

This Review is part of a thematic series on Unanswered Questions in Heart Failure, which includes the following articles:

Is Depressed Contractility Centrally Involved in Heart Failure?

What is the Role of β -Adrenergic Signaling in Heart Failure?

What Mechanisms Underlie Diastolic Dysfunction in Heart Failure?

Is the Failing Heart Energy Starved?

What Causes Sudden Death in Heart Failure?

Is Abnormal Cell Growth and Hypertrophy the Cause of Heart Failure?

Steven Houser, Guest Editor

Is the Failing Heart Energy Starved? On Using Chemical Energy to Support Cardiac Function

Joanne S. Ingwall, Robert G. Weiss

Abstract—The requirement of chemical energy in the form of ATP to support systolic and diastolic work of the heart is absolute. Because of its central role in cardiac metabolism and performance, the subject of this review on energetics in the failing heart is ATP. We briefly review the basics of myocardial ATP metabolism and describe how this changes in the failing heart. We present an analysis of what is now known about the causes and consequences of these energetic changes and conclude by commenting on unsolved problems and opportunities for future basic and clinical research. (*Circ Res.* 2004;95:135-145.)

Key Words: adenosine triphosphate ■ phosphocreatine ■ creatine kinase ■ familial hypertrophic cardiomyopathy ■ heart failure

The energy starvation hypothesis suggesting that the failing heart is energy-starved is decades old.^{1,2} Because ATP is required for normal systolic and diastolic contractile performance, the idea that the failing heart is unable to meet the hemodynamic requirements of the body because there is not enough chemical energy available is logical. The hypothesis was initially set aside for several reasons. First, it was unclear whether the concentration of ATP ([ATP]) decreased. Second, it was reasoned that even if there were decreases in [ATP] in the failing heart, the remaining ATP should be sufficient to supply the ATP-requiring reactions in the myocyte. Third, our understanding of how ATP synthesis and use are regulated was remarkably incomplete. A good example of our ignorance about cardiac energetics was the use of inotropic agents to increase performance of the failing human heart. While increasing performance, these agents did so at

great energetic cost and often resulted in increased, rather than decreased, heart failure mortality.

There is now renewed interest in the energy-starvation hypothesis.^{3,4} New biophysical tools such as nuclear magnetic resonance (NMR) spectroscopy, positron emission tomography (PET), and transgenesis using the mouse have allowed old questions to be revisited and new ones to be formulated. Combining old and new strategies to address the “energy starvation” hypothesis, we have learned much. We now know when and by how much [ATP] decreases in the hypertrophied and failing heart. We now know that despite increases in some ATP synthesizing pathways such as glycolysis, other pathways such as the creatine kinase (CK)–phosphocreatine (PCr) system decrease. Finally, we now have a better understanding of how the myocyte accomplishes the tasks of maintaining (near) normal ATP supply

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and high chemical driving forces for the ATP-requiring reactions when the left ventricular (LV) chamber thickens or dilates, wall stress increases, or the ventricular pump fails to recruit its contractile reserve.

ATP as the Universal “Currency” of Energy

The American Heritage Dictionary defines *energy* as “the capacity for doing work” and as “a source of usable power.”⁵ For the heart, “work” includes excitation, contraction, relaxation, and the molecular synthesis and degradation. The requirement of chemical energy in the form of ATP to support systolic and diastolic work of the heart is absolute. Hence, the focus of this invited review is on the “source of usable power,” namely ATP. The concept that the potential energy stored in phosphoryl bonds of ATP could be released for use and then regenerated through substrate metabolism within the cell was described more than 60 years ago.⁶ Krebs et al⁷ described phosphoryl bonds as the “energy currency” of the cell nearly 50 years ago. The basic concept of the phosphoryl bonds serving as “currency” of energy is still valid. Here, we briefly review the basics of ATP metabolism and then describe how this changes in the failing heart. We present an analysis of what is now known about the causes and consequences of these energetic changes and conclude by commenting on unsolved problems and opportunities for future basic and clinical research. Other important aspects of energetics are discussed in other reviews in this series. Tools assessing total energy demands of the heart have been elegantly described,^{8–9a} and their relation to heart failure is described by David Kass. The role of calcium in heart failure is the focus of another review by Houser and Margulies.¹⁰ Detailed reviews of substrate metabolism are available elsewhere.^{3,11–14} Similarly, the energetics of skeletal muscle of patients and animals with heart failure is described elsewhere.^{13,15}

ATP and the Heart

Central to understanding cardiac energetics is the integration of ATP-producing and ATP-utilizing pathways (Figure 1).¹⁶ The primary ATP-utilizing reactions (shown on the right in Figure 1) are actomyosin ATPase in the myofibril, the Ca^{2+} -ATPase in the sarcoplasmic reticulum, and the Na^+ , K^+ -ATPase in the sarcolemma. Also shown is a growing polypeptide chain representing the requirement of ATP for (macro)molecular synthesis (in the form of GTP for protein synthesis); ATP is also used to degrade molecules. [ATP] is maintained constant, ≈ 10 mmol/L, by the highly regulated integration of the pathways for ATP use and its synthesis. ATP synthesis by oxidative phosphorylation in the mitochondria is usually sufficient to maintain normal [ATP], even when the work output of the heart changes 3- to 5-fold. Quantitatively small contributions to ATP synthesis also occur from substrate level phosphorylation in the glycolytic pathway and, to a lesser extent, in the tricarboxylic acid cycle.

