Modulation of Myocardial Energetics
Emerging Evidence for a Therapeutic Target in Cardiovascular Disease

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The traditional paradigm for heart failure management centered on mitigating the hemodynamic changes that occur in response to the failing heart. Subsequently, pharmacological modulation of neurohormonal activation and more recently cardiac resynchronization have been shown to reverse ventricular remodeling and to slow disease progression. Despite these advances in therapy, successful treatment of heart failure remains challenging, with rates of hospitalization in the United States exceeding 1 million per year and the annual number of heart failure–related deaths increasing steadily. Unfortunately, the history of drug development for heart failure has been marked by many disappointing results, most notably the excess mortality associated with oral positive inotropes that were targeted at improving hemodynamics. In addition, more recent interventions aimed at interrupting endothelin and cytokine signaling or reducing oxidative stress have yet to fulfill hopes for novel biological therapies. Thus, new therapeutic strategies are needed to alter the natural history of the disease and to slow or reverse current epidemiological trends. The report by Lee and colleagues in this issue of Circulation points toward the promise of an alternative approach based on favorably influencing the efficiency of myocardial energetics, thereby increasing cardiac performance without depending on changes in oxygen consumption or improvement in hemodynamics.

Modulation of Myocardial Energetics
The study of agents aimed at enhancing myocardial energy efficiency has focused principally on shifting myocardial substrate use toward more oxygen-efficient pathways. Although the complete oxidation of fatty acids to CO₂ yields more adenosine triphosphate (ATP) per molecule of CO₂ produced than does complete oxidation of glucose, a greater amount of oxygen is required to completely oxidize a fatty acid of equivalent carbon-chain length. Therefore, for a given amount of oxygen consumed, metabolism of glucose is more “oxygen efficient,” producing ~15% more ATP (Figure). In the setting of heart failure, the blood concentration of free fatty acids increases as a consequence of catecholamine-induced activation of lipolysis, as well as upregulation of genes associated with free fatty acid use via peroxisome proliferator–activated receptor-α activation. Furthermore, free fatty acids promote their own uptake and oxidation and antagonize the uptake of glucose, lactate, and pyruvate, in part through direct inhibition of pyruvate dehydrogenase. Mitochondrial effects of free fatty acids include uncoupling of cellular respiration, resulting in decreased ATP production and oxygen wasting. Thus, elevated blood levels of free fatty acids augment lactate and proton accumulation, decrease cellular pH, and disrupt cellular function. Other consequences of excess free fatty acids include impaired calcium handling, oxidative stress, and myocyte apoptosis. It is plausible that these changes in the cellular milieu underlie the impaired ventricular performance, decreased myocardial efficiency, and increased risk of arrhythmias and postinfarction angina associated with elevated concentrations of free fatty acids.

The cellular pathways of substrate use present several avenues for cardioprotective intervention with “metabolic” agents (Figure). Carbohydrate metabolism may be directly increased with agents such as dichloroacetate that directly activate pyruvate dehydrogenase and thus increase oxidation of pyruvate or with drugs such as the thiazolidinediones and carvedilol that increase insulin sensitivity. Alternatively, the rate of fatty acid oxidation may be decreased by 1 of 3 major strategies: (1) Decreasing the circulating levels of free fatty acids and/or their uptake by cardiac myocytes, eg, by treatment with glucose, insulin and potassium; (2) inhibiting the mitochondrial uptake of fatty acids via suppression of carnitine palmitoyl transferase (CPT) I or II; or (3) directly inhibiting the enzymes that participate in fatty acid β-oxidation.

Perhexiline, the agent studied by Lee et al., has been recognized since the late 1960s to reduce the frequency of chronic stable angina but only recently has been proposed to exert its clinical effects through inhibition of CPT I and, to a lesser degree, CPT II. In addition to reducing angina, perhexiline has been shown to attenuate the increase in diastolic tension associated with myocardial ischemia and to improve myocardial efficiency in animal models. Despite these potential favorable actions, the direct myocardial and hemodynamic effects of perhexiline in patients with heart failure are unknown. Furthermore, clinical interest in the chronic administration of perhexiline has been diminished by an association with infrequent but serious hepatotoxicity and neuropathy that necessitates regular monitoring of plasma levels and makes perhexiline relatively contraindicated in patients with hepatic or renal dysfunction.
Trimetazidine, a piperazine salt that reduces angina without evidence of direct hemodynamic effects, is believed to act through partial inhibition of fatty acid β-oxidation.\(^3\) Available evidence suggests that the primary molecular target of trimetazidine is the mitochondrial enzyme long-chain 3-ketoacyl coenzyme A thiolase, inhibition of which triggers a balancing increase in pyruvate oxidation and reduces the accumulation of lactate. Consistent with this mechanism, trimetazidine does not appear to increase glycolysis directly.

