

# Clinical benefits of trimetazidine in patients with coronary artery disease and diabetes mellitus

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## Abstract

The heart is capable of using fatty acids and glucose as its main sources of energy, with their balance depending on many physiological and pathological situations. In the presence of ischemia, there is a switch to oxidation of fatty acids, which has deleterious effects on the function of the heart. Trimetazidine reduces fatty acid oxidation and increases glucose oxidation, which tends to normalize the metabolism and function of the heart in ischemia and diabetes. It has been shown that trimetazidine reduces angina and ischemia in patients with stable coronary artery disease – an effect that has also been observed in patients with coronary artery disease who have diabetes mellitus.

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## Introduction

The prevalence of diabetes mellitus has increased dramatically over recent decades, and this trend is expected to continue in the foreseeable future. Most cases of diabetes are attributed to type 2 (non-insulin-dependent) diabetes mellitus, which carries a high cardiovascular risk. Indeed, cardiovascular disease is the leading cause of death in these patients, atherosclerosis being responsible for around 80% of deaths [1].

Many pathogenic factors can pave the road to the development and progression of atherosclerosis in diabetes mellitus; among them, hyperglycemia, hypertension, dyslipidemia, insulin resistance, hypercoagulability, impaired fibrinolysis, and endothelial dysfunction are key [2]. Furthermore, these factors can also play a part in worsening the clinical presentation and prognosis of patients with diabetes who have coronary artery disease, such as those with

myocardial infarction. As the same adverse prognosis has been observed in diabetic patients with other types of heart disease, such as left ventricular hypertrophy and dilated cardiomyopathy, the cause is most probably a derangement of cardiac metabolism produced by diabetes mellitus, not a differential pathophysiology of the atherosclerotic plaque in this disease [3].

## Effect of diabetes mellitus and ischemia on cardiac metabolism and function

Under normal circumstances, the heart is an “omnivorous” organ, capable of oxidizing different classes of substrates, such as carbohydrates or free fatty acids (FFAs), for the production of energy (*Figure 1*) [4]. The normal heart obtains 60–90% of its energy from FFA oxidation, and the remainder from glucose and lactate. FFA metabolism yields more ATP per gram,

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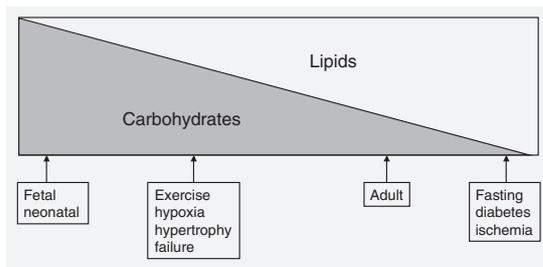


Figure 1. Metabolic substrates of the heart. The heart can use several metabolic substrates, but the contribution of each of them to ATP synthesis varies depending on the age of the patient and on several conditions (physiological or pathological). Fatty acids are the predominant substrate for the adult heart, whereas carbohydrates are the preferred fuel for fetal hearts. Moreover, in adults the heart can shift its metabolic substrate in response to substrate availability (fasting, exercise) or in response to altered regulatory mechanisms (heart failure, ischemia, diabetes). (Modified from Tian [4].).

but requires a greater oxygen consumption because it is less efficient. The ability of the heart to switch from one substrate to another allows it to adapt efficiently to many different factors, such as substrate availability, tissue perfusion, hormonal regulation, and the amount of cardiac work, and is therefore fundamental to its health.

Type 2 diabetes mellitus disturbs the capability of the heart to use different metabolic substrates and makes it dependent almost exclusively on the metabolism of fatty acids. Peripheral insulin resistance produces an increase in the delivery of fatty acids to the heart. The increased uptake of fatty acids by the heart produces a decrease in glucose oxidation by the organ as a result of the Randle phenomenon and the activation of peroxisome proliferator activated  $\alpha$ . Fatty acids also inhibit insulin signaling pathways, which produces a further reduction in the oxidation of glucose by the heart. As a consequence of all of these changes, fatty acid oxidation increases and glucose oxidation decreases in the diabetic heart [5]. However, because of the hyperglycemia present in diabetes mellitus, glucose uptake by the heart is frequently within normal ranges in diabetes mellitus.

These metabolic changes in the hearts of patients with diabetes result in a derangement of cardiac function that can have a specific clinical expression [6]. Fatty acid oxidation is less efficient than glucose oxidation, because less ATP is produced per mole of oxygen used. Furthermore, other factors such as an increase in mitochondrial uncoupling, an overproduction of reactive oxygen species with consequent deleterious effects, and an accumulation of glucose and fatty acid metabolic intermediates in the cells also contribute to further deterioration of cardiac cellular function and survival.

Several studies in experimental models have shown that the metabolic modification of the heart in diabetes mellitus produces an improvement in cardiac function [7]. This, together with the fact that magnetic resonance spectroscopy enables study of the metabolic status of the heart [8,9], has increased interest in this type of study in humans. A recent study performed with pioglitazone and metformin failed to demonstrate that a change in cardiac metabolism translates into a change in cardiac function in men with diabetes mellitus [10], whereas other authors have found an improvement in cardiac function in patients with myocardial dysfunction and diabetes mellitus treated with a metabolic modulator such as trimetazidine [11].

