On the Hypothesis that the Failing Heart Is Energy Starved: Lessons Learned from the Metabolism of ATP and Creatine

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Adenosine triphosphate (ATP) and phosphocreatine fall in the failing heart. New insights into the control of ATP synthesis, supply, and utilization, and how this changes in the failing heart, have emerged. In this article, we address four questions: What are the mechanisms explaining loss of ATP and creatine from the failing heart? What are the consequences of these changes? Can metabolism be manipulated to restore a normal ATP supply? Does increasing energy supply have physiologic consequences (ie, does it lead to improved contractile [systolic and/or diastolic] performance)? In part 1 we focus on ATP, in part 2 on creatine, and in part 3 on the relationship between creatine and purine metabolism and purine nucleotide signaling.

Introduction

Shown by investigators using many different tools studying human myocardium and a wide variety of animal models of heart failure, it is now widely accepted that one characteristic of the failing heart is persistent and progressive loss of adenosine triphosphate (ATP) as well as phosphocreatine (PCr). Now that this once controversial issue has been resolved, the questions to be asked are the following: How does this occur? What are the consequences of these changes? Can metabolism be manipulated to restore a normal ATP supply? Does increasing energy supply have physiologic consequences (ie does it lead to improved contractile [systolic and/or diastolic] performance)? In this article, we describe the energetic phenotype of the failing heart from two points of view: using what we know about basic biochemistry of ATP reactions and what we are learning from analyses of the human heart and of animal models of heart failure, especially new mouse models. In part 1 we focus on ATP, in part 2 on creatine (Cr), and in part 3 on Cr and its relationship to purine signaling pathways. Demonstrating renewed interest in this subject, there have been several recent reviews published on the energetics of the failing heart [1–12]. Here, the references chosen are meant to be illustrative, not inclusive, and to add to the literature previously summarized.

ATP Progressively Falls in the Failing Heart

The basics

The normal mammalian heart maintains cytosolic ATP at a constant level of approximately 10 mM despite large fluctuations in ATP demand. Metabolism is designed so that the rate of ATP synthesis via re-phosphorylation of adenosine diphosphate (ADP) closely matches the varying rate of ATP utilization by myosin, ion pumps, synthesis and degradation of large and small molecules, and so forth. The primary source of ATP re-synthesis is via fatty acid oxidation in the mitochondria; the contribution from glycolysis is quantitatively small, less than 10%. Phosphoryl transfer between sites of ATP production and utilization occurs via creatine kinase (CK), adenylate kinase, and glycolysis. Because the velocity of the CK reaction is approximately 10 times faster than the ATP synthesis rate via oxidative phosphorylation, CK also functions to supply ATP from PCr during acute conditions of energy demand. ATP synthesis pathways not only function to maintain constant ATP, but they also function to maintain a high ratio of ATP to the products of ATP hydrolysis, namely ADP and inorganic phosphate (Pi). This ratio is the variable term in the expression for the free energy of ATP hydrolysis, $\Delta G_{\sim ATP}$

Table 1. Cytosolic purine nucleotide concentrations in control, hypertrophied, and failing myocardium

Study	Myocardium	ATP , *mM*	ADP, *μM*	AMP, *μM*
	Animal models			
Luptak et al. [13•]	Control rat	10	11	0.01
	50% LVH due to aortic banding	8.8	**39**	**0.16** ↑
Shen et al. [14]	Control dog	10	64	0.42
	Pacing-induced HF	8.0	**49**	**0.34** ↓
Nascimben et al. [15]	Nonfailing hamster	8.7	74	0.60
	Failing hamster	6.4	**36**	**0.20** ↓
Liao et al. [16]	Control turkey	8.5	47	0.25
	Furazolidine DCM	6.5	**23**	**0.08** ↓
	Human myocardium			
Nascimben et al. [17]	Control	10	43	0.17
	Failing	7.6	**31**	**0.14** ↓

Numbers in **bold** are statistically different from control.
ADP—adenosine diphosphate; AMP—adenosine monophosphate; ATP—adenosine triphosphate; DCM—dilated cardiomyopathy; HF—heart failure; LVH—left ventricular hypertrophy.

