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Clinical benefits of trimetazidine in heart failure

Giuseppe M.C. Rosano, MD, PhD, FESC, FHFA
Cardiovascular Clinical Academic Group, St George's Hospitals NHS Trust University of London, United Kingdom – Dept of Medical Sciences, IRCCS San Raffaele, Rome, Italy

Correspondence: Giuseppe M.C. Rosano, MD, PhD, FESC, FHFA, Cardiovascular Clinical Academic Group, St George's Hospitals NHS Trust University of London, Cranmer Terrace, London SW15 1BA, United Kingdom
E-mail: grosanosgul.ac.uk

Abstract

Heart failure is a clinical condition associated with an impaired ability to convert metabolic substrates into high-energy substrates. The metabolic alterations occurring in heart failure result in a 30% to 40% decrease in cardiac adenosine triphosphate (ATP) levels and in a significant decrease in phosphocreatine, the heart's main store of high-energy phosphates. It is becoming evident that modulation of cardiac metabolism is an important tool for the treatment of patients with heart failure and/or with conditions that increase the risk of developing it, such as ischemic heart disease and diabetes. Unlike hemodynamic drugs, trimetazidine acts directly at the cardiac-cell level; by increasing high-energy phosphate availability, it improves contractility and reduces angina. Four meta-analyses have evaluated the effect of trimetazidine on left ventricular function, exercise tolerance, and clinical outcomes in patients with heart failure, all concluding that trimetazidine improves New York Heart Association class, functional capacity, and left ventricular ejection fraction, and reduces the occurrence of hospitalization for heart failure and cardiovascular mortality. The effects of trimetazidine on functional parameters and clinical outcome in heart failure are associated with a good safety profile. Therefore, trimetazidine represents an important therapeutic resource for the treatment of patients with heart failure in whom it has a significant benefit on quality and quantity of life. ■ *Heart Metab*. 2017;74:24-28

Keywords: cardiac energy metabolism; heart failure; trimetazidine

Heart failure is a clinical condition associated with an impaired ability to convert metabolic substrates into high-energy substrates.[1-5] Ample evidence suggests that in heart failure and in most of its predisposing conditions such as diabetes, arterial hypertension, and coronary artery disease, there is an elevated rate of myocardial fatty acid oxidation and reduced glucose oxidation.[6-8]

Metabolic alterations in heart failure

The preferential myocardial utilization of free fatty acid (FFA) in heart failure is the consequence of a maladaptive process that leads to an impaired production of high-energy phosphates.[8] This maladaptive process is more evident in diabetic patients. Studies have shown that, despite higher plasma levels of glucose, these patients exhibit a greater FFA extraction and utilization by their cardiac myocytes and that a direct relationship exists between the degree of insulin resistance and left ventricular dysfunction.[9,10] These changes are associated with an increased oxygen utilization and decreased energy production and metabolic efficiency.[11] Studies in patients with congestive

Abbreviations

ATP: adenosine triphosphate; **HFrEF:** heart failure with reduced ejection fraction; **NYHA:** New York Heart Association; **SERCA:** sarcoplasmic/endoplasmic reticulum calcium–ATPase

heart failure found a 50% increased extraction and uptake of FFA coupled with a 60% decreased glucose uptake compared with subjects without heart failure.[6]

Glucose oxidation requires less oxygen per mole of adenosine triphosphate (ATP) generated than FFA oxidation; thus, FFA utilization is less metabolically efficient than gluose utilization and leads to a reduced production of ATP, which translates into a lower availability of high-energy phosphates for cellular processes and cardiac contraction than that afforded by glucose utilization. Therefore, glucose oxidation is preferable to FFA oxidation when oxygen availability is limited, such as in underperfused cardiac tissue. The metabolic alterations occurring in heart failure result in a 30% to 40% decrease in cardiac ATP concentration and in a significant decrease in its main storage molecule, phosphocreatine.[1-4]

