# The metabolic approach to improving prognosis in ischemic heart disease

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## Abstract

Recent studies have demonstrated that alterations in cardiac metabolism can be present in ischemic heart disease and heart failure, suggesting an increased utilization of non carbohydrate substrates for energy production, with a reduction in the efficiency of myocardial oxygen consumption. A direct approach to the manipulation of cardiac energy metabolism consists in modifying substrate utilization. Trimetazidine is a pharmacological agent that shifts the preference for energy substrate away from fatty acid metabolism and towards glucose metabolism. Recent findings suggest that trimetazidine has a positive influence on ventricular function, various prognostic factors (inflammation and biochemical markers), and, probably, prognosis. Metabolic therapy offers concrete help in the management of coronary artery disease and dilated cardiomyopathy.
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**Keywords:** Trimetazidine, heart failure, ischemic heart disease, prognosis

## Introduction

Cardiovascular diseases are the leading cause of mortality in development countries and they still represent a heavy economic burden [1]. The global number of deaths attributable to ischemic heart disease is very high and, since 1990, it has become the most frequent cause of chronic heart failure, demonstrable in about 65% of the patients [2]. Aspirin, β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin type 1 receptor blockers, and lipid-decreasing agents are currently the milestones of pharmacologic management, supplemented by lifestyle changes [3]. However, side effects of chronic drug treatment may affect quality of life, and they are the main reason for poor patient compliance. Coronary artery bypass surgery and angioplasty are interventional procedures that are frequently used for ischemic heart disease, although they can be invasive and costly, and need to be repeated. In spite of these therapeutic options, mortality rates remain high, and many patients continue to have symptoms. An alternative strategy to improve prognosis and quality of life could be to treat the metabolic causes or consequences of ischemia [4].

## The metabolic approach in ischemic heart disease and heart failure

The main problem in the management of ischemic heart disease is prevention of ventricular remodeling, the pivotal mechanism contributing to evolution from left ventricular dysfunction to irreversible heart failure in patients with the condition [5]. This progressive process is linked to neurohormonal activation. Prevention of remodeling appears to be consistent with improvement in clinical outcome. In patients with left ventricular dysfunction or heart failure, treatment by combination neurohormonal blockade with ACE

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Table I. Effects of trimetazidine on modifiable prognostic factors in patients with ischemic cardiomyopathy and heart failure.

| Prognostic factor | Effect of trimetazidine |
| --- | --- |
| Diabetes mellitus | Beneficial effects in patients with coronary artery disease with or without left ventricular dysfunction |
| Renal function | Reduction of oxidative stress and ischemia-reperfusion injury in experimental study. Few data in humans. |
| NYHA class | Improvement in short- and long-term follow-up study |
| LVEF | Improvement in short- and long-term follow-up study |
| Biochemical markers: | |
| ● C-reactive protein | Reduced |
| ● Brain natriuretic peptide | Reduced |
| ● Troponin T | Unknown in patients with heart failure. Reduced after coronary angioplasty and coronary artery bypass graft |
| PCr/ATP ratio | Improved in short-term follow-up study |

NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; PCR/ATP, phosphocreatine/adenosine triphosphate.

inhibition and β-blockade is the standard evidence-based recommendation [6–8]. Recent studies have investigated the possibility of increasing cardiac performance without affecting oxygen consumption and hemodynamics, using agents aimed at enhancing myocardial energy efficiency. These drugs shift energy substrate utilization away from fatty acid metabolism and towards glucose metabolism, which is more efficient in terms of production of adenosine triphosphate (ATP). A decrease in circulating free fatty acid concentrations is obtained by the administration of glucose–insulin solutions [9] or β-blockers [10,11], or, alternatively, by agents that directly inhibit fatty acid oxidation, such as inhibitors of mitochondrial uptake of free fatty acids (via suppression of carnitine palmitoyl transferase I and II), or direct inhibitors of 3-ketoacyl coenzyme A thiolase (3-KAT), the last enzyme involved in β-oxidation. Of the latter class of pharmacological agents, trimetazidine and ranolazine are the only available drugs. Trimetazidine in particular, has been shown to affect myocardial substrate utilization by inhibiting oxidative phosphorylation, and by shifting energy production from free fatty acids to glucose oxidation by selective block of long-chain 3-KAT [12]. However, recent studies have outlined the potential benefits that trimetazidine may offer in myocardial dysfunction because of its ability to increase utilization of glucose and lactate, which are more efficient fuels for aerobic respiration, improving oxygen consumption of the myocardium by 16–26% [13].

