

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.
Copyright © 2007 Massachusetts Medical Society.

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 transporter³¹ 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 cre-

atine 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 (³¹P-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, ³¹P-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 acids³⁸⁻⁴¹ and rates of oxidative phosphorylation⁴² 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.

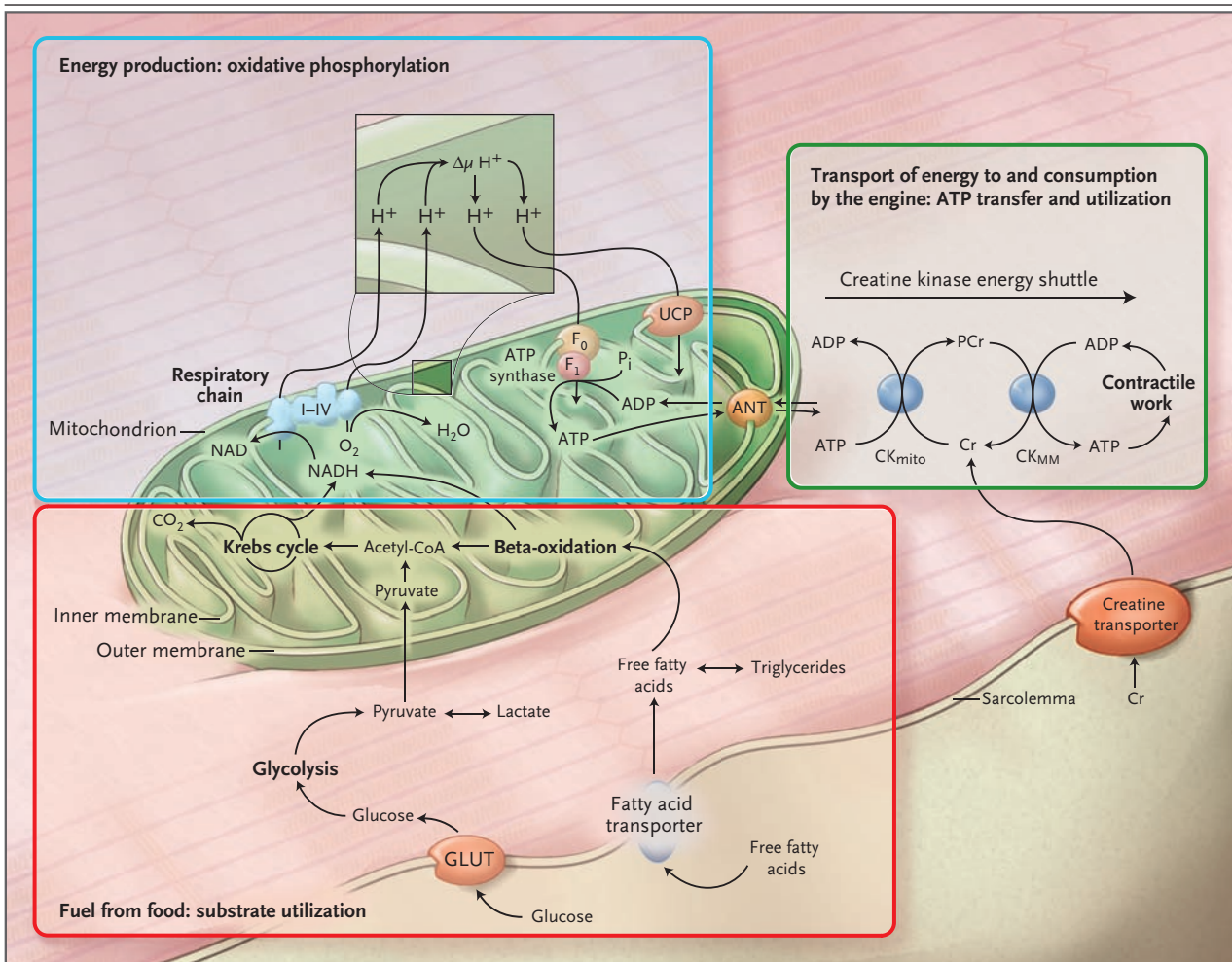


Figure 1. Cardiac Energy Metabolism.

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 (CO₂). 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 F₁, F₀ 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.