It is important to emphasize that the energetic state of the heart is not defined simply by the concentration of ATP. The amount of ATP made and used per minute (turnover) is many times greater than the size of the ATP pool. Thus, maintaining a high ATP supply is critically important for maintaining

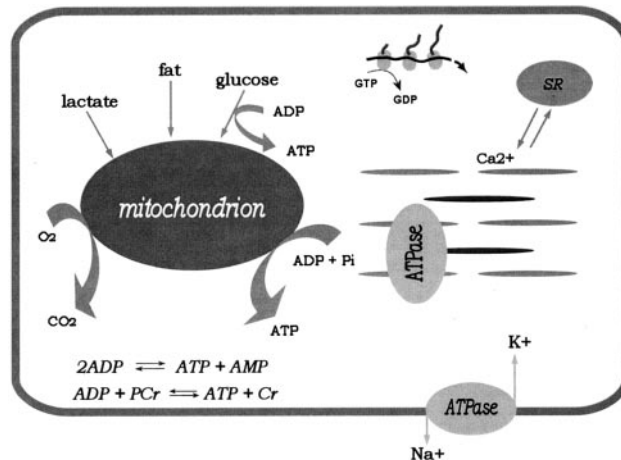


Figure 1. A cartoon¹⁶ summarizing the integration of the ATP synthesizing and utilizing reactions. The primary ATP utilizing reactions (shown on the right) are actomyosin ATPase in the myofibril, the Ca^{2+} -ATPase in the sarcoplasmic reticulum, and the Na^+ , K^+ -ATPase in the sarcolemma. Also shown is a polypeptide chain representing the requirement of ATP for macromolecular synthesis. The primary ATP synthesizing pathways (left) are oxidative phosphorylation in the mitochondria and the glycolytic pathway. The creatine kinase and adenylate kinase phosphotransfer reactions are also shown. Adapted from Ingwall,¹⁶ with permission.

cardiac performance. The ability of the complex metabolic machinery in the heart to oxidize a variety of carbon-based fuels for ATP synthesis ensures that [ATP] remains constant despite varying ATP turnover rates.

ATP-requiring reactions are inhibited by the accumulation of the products of ATP hydrolysis, namely ADP and inorganic phosphate (Pi): $\text{ATP} \rightarrow \text{ADP} + \text{Pi}$. To determine whether ATP-requiring reactions are limited because of insufficient chemical-driving forces, we need to know the concentrations of ADP and Pi as well as [ATP]. The ratio $([\text{ATP}]/[\text{ADP}][\text{Pi}])$, the phosphorylation potential (PP), determines the free energy available ($\Delta G_{\sim\text{ATP}}$) from the hydrolysis of ATP to drive ATP-requiring reactions. The chemical-driving force can be thought of as a battery used to fuel chemical reactions. Intracellular [ATP], [ADP], [Pi], and PP in normal ventricular tissue are ≈ 10 mmol/L, < 50 $\mu\text{mol/L}$, < 1 mmol/L, and > 200 mmol/L⁻¹, respectively. Note that classical biochemical tools used to analyze extracts of even carefully freeze-clamped tissue cannot provide accurate measures of free [ADP] or [Pi].¹⁷ For example, measures of total [ADP] in tissue extracts are in the 1 to 2 mmol/L range, whereas the size of the metabolically active pool or free ADP is 10 to 50 $\mu\text{mol/L}$, ie, ≈ 2 orders of magnitude lower. The physiologically relevant entity is the free [ADP]; it can be calculated from the CK equilibrium expression.^{18,19} [Pi] can also be overestimated, by as much as 10-fold. It is now possible to measure [ATP] and [Pi] and to obtain good estimates for [ADP] while simultaneously measuring indices of cardiac performance using ³¹P NMR spectroscopy, making it a useful tool for the study of energetics.

The heart uses energy reserve systems to maintain a high phosphorylation potential (and hence a favorable free energy of ATP hydrolysis, $\Delta G_{\sim\text{ATP}}$) to drive ATPase reactions during

variations in work output. The primary energy reserve compound in the heart is PCr, which is present in concentrations twice that of ATP. The enzyme CK transfers the phosphoryl group between ATP and PCr at a rate ≈ 10 -times faster than the rate of ATP synthesis by oxidative phosphorylation:²⁰ $\text{PCr} + \text{ADP} + \text{H}^+ \leftrightarrow \text{creatine} + \text{ATP}$. Under conditions when ATP demand exceeds ATP supply, as in acute pump failure in ischemia and in chronic conditions of high wall stress, use of PCr via the CK reaction is one way that the heart maintains constant [ATP]. The CK reaction also maintains a low [ADP] and [Pi], thereby maximizing the phosphorylation potential.²¹ The enzyme adenylate kinase also functions to maintain high levels of ATP by transferring phosphoryl groups among the adenine nucleotides: $2\text{ADP} \leftrightarrow \text{ATP} + \text{AMP}$. Glycogen is an indirect energy store in that its glucosyl units can be used to generate ATP through glycolytic and oxidative metabolism.^{22,23}

ATP and the Failing Heart

Based on analysis of human biopsy specimens, we now know that [ATP] is $\approx 25\%$ to 30% lower in the failing human heart.^{24,25} This has been confirmed in heart failure patients by absolute quantification of [ATP] using ^{31}P NMR spectroscopy.²⁶ Longitudinal studies of animal models of heart failure have provided us with insights into when and why ATP is lost from the myocardium. Results using a dog model of heart failure (pacing-induced)²⁷ show that the loss of ATP in the failing myocardium is slow and progressive: $\approx 0.35\%$ of the ATP pool per day. This low rate means that a decrease in ATP content would not be easy to detect until the heart was in severe failure, explaining the conflicting literature results on this topic. This conclusion is well-supported by results using other animal models of compensated and uncompensated LV hypertrophy (LVH).^{28–32}

Studies in animal models of heart failure show that the loss of ATP in the failing heart is caused by loss in the total adenine nucleotide (TAN) pool.^{27,30,31} The failing heart is a unique example of a well-oxygenated heart^{33–35} in which a chronic mismatch between ATP synthesis and degradation results in loss of ATP and TAN; previously, ATP and TAN loss were observed only for conditions of hypoxia and ischemia. Whether ATP and TAN losses occur because de novo purine synthesis is slowed (or fails to increase to support a larger myocyte mass) or because reactions converting adenine nucleotides to diffusible purine nucleosides and bases are accelerated remain to be determined. Why [ATP] decreases by only $\approx 25\%$ is not known, and the length of time the heart can tolerate this new steady-state also remains to be defined.

