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Review

# Rationale and benefits of trimetazidine by acting on cardiac metabolism in heart failure

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ABSTRACT

Heart failure is a systemic and multiorgan syndrome with metabolic failure as a fundamental mechanism. As a consequence of its impaired metabolism, other processes are activated in the failing heart, further exacerbating the progression of heart failure.
Recent evidence suggests that modulating cardiac energy metabolism by reducing fatty acid oxidation and/or increasing glucose oxidation represents a promising approach to the treatment of patients with heart failure.
Clinical trials have demonstrated that the adjunct of trimetazidine to the conventional medical therapy improves symptoms, cardiac function and prognosis in patients with heart failure without exerting negative hemodynamic effects.
This review focuses on the rationale and clinical benefits of trimetazidine by acting on cardiac metabolism in heart failure, and aims to draw attention to the readiness of this agent to be included in all the major guidelines dealing with heart failure.



## 1. Introduction

Despite advances in the treatment of heart failure, the disease continues to remain a costly and deadly condition, the management of which requires a lot of human and economic resources [1,2]. Heart failure is a complex syndrome with several features, including abnormal myocardial structure and function and neurohumoral activation. Therefore, pharmacological treatment of heart failure has focused on the suppression of neurohumoral activation, as well as regulation of the fluid volume overload, hemodynamics and optimization of heart rate control [3]. However, the growing understanding of the role of other mechanisms in the pathogenesis of heart failure, such as inflammatory activation and metabolic impairment, determined the search for new therapeutic approaches in addition to the therapy recommended by the guidelines.

Currently, multiple myocardial metabolic abnormalities have been revealed in heart failure. Moreover, beyond myocardial metabolic failure, systemic (peripheral) metabolic regulation has been found to contribute both to major symptoms (muscle weakness, fatigue, exercise limitation, and dyspnea) and to disease progression [4]. As a consequence, heart failure is conceived as a systemic and multi-organ syndrome with metabolic failure as the basic mechanism. Recently, impaired mitochondrial oxidative metabolism in heart failure, defined with the term "metabolic remodeling", was described as a component of a broader and more general concept of remodeling covering hemodynamic, neurohumoral, metabolic, and inflammatory processes, causing changes in cardiomyocytes, endothelium, vascular smooth muscle cells as well as interstitial cells and matrix [5]. This concept allows

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considering therapies targeting the cardiac metabolism along with conventional treatment of heart failure.

The list of new therapies targeting heart metabolism is constantly expanding, but most of them are not available in clinical practice yet. Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride) is an anti-ischemic metabolic modulator, which has been approved in more than 80 countries worldwide for the symptomatic treatment of chronic stable angina. Furthermore, there has been growing evidence that trimetazidine reduces ischemia-reperfusion injury after myocardial revascularization procedures [6–8] and improves cardiac function in heart failure [9–11]. There are now more than 100 articles available on PubMed that report on experimental or clinical trials proving the beneficial efficacy of trimetazidine in heart failure.

This review focuses on the rationale and clinical benefits of trimetazidine by acting on cardiac metabolism in heart failure, and aims to draw attention to the additional advantages that might be obtained by adding this agent to the standard therapy of heart failure.

## 2. Metabolic processes in the normal and failing heart

Due to its continuous contractile activity, the heart has a very high energy demand. About 95% of this energy is normally obtained by the production of ATP from mitochondrial oxidative metabolism, while the remaining 5% originate from glycolytic ATP production (Fig. 1A). The source of fuel for mitochondrial oxidative metabolism normally originates from a balance between fatty acids and carbohydrates (glucose and lactate), and to a lesser degree ketones and amino acids [12]. Dramatic alterations in energy metabolism occur in the failing heart, which contribute to the severity of contractile dysfunction [12]. A failing heart is "an engine out of fuel" [13], which is evidenced by a decrease in phosphocreatine and ATP levels in the failing myocardium [14–16]. Impaired mitochondrial integrity and function in heart failure result in a switch from mitochondrial oxidative metabolism to an increase in glucose uptake and glycolysis [17–21]. This increase in glucose uptake and glycolysis can occur even though mitochondrial glucose oxidation is impaired [22–26], resulting in an uncoupling of glycolysis from glucose oxidation [27–29]. This uncoupling produces lactate and $H^+$s, which decreases the efficiency of the heart (Fig. 1B) [12].

