

Understanding the metabolic phenotype of heart disease

Rong Tian

NMR Laboratory for Physiological Chemistry, Division of Cardiovascular Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence: Dr Rong Tian, 221 Longwood Ave, Room 252, Boston, MA 02115, USA.
Tel: +1 617 732 6729; fax: +1 617 732 6990; e-mail: rtian@rics.bwh.harvard.edu

Abstract

Substantial changes in cardiac energy metabolism have been observed in a variety of heart diseases. Understanding the functional role of these changes is critical for developing the concept of metabolic intervention for heart disease. The use of genetically engineered mice in recent studies has made it possible to alter cardiac metabolism independently of secondary influence by disease and, thus, allow the causal role of metabolic remodeling in the pathogenesis and progression of heart disease – in particular, heart failure – to be tested. Results from these studies also shed light on the potential tactics for targeting energy metabolism in heart failure.

■ *Heart Metab.* 2006;32:5–8.

Keywords: energetics, heart failure, transgenic mice, fatty acid oxidation, glucose metabolism, metabolic therapy

Introduction

Cardiovascular disease is the leading cause of death in developed countries. Improved survival after an acute ischemic episode in recent years has, paradoxically, resulted in an increased diagnosis of heart failure in patients post-myocardial infarction. Despite the success of neurohormonal inhibition, many patients with heart failure still experience progression of their disease, and heart failure remains the number one killer in the USA [1]. The recent failure of trials of treatment with endothelin-1 receptor blockers and cytokine antibodies has fueled the search for alternative options in chronic therapy in order to achieve further improvement in the limited prognosis of patients with heart failure.

Targeting energy metabolism for heart failure therapy is worth considering, not only because the heart is an organ with high energy consumption, but also because failing hearts are energy-deprived. Studies in animal models and in patients have shown a significant decrease in myocardial content of the energy reserve compound, phosphocreatine, which

can rapidly regenerate ATP in case of abrupt increases in energy demand [2–4], followed by the eventual depletion of myocardial ATP content at the end-stage of heart failure [4]. Long-term follow-up studies in patients with idiopathic dilated cardiomyopathy have demonstrated that decreased phosphocreatine is an independent predictor of mortality [3], suggesting that impaired myocardial energetics contributes significantly to the progression of heart failure. This notion is further supported by consistent observations in clinical trials in patients with heart failure showing that energy-costly treatments such as positive inotropic agents (β -receptor mimetic drugs, phosphodiesterase inhibitors) increase mortality, whereas energy-sparing treatments such as angiotensin-converting enzyme inhibitors, angiotensin II blockers or β -receptor blockers reduce mortality. These observations collectively suggest that myocardial energy metabolism plays an important part in the progression of heart failure. Thus a better understanding of the metabolic phenotype may offer new opportunities to mend the failing heart.

Energy metabolism in animal models of heart failure

An important change in energy metabolism observed in animal models of cardiac hypertrophy and failure is a shift in the preference of substrates for energy generation. Although the heart is able to utilize a variety of substrates, preference in substrate utilization has been documented and it can change in response to altered substrate availability or altered regulation of metabolic pathways. As illustrated in *Figure 1*, substrate preference of the heart changes under several physiological and pathological situations. For example, glucose and lactate (collectively referred to as carbohydrates) are the primary carbon substrates for fetal hearts, whereas fatty acids become the predominant fuel in adult hearts, supporting more than 67% of the total ATP synthesized [5–7]. In contrast, hypertrophied and failing hearts demonstrate increased reliance on glucose as a fuel while decreasing its fatty acid utilization, an apparent recurrence of the fetal metabolic profile [8–10].

Studies using animal models of heart failure show that the shift of substrate preference is associated with downregulation of peroxisome proliferator-activated receptor α (PPAR α), a transcription factor controlling the expression of key enzymes for fatty acid oxidation [11,12]. Subsequent studies using transgenic mouse hearts deficient in PPAR α have demonstrated a similar shift in substrate selection, supporting a causal role of PPAR α in altered substrate utilization in cardiac hypertrophy and failure [13]. Furthermore, impaired myocardial energetics also leads to activation of AMP-activated protein kinase, a cellular energy sensor [14]. Increased AMP-activated protein kinase activity promotes glucose uptake and glycolysis and thus enhances the shift of substrate utilization toward glucose [14,15].

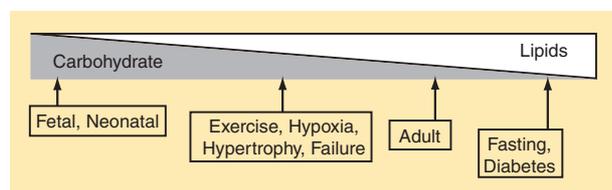


Figure 1. Substrate preference of the heart. Although the heart is able to use several substrates, the contribution of each class of substrate to ATP synthesis varies depending on the developmental stage and the (patho)physiological conditions. Fatty acids are the predominant fuel for the adult heart, whereas carbohydrates are the preferred substrates for fetal hearts. Furthermore, the adult heart can shift its substrate utilization profile in response to altered substrate availability such as during fasting and exercise or in response to altered regulatory mechanisms such as in heart failure.

