EDITORIAL COMMENT

Metabolism—The Lost Child of Cardiology*

Heinrich Taegtmeyer, MD, DPHIL, FACC
Houston, Texas

This issue of the *Journal* features an experimental study on the triad of hypertrophy, ischemia and reperfusion (1). The results offer the promise that a targeted pharmacologic intervention may improve metabolism and function of the postischemic heart. Although this is not a completely novel concept, the link between energy substrate metabolism and function of the reperfused heart is not always appreciated. The importance of these findings is therefore better appreciated when viewed in a broader context.

Although metabolism of fuels provides the heart with the energy required for contraction, a discussion of myocardial energy substrate metabolism has all but disappeared from textbooks of cardiology. In the 1970s, when I was a cardiology fellow at the Peter Bent Brigham Hospital in Boston, case presentations used to end with the phrase "coronary sinus lactate levels are pending," an oblique reference to the hypothesis that small-vessel coronary artery disease can be detected by a rise in sinus lactate levels due to a shift from aerobic to anaerobic glucose metabolism (2). The clinical usefulness of these measurements, however, never materialized. Over the years, metabolism became a lost child of cardiology.

Almost concurrently, the study of cardiac metabolism evolved into an attractive discipline to biochemists and physiologists who saw in the heart an ideal model system for the examination of metabolism and function of an intact organ (quite literally, a conveniently packaged bag of enzymes). The understanding of metabolic regulation at a cellular level advanced rapidly in the 1960s and 1970s (3). By using a strictly reductionist approach, a system of enormous complexity was unraveled. Indeed, a general approach at that time included reducing metabolism and function to molecular science, identifying and purifying the relevant molecules and finding activators or inhibitors which they bound.

Two major advances in technology brought the intact heart back into focus: In the 1980s, nuclear magnetic resonance spectroscopy revitalized the field of bioenergetics

(4,5), and positron emission tomography delivered the promise of regional assessment of metabolic activity (6). However, the results obtained with these new techniques were largely predictable. Despite the undisputed clinical usefulness, few truly new paradigms emerged from this work.

Energy transfer in the heart. Because the whole is greater than the sum of its parts, an understanding of the control and regulation of energy substrate metabolism remains an important field of research. Energy is the capacity to do work. The release of energy from fuels is achieved by the step-by-step processes of enzymatically controlled fuel metabolism and mitochondrial oxidative phosphorylation, in which the energy content of fuels is transferred to the high energy phosphate bonds of adenosine triphosphate (ATP). Metabolism and contraction of the heart are therefore inseparably linked, which means that ATP must be continuously remade by the dynamo of metabolism. The high turnover rate of ATP means that energy passes through it for all but a fleeting moment. As a result, there is also no correlation between ATP content and ATP turnover in the normal or reperfused heart (5,7).

The first law of thermodynamics is that energy cannot be created or destroyed by any process. It can only be converted from one form into another form. In the heart, like in all cells of the body, efficient energy transfer arises from the interaction of a series of moiety conserved cycles (3). The cell's key task is to match rates of ATP production to rates of ATP consumption; this is made difficult because the primary site of ATP production (mitochondria) is separate from the primary site of ATP utilization (sarcomeres). The mechanism by which the precise matching between ATP production and utilization occurs is presently unknown. We can say with certainty, however, that "all is in flux."

Which fuel? The heart is a metabolic omnivore and is able to meet its need for energy from the oxidation of fatty acids, glucose, lactate and other oxidizable substrates. Studies in the isolated working rat heart, where substrate concentrations can be precisely controlled, have shown that fatty acids inhibit glucose oxidation to a greater extent than glucose inhibits fatty acid oxidation, and that the heart functions best when it oxidizes the two substrates simultaneously (8). This principle is appropriately illustrated by the development of hypertrophy and failure in tissue-specific knock-out models of enzymes of glucose (9) or fatty acid metabolism (10) and by the recently described lipotoxic heart disease in obese rats (11).

