Editorial

Metabolic Modulation
A Means to Mend a Broken Heart

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Heart failure is a clinical syndrome characterized by progressive deterioration of heart pump function that is very common in our society. It is a highly lethal disease with an annual mortality rate ranging from 5% to 10% in those with mild symptoms to 30% to 40% in those with severe symptoms. The morbidity associated with heart failure is also substantial such that heart failure is currently the leading cause of hospitalization in the United States, with direct costs related to treatment amounting to $20 000 million annually. As a result, the socioeconomic impact of heart failure is great. The need to prevent and, when necessary, effectively treat heart failure is, therefore, of utmost importance.

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Angiotensin-converting enzyme inhibitors, β-adrenergic receptor antagonists, and diuretics, with or without aldosterone antagonists and digoxin, are mainstays of long-term pharmacological treatment of heart failure. Use of inotropic therapy to increase contractility in heart failure is not routinely used due to the fact that currently used inotropic agents simultaneously increase myocardial oxygen demand, a clinically undesirable effect. Development of agents that increase performance of the dysfunctional heart in the absence of significant alterations in oxygen demand would have great clinical utility. An experimental study by Hasenfuss et al featured in this issue of Circulation presents data showing that pyruvate, which dose-dependently improved performance in myocardium from failing human hearts, may be one such agent.

A number of abnormalities in both energy metabolism and contractile function have been identified in failing cardiac muscle. Metabolic changes include decreases in high energy phosphorylation potential, decreases in mitochondrial oxidative phosphorylation capacity, and a switch to a more fetal glycolytic metabolism. Contractile-related changes involve switches in myosin isoform profile, as well as alterations in calcium cycling during diastole and systole. The study by Hasenfuss et al used muscle strips obtained from end-stage failing human hearts to show that pyruvate can increase contractile force and improve calcium cycling in the myocardium. Overall, the findings of the study are significant because they provide a direct link between energy metabolism and alterations in contractile function in the failing heart. The study also highlights the potential of using "metabolic modulation" as an approach to improving contractile function in the failing heart. The study does not differentiate as to whether pyruvate acts directly on contractile proteins or calcium transients, or whether the actions of pyruvate occur indirectly as a result of pyruvate effects on energy metabolism. However, it provides a good rationale for performing future studies that address these issues.

Pyruvate, a product and substrate of myocardial energy metabolism, has a number of cellular actions that may account for the improvement in failing human heart. As Hasenfuss et al point out, its beneficial effects are likely, at least in part, attributable to its effects on myocardial energy metabolism. This viewpoint and the results of the present study support the evolving concept that modulation of myocardial metabolism is a novel, alternative approach to improve performance of dysfunctional myocardium, whether it be in the setting of acute myocardial ischemia-reperfusion, cardiac hypertrophy, or chronic heart failure.

Hearts use a variety of energy substrates, with the oxidation of fatty acids and carbohydrates providing the majority of the heart’s energy requirements. However, oxidation of long-chain fatty acids can be reduced in failing hearts as well as in hypertrophied hearts. As a result, energy production in hypertrophied and failing hearts becomes more dependent on metabolism of carbohydrates, such as glucose. In hypertrophied but nonfailing hearts, glycolysis of exogenous glucose is accelerated, presumably as a compensatory response to low rates of fatty acid oxidation. Despite the acceleration of glycolysis, glucose oxidation is not correspondingly increased and may, in fact, be lower than in nonhypertrophied hearts. As a result, the balance (or coupling) between glycolysis and glucose oxidation is lower in hypertrophied hearts than in nonhypertrophied hearts. This pattern of glucose utilization (ie, low coupling of glycolysis and glucose oxidation) is known to be associated with myocardial dysfunction, especially in the setting of ischemia-reperfusion.

The concept of modulation (or optimization) of energy metabolism to improve performance of dysfunctional myocardium is not new (see reference 10 for review). Beneficial effects of pharmacological agents that influence myocardial energy substrate metabolism, including pyruvate, have been shown in experimental and clinical studies of acute ischemia-reperfusion, cardiac hypertrophy, and heart failure. Although the mechanisms by which these agents...
influence myocardial metabolism differ (see Figure), all generally alter it by shifting energy metabolism away from fatty acids toward carbohydrates. Specifically, the agents improve coupling of glycolysis and glucose oxidation by stimulating glucose oxidation via activation of the pyruvate dehydrogenase complex (PDC). Some agents, such as pyruvate and dichloroacetate, activate PDC directly by inhibiting PDC kinase. Other agents activate PDC indirectly by reducing fatty acid oxidation, either by inhibiting carnitine palmitoyltransferase-1 (eg, etomoxir, oxefnicine) or mitochondrial \( \beta \)-oxidation (eg, trimetazidine, ranolazine). Carnitine and its derivative, propionyl L-carnitine, also indirectly activate PDC by reducing the acetyl-CoA/CoA ratio in the mitochondria. In the setting of acute ischemia-reperfusion, glucose-insulin-potassium therapy reduces fatty acid oxidation by lowering circulating fatty acid concentration and, thereby, indirectly activates the PDC. Of great importance, the beneficial effects of these agents can occur independently of significant increases in oxygen demand.