PCr and the Failing Heart

Creatine is not made in the heart but accumulates against a large concentration gradient by means of a facilitated creatine transporter.^{36,37} In the normal heart, approximately two-thirds of the total creatine pool is phosphorylated via the CK reaction to form PCr and hence is chemically trapped.

The observation that the total creatine pool is as much as 60% lower in LVH and heart failure was originally made in animal models.^{28,29} This was confirmed in human myocardial biopsy specimens in the mid 1980s in patients with severe

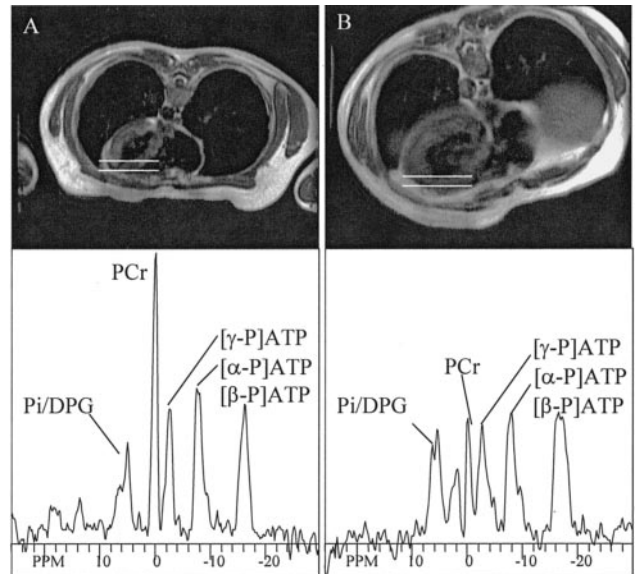


Figure 2. Changes in cardiac ^{31}P NMR spectra in heart failure. ^1H NMR images (upper panel) and spatially localized ^{31}P NMR spectra (bottom panel) are shown from a normal individual (left, A) and in a patient with idiopathic dilated cardiomyopathy (right, B). ^{31}P NMR spectra were obtained from the regions of the anterior left ventricular wall denoted on the ^1H NMR images between the white lines. In NMR spectra, the peak position is determined by the chemical moiety and the peak area is related to the amount of the chemical compound. The peaks, from left to right, are inorganic phosphate, creatine phosphate, and the $[\gamma\text{-P}]$, $[\alpha\text{-P}]$, and $[\beta\text{-P}]$ of ATP. In the normal human heart, the relative amount of creatine phosphate (PCr) is nearly twice that of ATP (lower left panel). In heart failure (lower right panel), the relative amount of PCr to ATP is reduced dramatically at rest. In measurements from several regions of this patient's failing heart, mean [ATP] is reduced by $\approx 15\%$ and [PCr] by $>40\%$ from that in normal subjects (R.G. Weiss and P.A. Bottomley, 2003, unpublished data).

aortic stenosis³⁸ and in the 1990s in patients with severe heart failure.⁴ A recent study using ^1H NMR spectroscopy demonstrated creatine depletion in human heart failure and, moreover, that the magnitude of the decrease was related to heart failure severity.³⁹

Because CK is relatively abundant even in the failing heart,^{25,28–32,38,40} a lower total creatine pool means that [PCr] must also be lower. ^{31}P NMR studies in the early 1990s by several groups^{41–44} showed that [PCr]/[ATP] is lower in dilated cardiomyopathy and heart failure. In Figure 2, typical ^{31}P NMR spectra obtained noninvasively from normal and failing human hearts illustrate the changes in [ATP] and [PCr] that characterize the failing heart. Because we now know that [ATP] is also lower in severely failing human myocardium,^{24,26} the decrease in [PCr] reported by the ratio of [PCr] to [ATP] is underestimated in severe heart failure.²⁷ Importantly, the [PCr]-to-[ATP] ratio is a good predictor of mortality in patients with dilated cardiomyopathy.⁴⁵ In fact, over the course of several years, a low cardiac [PCr]/[ATP] is a better predictor of overall and cardiovascular mortality than New York Heart Association Class and LV ejection fraction (Figure 3).

The observations that [PCr]/[ATP] and [PCr] are lower in both compensated LVH as well as failing hearts suggest that

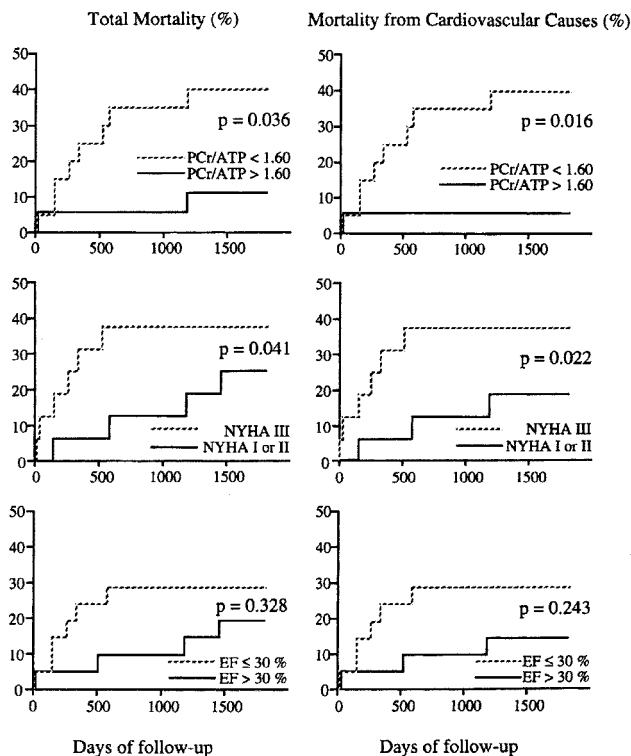


Figure 3. Relationship between overall mortality (left panel) and cardiovascular mortality (right panel) in subjects with dilated cardiomyopathy and heart failure based on cardiac PCr/ATP (top row), NYHA Class (middle row), and left ventricular ejection fraction (bottom row). Note that cardiac energetics as measured by the myocardial PCr/ATP is a better predictor of overall and cardiovascular mortality than the usual clinical indices of ejection fraction and NYHA symptomatology. Reproduced from Figure 3 of Neubauer et al,⁴⁵ with permission.

