Use of trimetazidine to treat diabetes patients with heart failure

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Abstract
Heart failure (HF) occurs commonly in modern society and is a major cause of morbidity and mortality all over the world. Cardiac energy metabolism is altered in HF and has been demonstrated to be an important factor in the development of HF in clinical and animal research. Trimetazidine is a metabolism modulator, which shifts energy production from free fatty acid to glucose oxidation. There is evidence demonstrating that trimetazidine can improve cardiac function and prognosis, even affecting cardiac electrophysiology. In this paper, recent literature on the beneficial therapeutic effects of trimetazidine on left ventricular dysfunction and HF is reviewed and discussed, especially in diabetes patients with HF. ■ Heart Metab; 2013;61:25–28

Keywords: Energy metabolism; heart failure; trimetazidine.

Introduction
Heart failure (HF) is a clinical syndrome characterized by the abnormality of cardiac structure and/or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues [1]. Approximately 1–2% of the adult population in developed countries has HF [1]. In the USA, the total number of HF-related hospitalizations increased from 3 891 737 in 2001 to 4 244 865 in 2009 [2]. The incidence of HF has brought about an enormous financial burden, estimated to be US$39.2 billion each year in the USA [3]. The causes of HF commonly are cardiac ischemia, cardiac hypertrophy, myocarditis, diabetic cardiomyopathy (DCM) and other secondary cardiomyopathies. According to the European Society of Cardiology guidelines on HF in 2012, coronary artery disease (CAD) is the cause of approximately two-thirds of cases of systolic HF [1]. Meanwhile, in the last Heart Failure Pilot Survey, it was reported that 64% of patients with acute HF and 85% with chronic HF had an ischemic etiology [4].

Energetic modulation during HF
In order to preserve normal cardiac ejection, the myocardium requires more energy than any other tissues. Herrmann [5] reported that HF was a state of energy starvation in 1939. Ever since then, evidence has demonstrated that altered energetic modulation may play an important role in the mechanisms of HF [6]. The energy that the heart uses (ATP) is produced in myocardium mainly by oxidizing fatty acids (60–90%), carbohydrates (10–40%) and some amino acids. Metabolism insufficiency in HF has been described in detail by Neubauer [6]. In brief, the metabolic machinery of the heart has three main components: substrate utilization, oxidative phosphorylation and ATP
transfer and utilization. When HF occurs, all three components change. Despite some inconsistent results, there is consensus that the failing heart relies more on glucose as its preferential substrate for ATP synthesis [7, 8], that is, there is a shift of metabolism away from a preference for fatty acids to more carbohydrate oxidation, which may be a compensatory or protective mechanism for HF [9]. In advanced HF, both fatty acids and glucose metabolism decline. In earlier HF, the phosphocreatine and total creatine levels are reduced, although ATP levels remain normal. The eventual outcome of the loss of high-energy phosphates and creatine kinase activity is contractile dysfunction and particularly the loss of inotropic reserve of myocardium. At the same time, the free ADP levels rise when HF occurs, which can inhibit the function of many intracellular enzymes, causing contractile dysfunction.

**Effects of trimetazidine in HF**

According to experimental and clinical data, targeting cardiac energy metabolism can be beneficial in HF [10]. One of strategies is due to an improvement of substrate utilization. Furthermore, trimetazidine may improve cardiac function by other mechanisms such as preservation of intracellular levels of phosphocreatine and ATP [11], reduction of calcium overload and free radical-induced injury, inhibition of cell apoptosis, improvement of endothelial function, and inhibition of cardiac fibrosis [12] (see Figure 1).

There is controversy about the beneficial and adverse effects of a reduction in fatty acid oxidation for HF. However, multiple results have suggested that partial inhibition of fatty acid oxidation is promising. Trimetazidine is the first competitive inhibitor of long chain 3-ketoacyl-coenzyme A thiolase on the market, and can decrease the oxidation of fatty acids and pro-

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**Abbreviations**

CAD: coronary artery disease; DCM: diabetic cardiomyopathy; HF: heart failure
mote the metabolism of glucose in HF [13], thereby decreasing oxygen utilization, especially in ischemia. Some studies have shown that trimetazidine brings about beneficial effects in patients with HF, including ischemic and nonischemic etiologies. However, other studies have shown limited benefits, because the small sample sizes produced underpowered results and metabolic therapy was just indicated by the guidelines [1]. We therefore performed a meta-analysis to explore the potential therapeutic effects of trimetazidine in the management of chronic HF in 2011 [12]. In the meta-analysis we found that trimetazidine could improve left ventricular ejection fraction, subjective and objective measures of functional status in HF, and perhaps most intriguingly reduced all-cause mortality. At the same time, the addition of trimetazidine to current optimal HF treatment does not increase the incidence of cardiovascular events and hospitalization. These data confirm that trimetazidine might be an effective strategy for treating HF. Ashrafian and Neubauer [14] commented that the study may present a credible argument that trimetazidine might be effective across almost all measures of cardiac function and provide the strongest statistical rationale to date that metabolic modulation may be successful in HF.

Effects of trimetazidine in diabetes patients with HF

DCM has become a more significant cause of HF, along with the increase in newly diagnosed cases of diabetes mellitus throughout the world. The utilization of substrate in myocardium presents a preference that varies in physiologic or pathologic demands, in order to produce enough energy for preserved cardiac function. However, in diabetes, the high levels of blood glucose and fatty acids cause this preference to be constrained [15]. The diabetic heart thus relies on fatty acid β-oxidation with increased oxygen consumption for ATP synthesis even in HF or myocardial ischemia. Trimetazidine might then improve the detrimental consequences. Evidence has suggested that trimetazidine could reduce silent and symptomatic episodes of transient myocardial ischemia in diabetes patients with CAD [16]. Another clinical trial that included diabetes patients with idiopathic dilated cardiomyopathy proved that trimetazidine could improve the left ventricular ejection fraction, improve left ventricular end-systolic volume, reduce C-reactive protein concentrations, reduce plasma N-terminal pro brain natriuretic peptide levels, and increase the 6-minute walking distance after 6 months’ follow-up [17]. These results indicated that trimetazidine might be an effective therapeutic strategy.

Electrophysiological effect of trimetazidine in HF

In recent years, some studies have been carried out on the electrophysiological effect of trimetazidine in HF. A clinical trial, which included 36 patients with HF treated by trimetazidine added to optimal treatment for HF, suggested that trimetazidine may improve the maximum P-wave duration and P-wave dispersion in association with improved left ventricular function. This suggests that trimetazidine may decrease the risk of atrial fibrillation in HF [18]. Another study showed that the addition of trimetazidine can effectively reduce QTC, Tpeak-Tend and Tpeak–Tend dispersion [19]. However, this effect appears mainly confined to patients with post-ischemic HF. These effects of electrophysiology indicate that trimetazidine could be used for reducing the risk of major arrhythmias, which may be by means of an undiscovered mechanism.

Conclusion

Energy metabolism treatment is a more recent theory in HF. Some energy metabolism modulators including trimetazidine, coenzyme Q [10], and phosphocreatine, which regulate the cell metabolism by means of different mechanisms, have been proved effective in HF. However, despite our recent meta-analysis showing that these benefits also translate into improved survival, larger and long-term follow-up clinical studies are required to confirm the efficacy in HF.

REFERENCES

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