

Trimetazidine in the new 2016 European guidelines on heart failure and beyond

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Abstract

This article focuses on the management of concomitant angina in patients with heart failure, as described in the 2016 European guidelines for the diagnosis and treatment of acute and chronic heart failure. Trimetazidine has been included in this new guideline because it is considered an effective and safe antianginal treatment in patients with angina and heart failure. It is well-known that impairment of cardiac metabolism plays an important role in the pathophysiology of heart failure. Trimetazidine shifts the myocardial energy metabolism from fatty acid β -oxidation toward glucose oxidation, resulting in a greater production of high-energy phosphates. Adding trimetazidine to a β -blocker (or to an alternative treatment to β -blocker), is considered as an effective and safe step to eliminate angina. Along with this, trimetazidine improves New York Heart Association functional capacity, delays or reverses left ventricular remodeling, and reduces B-type natriuretic peptide levels in heart failure patients. Trimetazidine improves exercise duration, left ventricular function, and quality of life in patients with heart failure with reduced ejection fraction. The rationale and perspectives of using this agent in patients with heart failure with midrange and preserved ejection fraction are also discussed. ■ *Heart Metab.* 2016;71:23-26

Keywords: heart failure; guidelines; myocardial metabolism; trimetazidine

Introduction

The spring of 2016 was marked by the issuance of two guidelines devoted to heart failure. The first document, the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure, was developed with the special contribution of the Heart Failure Association of the ESC.¹ The second one was produced by the American College of Cardiology, the American Heart Association, and the

Heart Failure Society of America in collaboration with the International Society for Heart and Lung Transplantation.² Whereas the American guidelines are focused only on the update of pharmacological therapy, for example, about agents used in the United States, such as angiotensin receptor–neprilysin inhibitor (valsartan/sacubitril) and I_f inhibitor (ivabradine), the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure represent a complete update of their 2012 version.³

Abbreviations

ESC: European Society of Cardiology; **HFpEF:** heart failure with preserved ejection fraction; **HFrEF:** heart failure with reduced ejection fraction; **NYHA:** New York Heart Association; **PCr/ATP:** phosphocreatine/adenosine triphosphate; **RALI-DHF:** RAnoLazIne for the treatment of Diastolic Heart Failure [study]

It is well-known that impairment of cardiac metabolism plays an important role in the pathophysiology of heart failure. Therefore, there is nothing surprising in the fact that the list of new therapies targeting cardiac metabolism is constantly expanding; however, most of these new therapies are not yet available in clinical practice. Studies of mitochondria-targeted peptides (coenzyme Q10, Szeto-Schiller peptides, especially elamipretide), manganese superoxide dismutase mimetics, hormone replacement therapy, and iron chelators attract particular attention. The place of these agents in the guidelines on heart failure needs to be determined by further experimental and clinical research. However, one of the changes made by the 2016 European guidelines on heart failure¹ was the addition of trimetazidine in the guideline's section devoted to the pharmacological management of angina in patients with heart failure (class IIb, level of evidence A recommendation).

Trimetazidine's clinical benefits in patients with heart failure

Trimetazidine has been demonstrated to act directly at the level of the cardiomyocyte by blocking long-chain 3-ketoacyl coenzyme A thiolase, the key enzyme in the β -oxidation pathway and, therefore, inhibiting free fatty acid oxidation. Trimetazidine shifts the myocardial energy metabolism from fatty acid β -oxidation toward glucose oxidation, resulting in a greater production of high-energy phosphates. The beneficial effect of trimetazidine in heart failure is also attributed to improvement in endothelial function, reduction in calcium overload and free radical-induced injury, and inhibition of cell apoptosis and cardiac fibrosis.⁴⁻⁷ Using ³¹P-magnetic resonance spectroscopy to measure the cardiac phosphocreatine/adenosine triphosphate (PCr/ATP) ratio, investigators showed that trimetazidine preserves myocardial high-energy phosphate levels in patients with heart failure.⁸ Thus, trimetazidine

acting at the cellular level in the failing heart provides a significant improvement in functional class and left ventricular function in heart failure patients.⁸ It has also been observed that trimetazidine improves skeletal muscle metabolism.⁹ The effects of trimetazidine on symptoms, exercise capacity, and left ventricular function in patients with heart failure are concordant in all clinical studies. Moreover, several studies have demonstrated the ability of trimetazidine to prevent cardiovascular events and hospitalization in patients with heart failure with *reduced* ejection fraction (HFrEF).¹⁰⁻¹² Four meta-analyses have been performed to estimate the effects of trimetazidine in patients with heart failure. All of them concluded that trimetazidine improves functional capacity and left ventricular ejection fraction, delays or reverses left ventricular remodeling, and reduces B-type natriuretic peptide level in heart failure patients.¹³⁻¹⁶

Management algorithm for the treatment of stable angina pectoris with symptomatic (NYHA class II-IV) HFrEF

According to the new ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, the management algorithm for the treatment of stable angina pectoris with symptomatic (New York Heart Association [NYHA] class II-IV) HFrEF may be represented as follows¹:

A β -blocker (class I, level of evidence A) is recommended as the preferred first-line treatment to relieve angina because of the associated benefits of this treatment, such as reduction in the risks of heart failure hospitalization and premature death. On top of β -blocker or in case a β -blocker is not tolerated, ivabradine (class IIa, level of evidence B) should be considered as an antianginal drug in HFrEF patients with sinus rhythm and a heart rate at or above 70 beats per minute. For additional angina symptom relief, there are several drugs recommended, as follows:

Short- and long-acting nitrates: Long-acting nitrates, despite being an effective antianginal treatment, have not been extensively studied in heart failure.