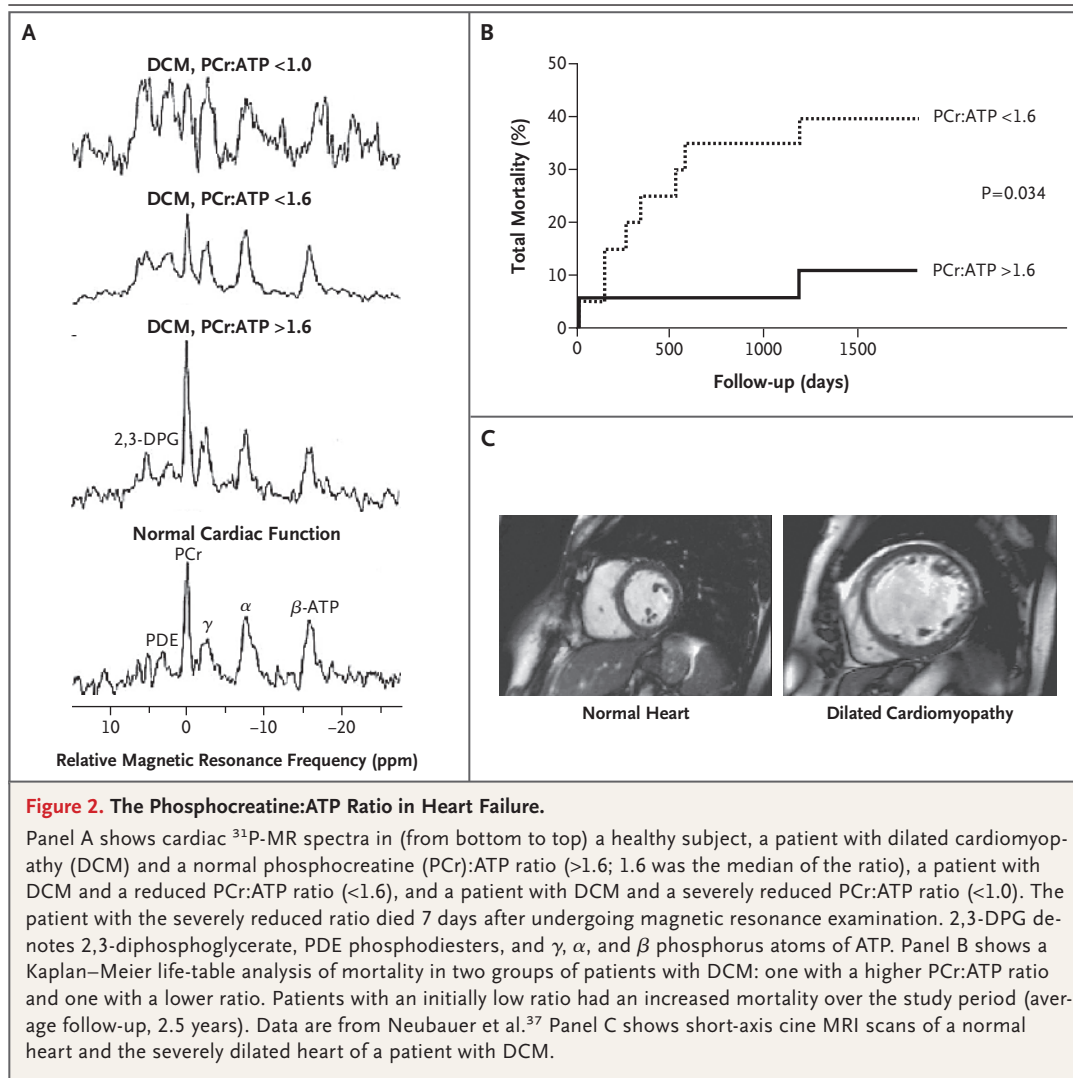
DERANGEMENT OF ENERGY METABOLISM IN HEART FAILURE

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 metabo-

lism: 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



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 impaired⁴¹; and the levels of uncoupling proteins (which cause mitochondria to produce heat rather