which is the expression defining the chemical driving force for all ATP-requiring reactions. Maintaining a high chemical driving force is essential for normal myocyte function and viability. ($\Delta G_{\sim ATP}$ is calculated from the constant value for ATP hydrolysis under standard conditions, $\Delta G^{o}_{\sim ATP}$ corrected for the actual concentrations of ATP, ADP, and Pi in the cytosol. The expression is: $\Delta G_{\sim ATP} = \Delta G^{o}_{\sim ATP}$ - RT *ln* [ATP] / [ADP] [Pi] where ΔG^{o} is the standard free energy change of ATP hydrolysis (-30.5 kJ/mol under standard conditions where each substrate and product is present at a concentration of 1 mol/L, standard temperature, pH 7, and 1 mM Mg^{2+}), R is the gas constant (8.3 J/mol/K), and T is the temperature in degrees Kelvin. The argument of the *ln* (ie, the natural log) term is the phosphorylation potential [ATP] / [AMP] [Pi] where Pi is inorganic phosphate.)

The failing myocardium

The tissue content of ATP progressively falls in the failing heart. In the severely failing human myocardium and in animal models of severe failure, ATP falls by as much as approximately 30%. Table 1 [13•,14–17] shows values for cytosolic ATP for normal and failing myocardium for a variety of animal models of heart failure and for failing human myocardium. The fact that ATP falls in the failing heart means that the metabolic network that maintains the balance between ATP supply and demand no longer functions normally. The loss of ATP in the severely failing heart is a unique example of chronic metabolic failure to meet ATP demand in the well-oxygenated myocardium.

The proximal mechanism

The proximal mechanism explaining the loss of ATP is loss of the adenine nucleotide pool (ie, the sum of all purine decreases). The primary pathway for ATP degradation in the cell is: ATP → ADP → adenosine monophosphate (AMP) → adenosine → inosine → hypoxanthine. Phosphorylated metabolites do not readily cross the cell wall but nucleosides and bases readily diffuse to the extracellular space moving down their concentration gradients. Activation of the gatekeeper of the adenine pool, cytosolic AMP-dependent 5'-nucleotidase (5'-NT), which converts AMP to adenosine, is sufficient to explain the decrease in the cytosolic content of adenine-containing compounds in the failing heart. In the normal myocardium, loss of purine is matched by de novo purine synthesis from glycine, glutamine, aspartate, and formate. Experiments determining whether de novo purine synthesis decreases in the failing myocardium remain to be done.

The long-term mechanism

The long-term mechanism explaining loss of ATP is decreased capacity for ATP synthesis relative to ATP demand. Based on measurements of uptake and oxidation rates of fatty acids and glucose in intact hearts and mRNA levels encoding key proteins and, more importantly, their enzyme activities in these pathways, there is little doubt that the relative contribution of fatty acid versus glucose oxidation to ATP synthesis changes in the hypertrophied and failing myocardium. Recently, attention has been given to determining absolute contributions of glucose versus fatty acid oxidation to ATP synthesis, and to when during the progression from compensated hypertrophy to severe failure these metabolic changes occur [18–20]. This is not a trivial problem because none of the tools available to estimate substrate contributions to ATP synthesis rate (use of isotopic labels detected as radioactivity or by ^{13}C nuclear magnetic resonance [NMR]) are without their limitations, and

longitudinal analyses of even relatively inexpensive animal models of heart failure are still costly. Consensus is emerging that in the compensated hypertrophied heart, glucose uptake and utilization increases, and that in severe failure, fatty acid oxidation (FAO) decreases due to a downregulation of gene expression of enzymes controlling fatty acid uptake and FAO by nuclear transcriptional factors such as peroxisome proliferator–activated receptor (PPAR)-α [21,22] and transcriptional coactivators such as proliferator-activated receptor-γ coactivator-1 α (PGC-1α) [23,24].