Trimetazidine (class IIb, level of evidence A): Trimetazidine has been recognized in new 2016 heart failure guidelines as an effective antianginal therapy and safe in heart failure; thus, it is recommended when angina persists despite treatment with a β -blocker or alter-

native. Along with this, trimetazidine improves NYHA functional capacity, exercise duration, left ventricular function, and quality of life in patients with HFpEF.^{17,18}

Amlodipine (class IIb, level of evidence B): Amlodipine has been studied in sizeable numbers of patients with HFpEF/left ventricular dysfunction and shown to be effective and safe.

Other antianginals: The safety of other antianginal agents in HFpEF, such as ranolazine and nicorandil, are uncertain, so they received a class IIb, level of evidence C recommendation. In heart failure patients, ranolazine and nicorandil may be considered only in those unable to tolerate a β -blocker to relieve angina. This is unlike the previous version of the ESC guidelines on heart failure,³ where ranolazine was considered as an alternative to β -blockers or a second-line antianginal agent (class IIb, level of evidence C).

Furthermore, with regard to ranolazine, new ESC guidelines have once again emphasized that its safety in heart failure patients is unclear. It is currently approved as an antianginal agent; however, the impact of ranolazine on heart failure has only been investigated in a few clinical trials.^{19,20} Ranolazine has been shown to significantly increase left ventricular ejection fraction in patients with systolic and diastolic heart failure. The RALI-DHF study (RAnoLazIne for the treatment of Diastolic Heart Failure)²⁰ revealed that ranolazine improves measures of hemodynamics; however, there were no significant effects on relaxation parameters or N-terminal pro-B-type natriuretic peptide concentration in patients with heart failure with *preserved* ejection fraction (HFpEF). Apparently, the value of ranolazine in the management of heart failure itself has yet to be clarified. It is very important to mention that other drugs, specifically diltiazem and verapamil, are thought to be unsafe in patients with HFpEF.

Myocardial revascularization: Percutaneous and surgical revascularization are complementary approaches for symptomatic relief of angina in HFpEF, but whether these interventions improve outcomes is not entirely clear. Myocardial revascularization is recommended when angina persists despite treatment with antianginal drugs.

Further perspectives in the treatment of HFpEF and HFmrEF patients

Is it possible to extend the use of trimetazidine to HFpEF patients and to those with heart failure

with *midrange* ejection fraction (HFmrEF)? It seems quite logical to consider use of trimetazidine to manage angina in these categories of patients. However, the impact of this agent on the disease course itself for HFmrEF and HFpEF needs to be clarified. Whereas the term HFmrEF first appeared in the 2016 European guidelines on heart failure, the term HFpEF has long been in the spotlight of such guidelines. Nevertheless, despite the irrefutable clinical significance of HFpEF—its morbidity and mortality rates on par with HFpEF—a wide range of issues about underlying pathophysiology and clinical management remain controversial, as discussed in this issue.

Phan et al have investigated the association between exercise-related changes in left ventricular relaxation, vasculoventricular coupling, and myocardial energy deficiency in patients with HFpEF.²¹ The study included 37 patients with HFpEF and 20 control subjects. Vasculoventricular coupling and left ventricular relaxation were assessed via radio-nuclide ventriculography while patients were at rest and during exercise. Cardiac energetic status (PCr/ATP ratio) was measured using ³¹P-magnetic resonance spectroscopy. At rest, both time to peak filling normalized for R-R interval and vasculoventricular coupling were similar in HFpEF patients and control subjects. On the other hand, the cardiac PCr/ATP ratio was significantly lower in HFpEF patients than in control subjects, indicating lower energy reserves. The relative changes in stroke volume and cardiac output during submaximal exercise were significantly lower in HFpEF patients than in control subjects. The time to peak filling normalized for R-R interval decreased during exercise in control subjects but increased in HFpEF patients. Vasculoventricular coupling decreased on exercise in control subjects but was unchanged in HFpEF patients. The authors stressed that patients with HFpEF manifest a significant reduction in PCr/ATP ratio at rest, indicating impairment of myocardial energy reserves. Moreover, during exercise, the energetically demanding active phase of relaxation during diastole lengthened and there was also a failure of the normal increase in contractile function on exercise in patients with HFpEF. These data suggest that trimetazidine treatment, due to its improvement in the energetic status in HFpEF, might be considered as a promising strategy to manage this category of patients.

Conclusion

Finally, the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure have established the position of trimetazidine as a new therapeutic strategy for the management of patients with angina and HF_rEF. Future research should reveal whether agents targeting cardiac metabolism can be used in HF_mrEF and HF_pEF patients without angina, as well as in patients with nonischemic etiology of heart failure. ■

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