Heart Metab. (2018) 77:24-27

Heart failure: a metabolic issue?

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Abstract

Ischemic heart disease and heart failure share a common pathophysiological pathway: the development of cardiac metabolic derangements. The heart derives most of its energy from β-oxidation of free fatty acids. High rates of fatty acid oxidation inhibit glucose oxidation. For any given amount of oxygen consumed, metabolism of glucose is more "oxygen efficient," producing about 15% more adenosine triphosphate (ATP). In patients with chronic heart failure, neurohormonal activation is thought to be responsible for enhanced free fatty acid delivery to the heart, which is responsible for myocardial lipotoxicity. Given such metabolic derangements, pharmacological approaches aimed at rebalancing myocardial metabolism may play a key role in the treatment of patients with heart failure. Trimetazidine, the first and most prescribed metabolic modulator, has been shown to improve left ventricular function in patients with chronic heart failure. Furthermore, trimetazidine has been shown to improve skeletal muscle performance in patients with heart failure, as well as in normal subjects. This unique combination of cardiac and peripheral effects result in a marked improvement in exercise tolerance and New York Heart Association class and support a larger use of trimetazidine and other metabolic modulators in the management of heart failure. ■ *Heart Metab*. 2018;77:24-27

Keywords: heart failure; New York Heart Association; trimetazidine

Introduction

As the understanding of the metabolic derangements associated with both ischemic heart disease and heart failure increases, so too does the number of new therapeutic opportunities.

The healthy heart derives most of its energy from free fatty acid β-oxidation, which accounts for approximately two-thirds of the energy (adenosine triphosphate [ATP]) production, with the other source of energy being glucose oxidation. Although complete fatty acid oxidation yields more ATP per molecule of fatty acid than does glucose oxidation, a greater amount of oxygen is required to produce an equivalent amount of ATP. Therefore, for any given amount of oxygen consumed, metabolism of glucose is more "oxygen efficient," producing about 15% more ATP.

In the setting of heart failure, the blood concentration of free fatty acid increases as a consequence of catecholamine-induced activation of lipolysis, as well as upregulation of genes associated with free fatty acid use via the peroxisome proliferator–activated receptor. Furthermore, free fatty acids antagonize the uptake of glucose. Elevated levels of free fatty acid in the blood augment lactate and proton accumulation, decrease cellular pH, and disrupt cellular function.[1]

Although abnormalities in myocardial energy metabolism are associated with heart failure, recent data

suggest that heart failure itself may promote metabolic changes, such as insulin resistance, in part through neurohumoral activation, generating a vicious cycle in which metabolic abnormalities further aggravate and precipitate heart failure.[2,3] Neurohumoral homeostasis is maladaptively activated in response to a chronic reduction in cardiac output, as characterized by the persistent activation of the sympathetic nervous system and the interlinked renin-angiotensin-aldosterone system. In addition to this increased catecholamine secretion, reduced cardiac catecholamine reuptake can be observed. Increased catecholamines have direct detrimental effects on the heart, which cause marked enzyme loss as an index of diffuse myocardial damage and substantial oxygen wastage even in the absence of free fatty acids in the perfusate. Furthermore, norepinephrine promotes both coronary vasoconstriction and increased plasma free fatty acid levels, which further promote oxygen wastage. Therefore, addressing metabolic issues in patients with heart failure and improving cardiac metabolism could represent a potential therapeutic target for improving patient prognosis.

Innovative approaches to manage heart failure

Given this biochemical background, it seems logical to consider pharmacological manipulation of cardiac energy metabolism as an attractive therapeutic option for patients with heart failure. Optimization of cardiac energy metabolism is largely based on promoting cardiac glucose oxidation and suppressing fatty acid β-oxidation. This optimization has been proven to enhance cardiac function and protect myocardial tissue against ischemia-reperfusion injury, as well as attenuating the progression to chronic heart failure. The rate of fatty acid oxidation may be decreased by directly inhibiting the enzymes that participate in fatty acid oxidation.[4]

In 2003, Rosano et al reported that trimetazidine improves left ventricular function in diabetic patients with coronary artery disease.[5] This observation was confirmed by Belardinelli et al a few years later.[6] In 2006, Fragrasso et al evaluated the efficacy of trimetazidine in patients with heart failure.[7] A total of 55 patients with heart failure were randomly allocated in an open-label fashion either to conventional therapy plus trimetazidine (20 mg three times daily) or to conventional therapy alone. Mean follow-up was 13±3 months. At study entry and at follow-up, all patients underwent exercise testing and two-dimensional echocardiography. Among others, New York Heart Association (NYHA) functional class and ejection fraction were evaluated. In the trimetazidine group, the NYHA functional class significantly improved compared with the conventional therapy group ($P<0.0001$). Trimetazidine significantly decreased left ventricular end-systolic volume (from 98±36 mL to 81±27 mL; $P=0.04$) and increased the ejection fraction from 36±7% to 43±10% ($P=0.002$). On the contrary, in the conventional therapy group, both left ventricular end-diastolic and end-systolic volumes progressively deteriorated, increasing from 142±43 mL to 156±63 mL ($P=0.2$) and from 86±34 mL to 104±52 mL ($P=0.1$), respectively. Accordingly, ejection fraction significantly decreased from 38±7% to 34±7% ($P=0.02$). This study confirmed that trimetazidine contrasts with chronic heart failure natural history, as shown by the decrease in ejection fraction observed in patients on standard therapy alone.[8]