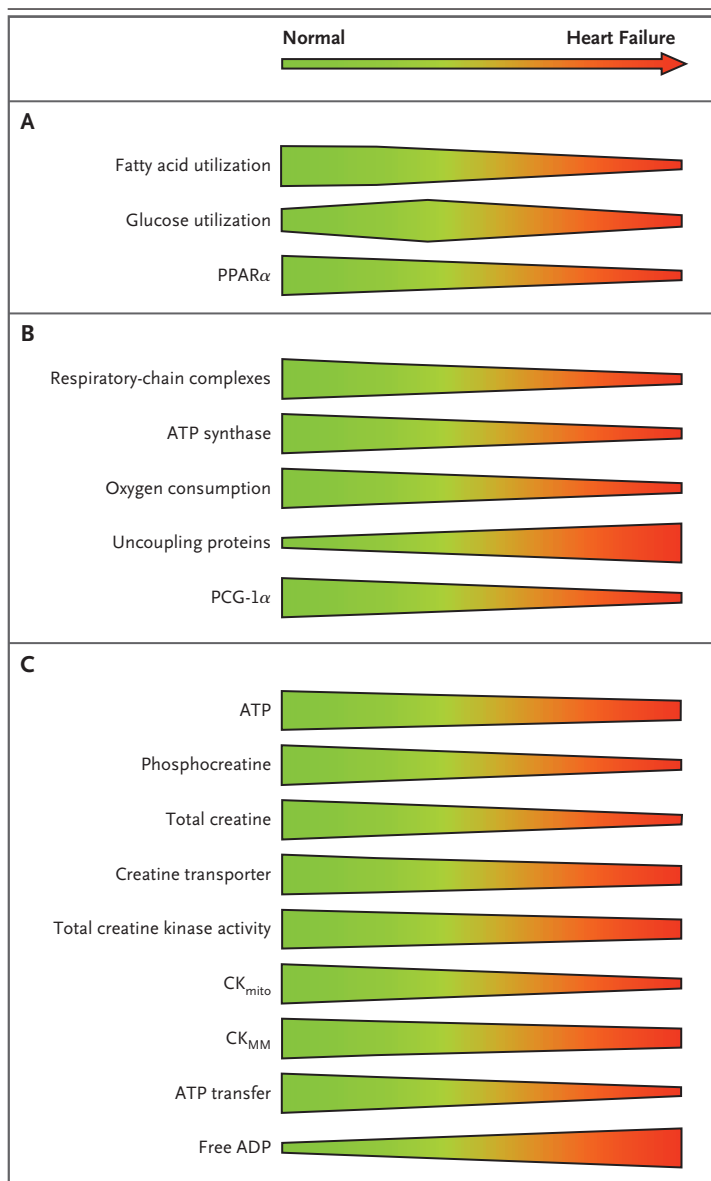


Figure 3. Changes in Cardiac Energy Metabolism in Heart Failure.

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 (PPAR α). 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 PPAR α coactivator 1 α (PCG-1 α). 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 perimyo-fibrillar 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 classes⁶³ and with indexes of systolic⁸³ and diastolic⁸⁴ 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 indexes³⁷ (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: PPAR α , PPAR β , and PPAR γ . All three affect cardiac lipid metabolism, but the primary regulator appears to be PPAR α , which controls the expression of enzymes directly involved in fatty acid oxidation. In cardiac hypertrophy in both animal models⁸⁸ and humans,^{89,90} the expression of PPAR α is decreased in proportion to the depression of fatty acid utilization. For this reason, the down-regulation of PPAR α 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, PPAR γ coactivator-1 (also known as PCG-1 α), 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 PPAR α and PPAR β and nuclear respiratory factors 1 and 2. Experimental studies suggest that the inhibition of PCG-1 α ,^{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-1 α 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 models⁹⁴⁻¹⁰³ 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 patients¹¹³; 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 non-ischemic origin, 2 months of treatment with the fatty acid oxidation inhibitor perhexiline¹¹⁵ or 3 months of treatment with the carnitine palmitoyl transferase 1 inhibitor etoxomir¹¹⁶ 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 PPAR α ¹¹⁹ and that PPAR activators may have beneficial,¹²⁰ adverse,¹²¹ or no¹²² 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
PPAR α	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-1 α	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 coxylase 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-1 α 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-sensitizing¹²⁴ 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 GlaxoSmith-Kline 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.