loss of creatine cannot be a specific marker of the failing heart. Instead, loss of PCr is a more general marker of a mismatch in the integration of the pathways maintaining sufficient ATP supply to meet the demand for ATP utilization. Mechanisms accounting for decreased [PCr] include decreased number of creatine transporters³⁷ and changes in CK isozyme expression leading to a lower ratio of [PCr]-to-[total creatine].²¹

The Failing Heart Is Energy-Poor

The evidence amassed to date suggests that the following sequence of events occurs in the progression to myocardial pump failure. [PCr] decreases in hypertrophy and failure because of a mismatch in ATP supply and demand. This is followed by a loss in [creatinine] by as much as 60% and by a decrease in [ATP]. The loss of creatine is cardiac-specific and is nearly an order of magnitude faster than loss of ATP.²⁷ ATP slowly and progressively decreases in the dysfunctional and failing myocardium to a lower limit of $\approx 70\%$ to 75% of normal values. The loss of ATP is caused by loss of purines. Early in the evolution of heart failure, [ADP] (and Pi) increases, leading to a decrease in $\Delta G_{\approx ATP}$, but with time, as the absolute concentrations of ATP, ADP, and creatine decrease in the failing heart, and the ratio of [ATP]-to-[ADP] and $\Delta G_{\approx ATP}$ are reset to near normal values. How long any of these states remain stable is not known.

The observation that [ATP] decreases in the failing heart means that the normal well-designed well-integrated metabolic machinery has failed. Moreover, because the [ATP]-poor state persists in the failing heart, the normal mechanisms that slowly replete the ATP pool after myocardial ischemia and infarction must also “fail.” The decrease in [ATP] is important, not because [ATP] decreases to values below the K_m for ATP of the ATPase reactions; it does not. It is important because it signals a massive change in normal metabolic regulation, one that is unable to support normal levels of either ATP or PCr. Here we list the primary changes in the ATP synthesis pathways now thought to occur in the failing heart.

On the Failure of ATP Synthesis Pathways to Prevent the Decrease in [ATP]

Mitochondrial protein activities measured in heart failure models as diverse as the pacing dog⁴⁶ and the aortic banded rat⁴⁷ have been shown to be decreased, but whether the changes are large enough to limit the capacity for MVO_2 is not entirely clear.^{27,46,48} Based on elegant measures of myoglobin saturation using NMR spectroscopy, what is clear is that the hypertrophied/ failing heart is not hypoxic.^{34,35}

At least some of the mechanisms responsible for the decreases in fatty acid oxidation in hypertrophied and failing heart have been identified.⁴⁹ The coordinated downregulation of gene expression of enzymes controlling fatty acid oxidation is caused, at least in part, by decreases in expression of the nuclear receptors proliferator-activated receptor- α and retinoid X receptor- α ^{46,48} and the master transcriptional regulator of mitochondrial biogenesis peroxisome proliferator-activated receptor γ co-activator (PGC1- α).⁴⁷

The first observation of molecular remodeling or reprogramming in a model of LVH was a change in isozyme distribution of the glycolytic enzyme lactate dehydrogenase.⁵⁰ It is now widely accepted that glucose uptake and utilization increase in hypertrophied and mildly failing heart.^{51–54} It is not yet clear how long this is sustained.

The large decrease in CK reaction velocity caused by decreases in both CK muscle-type isozyme activities and in creatine is only partially compensated for by increases in adenylate kinase reaction velocity and glycolytic rate.⁵⁵

The sum of all these changes in ATP synthesis pathways fails to meet the chronic demand for ATP utilization in the failing heart. [ATP] decreases.

The decrease in fatty acid oxidation and increased reliance on glucose utilization in hypertrophied and failing hearts has often been described as a shift to the “fetal phenotype.” It is important to point out that the “shift” is only partial, and even when the proportion of ATP synthesized from glucose increases many fold, aerobic metabolism is still dominant.

On Causes and Consequences

What are the causes and consequences of these metabolic changes? Are they a cause or a consequence of the hemodynamic changes that occur in the hypertrophied and failing heart? Is any one of these changes sufficient to cause heart failure? Do they contribute to the progressive decline in pump function?

In any discussion of *causes and consequences*, we need to distinguish among the cause of a specific molecular change, its consequence if any on systolic and diastolic function of the heart, and when the change occurs during the evolution to failure. To distinguish *cause versus consequence*, we can create gain and loss of function models for each molecular change identified in the failing heart and determine the consequences in the context of the normal heart and in the far more complex setting of the failing heart. This is a formidable challenge for at least 2 reasons. One is that it is unlikely that any single change leads to heart failure. Even the familial hypertrophic cardiomyopathy (FHC)-associated mutations are lethal in only a subset of carriers of the defective gene.⁵⁶ The second is that the cell is designed to compensate for the loss of any important enzyme or pathway. Energetics is the prime example of this basic biologic principle. Myocytes are designed to make large amounts of ATP needed to meet varying needs of contraction from a variety of carbon-based substrates. When one pathway fails, there are others to compensate.