In an international, multicenter, retrospective cohort study, with data from 669 patients, a Kaplan-Meier analysis for global mortality showed an 11.3% improved global survival ($P=0.015$) and an 8.5% improved survival for cardiovascular death ($P=0.050$) in the trimetazidine group.[9] Trimetazidine also showed a good risk reduction profile for cardiovascular death causes (hazard ratio [HR], 0.072; 95% CI, 0.019-0.268; $P=0.0001$). The rate of hospitalization for cardiovascular causes was reduced by 10.4% at 5 years ($P<0.0005$) with a 7.8-month increase in hospitalization-free survival. The authors concluded that trimetazidine, on top of optimal medical therapy, was effective in reducing mortality and improving event-free survival in patients with chronic heart failure. Similarly, short- and long-term administration of trimetazidine was beneficial in patients with diabetes and ischemic cardiomyopathy[10] and in patients with idiopathic-dilated cardiomyopathy.[11] These data have further confirmed the results of previous studies in which it had been shown that trimetazidine can improve left ventricular function, exercise capacity, and NYHA class in diabetic patients and elderly patients. Furthermore, the addition of trimetazidine to exercise training has resulted in greater improvements in functional capacity, left ventricular ejection fraction, and endothelium-dependent dilation in patients with chronic heart failure.[12]

These results have been confirmed in a meta-analysis conducted by Gao et al, which included 17 randomized controlled trials of trimetazidine for heart failure, with data from 955 patients.[13] Trimetazidine therapy was associated with a significant improvement in left ventricular ejection fraction in patients with both ischemic (weighted mean difference (WMD) with placebo, 7.37%; 95% CI, 6.05-8.70; *P*<0.01) and nonischemic heart failure (WMD, 8.72%; 95% CI, 5.51-11.92; *P*<0.01). With trimetazidine therapy, left ventricular end-systolic volume was significantly reduced (WMD, 10.37 mL; 95% CI, 15.46-5.29; *P*<0.01) and NYHA classification was improved (WMD, 0.41; 95% CI, 0.51-0.31; *P*<0.01) as was exercise duration (WMD, 30.26 s; 95% CI, 8.77-51.75; *P*<0.01). More importantly, trimetazidine had a significant protective effect for all-cause mortality (risk reduction [RR], 0.29; 95% CI, 0.17-0.49; *P*<0.00001) and cardiovascular events and hospitalization (RR, 0.42; 95% CI, 0.30-0.58; *P*<0.00001).

In another study, trimetazidine use was associated with improved myocardial perfusion and contractile response in patients with chronically dysfunctional myocardium and ischemic cardiomyopathy.[14] In contrast with this data, a more recent study showed that the addition of trimetazidine (6 months, at a dose of 35 mg twice daily) in patients with stable nonischemic heart failure resulted in no observed changes in left ventricular ejection fraction, 6-minute walk test distance, maximum O_2 uptake, functional class, or quality of life.[15]

Skeletal muscle performance in heart failure

Clinical classifications of chronic heart failure are based on exercise tolerance, including the most popular one, proposed many decades ago by the NYHA. Traditionally, the reduced exercise capacity of patients with heart failure is attributed to the malfunctioning cardiac pump. More recently, "peripheral" factors have been identified that may contribute to the limited exercise capacity associated with chronic heart failure. Morphological and functional abnormalities found in both skeletal muscle and respiratory muscles, including muscle atrophy, fiber type changes, reduced mitochondrial enzymes, decreased mitochondrial volume density, and alterations at the vascular/skeletal muscle interface (greater sympathetic vasoconstrictor tone, decreased capillarity, and smaller capillary diameter) may all contribute to dyspnea and fatigue, in addition to or independently from "central" derangements.

Trimetazidine has been consistently shown to improve the NYHA class and quality of life in patients with heart failure. Given the similarities between energy metabolism in cardiac and skeletal muscle, it is not surprising that trimetazidine also improves skeletal muscle performance.[16] This boosting effect of trimetazidine on skeletal muscle performance is so relevant that trimetazidine has been listed among the doping substances by international sport authorities and that Olympic athletes have been disqualified for taking trimetazidine in international competitions. So, in patients with heart failure, it is not clear how much of the increased exercise tolerance is due to the cardiac effects of trimetazidine and how much is due to the peripheral effects.

Conclusions

In patients with heart failure, trimetazidine slows the progression of the disease and improves the patients' quality of life and prognosis. The failing heart and the ischemic heart are both energy-starved organs dependent on inefficient fatty acid oxidation. Trimetazidine, inducing a "switch" in substrate use, renders the heart more oxygen efficient. Through this and other mechanisms, modulation of cellular energetics by trimetazidine has the potential to improve cardiac performance and reduce symptoms in patients with heart failure without relying on the alteration in hemodynamics or further neurohormonal modulation.

Given the favorable effects on skeletal muscle performance that contribute to the increase the exercise tolerance, the absence of contraindications, and the clinical tolerability, trimetazidine should have a larger role in the medical therapy of heart failure, independently from clinical severity and from the pathogenetic mechanism. ■

Acknowledgments: *To the precious editorial assistance of Sherri Smith.*

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