## The metabolic approach: clinical relevance in patients with ischemic heart disease

Many studies have been undertaken to determine which factors increase mortality and morbidity in patients with ischemic heart disease and heart failure, across a variety of clinical settings. Factors that have

been shown to be predictors of mortality are increasing age, history of diabetes mellitus or renal dysfunction, measures of higher functional disability such as New York Heart Association (NYHA) class, lower left ventricular ejection fraction (LVEF), lower sodium concentrations and lower quality-of-life scores [14–16]. Recently, intense interest has emerged in the predictive value of plasma biochemical markers such as C-reactive protein, B-type natriuretic peptide, and cardiac troponin T [17–19]. Recent studies revealed evidence that trimetazidine treatment could have a positive influence on these prognostic factors (Table I). For all these reasons, expanded upon below and summarized in *Figure 1*, a therapeutic approach using trimetazidine could exert a positive influence on left ventricle remodeling, with potential prognostic relevance in patients with ischemic cardiomyopathy.

## Effects of trimetazidine in patients with ischemic cardiomyopathy

On the basis of the hypothesis that free fatty acid inhibitors could act as metabolic modulators in the protection of ischemic myocardium, the effects of trimetazidine have been assessed in patients with ischemic cardiomyopathy. In these patients, mortality rate and quality of life are unsatisfactory and left ventricular dysfunction is the result of myocardial fibrosis, or hibernating or stunned myocardium. The therapeutic management of hibernating and stunned myocardium is fundamental in ischemic cardiomyopathy, because they are potentially reversible conditions.

Belardinelli et al [20] reported that trimetazidine exerted beneficial effects on chronically dysfunctional myocardium. Forty-four patients with ischemic cardiomyopathy and a previous acute myocardial infarction, multivessel coronary artery disease, and ventricular dysfunction (ejection fraction 33%) were treated with trimetazidine. After 2 months of treatment,
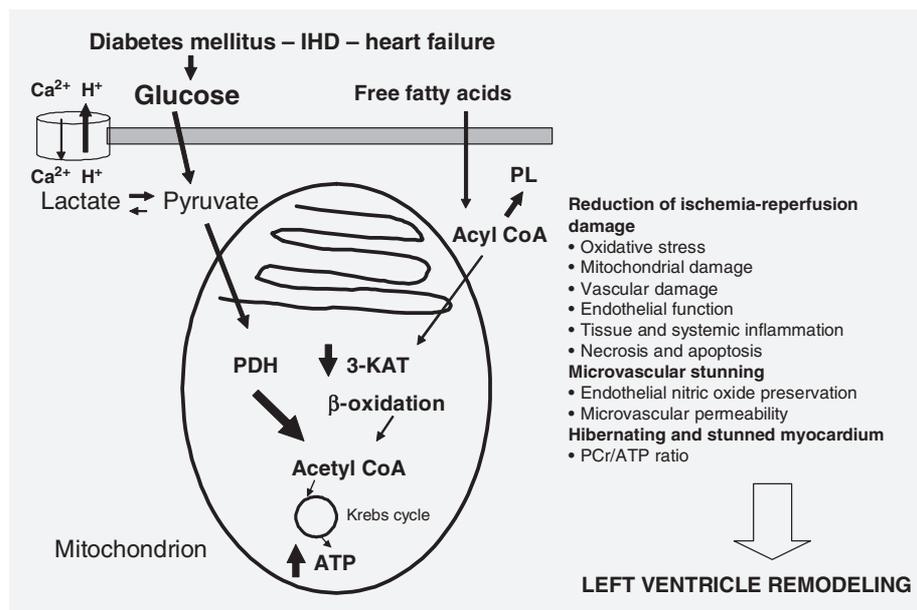
*Figure 1. Biological and metabolic effects of trimetazidine in patients with ischemic heart disease (IHD). Trimetazidine reduces fatty acid oxidation and stimulates glucose utilization by selective inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase (3-KAT). The coupling of glycolysis with glucose oxidation is improved, and production of adenosine triphosphate (ATP) is increased. The deleterious effects of acidosis and intracellular $Ca^{2+}$ overload in ischemic, hypoxic, and overstretched cells are limited or abolished. Trimetazidine exerts a cardioprotective effect by rapidly restoring the phosphorylation processes, preserving the phosphocreatine (PCr)/ATP ratio, protecting cardiac cells against intracellular acidosis, preventing intracellular accumulation of sodium and calcium ions, and, finally, by reducing oxidative damage. All these properties protect the myocardial cell against necrotic and apoptotic cell death. These two steps are considered fundamental in regulating left ventricle remodeling and progressive decline of the contractile function occurring during the evolution of dilated cardiomyopathy. CoA, coenzyme A; PDH, pyruvate dehydrogenase; PL, phospholipids.*

there was a significant improvement in the contractile response to low-dose dobutamine in chronically dysfunctional myocardium. Fragasso et al [21] demonstrated that trimetazidine restored the energetic status of myocardium in patients with heart failure. In these patients, the phosphocreatine (PCr)/ATP ratio, an important index of energetic status, was similar to that in healthy individuals, and significantly improved compared with that in a placebo group. These results appear particularly interesting, especially in view of previous evidence suggesting the PCr/ATP ratio to be a significant predictor of mortality [22].

