abolished insulin-stimulated glucose transport	Cardiac hypertrophy[97]
PCG-1α	Reduced oxidative phosphorylation and fatty acid oxidation	Loss of contractile reserve[98]
Heart-specific Tfam, a nuclear-encoded mitochondrial DNA replication transcription factor	Reduced activity of respiratory-chain complexes, reduced fatty acid oxidation, increased glucose utilization	Cardiac hypertrophy, dilatation, heart failure, conduction defects[99]
Adenine nucleotide translocase 1	Impaired ADP-stimulated mitochondrial respiration	Cardiac hypertrophy[100]
Mitochondrial and myofibrillar CK isoenzymes	Loss of mitochondrial CK, loss of mitochondrial and myofibrillar CK	Hypertrophy and dilatation, impaired contractile reserve, shortened diffusion distances between mitochondria and myofibrils[101,102]
Guanidino acetate methyl transferase	Deficient creatine biosynthesis, accumulation of precursor guanidino acetate, CK reaction velocity 1%	Loss of inotropic reserve, increased susceptibility to ischemia and reperfusion injury[103]
Human inborn errors of metabolism		
Systemic carnitine deficiency	Defective carnitine biosynthesis, transmembrane transport, intestinal uptake or tubular reabsorption	Dilated cardiomyopathy, cardiac arrest, cardiomegaly — oral carnitine therapy reverses phenotype[104]
Malonyl carboxylase deficiency	Elevation of malonyl–CoA, a potent inhibitor of carnitine palmitoyl transferase 1	Cardiomyopathy, decreased contractility, heart failure[105]
Carnitine palmitoyl transferase 2 deficiency	Impaired mitochondrial acyl–CoA transport	Cardiac hypertrophy, fatal cardiomegaly, dysrhythmias[106]
Short-chain, medium-chain, long-chain, and very-long-chain acyl–CoA dehydrogenase	Dysfunction of enzymes of fatty acid beta-oxidation	Short-chain acyl–CoA dehydrogenase: mild left ventricular dysfunction, biatrial hypertrophy[107] Medium-chain acyl–CoA dehydrogenase: cardiac involvement rare[107] Long-chain and very-long-chain acyl–CoA dehydrogenase: severe dilated or hypertrophic cardiomyopathy[107]
Kearns–Sayre syndrome, MELAS, Barth syndrome: mutations of mitochondrial DNA; Leigh's syndrome: mutation of mitochondrial or nuclear DNA	Various deficiencies of respiratory-chain complexes	Dilated cardiomyopathy, hypertrophic cardiomyopathy, conduction defects, ventricular ectopy[107,108]

* Many of these deficiency models and syndromes also have extracardiac manifestations not listed here. CoA denotes coenzyme A, CK creatine kinase, and MELAS mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

increasing PCG-1α activity as a means of up-regulating oxidative phosphorylation enzymes may be a promising approach.[93] An alternative is to reduce free fatty acid levels, which should repress mitochondrial uncoupling proteins, thereby increasing ATP synthesis.

MANIPULATION OF HIGH-ENERGY PHOSPHATE METABOLITES

A third strategy for metabolic intervention is the direct manipulation of high-energy phosphate stores, their availability, or the efficiency of their utilization. Creatine and phosphocreatine levels

can be augmented by increasing the creatine transporter function.[123] Although massive increases in the creatine transporter function are detrimental (because a substantially supranormal creatine level increases the free ADP level), future studies will show whether reversing the decrease in creatine and phosphocreatine levels by moderate stimulation of creatine transporter activity is beneficial in heart failure. Finally, it may be feasible to improve the myofibrillar efficiency of ATP utilization with new calcium-sensitizing[124] or myosin activator compounds.

CONCLUSIONS

Metabolic therapy is a promising new avenue for the treatment of heart failure, and suitable targets for therapy are substrate utilization, oxidative phosphorylation, and the availability of high-energy phosphates. A multipronged effort is needed to fully investigate this concept. Experimental studies will, for example, further clarify the mechanisms leading to energetic derangement and will suggest new molecular targets for therapeutic intervention. New metabolic modulator compounds need to be developed by academia and industry. Proof-of-principle clinical studies may use the myocardial phosphocreatine:ATP ratio to monitor the early energetic response of the heart to metabolic therapy, and this method may provide a surrogate marker of long-term prognostic effects. Finally, large-scale clinical trials will have to prove or disprove the clinical efficacy of metabolic modulators. There is substantial hope that such a combined effort will lead to new therapies targeted at cardiac energetics. These therapies may improve the symptoms and prognosis of patients with the life-threatening illness of chronic heart failure.

Supported by grants from the British Heart Foundation and the Medical Research Council, London.

Dr. Neubauer reports serving as a consultant to GlaxoSmithKline and receiving grant support from Siemens Medical Solutions. No other potential conflict of interest relevant to this article was reported.

I thank Kieran Clarke, Joanne S. Ingwall, Rong Tian, and Hugh Watkins for their review of the manuscript and helpful suggestions and all the colleagues, research fellows, students, and technicians who have worked on cardiac energetics with me.

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