Because mitochondrial oxidative metabolism is critically dependent on the supply of oxygen to the heart, any decrease in oxygen supply to the myocardium, such as is seen in myocardial ischemia, can result in a decrease in the production of ATP. There is an initial adaptive increase in glycolysis, aimed at producing ATP in the absence of oxygen, which is followed by a significant increase in the oxidation of fatty acids. Therefore, fatty acid oxidation becomes the main residual source of mitochondrial oxidative metabolism in myocardial ischemia. The high glycolysis coupled to low glucose oxidation results in the production of lactate and protons, which leads to a reduction in the pH of cell, calcium overload, and contractile dysfunction. These changes are even more marked in diabetic individuals with coronary artery disease [12].

The optimization of cardiac metabolism represents an interesting approach to the treatment of heart disease that is aimed at switching the fuel preference of the heart to glucose instead of fatty acid. This can be attained through different strategies: direct inhibition of mitochondrial fatty acid oxidation (trimetazidine and ranolazine), prevention of the mitochondrial uptake of fatty acids (etomoxir), reduction of the circulating concentrations of free fatty acids (infusion of glucose–insulin–potassium solution), or direct stimulation of glucose oxidation and improvement in its coupling to glycolysis (dichloroacetate) [13,14].

### Trimetazidine in diabetes and myocardial ischemia

As inhibition of fatty acid oxidation and stimulation of glucose oxidation can improve cardiac efficiency and function in the heart, trimetazidine, a piperazine derivative that belongs to the family of partial fatty acid oxidation inhibitors, offers one interesting approach to the modification of the metabolic phenotype of the heart in diabetes and ischemia, switching the substrate for oxidation from fatty acid to glucose.

Trimetazidine inhibits the enzyme of fatty acid  $\beta$ -oxidation, long-chain 3-ketoacyl coenzyme A thiolase (3-KAT). Through the inhibition of myocardial fatty acid oxidation, glucose and pyruvate oxidation are increased (pyruvate dehydrogenase activity is increased) and lactate production is decreased at the time of ischemia. As a consequence, the deleterious metabolic consequences of ischemia are corrected independently of hemodynamic factors [15].

Trimetazidine has been shown to be an effective drug for the treatment of angina pectoris and ischemia in chronic coronary artery disease. In a Cochrane review of the clinical efficacy and tolerability of trimetazidine in patients with stable angina, a total of 23 randomized trials involving 1378 patients were included. Compared with placebo, trimetazidine reduced both the weekly rate of angina attacks (by 40%;  $P < 0.0001$ ) and consumption of nitrate medication ( $P < 0.0001$ ). Objectively, trimetazidine improved exercise time to 1 mm ST-segment depression ( $P = 0.0002$ ). Furthermore, the effects of trimetazidine were found to be similar to those of hemodynamic antianginal agents, but with a lower incidence of adverse effects. The benefits were obtained with trimetazidine used both as monotherapy and in combination with other agents [16].

We studied a total of 580 patients with type 2 diabetes mellitus and coronary artery disease (the DIETRIC study) treated with trimetazidine in association with other anti-ischemic drugs, with the aim of analyzing the anti-ischemic effect of trimetazidine. The clinical response and results of a treadmill stress test at 6 months were assessed. The weekly number of angina crises ( $P < 0.001$ ) and the use of glyceryl trinitrate pills ( $P < 0.001$ ) were reduced by trimetazidine. Furthermore, there were increases in total exercise time ( $P < 0.001$ ) and in time to a 1 mm ST-segment depression ( $P = 0.02$ ) in the 6 months stress test, in addition to an excellent tolerance of the drug [17] (Figure 2). Similar observations in small randomized trials have been made by other authors [18,19].

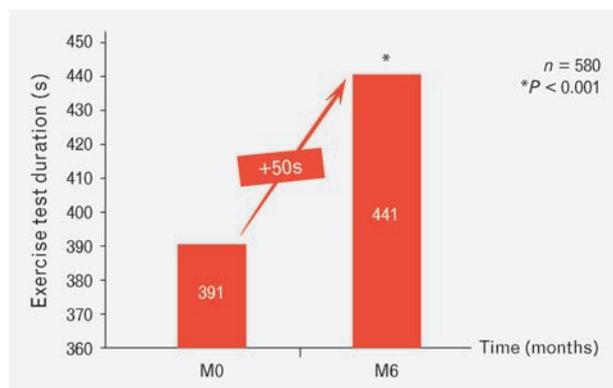


Figure 2. Exercise test at baseline and after Trimetazidine treatment. Trimetazidine significantly increases exercise test duration after 6-month of treatment ( $P < 0.001$ ).

Although there are no data concerning improved prognosis after treatments with trimetazidine, small trials have revealed an interesting trend. It has been demonstrated recently, in 116 patients with coronary artery disease and left ventricular dysfunction undergoing cardiac rehabilitation, that the addition of trimetazidine to exercise training produced greater improvements in functional capacity, left ventricular ejection fraction, and endothelium-dependent dilation than were achieved with trimetazidine or exercise training alone. Some of the patients studied had diabetes, and this randomized study revealed a synergistic role of trimetazidine with exercise [20]. Furthermore, the addition of trimetazidine to the standard treatment in patients with diabetic cardiomyopathy can improve left ventricular systolic function and functional capacity despite no change in myocardial perfusion [21].

## Summary

Trimetazidine is an anti-ischemic drug that modulates the metabolism of the heart and improve symptoms and quality of life in patients with angina pectoris. Its profile is especially useful in patients with diabetes mellitus, as it tends to normalize the metabolic functional changes in the heart that are induced by diabetes mellitus [22]. ■

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