One of the earliest enzymes to be studied in the context of the energetics of hypertrophy and failure, the CK system in hypertrophy and failure has been much written about. CK activity and Cr, and therefore PCr, are both lower in the hypertrophied and failing myocardium, resulting in greatly decreased CK reaction velocity [17,25,26].

The major consequence of this complex molecular reprogramming is that the total capacity for ATP synthesis decreases, demand for ATP outstrips supply, and ATP falls. In summary, energy reserve, also referred to as metabolic reserve, is lower in the failing heart.

Consequences of decreased capacity for ATP synthesis

Although there is no doubt that decreasing ATP synthesis rates leads to decreased contractile performance in acute settings such as hypoxia and ischemia, testing whether a chronic mismatch between ATP supply and demand as occurs in the failing heart leads to contractile dysfunction is more difficult. So many changes occur in the hypertrophied and failing myocardium that it is difficult to prove cause and effect or even to define consequences. The use of genetically modified mouse hearts in which a single change has been made in a metabolic pathway has been critical in advancing our understanding of the consequences of decreased capacity for ATP synthesis. Here we present some recent examples of this.

PGC-1α, a master regulator of energy metabolism, is a potent transcriptional coactivator of nuclear receptors and DNA-binding transcription factors, including the PPAR-γ and -α, retinoid receptors, the estrogen receptor, and nuclear respiratory factors 1 and 2 [23]. PGC-1α activates genes encoding proteins comprising entire metabolic pathways that control ATP synthesis in mitochondria, namely FAO and oxidative phosphorylation. Modeling the observation that PGC-1α is downregulated in the hypertrophied and failing heart, PGC-1α null mice have been used to define the consequences of reduced PGC-1α on ATP synthesis in the heart. Although PGC-1α is not required for mitochondrial biogenesis in the heart, the absence of PGC-1α not only led to reduced gene expression for proteins required for FAO and oxidative phosphorylation, but their enzyme activities were reduced and ATP was decreased to levels observed in the failing heart [24]. Central to defining the consequences of reduced ATP synthesis in the heart, PGC-1α null hearts had reduced contractile reserve. Similarly, hearts without one of the major targets for PGC-1α, the transcriptional receptor PPAR-α, also have decreased FAO and increased glycolysis and glucose oxidation [27–29]. Importantly, mouse hearts with no PPAR-α also fail to increase work with inotropic challenge, suffer a loss of ATP during inotropic challenge, and develop cardiomyopathy [13•,30,31]. Thus, PGC-1α and PPAR-α null mice have a strikingly common phenotype mimicking the energetic phenotype of the failing heart: decreased ATP synthesis by FAO and oxidative phosphorylation and increased dependence on glucose utilization. The consequence of this metabolic reprogramming is that hearts are unable to increase and sustain high workloads and they lose ATP. The fall of PGC-1α and PPAR-α in the failing heart likely contributes to the decreases in ATP synthesis and contractile reserve.

Genetic manipulation in the mouse has identified other players in the control of ATP production, which bear studying in the context of heart failure. For example, mouse hearts deficient in the mitochondrial transcription factor A (Tfam) gene develop cardiac dysfunction [32]. These hearts demonstrate an early switch in metabolism characterized by respiratory chain dysfunction and downregulation of genes encoding PPAR-α and its target genes despite increased mitochondrial mass and upregulation of genes important for glycolysis. Importantly, this metabolic remodeling took place prior to cardiac dysfunction, suggesting cause and consequence. Lending further support to the essential role of ATP production to the failing heart, ablating muscle LIM protein in mice led to regional decreases in mitochondrial density and decreases in PGC-1α [33]. The consequences of a decrease in energy reserve via CK for contractile performance have been studied using a variety of approaches, all of which have shown that loss of the energy reserve system leads to abnormal energetics with decreased rate of ATP synthesis via CK, increased free ADP (correlated with loss of sarcomeric mitochondrial CK isozyme [34]), and a lower $\Delta G_{\sim ATP}$. They also show decreased contractile reserve, suggesting a causal link between energy reserve and contractile reserve.