REFERENCES

- Heart disease and stroke statistics: 2005 update. Dallas: American Heart Association, 2005.
- Dayer M, Cowie MR. Heart failure: diagnosis and healthcare burden. *Clin Med* 2004;4:13-8.
- McMurray JJ, Pfeffer MA. Heart failure. *Lancet* 2005;365:1877-89.
- The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
- Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;327:669-77.
- Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
- CIBIS Investigators and Committees. A randomized trial of β -blockade in heart failure: the Cardiac Bisoprolol Insufficiency Study (CIBIS). *Circulation* 1994;90:1765-73.
- Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;334:1349-55.
- Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-50.
- Cleland JGF, Daubert J-C, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-49.
- Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation* 2005;111:2837-49. [Erratum, *Circulation* 2005;112(4):e75.]
- Herrmann G, Decherd GM. The chemical nature of heart failure. *Ann Intern Med* 1939;12:1233-44.
- Wollenberger A. On the energy-rich phosphate supply of the failing heart. *Am J Physiol* 1947;150:733-6.
- Olson RE, Schwartz WB. Myocardial metabolism in congestive heart failure. *Medicine (Baltimore)* 1951;30:21-41.
- Olson RE. Myocardial metabolism in congestive heart failure. *J Chronic Dis* 1959;9:442-64.
- Ingwall JS, Weiss RG. Is the failing heart energy starved? On using chemical energy to support cardiac function. *Circ Res* 2004;95:135-45.
- Taegtmeyer H. Metabolism — the lost child of cardiology. *J Am Coll Cardiol* 2000;36:1386-8.
- Idem*. Cardiac metabolism as a target for the treatment of heart failure. *Circulation* 2004;110:894-6.
- Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev* 2005;85:1093-129.
- Ventura-Clapier R, Garnier A, Veksler V. Energy metabolism in heart failure. *J Physiol* 2004;555:1-13.
- Morrow DA, Givertz MM. Modulation of myocardial energetics: emerging evidence for a therapeutic target in cardiovascular disease. *Circulation* 2005;112:3218-21.
- Lopaschuk GD, Rebecka IM, Allard MF. Metabolic modulation: a means to mend a broken heart. *Circulation* 2002;105:140-2.
- Essop MF, Opie LH. Metabolic therapy for heart failure. *Eur Heart J* 2004;25:1765-8.
- van Bilsen M, Smeets PJ, Gilde AJ, van der Vusse GJ. Metabolic remodeling of the failing heart: the cardiac burn-out syndrome? *Cardiovasc Res* 2004;61:218-26.
- Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
- Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;362:759-66.
- Katz AM. Heart failure: pathophysiology, molecular biology and clinical man-