Here we present 7 examples in which the relationship between cardiac pathophysiology and some aspect of energetics have been defined. Several examples focus on phosphotransferase reactions, a subject for which much is known.

On the Causes of Altered Energetic Phenotype Characteristic of the Failing Heart: The Relationship Between LV Pressure and Molecular Phenotype

Myocyte size, location, and ability to adapt to stress, as well as hemodynamic factors, all play important roles leading to altered gene expression in the failing heart. This is well-illustrated by an early study in which cell size and enzyme activities of several proteins known to change in cardiac hypertrophy and failure were measured in myocytes isolated from different regions of hypertensive and nonhypertensive hypertrophied rat hearts (2 kidney, 1 clip model).⁵⁷ Some proteins increased in proportion to myocyte size while others were relatively diluted, and still others increased out of proportion to myocyte size. Regulation of gene expression differed among neighboring cells within the same organ. This myocyte study showed that gene expression changed in response to sustained hemodynamic load.

The idea that sustained increased hemodynamic load *causes* changes in gene expression in some but not all proteins involved in energy utilization and synthesis is well-supported by a recent study showing that the decreases in MM-CK and mitochondrial (sMt)-CK isozymes, but not the increase in MB-CK, were reversed in heart failure patients given a ventricular assist device.⁵⁸ These observations suggest that unloading the failing heart leads to a reversal toward the normal adult phenotype. The molecular details of how this occurs remain unknown, and additional reversal strategies need to be pursued.

Consequences of Reduced Phosphotransferase Activity: CK Activity and the Ability to Recruit Contractile Reserve

The relationship between energy reserve supplied from the transfer of the phosphoryl group between ATP and PCr via

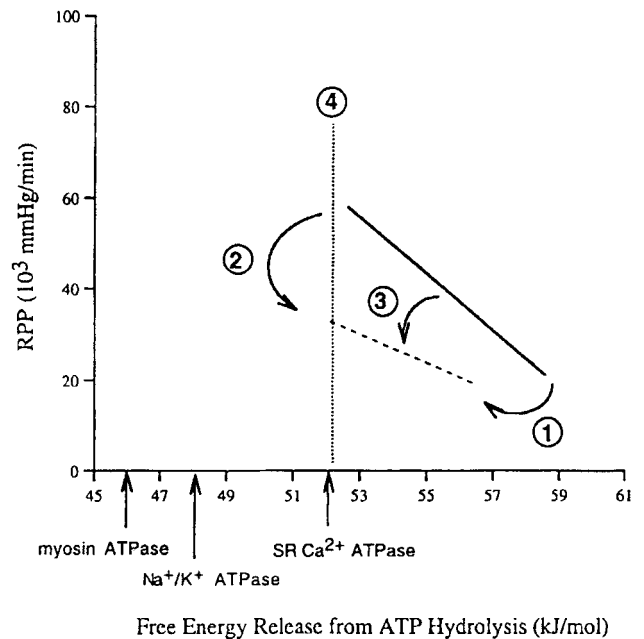


Figure 4. Linear fits of the relationship between isovolumic contractile function, estimated as the rate pressure product (RPP), and the free energy release from ATP hydrolysis (ΔG_{ATP}) for normal rat hearts (solid line) and hearts with $\approx 1\%$ creatine kinase (CK) activity (dashed line). RPP was increased by increasing $[\text{Ca}^{2+}]$ in the perfusate from 1.75 to 4.0 mmol/L. Each line fit is based on data obtained from 6 hearts. Literature values for $|\Delta G_{\text{ATP}}|$ determined for the primary ATPases of the myocytes are shown on the x-axis. The circled numbers indicate the following: (1) CK-inhibited hearts operate at a lower ΔG_{ATP} ; (2) the increase in RPP in creatine kinase-inhibited hearts for the equivalent inotropic challenge was less than for normal hearts; (3) the decrease in the slope of the RPP- ΔG_{ATP} relation for the CK-inhibited hearts compared with normal hearts shows that there is a large expenditure of free energy for a small change in RPP; and (4) for both normal and CK-inhibited hearts, essentially no data points fall beyond the value for ΔG_{ATP} for the calcium ATPase. At least under these conditions, there appears to be a limiting threshold. Adapted from Tian and Ingwall,⁵⁹ with permission.

the CK system and contractile reserve (by which we mean the ability of the heart to increase cardiac performance in response to demand) has been defined for the normal heart by inhibiting the velocity of the CK reaction acutely and chronically using several different approaches. In one set of studies, energy reserve was acutely decreased by $\approx 99\%$ by chemically inhibiting CK activity.^{59,60} Because the velocity of the CK reaction is directly proportional to maximal enzyme activity (V_{max}), this maneuver effectively eliminated the primary energy reserve system in the heart. Care was taken to test whether MVO_2 , the MVO_2 -work relation, adenylate kinase capacity, and glycolytic rates were normal in these hearts; none of these differed from control hearts; so, of all the ATP supply reactions, only the CK reaction was eliminated. The primary consequences of eliminating CK activity were (Figure 4): (1) at any workload, hearts with low levels of CK activity operate at a lower ΔG_{ATP} ; this means that they have less free energy available from ATP hydrolysis to support an increase in work; (2) for the equivalent inotropic challenge, the increase in contractile reserve in CK-inhibited hearts was much less than for normal hearts; and (3) for the

same energy expenditure, there is less work output in CK-inhibited hearts. Thus, reducing energy reserve via the CK system limits the contractile reserve of the heart.