Rescuing the failing heart by regulating gene expression

In addition to using loss-of-function approaches to establish cause and effect, gain-of-function strategies are critically important in testing whether loss of metabolic reserve contributes to contractile dysfunction. This approach has proven to be technically difficult due to the robust nature of the promoter most widely used to overexpress genes encoding cardiac proteins in attempts to rescue the heart failure phenotype, α-myosin heavy chain. A good example of this is the unintended consequences of increasing PGC-1α expression in the mouse heart. Massive overexpression of PGC-1α led to mitochondrial proliferation to such an extent that the sarcomeres became displaced, leading to cardiomyopathy and heart failure [35]. However, short-term PGC-1α overexpression resulted in reversible

contractile dysfunction [36], suggesting causative links among PGC-1α expression, mitochondrial biogenesis, ATP synthesis, and contractile performance.

Restoring PPAR-α to hearts with reduced PPAR-α reversed the shift from lower FAO and increased glycolysis characteristic of the hypertrophied myocardium [28]. This suggests that the presumably compensatory increase in glucose utilization caused by eliminating PPAR-α is not sufficient to supply enough ATP to match ATP utilization during hemodynamic overload (ie, the metabolic reserve of the heart was not sufficient to support increased contractile demand). A recent test of this important hypothesis has been made using PPAR-α null mice overexpressing GLUT1, the constitutive insulin-independent glucose transporter in the heart [13•]. PPAR-α null mouse hearts demonstrated a threefold decrease in FAO and a threefold increase in carbohydrate used for ATP synthesis. Although these hearts could sustain baseline function, they were not able to sustain high workloads and, importantly, ATP fell. PPAR-α null mouse hearts had higher than normal oxygen consumption yet produced less ATP, demonstrating mitochondrial uncoupling. Importantly, increasing glucose uptake and utilization further by crossing the PPAR-α null mouse with the GLUT1 overexpresser rescued the PPAR-α phenotype: hearts were now able to sustain increased work without losing ATP. Oxygen consumption and ATP synthesis rates returned to near normal. These results have several important implications. First, they show that reduced ATP synthesis is responsible for the loss of ATP and contractile dysfunction during high workload in hearts without PPAR-α. Second, they show that glucose utilization, if sufficiently high, can support and sustain high workload. Third, they lend strong support for the concept that metabolic remodeling designed to increase ATP production is an effective strategy for treating heart failure.

Cr Progressively Falls in the Failing Heart

The basics

Cr accumulates in excitable tissues. In the myocardium, cytosolic Cr is 30 to 45 mM, of which 20 to 24 mM is phosphorylated by CK to PCr. It has been widely accepted that Cr is not made in excitable tissues but rather is supplied to muscles and brain via the bloodstream through the action of the electrogenic transporter belonging to a superfamily of Na^+,Cl^--coupled transporters of neurotransmitters, including dopamine and norepinephrine and amino acids including the α-amino acid glycine and the β-amino acid taurine. Creatine transporter (CrT) in the sarcolemma moves Cr against a large concentration gradient and is saturated at typical blood Cr levels. The primary sources for blood-borne Cr are diet (meat) and a two-step biosynthesis that occurs primarily in the kidney, liver, and pancreas. Figure 1 shows the steps for Cr biosynthesis and the structure of PCr. Cr, a β-amino acid, is made by the transfer of glycine onto the arginine side chain catalyzed by arginine: glycine amidinotransferase (AGAT) to form guanidinoacetate. The methyl group is transferred to the guanidino group via guanidinoacetate methyltransferase (GAMT). A spatiotemporal developmental study of the rat found that skeletal muscles have both AGAT and GAMT, blood vessels express only AGAT, and the heart does not have detectable levels of either AGAT or GAMT [37].

Cr accumulation in the heart is well explained by the amount of CrT on the sarcolemma. Using strategies designed to increase or decrease plasma Cr (feeding rats a diet either with supplemental Cr or with β-guanidinopropionic acid, a known competitive inhibitor of the CrT), it has been shown that Cr transport is determined by the amount of CrT protein on the plasma membrane; total CrT measured in heart homogenates was unchanged [38]. Cr deficiency syndrome due to mutations in AGAT, GAMT, and CrT led to severe neurologic pathology and epilepsy with no apparent muscle involvement [39].