Failing and hypertrophied hearts are known to have abnormalities in calcium homeostasis that likely contribute to the poor contractile function of these hearts. In association with improved performance of failing myocardium, the authors of the present study found that pyruvate caused alterations in the pyruvate dehydrogenase complex (PDC). Some agents, such as pyruvate and dichloroacetate, activate PDC directly by inhibiting PDC kinase. Other agents activate PDC indirectly by reducing fatty acid oxidation, either by inhibiting carnitine palmitoyltransferase-1 (eg, etomoxir, oxefnicine) or mitochondrial \( \beta \)-oxidation (eg, trimetazidine, ranolazine). Carnitine and its derivative, propionyl L-carnitine, also indirectly activate PDC by reducing the acetyl-CoA/CoA ratio in the mitochondria. In the setting of acute ischemia-reperfusion, glucose-insulin-potassium therapy reduces fatty acid oxidation by lowering circulating fatty acid concentration and, thereby, indirectly activates the PDC. Of great importance, the beneficial effects of these agents can occur independently of significant increases in oxygen demand.10

A relative imbalance between glycolysis and glucose oxidation, as occurs in hypertrophied hearts9,14 and in hearts exposed to acute ischemia-reperfusion, results in increased lactate release and accelerated production of protons, the latter of which arises from hydrolysis of glycolytic-generated ATP. By way of ion exchange mechanisms, increased production of protons can lead to greater influx of Na\(^+\) and, ultimately, Ca\(^{2+}\). Utilization of ATP to maintain homeostasis of these ions under these circumstances redirects ATP use away from contractile activity, an effect that decreases the efficiency of converting energy stored in ATP into contractile work. Thus, interventions that reduce the imbalance between glycolysis and glucose oxidation (particularly by stimulating flux through PDC) should lower proton production and the resultant influx of Na\(^+\) and Ca\(^{2+}\) and, ultimately, lead to improved cardiac function and efficiency. Net proton production is lowered when glucose oxidation is stimulated because 1 proton accompanies each pyruvate molecule into the mitochondria where it is consumed.10 In the setting of myocardial dysfunction due to acute ischemia-reperfusion, it has been shown that use of pharmacological agents that stimulate glucose oxidation improves contractile function and efficiency in association with the expected changes in proton and Na\(^+\) concentrations.20,21 In addition to effects on ion homeostasis, the beneficial effects of such agents are also likely related, in part, to an improved energetic state of the myocardium.12

The Hasenfuss et al study4 has clinical relevance in a number of scenarios, including ventricular dysfunction following ischemia, cardiac hypertrophy, or acute decompensation of a chronically failing heart. Furthermore, postischemic ventricular dysfunction following pediatric and adult cardiac surgery is likely the most important cause of morbidity and mortality. The general approach to managing acute heart failure in these settings is to improve performance of the dysfunctional heart by administering catecholamines. Although inotropic stimulation with catecholamines will generally improve contractility and cardiac output, the benefits are often short-lived and are associated with significant detrimental effects. The adverse effects of this approach are likely related to the increase in myocardial oxygen consumption associated with their use. The augmented contractility with catecholamines comes at the expense of a reduction in myocardial efficiency with an increase in oxygen use per unit work. As such, the administration of catecholamines to improve function of the failing heart has been likened to “whipping a sick, tired, and energy-starved horse” with the aim of making it work harder. A better solution to this problem would be to “feed the horse” through metabolic intervention. Pyruvate, which is well known to have beneficial effects on the metabolism and function of the posts ischemic heart, is convincingly shown in the Hasenfuss et al study4 to be an agent that improves performance of myocardium from failing human hearts, presumably by “feeding” rather than “whipping” the heart.

Unfortunately, pyruvate is not well suited for routine clinical use. Because of its potency and large volume of distribution, clinical use would require the infusion of pyruvate directly into the left main coronary artery to obtain adequate coronary arterial pyruvate concentrations (3 to 6 mmol/L). Systemic administration of pyruvate, which exists...
as a sodium salt, is not practical because the vast quantities required would likely result in a significant sodium load to patients already suffering from heart failure.

As with any study, the results of the present investigation also raise a number of issues and questions that must be addressed. First, it is apparent that the myocardial utilization profile of substrates of both exogenous and endogenous (eg, glycogen, triglyceride) origin in failing hearts from experimental animals and humans needs to be characterized in detail. Second, the demonstration that the results obtained in the present study can be reproduced in the presence of a mixture of exogenous substrates and hormones at physiologically relevant concentrations is required; myocardium was provided only carbohydrate as a fuel source and insulin concentration exceeded the physiological range in the present investigation. Third, do pharmacological agents known to stimulate glucose oxidation improve function of failing myocardium in association with the changes in proton concentration and Ca\(^{2+}\) homeostasis observed in the present study?

The increasing prevalence of heart failure, the continued high morbidity and mortality of patients with heart failure treated with currently available therapeutic agents, and the socioeconomic burden of heart failure clearly indicate a need for new approaches to treat this significant health problem. The Hasenfuss et al study,\(^4\) which nicely demonstrates the relationship between myocardial energy metabolism, ion homeostasis, and contractile function in the context of the human failing heart, points to an alternative therapeutic approach. The time has now come to seriously consider metabolic modulation as a novel means to mend a broken heart.

References

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