- agement. Philadelphia: Lippincott Williams & Wilkins, 2000.
28. Bessman SP, Geiger PJ. Transport of energy in muscle: the phosphorylcreatine shuttle. *Science* 1981;211:448-52.
 29. Ingwall JS. ATP and the heart. Norwell, MA: Kluwer Academic, 2002.
 30. Wallimann T, Wyss M, Brdiczka D, Nicolay K, Eppenberger HM. Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: the 'phosphocreatine circuit' for cellular energy homeostasis. *Biochem J* 1992;281:21-40.
 31. Guimbal C, Kilimann MWA. A Na(+)-dependent creatine transporter in rabbit brain, muscle, heart, and kidney: cDNA cloning and functional expression. *J Biol Chem* 1993;268:8418-21.
 32. Wyss M, Wallimann T. Creatine metabolism and the consequences of creatine depletion in muscle. *Mol Cell Biochem* 1994;133-134:51-66.
 33. Garlick PB, Radda GK, Seely PJ. Phosphorus NMR studies on perfused heart. *Biochem Biophys Res Commun* 1977;74:1256-62.
 34. Ingwall JS. Phosphorus nuclear magnetic resonance spectroscopy of cardiac and skeletal muscles. *Am J Physiol* 1982;242:H729-H744.
 35. Bottomley PA. MR spectroscopy of the human heart: the status and the challenges. *Radiology* 1994;191:593-612.
 36. Neubauer S. Cardiac magnetic resonance spectroscopy. In: Lardo AC, Fayad ZA, Chronos NAF, Fuster V, eds. Cardiovascular magnetic resonance: established and emerging applications. London: Martin Dunitz, 2003:39-60.
 37. Neubauer S, Horn M, Cramer M, et al. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circulation* 1997;96:2190-6.
 38. Vitale GD, deKemp RA, Ruddy TD, Williams K, Beanlands RS. Myocardial glucose utilization and optimization of (18)F-FDG PET imaging in patients with non-insulin-dependent diabetes mellitus, coronary artery disease, and left ventricular dysfunction. *J Nucl Med* 2001;42:1730-6.
 39. Wallhaus TR, Taylor M, DeGrado TR, et al. Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure. *Circulation* 2001;103:2441-6.
 40. Davila-Roman VG, Vedala G, Herrero P, et al. Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 2002;40:271-7.
 41. Lewandowski ED. Cardiac carbon 13 magnetic resonance spectroscopy: on the horizon or over the rainbow? *J Nucl Cardiol* 2002;9:419-28.
 42. Ning XH, Zhang J, Liu J, et al. Signaling and expression for mitochondrial membrane proteins during left ventricular remodeling and contractile failure after myocardial infarction. *J Am Coll Cardiol* 2000;36:282-7.
 43. Gudbjarnason S, Mathes P, Ravens KG. Functional compartmentation of ATP and creatine phosphate in heart muscle. *J Mol Cell Cardiol* 1970;1:325-39.
 44. Chandler MP, Kerner J, Huang H, et al. Moderate severity heart failure does not involve a downregulation of myocardial fatty acid oxidation. *Am J Physiol Heart Circ Physiol* 2004;287:H1538-H1543.
 45. Osorio JC, Stanley WC, Linke A, et al. Impaired myocardial fatty acid oxidation and reduced protein expression of retinoid X receptor-alpha in pacing-induced heart failure. *Circulation* 2002;106:606-12.
 46. Remondino A, Rosenblatt-Velin N, Montessuit C, et al. Altered expression of proteins of metabolic regulation during remodeling of the left ventricle after myocardial infarction. *J Mol Cell Cardiol* 2000;32:2025-34.
 47. Nascimben L, Ingwall JS, Lorell BH, et al. Mechanisms for increased glycolysis in the hypertrophied rat heart. *Hypertension* 2004;44:662-7.
 48. Murakami Y, Zhang Y, Cho YK, et al. Myocardial oxygenation during high work states in hearts with postinfarction remodeling. *Circulation* 1999;99:942-8.
 49. Ide T, Tsutsui H, Hayashidani S, et al. Mitochondrial DNA damage and dysfunction associated with oxidative stress in failing hearts after myocardial infarction. *Circ Res* 2001;88:529-35.
 50. Marin-Garcia J, Goldenthal MJ, Moe GW. Abnormal cardiac and skeletal muscle mitochondrial function in pacing-induced cardiac failure. *Cardiovasc Res* 2001;52:103-10.
 51. Pool PE, Spann JF Jr, Buccino RA, Sonnenblick EH, Braunwald E. Myocardial high energy phosphate stores in cardiac hypertrophy and heart failure. *Circ Res* 1967;21:365-73.
 52. Bittner V, Reeves RC, Digerness SB, Caulfield JB, Pohost GM. 31P NMR spectroscopy in chronic adriamycin cardiotoxicity. *Magn Reson Med* 1991;17:69-81.
 53. Nascimben L, Friedrich J, Liao R, Pualetto P, Pessina AC, Ingwall JS. Enalapril treatment increases cardiac performance and energy reserve via the creatine kinase reaction in myocardium of Syrian myopathic hamsters with advanced heart failure. *Circulation* 1995;91:1824-33.
 54. Neubauer S, Horn M, Naumann A, et al. Impairment of energy metabolism in intact residual myocardium of rat hearts with chronic myocardial infarction. *J Clin Invest* 1995;95:1092-100.
 55. Zhang J, Merkle H, Hendrich K, et al. Bioenergetic abnormalities associated with severe left ventricular hypertrophy. *J Clin Invest* 1993;92:993-1003.
 56. Zhang J, Wilke N, Wang Y, et al. Functional and bioenergetic consequences of postinfarction left ventricular remodeling in a new porcine model: MRI and 31 P-MRS study. *Circulation* 1996;94:1089-100.
 57. Zhang J, Toher C, Erhard M, et al. Relationships between myocardial bioenergetic and left ventricular function in hearts with volume-overload hypertrophy. *Circulation* 1997;96:334-43.
 58. Kalsi KK, Smolenski RT, Pritchard RD, Khaghani A, Seymour AM, Yacoub MH. Energetics and function of the failing human heart with dilated or hypertrophic cardiomyopathy. *Eur J Clin Invest* 1999;29:469-77.
 59. Razeghi P, Young ME, Alcorn JL, Moravec CS, Frazier OH, Taegtmeier H. Metabolic gene expression in fetal and failing human heart. *Circulation* 2001;104:2923-31.
 60. Taylor M, Wallhaus TR, Degrado TR, et al. An evaluation of myocardial fatty acid and glucose uptake using PET with [18F]fluoro-6-thia-heptadecanoic acid and [18F]FDG in patients with congestive heart failure. *J Nucl Med* 2001;42:55-62.
 61. Quigley AF, Kapsa RM, Esmore D, Hale G, Byrne E. Mitochondrial respiratory chain activity in idiopathic dilated cardiomyopathy. *J Card Fail* 2000;6:47-55.
 62. Hardy CJ, Weiss RG, Bottomley PA, Gerstenblith G. Altered myocardial high-energy phosphate metabolites in patients with dilated cardiomyopathy. *Am Heart J* 1991;122:795-801.
 63. Neubauer S, Krahe T, Schindler R, et al. 31P magnetic resonance spectroscopy in dilated cardiomyopathy and coronary artery disease: altered cardiac high-energy phosphate metabolism in heart failure. *Circulation* 1992;86:1810-8.
 64. Regitz V, Fleck E. Myocardial adenine nucleotide concentrations and myocardial norepinephrine content in patients with heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. *Am J Cardiol* 1992;69:1574-80.
 65. Starling RC, Hammer DF, Altschuld RA. Human myocardial ATP content and in vivo contractile function. *Mol Cell Biochem* 1998;180:171-7.
 66. Beer M, Seyfarth T, Sandstede J, et al. Absolute concentrations of high-energy phosphate metabolites in normal, hypertrophied, and failing human myocardium measured noninvasively with (31)P-SLOOP magnetic resonance spectroscopy. *J Am Coll Cardiol* 2002;40:1267-74.
 67. Nascimben L, Ingwall JS, Pualetto P, et al. Creatine kinase system in failing and nonfailing human myocardium. *Circulation* 1996;94:1894-901.
 68. Conway MA, Allis J, Ouwkerk R, Nioka T, Rajagopalan B, Radda GK. Detection of low phosphocreatine to ATP ratio in failing hypertrophied human myocardium by 31P magnetic resonance spectroscopy. *Lancet* 1991;338:973-6.
 69. Casademont J, Miro O. Electron trans-