Functional consequences of the altered substrate metabolism

Is the shift in substrate preference beneficial or detrimental, or of no functional significance for the heart? To address such a question, it is necessary to alter substrate preference by a mechanism that is independent of heart failure. This is made possible by studying transgenic mouse hearts in which substrate preference has been altered by genetic manipulations. In mouse hearts deficient in PPAR α , increased glucose utilization has been observed and it was sufficient to compensate for the decrease in fatty acid oxidation at baseline workload [13,16,17]. However, these hearts showed impaired energetics and contractile function when challenged with high workloads [17,18]. In contrast, myocardial glucose utilization increased by overexpression of an insulin-independent glucose transporter, GLUT 1, was not associated with an adverse phenotype [17,19], and the overexpression of GLUT 1 was able to correct the energetic and contractile defects in PPAR α -deficient hearts [17]. Analysis of substrate oxidation profiles using a carbon-13 nuclear magnetic resonance technique showed that the compensatory increases in glucose oxidation in hearts that were deficient in PPAR α at baseline had exhausted the reserve for a further increase at high workload, thus depleting the metabolic reserve and consequently the contractile reserve of the heart. Subsequent overexpression of GLUT 1 restored the ability to achieve a further increase in the contribution of glucose to oxidative metabolism [17].

An important lesson learned from these studies is that increased reliance on glucose *per se* is not harmful for the heart. However, the intrinsic adaptation to impaired fatty acid oxidation through an increase in glucose utilization is limited in the adult heart and comes with the cost of depleting the functional reserve of the heart. Such a scenario is clearly unfavorable for failing hearts that constantly struggle to accomplish their workload. This is even more problematic when one considers that heart failure is often associated with insulin insensitivity [20,21], thus further compromising the glucose utilization of the heart. Therefore, altered substrate metabolism, which is part of the myocardial remodeling process after an initial pathological event such as myocardial infarction or pressure or volume overload of the heart, may ultimately fail to satisfy the high energy demand of the heart coping with mechanical overload caused by the underlying diseases. The mismatch of energy supply and demand thus drives a vicious cycle that contributes to the ultimate failure of the heart.

Developing therapeutic concepts based on phenotyping

How do we restore the supply of energy to the overloaded heart? Several hypotheses derived from the metabolic phenotype discussed above have been tested (Figure 2). One obvious approach is to restore substrate preference by reactivating PPAR α . Although systemic benefits of the lipid-decreasing and anti-inflammatory effects of PPAR α agonists have been noted in several studies [22,23], increased myocardial fatty acid oxidation that results from reactivation of PPAR α is apparently detrimental to hypertrophied hearts [24,25]. Decreased fatty acid oxidation is probably beneficial for hearts with compromised perfusion, because of its oxygen-sparing effect [26]. Furthermore, a recent study showed that decreased PPAR α activity in ischemic cardiomyopathy protected the heart from lipotoxicity by shifting the fuel preference away from fatty acids [25]. This is consistent with earlier observations that partial inhibition of fatty acid utilization is cardioprotective [27].

Therefore, strategies for improving the energy supply of the failing heart without increasing fatty acid utilization would be highly desirable. The rescue of PPAR α -deficient hearts by overexpressing GLUT 1 suggests that improving myocardial glucose utilization can be an effective approach to increasing the capacity of the failing heart for ATP synthesis. Supportive of this concept, mouse hearts overexpressing GLUT 1 showed increased tolerance to chronic pressure overload, with delayed progression to heart failure and reduced mortality [19]. Similarly, in a large animal model of heart failure caused by dilated cardiomyopathy, enhancement of myocardial glucose uptake and utilization by recombinant glucagon-like peptide-1 improved left ventricular performance [28].

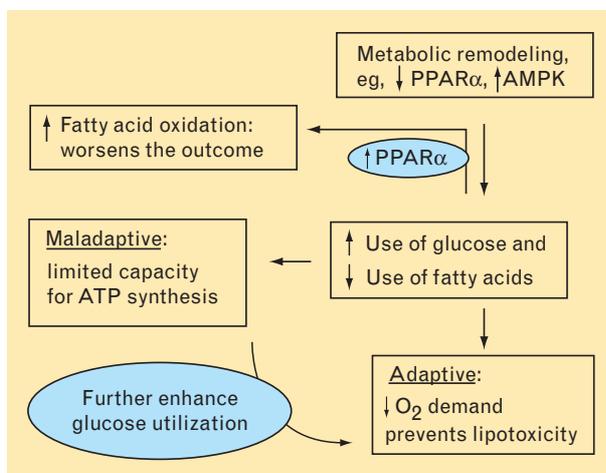


Figure 2. Working hypotheses regarding the adaptive and maladaptive aspects of the shift in substrate preference in heart failure, and proposed strategies for sustaining energy homeostasis.