Metabolism of glucose to lactate is the main source of energy for the ischemic heart. When lack of oxygen induces a shift from aerobic to anaerobic metabolism, there is rapid stimulation of glucose uptake, glycogenolysis, glycolytic flux and ATP hydrolysis (12). Such an increase in glycolysis is also observed in hypertrophied hearts perfused with low concentrations of fatty acids (13) and is consistent with an

increase in glycolytic enzyme activities (14). Despite this increase in glycolysis, rates of glucose oxidation are decreased in hypertrophied as compared with normal hearts, resulting in a greater amount of pyruvate converted to lactate and in an uncoupling of glycolysis from glucose oxidation (13). Hydrolysis of two ATPs for each molecule of glucose metabolized to lactate (and not oxidized) produces two hydrogen ions (H^+) (15). Acidosis is implicated in contractile dysfunction of the heart (16,17). The excess production of H^+ may contribute to impaired function of the failing heart.

In the isolated working rat heart, brief periods of ischemia (up to 20 min) result in a dissociation between the early return of oxidative metabolism and a delayed return of contractile function (18). Although it has long been appreciated that fatty acids decrease cardiac efficiency (19,20), the main reason for contractile dysfunction is thought to be the delayed clearance of protons from the cell. One hypothesis is that increased glucose oxidation during reperfusion reduces the proton load and improves functional recovery (21,22).

Metabolic adaptations. Ischemia followed by reperfusion, on the one hand, and hypertrophy on the other, represent two separate but interrelated processes. The former stimulates reactions realized instantly, which are immediately available, whereas the latter produces more gradually evolving reactions, which are of long-term adaptive benefit. *Immediate adaptation* involves reactions for which the organ has ready-made mechanisms in place. They include the sudden increase in glycogenolysis and glucose oxidation in response to a sudden increase in the work load of the heart (23) and the switching from aerobic to anaerobic metabolism in response to a lack of oxygen, with a resulting accumulation of metabolic products. *Long-term adaptation* involves reactions for which the heart possesses the genomic prerequisites that allow the gradual evolution of adaptive mechanisms in the face of repeated or persistent environmental stimuli (24). For example, the adaptive responses to training enable the organism to perform levels of physical work not possible in the inherited untrained state. Likewise, the heart's adaptation to pressure overload prevents the adaptive capacity of the organism from being exhausted when environmental requirements are excessive or sustained (25). Part of this adaptive process is a switch from fatty acids to glucose as the main fuel for respiration, which would be a beneficial adaptive response (26,27). This adaptive metabolic response can precede any trophic changes (14) and may, in its early phase, result in improved efficiency of the heart.

Within this conceptual framework, it is easy to propose that metabolic activity links gene expression with heart function. Although the exact mechanisms of this link are not yet completely understood, a growing body of evidence indicates that the overall metabolic adaptations are brought about, at least in part, by adjustments in the rate of transcription of genes encoding proteins involved in energy substrate metabolism (28).

Targeting metabolism to improve efficiency. As the study by Wambolt et al. (1) shows, adaptation turns into maladaptation when an acute stress (ischemia and reperfusion) is superimposed on an adaptive response. The excess production of protons from enhanced glycolytic metabolism results in contractile dysfunction by mechanisms that are not completely understood. The deleterious effects on contraction that accompany enhanced glycolytic flux are prevented by the addition of a drug that promotes pyruvate oxidation, thereby reducing its conversion to lactate. Dichloroacetate, like ranolazine, and probably also L-carnitine, activate the pyruvate dehydrogenase (PDH) complex by inhibiting pyruvate dehydrogenase kinase (PDK) (29–32). Restoring carbon flux through PDH may be all that is necessary to improve postischemic contractile function (30). Dichloroacetate, although not a specific inhibitor of PDK (33), is one member of the growing group of drugs that target metabolism and metabolic efficiency in the normal, stressed, ischemic or postischemic heart (34,35). These drugs include propionyl L-carnitine (36), etomoxir (34), trimetazidine (37) and troglitazone (38). Although acting at different sites, all of them cause a pharmacologic switch from fatty acid to glucose oxidation. Although it may have been possible to predict the results of the present study, the work exposes an important principle: Metabolic adaptation and maladaptation of the heart are potential targets for pharmacotherapy. Glucose is good for the heart as long as the heart can oxidize glucose. In the future, this concept of intervening in altered cellular metabolism may become as important as intervening in altered blood supply through revascularization of the ischemic heart.