Importantly, the consequences of acutely decreasing energy reserve on contractile reserve demonstrated by this experiment also apply to chronic conditions of decreased energy reserve. The velocity of the CK reaction was chronically decreased by replacing creatine in the diet of rats with one of two creatine analogs, β -guanidinopropionic acid or β -guanidinopbutyric acid.⁶¹ These creatine analogs are poor substrates for the CK reaction and, at the doses delivered, reduced [PCr] and CK reaction velocity by $\approx 70\%$. As observed for hearts with lower CK reaction velocity caused by acutely inhibiting the enzyme, isolated hearts that were creatine-depleted were unable to perform as much work as normal hearts. At any LV volume, contractile performance was lower than in controls. At peak work states, contractile performance assessed as the product of heart rate and developed pressure (RPP) in creatine-depleted hearts was only $\approx 60\%$ of control. Reduced [PCr] compromises the rate of phosphoryl transfer between mitochondria and sites of utilization not only in the sarcomere but also in the sarcoplasmic reticulum. Particularly noteworthy are observations using other models showing that changes in CK compartmentation alter adenine nucleotide channeling among organelles and calcium homeostasis.^{62–64}

Using transgenesis to chronically reduce either CK or adenylate kinase (the other major phosphotransferase) activity in the mouse heart, similar conclusions can be drawn. For mouse hearts with ablated muscle isoform of CK (MM-CK) and sMtCK activities (only BBCK activity remained), the same increase in RPP lead to a greater change in ΔG_{ATP} .⁶⁵ Studies using otherwise normal mouse hearts deficient in adenylate kinase 1 have shown that even though flux through the CK reaction and glycolysis increased to compensate for the loss in adenylate kinase, more ATP per contraction was used in adenylate kinase 1-deficient muscle.⁶⁶ Thus, in both acute and chronic phosphoryl-transfer-deficient states, there is a greater energy cost for work produced, and the efficiency of energy transduction is compromised.

How does this apply to the failing heart? The failing heart is “energy-starved” with respect to its capacity to rapidly resynthesize ATP via the CK system. Based on experiments in normal animal hearts and in models of heart failure showing similar relationships for energy reserve via the CK system and contractile reserve of the heart (for example, Figure 5),⁴⁰ we conclude that the decreased energy reserve of the failing heart contributes to its decreased contractile reserve. The energy-poor heart cannot recruit its contractile reserve without expending a disproportionate amount of energy and this property of the failing heart is associated with worse clinical outcomes (see below).

Consequences of Increased [ADP]: On the Energetic Causes of Diastolic Dysfunction

Diastolic dysfunction in the absence of systolic failure occurs in approximately half of all heart failure patients. One of the consequences of the decrease in [PCr] without a concomitant decrease in [creatine] observed during early stages of heart

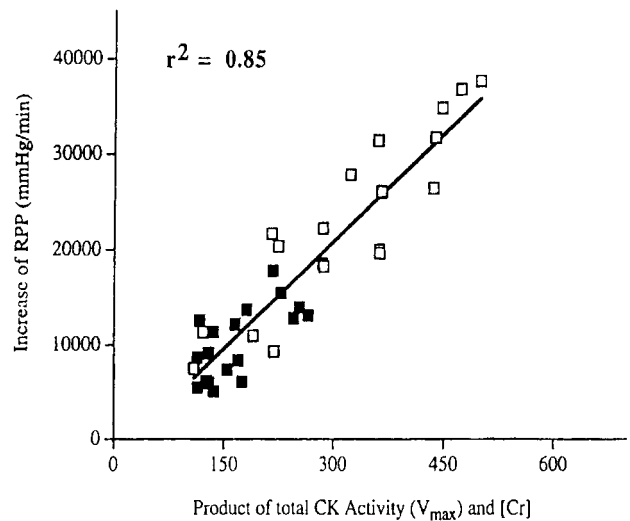


Figure 5. The relationship between the contractile reserve, estimated as the increase in the rate pressure product of isolated isovolumic hearts during high calcium perfusion, and the capacity of the creatine kinase reaction, estimated by the product of creatine kinase activity (V_{max}) and the total creatine content in hearts from Syrian cardiomyopathic hamsters (TO2 strain and normal hamsters) 4 weeks to 30 weeks old. The failing hearts had lower energy reserve and lower contractile reserve; importantly, data for the failing hearts fall on the normal relationship, but in the lower left-most portion of the relationship. Control heart (\square), cardiomyopathic heart (\blacksquare). Reproduced from Tian et al,⁴⁰ with permission.

failure is increased cytosolic [ADP]. The possibility that higher cytosolic [ADP] is sufficient to slow dissociation of the cross-bridges enough to slow relaxation in the intact heart as it does in skeletal muscle has been tested.^{67,68} Free [ADP] was manipulated in a whole heart (rat) preparation without substantially altering any of the other known regulators of contraction, namely ATP, Pi, H⁺, or Ca²⁺; the rate of ATP synthesis from glycolysis was also unchanged. In the normal heart, this was accomplished by chemically inhibiting CK to varying degrees.⁶⁸ In the heart hypertrophied because of aortic banding, the changes were the result of the perturbations in the CK-PCr that occur during hypertrophy and failure.⁶⁷ In both settings, a monotonic relationship between increased LV end diastolic pressure and increased [ADP] was found (Figure 6). Taken together, these studies demonstrate that increases in the average cytosolic [ADP] in the absence of changes in any of the other known regulators of myofilament function are sufficient to slow cross-bridge cycling and thereby contribute to the observed diastolic dysfunction.