Summary

The use of animal models as “proofs-of-concept” in understanding of the metabolic phenotype has generated valuable evidence for the therapeutic potential of manipulating cardiac metabolism. We anticipate that the concept will be further tested by clinical studies and eventually in large-scale clinical trials; however, in addition, basic research leading to the development of novel compounds that have high efficacy in myocardial metabolism and few side effects is urgently needed to advance the practice of metabolic therapy. ■

REFERENCES

1. American Heart Association. *Congestive Heart Failure Statistics*. New York: American Heart Association; 2005.
2. Neubauer S. High-energy phosphate metabolism in normal, hypertrophied and failing human myocardium. *Heart Fail Rev*. 1999;4:269–280.
3. 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;96:2190–2196.
4. Ingwall JS, Weiss RG. Is the failing heart energy starved? On using chemical energy to support cardiac function. *Circ Res*. 2004;95:135–145.
5. Fisher DJ. Oxygenation and metabolism in the developing heart. *Semin Perinatol*. 1984;8:217–225.
6. Lopaschuk GD, Belke DD, Gamble J, Itoi T, Schonekess BO. Regulation of fatty acid oxidation in the mammalian heart in health and disease. *Biochim Biophys Acta*. 1994;1213:263–276.
7. Lopaschuk GD, Spafford MA, Marsh DR. Glycolysis is predominant source of myocardial ATP production immediately after birth. *Am J Physiol Heart Circ Physiol*. 1991;261:H1698–H1705.
8. Barger PM, Kelly DP. Fatty acid utilization in the hypertrophied and failing heart: molecular regulatory mechanisms. *Am J Med Sci*. 1999;318:36–42.
9. Sambandam N, Lopaschuk GD, Brownsey RW, Allard MF. Energy metabolism in the hypertrophied heart. *Heart Fail Rev*. 2002;7:161–173.
10. Tian R. Transcriptional regulation of energy substrate metabolism in normal and hypertrophied heart. *Curr Hypertens Rep*. 2003;5:454–458.
11. 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;94:2837–2842.
12. Lehman JJ, Kelly DP. Gene regulatory mechanisms governing energy metabolism during cardiac hypertrophic growth. *Heart Fail Rev*. 2002;7:175–185.
13. Campbell FM, Kozak R, Wagner A, et al. A role for peroxisome proliferator-activated receptor alpha (PPARalpha) in the control of cardiac malonyl-CoA levels: reduced fatty acid oxidation rates and increased glucose oxidation rates in the hearts of mice lacking PPARalpha are associated with higher concentrations of malonyl-CoA and reduced expression of malonyl-CoA decarboxylase. *J Biol Chem*. 2002;277:4098–4103.
14. Tian R, Musi N, D’Agostino J, Hirshman MF, Goodyear LJ. Increased adenosine monophosphate-activated protein kinase activity in rat hearts with pressure-overload hypertrophy. *Circulation*. 2001;104:1664–1669.
15. Nascimben L, Ingwall JS, Lorell BH, et al. Mechanisms for increased glycolysis in the hypertrophied rat heart. *Hypertension*. 2004;44:662–667.
16. Lopaschuk GD, Kozak R, Dyck JRB, et al. The hearts of PPAR α null mice exhibit reduced fatty acid oxidation rates and altered response to loading. *Circulation*. 2000;102:II-8.
17. Luptak I, Balschi JA, Xing Y, Leone TC, Kelly DP, Tian R. Decreased contractile and metabolic reserve in PPAR α -null hearts can be rescued by increasing glucose transport and utilization. *Circulation*. 2005;112:2339–2346.

18. Loichot C, Jesel L, Tesse A, et al. Deletion of peroxisome proliferator-activated receptor- α induces an alteration of cardiac functions. *Am J Physiol Heart Circ Physiol*. 2006; 291:H161–H166.
19. 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;106:2125–2131.
20. Shah A, Shannon RP. Insulin resistance in dilated cardiomyopathy. *Rev Cardiovasc Med*. 2003;4 (suppl 6):S50–S57.
21. Witteles RM, Tang WH, Jamali AH, Chu JW, Reaven GM, Fowler MB. Insulin resistance in idiopathic dilated cardiomyopathy: a possible etiologic link. *J Am Coll Cardiol*. 2004;44:78–81.
22. Delerive P, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors in inflammation control. *J Endocrinol*. 2001;169:453–459.
23. Yue TL, Bao W, Jucker BM, et al. Activation of peroxisome proliferator-activated receptor- α protects the heart from ischemia/reperfusion injury. *Circulation*. 2003;108:2393–2399.
24. Young ME, Laws FA, Goodwin GW, Taegtmeyer H. Reactivation of peroxisome proliferator-activated receptor α is associated with contractile dysfunction in hypertrophied rat heart. *J Biol Chem*. 2001;276:44390–44395.
25. Dewald O, Sharma S, Adroge J, et al. Downregulation of peroxisome proliferator-activated receptor- α gene expression in a mouse model of ischemic cardiomyopathy is dependent on reactive oxygen species and prevents lipotoxicity. *Circulation*. 2005;112:407–415.
26. Essop MF, Opie LH. Metabolic therapy for heart failure. *Eur Heart J*. 2004;25:1765–1768.
27. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev*. 2005;85:1093–1129.
28. 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; 110:955–961.