However, this is not yet the time to rush to the pharmacy. First, the observations were made in isolated perfused hearts, and the systemic and toxic effects of the drugs may be considerable. Second, dichloroacetate has been advocated as a drug for the treatment of lactic acidosis (39) and congestive heart failure (40). Yet, the effect of the drug is only temporary and not sustained. Third, we still know far too little about the inner workings of the heart. For example, in the study by Wambolt et al. (1), proton production was only calculated, and neither pH nor the redox state nor lactate production was directly measured (refer to my earlier comment on "lactate levels pending"). Because the control of glycolytic flux is most likely distributed over several enzymes in the pathway (41), and because enzymes may be regulated by several allosteric and covalent regulators, we still do not precisely know the mechanism by which glycolysis and glucose oxidation are "out of step" in the hypertrophied and reperfused heart. As Wambolt et al. discuss, direct measurement of changes in intracellular pH, Na^+ and Ca^{2+} concentration would be necessary to support the conclusions. Many more small steps are needed to master metabolism and to understand the interplay between gene regulation and metabolic regulation of the heart. One example is

the mitochondrial involvement in apoptosis (42,43), and the metabolic regulation of this process (24). The message is clear: Heart muscle has its own fuel economy that responds to a wide spectrum of changes in its environment. More importantly, drugs that improve ischemia tolerance, or drugs that slow down programmed cell death, offer the promise of targeted metabolic interventions, either in the short term (by changing enzyme activities) or in the long term (by alternating gene expression), in the heart. We may be on our way to reclaim cardiology's lost child.

Acknowledgments

Reprint requests and correspondence: Dr. Heinrich Taegtmeyer, Division of Cardiology, University of Texas Houston Medical School, 6431 Fannin, Room 1.246, Houston, Texas 77030. E-mail: Heinrich.Taegtmeyer@uth.tmc.edu.