- port chain defects in heart failure. *Heart Fail Rev* 2002;7:131-9.
70. Murray AJ, Anderson RE, Watson GC, Radda GK, Clarke K. Uncoupling proteins in human heart. *Lancet* 2004;364:1786-8.
71. Shen W, Asai K, Uechi M, et al. Progressive loss of myocardial ATP due to a loss of total purines during the development of heart failure in dogs: a compensatory role for the parallel loss of creatine. *Circulation* 1999;100:2113-8.
72. Ten Hove M, Chan S, Lygate C, et al. Mechanisms of creatine depletion in chronically failing rat heart. *J Mol Cell Cardiol* 2005;38:309-13.
73. Neubauer S, Remkes H, Spindler M, et al. Downregulation of the Na(+)-creatinine cotransporter in failing human myocardium and in experimental heart failure. *Circulation* 1999;100:1847-50.
74. Vatner DE, Ingwall JS. Effects of moderate pressure overload cardiac hypertrophy on the distribution of creatine kinase isozymes. *Proc Soc Exp Biol Med* 1984;175:5-9.
75. Ingwall JS, Kramer MF, Fifer MA, et al. The creatine kinase system in normal and diseased human myocardium. *N Engl J Med* 1985;313:1050-4.
76. Laser A, Ingwall JS, Tian R, et al. Regional biochemical remodeling in non-infarcted tissue of rat heart post-myocardial infarction. *J Mol Cell Cardiol* 1996;28:1531-8.
77. Khuchua ZA, Ventura-Clapier R, Kuznetsov AV, Grishin MN, Saks VA. Alterations in the creatine kinase system in the myocardium of cardiomyopathic hamsters. *Biochem Biophys Res Commun* 1989;165:748-57.
78. De Sousa E, Veksler V, Minajeva A, et al. Subcellular creatine kinase alterations: implications in heart failure. *Circ Res* 1999;85:68-76.
79. Ye Y, Gong G, Ochiai K, Liu J, Zhang J. High-energy phosphate metabolism and creatine kinase in failing hearts: a new porcine model. *Circulation* 2001;103:1570-6.
80. Weiss RG, Gerstenblith G, Bottomley PA. ATP flux through creatine kinase in the normal, stressed, and failing human heart. *Proc Natl Acad Sci U S A* 2005;102:808-13.
81. Liao R, Nascimben L, Friedrich J, Gwathmey JK, Ingwall JS. Decreased energy reserve in an animal model of dilated cardiomyopathy: relationship to contractile performance. *Circ Res* 1996;78:893-902.
82. Liu J, Wang C, Murakami Y, et al. Mitochondrial ATPase and high-energy phosphates in failing hearts. *Am J Physiol Heart Circ Physiol* 2001;281:H1319-H1326.
83. Neubauer S, Horn M, Pabst T, et al. Contributions of 31P-magnetic resonance spectroscopy to the understanding of dilated heart muscle disease. *Eur Heart J* 1995;16:Suppl O:115-8.
84. Lamb HJ, Beyerbach HP, van der Laarse A, et al. Diastolic dysfunction in hypertensive heart disease is associated with altered myocardial metabolism. *Circulation* 1999;99:2261-7.
85. Ashrafian H, Redwood C, Blair E, Watkins H. Hypertrophic cardiomyopathy: a paradigm for myocardial energy depletion. *Trends Genet* 2003;19:263-8.
86. Crilley JG, Boehm EA, Blair E, et al. Hypertrophic cardiomyopathy due to sarcomeric gene mutations is characterized by impaired energy metabolism irrespective of the degree of hypertrophy. *J Am Coll Cardiol* 2003;41:1776-82.
87. Huss JM, Kelly DP. Nuclear receptor signaling and cardiac energetics. *Circ Res* 2004;95:568-78.
88. Barger PM, Brandt JM, Leone TC, Weinheimer CJ, Kelly DP. Deactivation of peroxisome proliferator-activated receptor-alpha during cardiac hypertrophic growth. *J Clin Invest* 2000;105:1723-30.
89. Sack MN, Rader TA, Park S, Bastin J, McCune SA, Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. *Circulation* 1996;94:2837-42.
90. Karbowska J, Kochan Z, Smolenski RT. Peroxisome proliferator-activated receptor alpha is downregulated in the failing human heart. *Cell Mol Biol Lett* 2003;8:49-53.