The failing myocardium

It has been known since the early 1980s that Cr and thus PCr fall in the hypertrophied and failing myocardium. ^{31}P and ^{1}H NMR spectroscopy have been used by many laboratories to show decreased PCr/ATP, and more recently, decreased absolute levels of Cr, PCr, and ATP in the hypertrophied and failing human myocardium, in accord with the large number of large and small animal studies [4]. Because ATP also falls, note that the fall in the PCr/ATP ratio in the failing myocardium underestimates the fall in PCr.

The proximal mechanism

Although the original report showing that the amount of CrT was decreased in the failing heart in proportion to the decrease in total Cr was limited by the use of a nonspecific antibody, an antibody specific for CrT yielded the same result [40]. A recent report using a rat model of chronic heart failure showed that the 30% decrease in total Cr was well matched to the 26% decrease in the rate of Cr uptake [41]. These data suggest that the loss of Cr in the hypertrophied and failing myocardium is due to a decrease of CrT on the plasma membrane. Thus, the recent report that human and rat myocardium expresses AGAT and that expression is reversibly elevated in heart failure was unexpected [42]. Whether the heart is capable of local Cr synthesis, as suggested in this report, or whether it is localized in the vessel wall, as suggested by the developmental study described above, remains to be determined.

The long-term mechanism

Cr and CrT activity are regulated. The amount of CrT on the membrane is set by the amount of plasma Cr, with less CrT protein on the membrane when plasma Cr is high and vice versa [38], thereby regulating cytosolic Cr. Cr-induced inward current measured in *Xenopus* oocytes was increased by coexpression with mTOR and

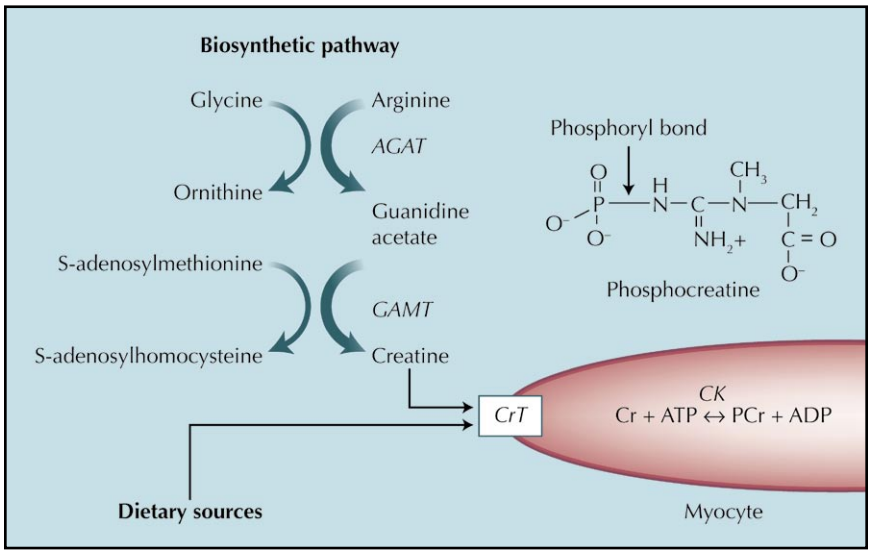

Figure 1. The primary sources for blood-borne creatine (Cr) are diet (meat) and a two-step biosynthesis that occurs primarily in the kidney, liver, and pancreas. Cr, a β-amino acid, is made by the transfer of glycine onto the arginine side chain catalyzed by arginine:glycine amidinotransferase (AGAT) to form guanidinoacetate. The methyl group is transferred to the guanidino group via guanidinoacetate methyltransferase (GAMT). Cr accumulates in muscles and brain through the action of the Cr transporter (CrT) in the sarcolemma. Cr is trapped by phosphorylation to phosphocreatine (PCr, see structure) by creatine kinase (CK). ADP—adenosine diphosphate; ATP—adenosine triphosphate; CrP—creatine phosphate.