REFERENCES

1. Wambolt RB, Lopaschuk GD, Brownsey RW, Allard MF. Dichloroacetate improves postischemic function of hypertrophied rat hearts. J Am Coll Cardiol 2000;36:1378–85.
2. Gorlin R, Brachfeld N, Messer J, Turner J. Physiologic and biochemical aspects of disordered coronary circulation. Ann Intern Med 1959;51:698–706.
3. Taegtmeyer H. Energy metabolism of the heart: from basic concepts to clinical applications. Curr Probl Cardiol 1994;19:57–116.
4. Ingwall J. Phosphorous nuclear magnetic resonance spectroscopy of cardiac and skeletal muscles. Am J Physiol 1982;242:H729–44.
5. Balaban RS. Regulation of oxidative phosphorylation in the mammalian cell. Am J Physiol 1990;258:C377–89.
6. Schelbert H. Measurements of myocardial metabolism in patients with ischemic heart disease. Am J Cardiol 1998;82:61K–67K.
7. Taegtmeyer H, Roberts AFC, Rayne AEG. Energy metabolism in reperfused rat heart: return of function before normalization of ATP content. J Am Coll Cardiol 1985;6:864–70.
8. Taegtmeyer H, Hems R, Krebs HA. Utilization of energy providing substrates in the isolated working rat heart. Biochem J 1980;186:701–11.
9. Abel E, Kaulbach H, Tian R, et al. Cardiac hypertrophy with preserved contractile function after selective deletion of GLUT4 from the heart. J Clin Invest 1999;104:1703–14.
10. Binas B, Danneberg H, McWhir J, Mullins L, Clark A. Requirement for the heart-type fatty acid binding protein in cardiac fatty acid utilization. FASEB J 1999;13:805–12.
11. Zhou Y, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci USA 2000;97:1784–9.
12. Depre C, Vanoverschelde J, Taegtmeyer H. Glucose for the heart. Circulation 1999;99:578–88.
13. Allard M, Schonekess B, Henning S, English D, Lopaschuk G. Contribution of oxidative metabolism and glycolysis to ATP production in hypertrophied hearts. Am J Physiol 1994;267:H742–50.
14. Taegtmeyer H, Overturf ML. Effects of moderate hypertension on cardiac function and metabolism in the rabbit. Hypertension 1988;11:416–26.
15. Gevers W. Generation of protons by metabolic processes in heart cells. J Mol Cell Cardiol 1977;9:867.
16. Katz AM, Hecht HH. The early "pump" failure of the ischemic heart. Am J Med 1969;47:497–502.
17. Orchard C, Kentish J. Effects of changes of pH on the contractile function of cardiac muscle. Am J Physiol 1990;258:C967–81.
18. Liu B, el Alaoui-Talibi Z, Clanachan AS, Schulz R, Lopaschuk GD. Uncoupling of contractile function from mitochondrial TCA cycle activity and MV_{O_2} during reperfusion of ischemic hearts. Am J Physiol 1996;270:H72–80.
19. Challoner D, Steinberg D. Effect of free fatty acid on the oxygen consumption of perfused rat heart. Am J Physiol 1966;210:280–6.
20. Burkhoff D, Weiss R, Schulman S, Kalil-Filho R, Wannenburg T, Gerstenblith G. Influence of metabolic substrate on rat heart function and metabolism at different coronary flows. Am J Physiol 1991;261:H741–50.
21. Lopaschuk GD, Spafford MA, Davies NJ, Wall SR. Glucose and palmitate oxidation in isolated working rat hearts reperfused after a period of transient global ischemia. Circ Res 1990;66:546–53.
22. Doenst T, Richwine R, Bray M, Goodwin G, Frazier O, Taegtmeyer H. Insulin improves functional and metabolic recovery of reperfused working rat heart. Ann Thorac Surg 1999;67:1682–8.
23. Goodwin G, Taylor C, Taegtmeyer H. Regulation of energy metabolism of the heart during acute increase in heart work. J Biol Chem 1998;273:29530–9.
24. Depre C, Taegtmeyer H. Metabolic aspects of programmed cell survival and cell death in the heart. Cardiovasc Res 2000;45:538–48.
25. Meerson F. The Failing Heart: Adaptation and Deadaptation. New York: Raven Press, 1983:1–5.
26. Bishop S, Altschuld R. Increased glycolytic metabolism in cardiac hypertrophy and congestive heart failure. Am J Physiol 1970;218:153–9.
27. Schonekess B, Allard M, Lopaschuk G. Recovery of glycolysis and oxidative metabolism during postischemic reperfusion of hypertrophied rat hearts. Am J Physiol 1996;271:H798–805.
28. Van Bilsen M, Van der Vusse G, Reneman R. Transcriptional regulation of metabolic processes: implications for cardiac metabolism. Pflugers Arch 1998;437:2–14.
29. McVeigh JJ, Lopaschuk GD. Dichloroacetate stimulation of glucose oxidation improves recovery of ischemic rat hearts. Am J Physiol 1990;259:H1079–85.
30. Lewandowski ED, White LT. Pyruvate dehydrogense influences postischemic heart function. Circulation 1995;91:2071–9.
31. Broderick TL, Quinney HA, Lopaschuk GD. Carnitine stimulation of glucose oxidation in the fatty acid perfused isolated working rat heart. J Biol Chem 1992;267:3758–63.
32. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic, and reperfused ischemic rat hearts. Circulation 1996;93:135–42.
33. Man K, Brosnan J. Inhibition of medium- and short-chain fatty acid oxidation in rat heart mitochondria by dichloroacetate. Metabolism 1982;31:744–8.
34. Zarain-Herzberg A, Rupp H. Transcriptional modulators targeted at fuel metabolism of hypertrophied heart. Am J Cardiol 1999;83:31H–37H.
35. Taegtmeyer H, King L, Jones B. Energy substrate metabolism, myocardial ischemia, and targets for pharmacotherapy. Am J Cardiol 1998;82:54K–60K.
36. Schonekess B, Allard M, Lopaschuk G. Propionyl L-carnitine improvement of hypertrophied heart function is accompanied by an increase in carbohydrate oxidation. Circ Res 1995;77:726–34.
37. Kantor P, Lucien A, Kozak R, Lopaschuk G. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res 2000;86:580–8.
38. Zhou P, Lu L, Xu Y, Schwartz G. Troglitazone improves recovery of left ventricular function after regional ischemia in pigs. Circulation 2000;101:1165–71.
39. Stacpoole P, Lorenz A, Thomas R, Harman E. Dichloroacetate in the treatment of lactic acidosis. Ann Intern Med 1988;108:58–63.
40. Bersin R, Wolfe C, Kwasman M, et al. Improved hemodynamic function and mechanical efficiency in congestive heart failure with sodium dichloroacetate. J Am Coll Cardiol 1994;23:1617–24.
41. Kashiwaya Y, Sato K, Tsuchiya N, et al. Control of glucose utilization in working perfused rat heart. J Biol Chem 1994;269:25502–14.
42. Gottlieb R. Mitochondria: ignition chamber for apoptosis. Mol Genet Metab 1999;68:227–31.
43. Kroemer G, Reed J. Mitochondrial control of cell death. Nat Med 2000;6:513–9.