Ranolazine is a second agent initially thought to achieve its clinical effects by partial inhibition of fatty acid oxidation.\(^6\) Although pharmacological effects on substrate use were observed in vitro, these findings generally occurred at concentrations in excess of the therapeutic range of plasma concentration. More recent experiments have pointed toward other potential effects on cellular energetics that may be responsible for the clinical effects of partial inhibition of fatty acid oxidation.\(^6\) Although pharmacological effects on substrate use were observed in vitro, these findings generally occurred at concentrations in excess of the therapeutic range of plasma concentration. More recent experiments have pointed toward other potential effects on cellular energetics that may be responsible for the clinical effects of partial inhibition of fatty acid oxidation.\(^6\)

Experimental and Clinical Evidence in Heart Failure

Although “metabolic” agents have undergone clinical evaluation principally for the treatment of ischemic heart disease,
Metabolic Therapy for Heart Failure and Mechanisms of Action

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
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<tr>
<td>Etoroxir</td>
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</tbody>
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both experimental and preliminary clinical data point toward a potential therapeutic role for this class in patients with heart failure (Table). For example, perhexiline increased cardiac output in isolated rat hearts without significantly increasing myocardial oxygen consumption, suggesting an improvement in myocardial efficiency.\(^9\) In addition, trimetazidine reduced ischemic contracture and improved posts ischemic recovery in a related heart model.\(^13\) Similarly, in animal models of ischemia/reperfusion, ranolazine has been shown to preserve tissue levels of ATP and to improve myocardial contractile performance. Moreover, acute administration of ranolazine improved contractile function without increasing myocardial oxygen consumption in dogs with chronic heart failure.\(^14\) Notably, ranolazine exerted no effect on heart rate or systemic blood pressure in this model. Beneficial metabolic and hemodynamic effects also have been demonstrated with acute administration of GLP-1 in dogs with pacing-induced heart failure.\(^12\)

Clinical studies of these agents in patients with heart failure are limited in number and scope. Etoroxir improved ejection fraction, exercise cardiac output, and clinical status in a small, open-label study of patients with mild to moderate heart failure.\(^15\) Similarly, small studies have demonstrated improvements in symptoms and cardiac function with trimetazidine in patients with ischemic heart failure.\(^16\) In an older study of 20 patients with ischemic cardiomyopathy treated with digoxin and diuretics only, blinded treatment with trimetazidine was associated with an absolute 9% increase in ejection fraction compared with a 16% decrease with placebo.\(^17\) The current study by Lee and colleagues\(^2\) adds importantly to this preliminary body of evidence. The randomized, double-blind design and the contemporary background therapy for heart failure are particular strengths of the study. In addition, the demonstration of consistent effects of perhexiline on left ventricular function, peak exercise capacity, and clinical status in patients with nonischemic heart failure provides evidence for potential benefits beyond reducing ischemia alone. The salutary effects of perhexiline on skeletal muscle metabolism also suggest peripheral and central benefits of metabolic therapy in heart failure. Unfortunately, the mechanism of action of perhexiline is not identified in this pilot study, and the long-term safety and efficacy of perhexiline in a broader heart failure population remain to be determined. Even with careful monitoring of plasma levels, the C4P2D6 metabolizer status of the patient, drug-drug interactions (eg, with amiodarone and selective serotonin reuptake inhibitors), and concomitant hepatic or renal dysfunction may limit applicability of this agent as adjunctive therapy for heart failure.

Application in Other Cardiovascular Conditions

The paradigm of achieving therapeutic effects through improved myocardial cellular energetics is likely to have cardiovascular applications beyond heart failure. Although studies of glucose, insulin, potassium, and more recently GLP-1 have focused on acute coronary syndromes, chronic metabolic therapy also offers hope. In fact, the reduction in ischemia and ischemia-related ventricular dysfunction achieved with perhexiline in clinical trials of chronic angina has supported the benefit of this strategy in ameliorating ischemic complications in patients with known coronary artery disease.\(^18\)\(^19\) Similarly, ranolazine has been shown to reduce angina and to improve exercise performance in at least 2 randomized placebo-controlled trials\(^\(20\)\); it now is being studied in the acute management of unstable coronary disease in the ongoing Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST elevation acute coronary syndromes (MERLIN)-TIMI 36 Trial. Lastly, it is possible that reductions in long-chain acylcarnitines achieved through blockade of CPT I may suppress electrical instability, leading to dysrhythmias. However, the development of cardiomyopathy and arrhythmias in children with inherited disorders of fatty acid oxidation and the lipotoxicity associated with chronic CPT I inhibition raise a cautionary note regarding the chronic alteration of metabolic pathways intrinsic to normal myocardial structure and function.\(^21\) Also, the lack of benefit of glucose, insulin, and potassium in acute myocardial infarction marks at least 1 unfulfilled acute metabolic intervention in acquired cardiovascular disease.

Conclusions

The failing heart has been described as an energy-starved organ dependent on inefficient fatty acid oxidation. Perhexiline, as insightfully studied by Lee and colleagues,\(^2\) offers hope of providing a pharmacological “switch” in substrate use, thereby making the heart more oxygen efficient. Through this or other mechanisms, modulation of cellular energetics has the potential to improve cardiac performance and reduce symptoms in patients with heart failure without relying on alteration of hemodynamics or further modulation of neurohormones. As such, agents acting via this approach are likely to complement rather than mimic established therapy and hold a possibility for clinical benefit in a range of cardiovascular diseases. Although the data presented by Lee et al are thought provoking, additional investigation is warranted to elucidate the long-term efficacy and safety of these strategies.

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References


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