91. Garnier A, Fortin D, Delomenie C, Momken I, Veksler V, Ventura-Clapier R. Depressed mitochondrial transcription factors and oxidative capacity in rat failing cardiac and skeletal muscles. *J Physiol* 2003;551:491-501.
92. Finck BN, Kelly DP. PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. *J Clin Invest* 2006;116:615-22.
93. Arany Z, Novikov M, Chin S, Ma Y, Rosenzweig A, Spiegelman BM. Transverse aortic constriction leads to accelerated heart failure in mice lacking PPAR-gamma coactivator 1alpha. *Proc Natl Acad Sci U S A* 2006;103:10086-91.
94. Exil VJ, Roberts RL, Sims H, et al. Very-long-chain acyl-coenzyme A dehydrogenase deficiency in mice. *Circ Res* 2003;93:448-55.
95. Kurtz DM, Rinaldo P, Rhead WJ, et al. Targeted disruption of mouse long-chain acyl-CoA dehydrogenase gene reveals crucial roles for fatty acid oxidation. *Proc Natl Acad Sci U S A* 1998;95:15592-7.
96. Luptak I, Balschi JA, Xing Y, Leone TC, Kelly DP, Tian R. Decreased contractile and metabolic reserve in peroxisome proliferator-activated receptor-alpha-null hearts can be rescued by increasing glucose transport and utilization. *Circulation* 2005;112:2339-46.
97. Abel ED, Kaulbach HC, Tian R, et al. Cardiac hypertrophy with preserved contractile function after selective deletion of GLUT4 from the heart. *J Clin Invest* 1999;104:1703-14.
98. Arany Z, He H, Lin J, et al. Transcriptional coactivator PGC-1 alpha controls the energy state and contractile function of cardiac muscle. *Cell Metab* 2005;1:259-71.
99. Hansson A, Hance N, Dufour E, et al. A switch in metabolism precedes increased mitochondrial biogenesis in respiratory chain-deficient mouse hearts. *Proc Natl Acad Sci U S A* 2004;101:3136-41.
100. Graham BH, Waymire KG, Cottrell B, Trounce IA, MacGregor GR, Wallace DC. A mouse model for mitochondrial myopathy and cardiomyopathy resulting from a deficiency in the heart/muscle isoform of the adenine nucleotide translocator. *Nat Genet* 1997;16:226-34.
101. Nahrendorf M, Spindler M, Hu K, et al. Creatine kinase knockout mice show left ventricular hypertrophy and dilatation, but unaltered remodeling post-myocardial infarction. *Cardiovasc Res* 2005;65:419-27.
102. Kaasik A, Veksler V, Boehm E, Novotova M, Minajeva A, Ventura-Clapier R. Energetic crosstalk between organelles: architectural integration of energy production and utilization. *Circ Res* 2001;89:153-9.
103. ten Hove M, Lygate CA, Fischer A, et al. Reduced inotropic reserve and increased susceptibility to cardiac ischemia/reperfusion injury in phosphocreatine-deficient guanidinoacetate-N-methyltransferase-knockout mice. *Circulation* 2005;111:2477-85.
104. Chapoy PR, Angelini C, Brown WJ, Stiff JE, Shug AL, Cederbaum SD. Systemic carnitine deficiency — a treatable inherited lipid-storage disease presenting as Reye's syndrome. *N Engl J Med* 1980;303:1389-94.
105. Matalon R, Michaels K, Kaul R, et al. Malonic aciduria and cardiomyopathy. *J Inher Metab Dis* 1993;16:571-3.
106. Hug G, Bove KE, Soukup S. Lethal neonatal multiorgan deficiency of carnitine palmitoyltransferase II. *N Engl J Med* 1991;325:1862-4.
107. Guertl B, Noehammer C, Hoefler G. Metabolic cardiomyopathies. *Int J Exp Pathol* 2000;81:349-72.
108. Russell LK, Finck BN, Kelly DP. Mouse models of mitochondrial dysfunction and heart failure. *J Mol Cell Cardiol* 2005;38:81-91.
109. Hugel S, Horn M, de Groot M, et al. Effects of ACE inhibition and beta-receptor blockade on energy metabolism in rats postmyocardial infarction. *Am J Physiol* 1999;277:H2167-H2175.
110. Hermann HP, Pieske B, Schwarzmueller E, Keul J, Just H, Hasenfuss G. Haemodynamic effects of intracoronary pyruvate in patients with congestive heart failure: an open study. *Lancet* 1999;353:1321-3.
111. Nikolaidis LA, Elahi D, Hentosz T, et al. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in