The heart has a tight reciprocal relationship between fatty acid oxidation and glucose oxidation, so that increases in fatty acid oxidation are associated with decreases in glucose oxidation and vice versa [12, 17]. Although overall mitochondrial oxidative metabolism is impaired in the failing heart, the decrease in glucose oxidation is more dramatic than alterations in fatty acid oxidation [24–26]. As such, the proportion of ATP derived from mitochondrial fatty acid oxidation exceeds that originating from glucose oxidation. This results in a less efficient heart, since: (1) more oxygen is required to produce ATP from fatty acid oxidation compared to glucose oxidation, and (2) low glucose oxidation increases lactate and $H^+$ production from the heart [12]. Consequently, one approach to improve cardiac efficiency in heart failure is to enhance glucose oxidation and, therefore, to promote a better coupling between glycolysis and glucose oxidation [27–29]. This can be achieved by inhibiting fatty acid oxidation or directly enhancing glucose oxidation. Inhibiting fatty acid oxidation to promote glucose oxidation involves exploiting the Randle cycle [30]. Acetyl CoA derived from fatty acid oxidation inhibits the rate-limiting enzymes of glucose oxidation, pyruvate dehydrogenase, thus lowering glucose oxidation. As a result, inhibition of fatty acid oxidation increases glucose oxidation. The rate of fatty acid oxidation can be regulated by: (1) lowering fatty acid supply to the heart; (2) inhibiting myocardial fatty acid uptake; (3) inhibiting mitochondrial fatty acid oxidation; or (4) by inhibiting directly mitochondrial fatty acid β-oxidation [31–41]. All of these scenarios result in a decrease in fatty acid oxidation, with a resultant increase in glucose oxidation (Fig. 1C). These approaches are also associated with an increase in cardiac efficiency, which can result in an improvement in contractile function in the failing heart [12].

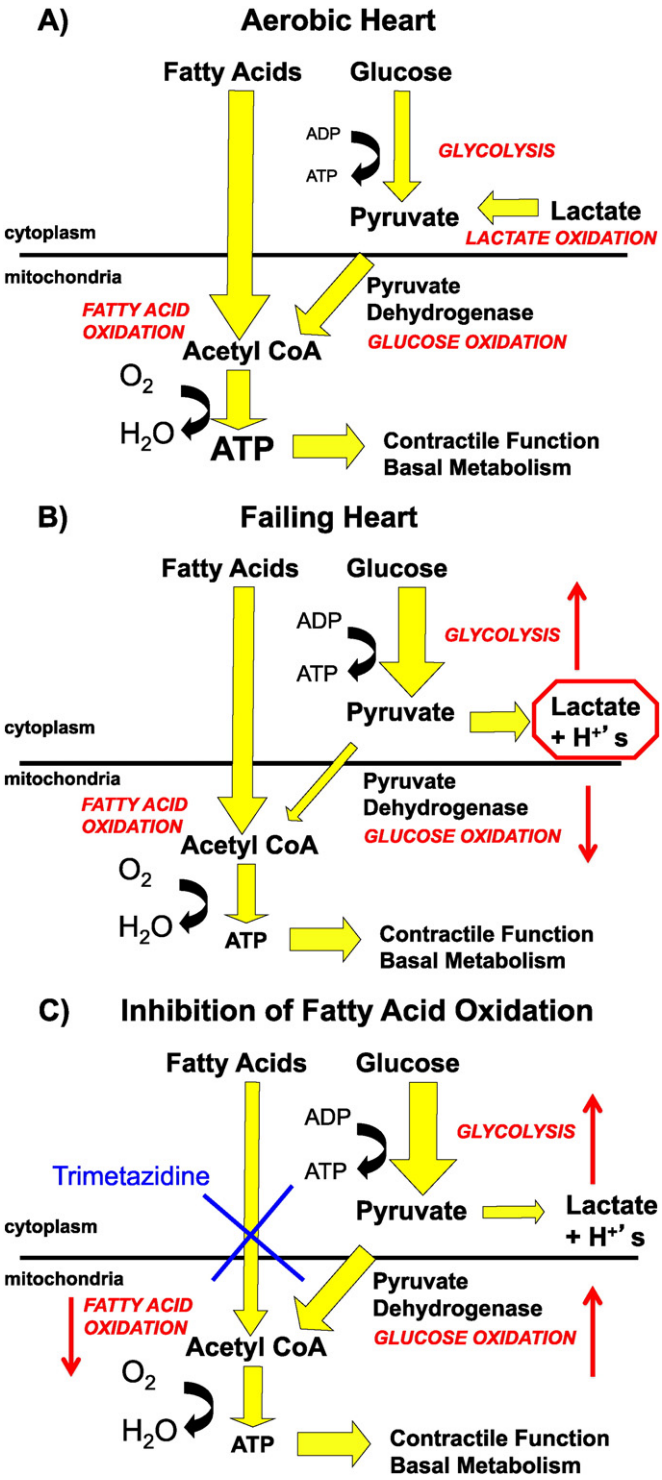


**Fig. 1.** Alterations in myocardial energy substrate metabolism in heart failure.

In the normal heart, fatty acids, glucose and lactate serve as the primary energy substrates to produce ATP via glycolysis, and mitochondrial oxidation of fatty acids, glucose and lactate (Fig. 1A). In the failing heart, decreases in glucose oxidation lead to energy deficit, that results in an increase in glycolysis (Fig. 1B). This results in an increase in lactate and proton production from glycolysis and glucose oxidation, that can lead to a decrease in cardiac efficiency. Inhibiting fatty acid oxidation (such as with trimetazidine) will increase glucose oxidation, and lessen the production of both lactate and protons (Fig. 1C). This can improve cardiac efficiency, resulting in an improvement in cardiac function.