ATP is required for almost all cellular processes; its reduced availability within the cardiac myocyte leads to diminished activity of the sarcoplasmic/endoplasmic reticulum calcium (Ca^{2+})-ATPase (SERCA) with a consequent impairment of active relaxation in early diastole. It also leads to reduced availability of ATP for actin-myosin cross-bridge cycling, leading to a further impairment of left ventricular function. The impact of glucose oxidation on left ventricular function is shown by the fact that, in animal models, after coronary artery ligation, the heart shows a better recovery of left ventricular function if glucose is used as substrate instead of FFA.[12] It is becoming evident that modulation of cardiac metabolism is an important tool for the treatment of patients with heart failure and/or with conditions, such as ischemic heart disease and diabetes, that increase the risk of developing it.

Therapeutic approaches to modulating cardiac energy metabolism

Several drugs have been shown to affect the metabolic processes in the failing heart, acting at different levels of glucose or FFA utilization. These include etomoxir, perhexiline, ranolazine, pyruvate, dichloroacetate, and trimetazidine.[13] Out of all these drugs, trimetazidine is the only one that has been consistently found to improve cardiac metabolism and to have relevant clinical cardiovascular effects in ischemic heart disease and in heart failure. Trimetazidine is approved for clinical use in more than 100 countries worldwide except in the United States, where it has never been filed for approval.[1] All the remaining small molecules have limited clinical application or significant safety issues that limit their use. Ranolazine is approved for the treatment of angina but has not shown efficacy in heart failure.

A closer look at trimetazidine

Several studies have shown that trimetazidine leads to a significant increase in cardiac ATP production and that this effect is associated with a significant clinical improvement and cardioprotection.[14,15] Fragasso et al have shown that the phosphocreatine/ATP ratio, an index of cardiac energy production, is lower in patients with coronary artery disease and in those with failing hearts than in normal subjects; they also show that in these patients, trimetazidine administration increases high-energy phosphate production by 33%, bringing it to the same level of that in normal subjects.[14]

Brottier et al first assessed the effect of long-term treatment with trimetazidine on top of standard treatment in 20 patients with advanced ischemic cardiomyopathy (New York Heart Association [NYHA] class III-IV) and found that it improved clinical status and left ventricular function compared with patients on placebo.[16] Our group has been the first to provide extensive evidence that metabolic modulation of the failing heart with trimetazidine has beneficial effects on cardiac function and on clinical events.[17-23] We have shown that trimetazidine is effective in improving left ventricular systolic and diastolic function in diabetic patients with heart failure, in those with ischemic heart failure, and in elderly patients with left ventricular dysfunction (*Figure 1*).[17,19] These initial findings have been confirmed by subsequent studies extending the evidence to patients with nonischemic heart failure and post myocardial revascularization.[24-30]

Patients with heart failure and reduced left ventricular function show a natural history of a progressive decline in left ventricular function, often despite

optimal medical therapy. Left ventricular function can be improved by interventions that directly increase cardiac contractility or reduce oxygen consumption. Drugs of the first class—such as amrinone, milrinone, flosequinan, and ibopamine—increase oxygen consumption and, in the long term, exhaust high-energy phosphate stores, leading to an impaired function of SERCA and Ca^{2+} accumulation that in turn increases the risk of arrhythmia. This is the reason why all these drugs have consistently shown an increase in the risk of death (mainly arrhythmic) in patients with heart failure. On the other hand, drugs that reduce oxygen consumption through different mechanisms (reduction in heart rate, reduction in preload or afterload) like angiotensin-converting enzyme (ACE) inhibitors, β-blockers, mineralocorticoid-receptor antagonists, ivabradine, and sacubitril/valsartan (LCZ696), improve contractility and long-term outcome. Trimetazidine has been shown to improve left ventricular function over the long term. Unlike the traditional approach, trimetazidine acts directly at the cardiac-cell level and, by increasing high-energy phosphate availability, it improves contractility and reduces angina. The increased ATP availability also leads to an improved diastolic function and decreases the levels of free Ca^{2+} in the sarcoplasmic reticulum during diastole, thereby decreasing the risk of arrhythmia. A