Consequences of Increased [AMP]: AMP-Dependent Protein Kinase and Cytosolic AMP-Specific 5'-Nucleotidase

When [ADP] increases, cytosolic [AMP] also must increase as a result of the adenylate kinase reaction: $2\text{ADP} \leftrightarrow \text{ATP} + \text{AMP}$.²⁷ A beneficial consequence of increased [AMP] is activation of AMP-dependent protein kinase (AMPK). AMPK acts as a “low-on-fuel” warning system.⁶⁹ By means of phosphorylation of specific proteins, increased AMPK activity remodels metabolic pathways for ATP synthesis toward greater metabolic efficiency. Activation of AMPK

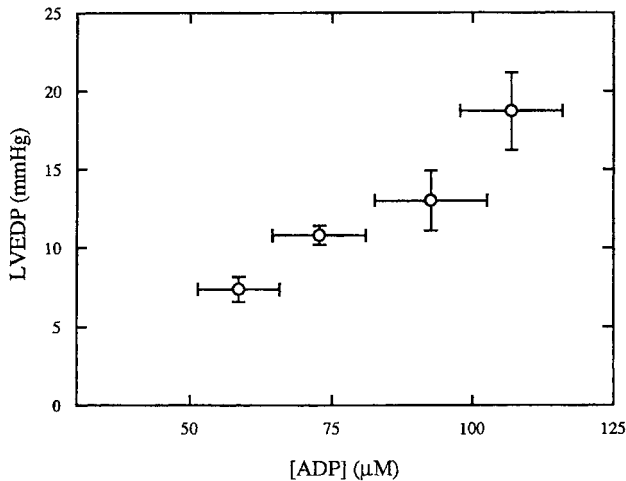


Figure 6. Relationship between the increase in [ADP] and the increase in LV end-diastolic pressure (EDP) in isolated perfused rat hearts in which [ADP] was altered by inhibiting creatine kinase to varying extents. Because all other known regulators of EDP were help-constant, these results show that increased [ADP] is sufficient to slow cross-bridge cycling in the heart. Reproduced from Tian et al,⁶⁸ with permission.

during *acute* low-energy states switches off ATP-consuming pathways such as fatty acid synthesis and activates ATP-producing pathways such as fatty acid oxidation and increased glucose uptake. AMPK has also been shown to function in this way in *chronic* low-energy states, including cardiac hypertrophy and failure⁷⁰ and skeletal muscle depleted of ATP.⁷¹ In hypertrophied (rat) hearts transitioning to failure, elevations in [AMP] and AMPK activity, isoform-specific alterations in AMPK expression and increased basal glucose uptake rates have all been observed.⁷⁰ Activation of AMPK led to a coordinate control of glucose supply and utilization, leading to higher rates of glycolytic ATP production. Increased AMPK activity also increases peroxisome proliferator-activated receptor γ co-activator (PGC-1 α) expression,⁷² a transcriptional co-activator that promotes mitochondrial biogenesis and oxidative phosphorylation.^{73–75}

But elevated [AMP] also has detrimental consequences. Increased [AMP] also activates cytosolic 5'-AMP-specific 5'-nucleotidase, the primary enzyme responsible for the conversion of AMP to adenosine in muscle cells.^{76–79} Increased adenosine concentrations leads to increased rate of purine and hence TAN loss. These 2 apparently conflicting consequences of increased [AMP] merit further study.

Increased Susceptibility of the Hypertrophied and Failing Heart to Acute and Chronic Stress

A characteristic of the failing myocardium is the failure to increase flux through the ATP synthesis pathways so that normal [ATP] and [PCr] are maintained. Once the state of diminished energy reserve is reached, regardless of cause, the heart has little contractile reserve and is at high risk for acute mechanical failure during an abrupt increase in work state, a hypoxic or ischemic insult, or an arrhythmia. Imposing a severe supply/demand mismatch on the already energetically compromised failing heart could lead to acute failure. One

demonstration of the greater susceptibility of the energy-depleted heart is the faster rate of loss of systolic performance during zero-flow ischemia in isolated mouse hearts deficient in the MM-CK and sMtCK genes.⁸⁰ Another is the example shown studying myocardial infarction in the rat.⁸¹ Myocardial [PCr] and CK reaction velocity were decreased by $\approx 90\%$ and [ATP] by 18% (a profile similar to the heart failure phenotype) in rats fed with the creatine analog β -guanidinopropionic acid, a competitive inhibitor of creatine transport and the CK reaction. Unlike control rat hearts that survived acute myocardial infarction, the 24-hour mortality of rats with severely compromised CK-PCr system was 100%.

The Effect of Ischemia on Energetics in the Failing Heart

Many patients with heart failure have underlying ischemic disease that contributes to both the onset and progression of heart failure. Because ischemia, defined as an imbalance of oxygen supply and demand, alters myocardial metabolism even before the onset of heart failure, this review focused primarily on animal and human studies without underlying coronary disease. In this way, we focus on heart failure per se and not the well-known metabolic consequences of ischemia or their complex interaction. It is unclear whether ischemia at the cellular level in the absence of coronary stenoses contributes to the onset or progression of heart failure as the determinants of oxygen demand, heart rate, and wall stress, increase. Recent studies, including those of myoglobin oxygenation, in several animal models indicate that inadequate oxygen supply or demand ischemia does not contribute significantly to heart failure progression.^{33–35}

Increased Energy Use With Normal ATP Supply: The Energetic Phenotype of Familial Hypertrophic Cardiomyopathy

One of the earliest ³¹P NMR spectroscopy studies of human hearts reported that the PCr/ATP was lower in hearts of young asymptomatic patients with primary hypertrophic cardiomyopathy (HCM).⁸² A subsequent analysis indicated that those with a familial history had more dramatic metabolic abnormalities, even though the extent of hypertrophy was comparable between the groups.⁸³ The re-analysis was prompted by a study showing greater ATP utilization (evidenced as decreased [PCr] and increased [Pi]) by using a transgenic mouse heart bearing the FHC-associated heterozygous R403Q mutation in cardiac myosin heavy chain.^{84,85} A recent study⁸⁶ of mouse hearts engineered to bear the FHC-associated R92Q mutation in the thin filament protein troponin T found even larger deficits in whole-heart energetics than observed for the myosin R403Q mutant. The most striking similarity between the hearts bearing FHC-related mutations in myosin heavy chain and troponin T is the unexpected defect in energetics despite apparently normal ATP supply.