- conscious dogs with pacing-induced dilated cardiomyopathy. *Circulation* 2004;110:955-61.
- 112.** Liao R, Jain M, Cui L, et al. Cardiac-specific overexpression of GLUT1 prevents the development of heart failure attributable to pressure overload in mice. *Circulation* 2002;106:2125-31.
- 113.** Vitale C, Wajngaten M, Sposato B, et al. Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. *Eur Heart J* 2004;25:1814-21.
- 114.** Di Napoli P, Taccardi AA, Barsotti A. Long term cardioprotective action of trimetazidine and potential effect on the inflammatory process in patients with ischaemic dilated cardiomyopathy. *Heart* 2005;91:161-5.
- 115.** Lee L, Campbell R, Scheuermann-Freestone M, et al. Metabolic modulation with perhexiline in chronic heart failure: a randomized, controlled trial of short-term use of a novel treatment. *Circulation* 2005;112:3280-8.
- 116.** Schmidt-Schweda S, Holubarsch C. First clinical trial with etomoxir in patients with chronic congestive heart failure. *Clin Sci (Lond)* 2000;99:27-35.
- 117.** Lionetti V, Linke A, Chandler MP, et al. Carnitine palmitoyl transferase-I inhibition prevents ventricular remodeling and delays decompensation in pacing-induced heart failure. *Cardiovasc Res* 2005;66:454-61.
- 118.** Chandler MP, Stanley WC, Morita H, et al. Short-term treatment with ranolazine improves mechanical efficiency in dogs with chronic heart failure. *Circ Res* 2002;91:278-80.
- 119.** Finck BN, Han X, Courtois M, et al. A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. *Proc Natl Acad Sci U S A* 2003;100:1226-31.
- 120.** Shiomi T, Tsutsui H, Hayashidani S, et al. Pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, attenuates left ventricular remodeling and failure after experimental myocardial infarction. *Circulation* 2002;106:3126-32.
- 121.** Lygate CA, Hulbert K, Monfared M, Cole MA, Clarke K, Neubauer S. The PPARgamma-activator rosiglitazone does not alter remodeling but increases mortality in rats post-myocardial infarction. *Cardiovasc Res* 2003;58:632-7.
- 122.** Frantz S, Hu K, Widder J, et al. Peroxisome proliferator activated-receptor agonism and left ventricular remodeling in mice with chronic myocardial infarction. *Br J Pharmacol* 2004;141:9-14.
- 123.** Wallis J, Lygate CA, Fischer A, et al. Supranormal myocardial creatine and phosphocreatine concentrations lead to cardiac hypertrophy and heart failure: insights from creatine transporter-overexpressing transgenic mice. *Circulation* 2005;112:3131-9.
- 124.** Ng TM. Levosimendan, a new calcium-sensitizing inotrope for heart failure. *Pharmacotherapy* 2004;24:1366-84.

Copyright © 2007 Massachusetts Medical Society.

POSTING PRESENTATIONS AT MEDICAL MEETINGS ON THE INTERNET

Posting an audio recording of an oral presentation at a medical meeting on the Internet, with selected slides from the presentation, will not be considered prior publication. This will allow students and physicians who are unable to attend the meeting to hear the presentation and view the slides. If there are any questions about this policy, authors should feel free to call the *Journal's* Editorial Offices.