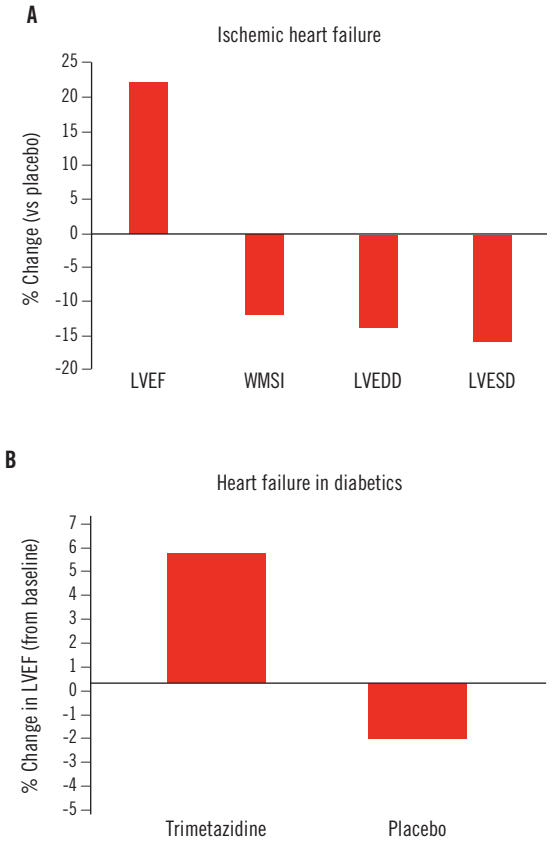

Fig. 1 *Effect of trimetazidine on left ventricular function in patients with heart failure. (**A**) Percent change in left ventricular function (various measures) in patients with ischemic heart failure treated with trimetazidine (compared with placebo). P<0.05 for all comparisons. (**B**) Percent change (from baseline) in left ventricular ejection fraction in diabetic patients with heart failure treated with trimetazidine. P<0.01 vs placebo.*
Abbreviation: *LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; WMSI, wall motion score index.*
Panel A after reference 19: *Vitale et al.* Eur Heart J. *2004;25(20):1814-1821. © 2004, Oxford University Press.*
Panel B after reference 17: *Rosano et al.* Cardiovasc Diabetol. *2003;2:16-24. © 2003, Rosano et al; licensee BioMed Central Ltd.*