with serum and glucocorticoid-inducible kinases (SGKs) 1 and 3 [43,44]. Importantly, rate (maximum velocity, V_{max}) was increased without changing affinity for Cr. The increases in the current with mTOR and SGK1 were not additive, suggesting a common mechanism of action. SGK1 is known to modify activity and abundance of many ion channels, such as Na,H-exchanger and other transporters such as for glucose. Cyclosporine A also changes the fraction of CrT on the membrane [45]. These results open a new line of research on the regulation of CrT and Cr in the heart.

Consequences of lower energy reserve and attempts to rescue the heart by increasing cytosolic Cr

Genetic modification in the mouse designed to manipulate the size of the myocardial Cr pool has expanded our understanding of the relationship between energy reserve via the CK system and contractile performance. Loss of function in the mouse was accomplished by replacing the Cr pool with its precursor guanidinoacetate by ablating GAMT in the pancreas and by taking care to ensure that Cr was not ingested by the mice (Fig. 1) [46•]. Hearts of these mice had undetectable levels of Cr and thus no PCr. As observed for hearts with low CK activity caused by a variety of maneuvers [4], hearts from GAMT null mice had normal contractile performance at baseline but reduced contractile reserve when challenged with the inotropic agent dobutamine. They also had increased susceptibility to ischemic injury. Thus, recapitulating the hypertrophied and failing heart, decreased energy reserve caused by decreasing the Cr pool led to decreased contractile reserve.

A gain-of-function strategy was used to test whether increasing CrT protein increased the cytosolic Cr pool in the mouse heart [47•]. The myocardial Cr pool increased on average twofold but, unexpectedly, the fraction of Cr that was phosphorylated was lower by approximately 50%, despite normal CK activity. As a consequence of the lower PCr to Cr ratio, cytosolic ADP increased and the driving force for adenosine triphosphatase reactions, $\Delta G_{\sim ATP}$, was lower. Importantly, these hearts developed left ventricular hypertrophy, dilatation, and dysfunction. This important experiment supports a causal relationship between decreased energy reserve and contractile dysfunction. It also demonstrates that it is possible to manipulate cytosolic Cr, suggesting a new experimental approach to the study of the energetics of the heart. Note that the consequences of decreasing PCr/Cr on contractile performance are more profound than decreasing CK activity alone. Decreasing CK activity alone using genetic modification led to little if any hypertrophy [34,48].

A different gain-of-function strategy is to use recovery from heart failure models to determine whether Cr returns toward control and whether this correlates with improved contractile function. Such models are rare, but recently these measurements were made in myocardium obtained during recovery from pacing-induced heart failure in the dog. Cr, as well as CK activity, and contractile performance all returned toward normal [49]. Although this positive result is correlative and not proof, a negative result would have argued against the importance of energy reserve in contractile performance.

Consequences of Changes in PCr/Cr on Purine Metabolism

The observation that increased free Cr and decreased PCr/Cr leads to contractile dysfunction, hypertrophy, and dilatation [47] raises the question of whether the loss of Cr in the failing heart is compensatory [14] or deleterious. The notion that loss of Cr could be compensatory may seem counterintuitive. Loss of Cr reduces the velocity of the CK reaction and thus reduces the primary energy buffer in the heart at a time when overall energy supply is compromised. However, loss of Cr also minimizes the increase in free ADP and thus maintains a near normal $\Delta G_{\sim ATP}$. This is a direct consequence of the

Table 2. Equilibrium expressions

For the CK reaction
$PCr + ADP + H^+ \leftrightarrow Cr + ATP$, is $K_{eq} = [ATP]\,[Cr] / [ADP]\,[PCr]\,[H^+]$. Rearranging, $[ADP] = [ATP]\,[Cr] / K_{eq}\,[PCr]\,[H^+]$. Typical values for ADP in the healthy heart are 20 to 50 μM.
For the adenylate kinase reaction
$2ADP \leftrightarrow ATP + AMP$, is $K_{eq} = [ATP]\,[AMP] / [ADP]^2$. Rearranging, $[AMP] = [ADP]^2 / [ATP]\,K_{eq}$. Typical values for AMP in the healthy heart are 0.2 to 0.7 μM.

