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The failing heart: an engine operating on "bad fuel"

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Abstract

The failing heart is energetically starved, where inefficient adenosine triphosphate (ATP) energy conversion and transfer is unable to match the high workload of the heart. Evidence emerging from the last decades of research suggests that such reductions in ATP cannot solely explain the onset of contractile dysfunction in human heart failure. Here, we propose that the "by-product" adenosine diphosphate (ADP) may be a key driver underlying impaired cardiac function, as minute elevations of intracellular ADP concentration augments the diastolic calcium (Ca^{2+}) level and associates with slowing of myocardial relaxation with limited ventricular compliance due to high diastolic pressure. Drug therapies should aim to lower use of ATP-consuming systems and to improve ADP conversion to ATP. ■ *Heart Metab*. 2016;71:37-39

Keywords: ADP elevation; cardiac contractility and energetics; cardiomyocyte contractile reserve; diastolic dysfunction

Introduction

It is well established that the failing heart is an "engine out of fuel," where limited energetic supply is not able to match the heart's mechanical demands.[1] In vivo global analysis of the myocardial energy metabolism by phosphorus nuclear magnetic resonance (^{31}P-NMR) showed a reduced phosphocreatine (PCr)/adenosine triphosphate (ATP) ratio—an indicator of energy deprivation—in various conditions of human heart failure (HF), including aortic valve disease, hypertrophic cardiomyopathy (HCM), and ischemic dilated cardiomyopathy (DCM).[1] Moreover, the decrease in PCr/ATP ratio correlates with disease severity in end-stage failing DCM patients.[2] Studies in animal models of HF also provided support for a compromised myocardial energy metabolism. These studies showed that the smaller PCr/ATP ratio is largely attributed to a more severe reduction in the pool of PCr (up to 50%) over ATP (≤25%),[3-5] which is confirmed by the equilibrium reaction of creatine kinase (CK).[6] CK regenerates the ATP pool at the myofilaments at the expense of PCr, preventing an accumulation of cytosolic adenosine diphosphate (ADP).[7] CK isoforms are reduced by approximately 30% in HF, and experimental blockade of cardiac CK or a decrease in [PCr] associates with contractile dysfunction in rats in response to inotropic stimulation.[4,8] Although [ATP] may decrease by 25%, the absolute ATP levels may never run sufficiently low to impair cardiac function. For instance, studies have shown that the reduction in [ATP] is not rate limiting for

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Abbreviations

ADP: adenosine diphosphate; **ATP:** adenosine triphosphate; **Ca^{2+}:** calcium; **CK:** creatine kinase; **HF:** heart failure; **PCr:** phosphocreatine; **^{31}P-NMR:** phosphorous nuclear magnetic resonance; **SERCA:** sarcoplasmic reticulum Ca^{2+}-ATPase

cardiomyocyte relaxation at rest and under stressful conditions. In HF, ATP decreases maximally from 10 to 7 mM;[5,9] however, as little as 0.1 mM ATP is sufficient for cardiac relaxation.[10] Additionally, estimates of the thermodynamic limits of the sarcoplasmic reticulum calcium (Ca^{2+})-ATPase (SERCA) suggest that decreases in the free energy released from ATP hydrolysis (ΔG_{ATP}) in HF precede any large drops in [ATP].[6] This is corroborated by findings in animal models of HF, where ATP levels measured by ^{31}P-NMR are practically unchanged, whereas substantial diastolic abnormalities are present.[8,9,11] These findings are consistent with the notion that ATP reduction cannot explain the onset of cardiac dysfunction.

A role for ADP in cardiac dysfunction

Recent data from our group and others suggest that the "by-product" ADP may be a key driver of impaired cardiac function.[8,9,11,12] Myocardial ADP levels in animal models are reported in the range of 10 to 50 µM in healthy animals and in the range of 40 to 140 µM in animals with disease, and the ADP level increases further during stress or vigorous exercise.[9] Selectively increasing ADP levels without altering cytosolic ATP levels increases left ventricle end-diastolic pressure and limits myocardial relaxation in rats.[8,9,11] Pathological ADP elevation may drive the myocardium into a diastolic HF phenotype by increasing residual actomyosin interactions at diastolic Ca^{2+} levels.[8] In a recent study, we showed that pathological ADP levels, in concert with diastolic [Ca^{2+}], lead to high myocardial stiffness and limited relaxation of the myocardium, associated with reduced ventricular compliance.[8] The ADP-mediated enhancement of myofilament Ca^{2+} activation was associated with increased diastolic [Ca^{2+}].[8] The high diastolic Ca^{2+} level probably results from Ca^{2+} buffering at the myofilaments (Ca^{2+} is "trapped to sticky myofilaments") and/or decreases in the free energy released from ATP hydrolysis (ΔG_{ATP}) due to an extremely high ADP level that exacerbates diastolic Ca^{2+} overload by reducing ΔG_{ATP} required for SERCA activity. Worth mentioning is the recently established link between increased myofilament Ca^{2+} sensitivity as a proarrhythmic factor.[13,14] This finding indicates that a high myofilament Ca^{2+} level is sufficient to "trap" more Ca^{2+} at the myofilaments, which in turn affects the electrical activity of the heart.

Apart from the ADP-mediated increase in myofilament Ca^{2+} sensitivity, high myofilament sensitivity to Ca^{2+} has been related to a reduction in troponin I phosphorylation due to desensitization and downregulation of the β-adrenergic receptor pathway during disease progression. High myofilament Ca^{2+} sensitivity[12,15,16] and myocardial energy deprivation are commonly seen in human HCM and end-stage HF[1] and may be sufficient to increase diastolic Ca^{2+} level. In the human failing heart, high myofilament Ca^{2+} activation coincides with high myosin-ATPase consumption at the myofilaments.[16,17] As a consequence, the continuous high energetic demand may elevate cytosolic ADP and Ca^{2+}, leading to a vicious cycle.

Basic studies on ADP-mediated cardiac effects may provide insight into how energy-sparing therapies exert a beneficial effect in human end-stage HF. For instance, the clinically approved trimetazidine[18] has been shown to improve symptoms and left ventricle function in HF patients, and this was associated with improved PCr/ATP ratio.[19] Using an animal model of chronic hypoxia, Wei and coworkers[20] demonstrated that trimetazidine prevented elevation of diastolic Ca^{2+} by promoting the metabolic shift from lipid to glucose oxidation. Although lipid oxidation provides highest energetic yield per molecule of substrate when compared with glucose, it is less efficient with regard to ATP synthesis per molecule of oxygen consumed.[21] Overall, these studies indicate that drug therapies that induce a metabolic shift may improve cardiac efficiency and optimize the balance between ATP and ADP and thereby improve diastolic performance of the heart.

Conclusion

In conclusion, rather than an "engine out of fuel," the heart may actually resemble an "engine running on bad fuel," where ADP elevation impairs diastolic performance. ADP elevates myofilament Ca^{2+} sensitivity and stiffness and thereby compromises myocardial relaxation and reduces ventricular compliance. These

ADP-mediated defects may be explained by the putative role of ADP to "trap" more Ca^{2+} at the myofilaments, but also by its potential effects on SERCA activity and on other ion pumps, due to alterations in ΔG_{ATP} requirements. Drug therapies should aim to lower use of ATP-consuming systems, in concert with improving myocardial metabolism efficiency. ■

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