The observation of increased energetic cost of cardiac function in hearts of FHC mutations shown by these mouse studies^{84,86} has been demonstrated in human FHC hearts using ³¹P NMR spectroscopy.⁸⁷ [PCr] relative to a presumably unchanged [ATP] was lower in 31 HCM patients with known

FHC mutations. The decrease in PCr/ATP was observed in patients with and without LV hypertrophy and in patients who were asymptomatic, suggesting that the decrease in [PCr] was caused by the mutant sarcomeric protein, not by LV hypertrophy. Taken together, these results suggest that a chronic mismatch between ATP utilization and supply can occur by increasing ATP utilization even in the absence of reduced ATP supply.

Finally, mutations in AMPK have also been identified as FHC-related,^{88,89} broadening the scope of the role of energetics in FHC and perhaps all forms of heart failure.

Interventions Designed to Alter Energetics in the Failing Heart: New Strategies for Therapy?

Is it possible to intervene and replete ATP and PCr? Strategies designed to expand the purine pool in the ischemic myocardium have had limited success. It is not clear whether the chemistry of the failing heart would be more amenable to these manipulations.

Although some athletes consume large amounts of creatine to expand the PCr pool (enhanced by carbohydrate loading), the magnitude of the increase in skeletal muscle is small. This is because the creatine pool size is set primarily by the number of creatine transporters.³⁷ Increasing the size of the creatine pool would increase the capacity for rapid ATP resynthesis via CK kinetically, but it would not change the thermodynamic driving force for ATP hydrolysis. A relatively small study suggested an improvement in LV ejection fraction in patients on chronic oral creatine supplementation but the increase in contractile function was modest and the impact of creatine supplementation on cardiac energetics was not studied.⁹⁰

Is It Possible to Intervene and Remodel the Pathways for ATP Synthesis?

The heart is capable of metabolizing multiple substrates to synthesize ATP and, as reviewed, the relative contribution of fatty acid oxidation decreases while glucose utilization increases in the failing heart.^{2,91} The reduction in fatty acid oxidation in the failing heart is caused by reduced expression of the nuclear receptors proliferator-activated receptor and retinoid X receptor⁴⁶ and to the master transcriptional regulator PGC1- α .⁴⁷ Further, this more "fetal"-like phenotype of reduced fatty acid oxidation and increased glucose contribution results from downregulation of adult gene transcripts rather than upregulation of fetal gene transcripts.^{11,92,93} Because glucose utilization is more efficient at generating ATP per O₂ consumed, it is thought that such a substrate switch is likely adaptive and thus beneficial.

The evidence showing that fatty acid oxidation decreases while glycolysis increases in the failing heart suggests a new strategy for therapy. Increasing the capacity for glucose uptake and utilization by overexpressing the insulin-independent glucose transporter, GLUT 1, was found to delay the natural history of the progression of heart failure.⁵⁴ Conversely, ablating the predominant insulin-dependent glucose transporter, GLUT4, depressed systolic function and eventually resulted in a dilated cardiomyopathy.^{94,95} Drugs

specifically designed to shift substrate utilization toward glucose (or have this as an unexpected consequence^{96,97}) are under development and may be effective therapy.

Future Directions

Much work remains to be performed to evaluate the role of energy depletion in heart failure at the basic and clinical levels. Although the extent of abnormalities in [ATP] have been characterized in many animal models of hypertrophy and heart failure, the evolution of those abnormalities and the attendant changes in [ADP] and $\Delta G_{\approx\text{ATP}}$ are still poorly characterized in the failing human heart. It is unclear whether reduced de novo purine synthesis, accelerated nucleoside loss, or both contribute to the slow loss of ATP in congestive heart failure. It is not even clear whether the 25% reduction in [ATP] in a failing myocardium has the same functional consequences as in a normal heart. Little information is available on whether energetic defects are reversible and, if so, could contribute to improved cardiac performance. Likewise, the timing and consequences of switches in substrate utilization during the development of heart failure are still incompletely understood. What is clear is that the development and implementation of new noninvasive quantitative methods for serial studies of energy metabolism, substrate utilization, and contractile performance in the same animal model or subject would be especially valuable for enhancing our understanding of the development and progression of heart failure.

Whether cause or consequence of the initiating event or a contributor to the progression to severe failure, it is also clear that what we have learned about cardiac energetics so far emphasizes the importance of considering the energetic state of the failing heart when treating heart failure patients. There is a need for detailed clinical studies of the role of metabolic interventions in heart failure. Observations from nearly all of the large randomized placebo-controlled trials of the most common heart failure medications performed to date are entirely consistent with a role for reduced energy production or "energy starvation" in heart failure. Specifically, pharmacologic interventions that reduce metabolic demand, such as ACE inhibitors,⁹⁸ angiotensin blockers,⁹⁹ and β -blockers,^{100,101} improve outcomes in heart failure. Conversely, agents that increase metabolic demand, such as positive inotropic drugs, do not improve outcomes and often increase mortality.¹⁰² Such observations provide necessary, but not sufficient, evidence for the energy starvation hypothesis as a fundamental cause of human heart failure.

What is probably most needed is a strategy for improving energy metabolism in the failing heart. While reduced energy reserve has been consistently associated with decreased contractile function in normal, hypertrophic, and ischemic hearts, there have been too few studies evaluating strategies that might improve metabolic reserve to test whether contractile reserve is improved in the failing heart or delay the inevitable progression to severe heart failure. Identification of novel pharmacologic, genetic, or mechanical methods to augment [ATP] or [PCr] stores, [ATP] synthesis, or $\Delta G_{\approx\text{ATP}}$ are critically needed. Such studies may also reveal whether changes in these essential metabolic factors play the same

roles during the initiation and regression of heart failure as during its progression. With a better understanding of how myocardial energy metabolism is altered during the onset and progression of heart failure and whether improved metabolism does indeed improve function in the failing heart, new targeted strategies should emerge to improve the function and outcomes of people with heart failure.

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