ADP—adenosine diphosphate; AMP—adenosine monophosphate; ATP—adenosine triphosphate; CK—creatine kinase; Cr—creatine; K_{eq}—equilibrium constant; PCr—phosphocreatine.

near equilibrium of the CK reaction: $[PCr]\,[ADP]\,[H^+] = [ATP]\,[Cr_{free}]\,K_{eq}$ and $[PCr] / [Cr] \propto [ATP] / [ADP]$. To satisfy these relationships for unchanged total Cr (sum of PCr and free Cr) and pH, free Cr and ADP must both increase when PCr decreases; and PCr/Cr_{free} and ATP/ADP both fall. However, if Cr_{free} and PCr both decrease, then ADP and ATP/ADP would remain close to normal. Maintaining low cytosolic ADP also keeps free AMP low. This is quantitatively important because cytosolic AMP calculated using the adenylate kinase equilibrium expression increases with the square of ADP.

It is worthwhile discussing the likely sequence of events that occurs as the acutely stressed heart transitions to the chronically stressed severely failing heart. In response to an acute increase in stress, PCr decreases, initially leading to increases in free Cr (and also Pi). ADP calculated from the CK equilibrium expression (Table 2) and AMP calculated from the adenylate kinase equilibrium expression (Table 2) also increase. The immediate consequences include 1) a decrease in CK reaction velocity, the major energy transferase; 2) a decrease in the phosphorylation ratio [ATP]/[ADP][Pi] and thus in $\Delta G_{\sim ATP}$, the driving force for myosin and ion pumps; 3) activation of cytosolic 5'-NT, leading to a loss of purines; and 4) activation of adenosine monophosphate–activated protein kinase (AMPK), a low-on-fuel sensor, leading to rapid reprogramming of metabolic pathways away from ATP-consuming reactions and toward ATP-sparing reactions. With time, loss of Cr reverses (2), (3), and (4); (1) remains. Elevated ADP falls and, despite a fall in ATP, ATP/ADP and $\Delta G_{\sim ATP}$ become more normal. As ADP falls, AMP also falls, reducing activation of 5'-NT and AMPK. Table 1 shows ATP, ADP, and AMP for an example of hypertrophied heart where ADP and AMP increase and four examples, including the human myocardium, where ATP falls but ADP and AMP are either unchanged or even lower than for control myocardium.

This analysis shows that the timing and magnitude of any change in PCr/Cr is critically important for understanding the metabolic remodeling that occurs during hypertrophy and failure, and ultimately the fate of ATP. It also suggests that whether loss of the ATP pool is attenuated or exacerbated depends on the balance between 5'-NT and AMPK activities. Surprisingly little is known about the time course of the activation/deactivation of AMPK in hypertrophy progressing to failure. Experiments carefully defining the time course of changes in cytosolic AMP (determined by NMR), and the magnitude of AMP-dependent and AMP-independent activation of AMPK and its targets, all remain to be made before we can assign a role of AMPK in the failing heart. One obvious question is: Does AMPK activity fall in the severely failing myocardium, thereby contributing to the downward spiral to contractile failure? Similarly, nothing is known about the kinetics of 5'-NT in the failing heart, despite its importance in preserving ATP pool. This is another important area for future studies.

Conclusions

New studies using gain and loss of CrT function, recognizing purine nucleotides as signals for metabolic remodeling, and new results defining transcriptional control of ATP synthesis pathways all provide strong support for a causal relationship between energy reserve and contractile reserve. They also contribute to a growing body of evidence explaining why clinical heart failure trials of energy-costly treatments increase mortality and lend support to new approaches that treat heart failure by reducing energy demand and the cost of contraction.

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