The beneficial effects of trimetazidine in patients with ischemic cardiomyopathy are also evident in long-term follow-up. Brottier et al [23] assessed the value of trimetazidine treatment with in patients with severe ischemic cardiomyopathy. After 6 months of treatment, the patients reported a considerable improvement in symptoms and showed a greater LVEF compared with the placebo group. These effects are also evident in longer follow-up. We reported that 12 months of treatment with trimetazidine induced a significant improvement in ejection fraction and NYHA functional class in patients with ischemic cardiomyopathy and LVEF <40% [24].

The beneficial effects of trimetazidine are also present in elderly and diabetic patients. Vitale et al [25] reported 47 patients (aged $78 \pm 3$ years) with ischemic

cardiomyopathy who were treated with trimetazidine and achieved significant improvement in ejection fraction and quality of life. Fragasso et al [26] reported an improvement in ejection fraction in diabetic patients with ischemic cardiomyopathy. These beneficial effects of trimetazidine were maintained in long-term follow-up, and contrast with the natural history of the disease, as shown by the progressive decrease in ejection fraction in the placebo group.

### Effects of trimetazidine on proinflammatory status

A proinflammatory state is recognized in chronic heart failure, and the degree of immune activation corresponds to disease severity and prognosis. In patients with heart failure, greater concentrations of C-reactive protein have been related to higher rates of readmission to hospital and mortality [27]. Trimetazidine exerts positive effects on the inflammatory status that characterizes ischemic cardiomyopathy. After ischemia, a significant reduction in the infiltration of neutrophils to the ischemic area is reported [28]. Recently, in an experimental model of ischemia-reperfusion damage, we demonstrated that trimetazidine reduced cellular damage and preserved endothelial function. This effect was related to a preservation of expression of endothelial nitric oxide

synthase [29]. The anti-inflammatory effects of trimetazidine are also evident in patients with ischemic cardiomyopathy, in which this drug reduces the plasma concentrations of C-reactive protein [24]. A reduction in inflammatory status could have relevant prognostic effects in the evolution of ischemic cardiomyopathy during trimetazidine treatment.

It has been also observed that trimetazidine was able to reduce the release of endothelin-1 in patients with heart failure [30]. Growth factors, vasoactive substances, and mechanical stress are involved in increases in endothelin-1. Despite the recognized adaptive advantage of endothelin-1 in supporting the contractility of the failing heart, persistent increases in its expression in the failing heart have a pathophysiologically maladaptive aspect, and are associated with the severity of myocardial dysfunction [30]. In patients with left ventricular dysfunction, the plasma concentration of B-type natriuretic peptide is also significantly reduced during treatment with trimetazidine [31]. If we consider B-type natriuretic peptide as a marker of myocardial load, trimetazidine treatment could positively redirect the neurohormonal pathway in patients with ischemic cardiomyopathy and reduce the cellular damage that characterizes chronic evolution of left ventricle remodeling.

## The metabolic approach: effects on prognosis

Although the findings to date are highly suggestive, it remains to be ascertained whether the benefits discussed above would translate into improved survival rates. The question of whether there are prognostic benefits during trimetazidine treatment in patients with ischemic cardiomyopathy is still under investigation. Improvement in ejection fraction, NYHA class, and biochemical markers in these patient probably influences prognosis. In patients with ischemic left ventricular dysfunction and multivessel coronary artery disease, El-Kady et al [32] reported positive effects of trimetazidine on prognosis: survival at 2 years was 92% among patients treated with trimetazidine and 62% among those treated with placebo. In a post-hoc analysis obtained from the 48 month extension of the Villa Pini d'Abruzzo trimetazidine trial [24], we observed that trimetazidine treatment reduced all-cause mortality (17% compared with 39% in controls) and admission to hospital because of heart failure (decreased by 47%) (unpublished observations).

## Conclusions

A metabolic approach could have a relevant role in the therapeutic management of heart failure. Trimetazidine treatment has a positive influence on ventricular function, quality of life, various prognostic factors (inflammation and biochemical markers), and, probably, prognosis. Although its true relevance to prognosis needs to be ascertained by multicenter, randomized, placebo-controlled trials, the selective inhibition of 3-KAT with trimetazidine represents a new therapeutic opportunity in the management of patients with ischemic heart disease and heart failure. ■

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