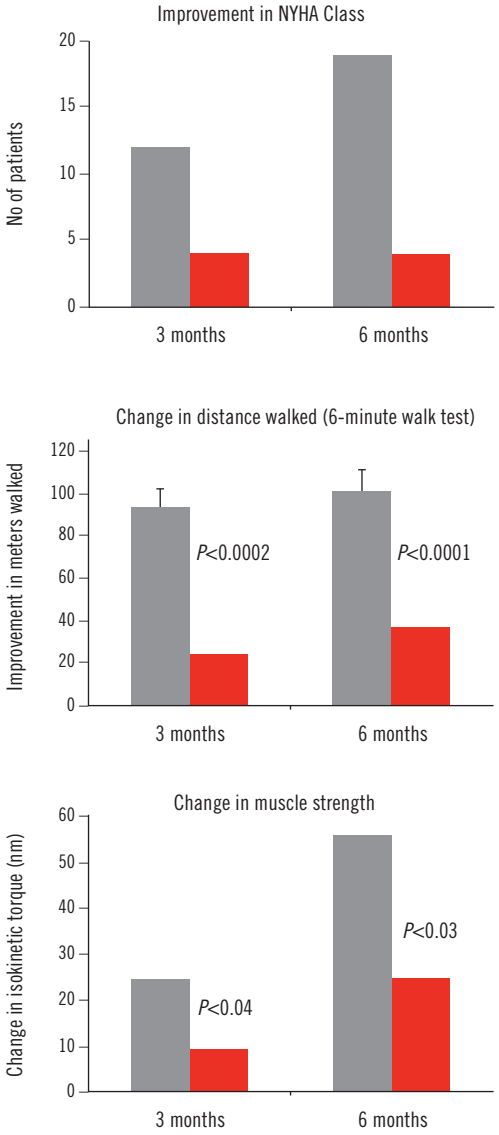

Fig. 2 *Effect of trimetazidine on exercise capacity and muscle strength in patients with heart failure with reduced ejection fraction (HFrEF). Gray bars indicate trimetazidine treatment. Red bars indicate placebo.*
Abbreviation: *6MWT, 6-minute walk test; NYHA, New York Heart Association; TMZ, trimetazidine.*
After reference 34: *Caminiti et al. Eur J Heart Fail. 2016;18(suppl 1):78. Abstract P335. © 2016, European Society of Cardiology.*

decrease in the occurrence of arrhythmia in patients receiving trimetazidine has been shown in patients with ischemic and nonischemic heart failure.[31,32]

The improvement in left ventricular function across the studies has been assessed in a meta-analysis by Gao et al that concluded that trimetazidine therapy was associated with a significant improvement in left ventricular ejection fraction in patients with both ischemic and nonischemic heart failure (weighted mean difference compared with placebo, 7.4% and 8.7% respectively).[33] These benefits are similar to those observed with ACE inhibitors.

The beneficial effect of inhibition of FFA oxidation with trimetazidine is not limited to the heart; it extends to skeletal muscle where trimetazidine increases muscle strength and reduces loss of muscle mass.[22,23] Overall, the central and peripheral effect of trimetazidine leads to an improvement in exercise capacity, NYHA class, and quality of life (*Figure 2*).[34]

Trimetazidine improves prognosis in patients with heart failure and reduced ejection fraction (HFrEF), as shown by a collaborative multicenter study coordinated by Fragasso.[35] In this international multicenter cohort study, trimetazidine reduced overall mortality and cardiovascular mortality by 30%; it also reduced hospitalization for heart failure by 10.4% at 5 years, with an improvement in hospitalization-free survival of 7.8 months at 5 years. Other studies have subsequently shown similar results, and recent meta-analyses have confirmed the effect of trimetazidine on mortality and morbidity. Four meta-analyses have evaluated the effect of trimetazidine on left ventricular function, exercise tolerance, and clinical outcomes in patients with heart failure, and all have concluded that trimetazidine improves NYHA class, functional capacity, and left ventricular ejection fraction, and reduces the occurrence of hospitalization for heart failure and cardiovascular mortality.[33,36-38] Three of these meta-analyses have also found a beneficial effect of trimetazidine on overall mortality.

The relevance of the body of evidence on trimetazidine in heart failure has also been endorsed by the recent guidelines of the European Society of Cardiology, which have included the drug in the algorithm for the treatment of patients with HFrEF.[39] Furthermore, during the assessment of the benefit/risk of trimetazidine, the European Medicines Agency acknowledged the beneficial effect of trimetazidine in patients with ischemic heart failure.[40]

Summary

The effects of trimetazidine on functional parameters and clinical outcome in heart failure are associated with a good safety profile. Because of the absence of an effect on heart rate or blood pressure, trimetazidine can be safely and effectively added to all cardiac medications used in heart failure. The modulation of cardiac metabolism with trimetazidine should always be considered in the treatment of patients with heart failure, when indicated. The evidence of trimetazidine in heart failure supports the well-established role of this drug in ischemic heart disease, where it can be used throughout the continuum of the disease from angina to heart failure. Its efficacy in patients with diabetes and cardiovascular disease suggests that it should be used as early as an alteration of cardiac function is detected. Its added benefits in the elderly are well proven and are associated with a sustained improvement in quality of life. Therefore, trimetazidine is an important therapeutic resource for the treatment of patients with heart failure, in whom it has a significant benefit on quality and quantity of life. ■

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