

The importance of a metabolic approach to anti-ischemic protection

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Abstract

Trimetazidine acting as a metabolic agent reduces symptomatic and silent ischemia – the total ischemic burden. Its cellular action in improving myocardial metabolism is cardioprotective and may explain the improvement in left ventricular function seen in the failing heart as a result of its use. The metabolic approach to myocardial ischemia is becoming increasingly important, with symptomatic and potentially prognostic benefits.

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Introduction

The management of the patient with ischemic heart disease can be viewed in terms of providing symptomatic benefit or improving prognosis – preferably, both [1]. This philosophy extends to all groups of patients, but the emphasis may change on an individual basis – we treat people as individuals and not as statistics. For example, for the same symptom limitation, an elderly person may be more focused on quality of life and accept some restriction in preference to an invasive strategy with its initial risks, whereas a younger individual with lower initial risks may elect to undergo intervention if the evidence base for a prognostic benefit is good enough. Although we consider the patient as an individual, we also need to recognize each patient's circumstances within their family, and the importance of involving relatives and friends in the management decisions. This is particularly important with respect to the elderly, who may live alone and, to some extent, be dependent on others to maintain their quality of life.

Targeting ischemia

Under normal aerobic conditions, free fatty acids (FFA) account for 60–90% of the energy generated in the adult heart, whereas carbohydrates contribute 10–40%. During ischemia, there is a shift towards glucose metabolism, which is advantageous because, to generate the same amount of ATP, fatty acids require 10–15% more oxygen than is required by glucose.

As ischemia increases, the myocardium increases its utilization of glucose, even though FFA oxidation remains the major energy substrate. In addition to requiring more oxygen to generate energy, an increase in the rate of FFA oxidation leads to suppression of glucose oxidation as a result of inhibition of pyruvate dehydrogenase. This leads to the accumulation of lactate and protons in the ischemic cells, acidosis, and a reduction in contractile function, in addition to decreasing the threshold to ventricular arrhythmias [2]. Reversing this process would be expected to benefit the ischemic heart clinically,

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and perhaps prognostically. Suppressing FFA oxidation leads to an increase in myocardial glucose utilization, and, because pyruvate dehydrogenase is not suppressed to the same degree, there is a decrease in lactate production.

Achieving the objective of decreasing oxygen demand can be indirect, using hemodynamic agents, or direct, using the metabolic agent, trimetazidine.

Hemodynamic approach

The traditional hemodynamic approach to reducing oxygen demand by the use of β -blockers, calcium antagonists, and nitrates is a well established anti-ischemic strategy [3]. The principal mechanism of achieving a reduction in oxygen demand is by decreasing blood pressure, contractility, and heart rate, with a debatable effect on improving oxygen supply secondary to coronary vasodilatation. Unfortunately, when titrated to effect, these agents reach a plateau of hemodynamic suppression, so that adding further dose increments or agents with a similar mechanism of action confers no benefit symptomatically, whereas adverse effects increase, especially in the elderly [4]. There is no evidence base for the use of several hemodynamic drugs with similar actions, yet it is widely practiced. Many patients are therefore receiving excessive medication and suffer side effects that limit their quality of life. Hemodynamic agents are undoubtedly beneficial; however, an alternative but complementary metabolic mechanism for reducing ischemia has been extensively investigated [5].

Metabolic therapy

In contrast to the hemodynamic approach, metabolic agents do not reduce oxygen demand or increase blood supply [5]. Trimetazidine is the most widely studied agent, and there is a strong evidence base for its effectiveness as an anti-anginal treatment, whether used as monotherapy or in combination with hemodynamic agents [4–6]. Trimetazidine inhibits 3-ketoacyl coenzyme A thiolase, which leads to a reduction in fatty acid oxidation and stimulation of glucose oxidation (Figure 1). By modifying the energy substrates, trimetazidine reduces ischemia and brings about an improvement in symptoms. Importantly, a significant literature now exists supporting a direct anti-ischemic effect of trimetazidine on myocardial cells that is recognized to be a cardioprotective action [6].

Recently, improvement in symptoms, left ventricular function and, possibly, prognosis have been identified in patients with heart failure who were treated with trimetazidine, taking the concept of cardioprotection into a clinical arena traditionally associated with a reduced quality of life and poor prognosis even when all conventional evidence-based approaches to treatments are utilized [7].

Patients with diabetes are well known to be at increased cardiovascular risk. A diabetic individual with no evidence of cardiovascular disease has a vascular risk similar to that of a non diabetic individual with coronary disease, and a diabetic person with coronary disease has a cardiac death rate twice that of a person who is not diabetic. The use of metabolic agents in diabetic patients represents a logical

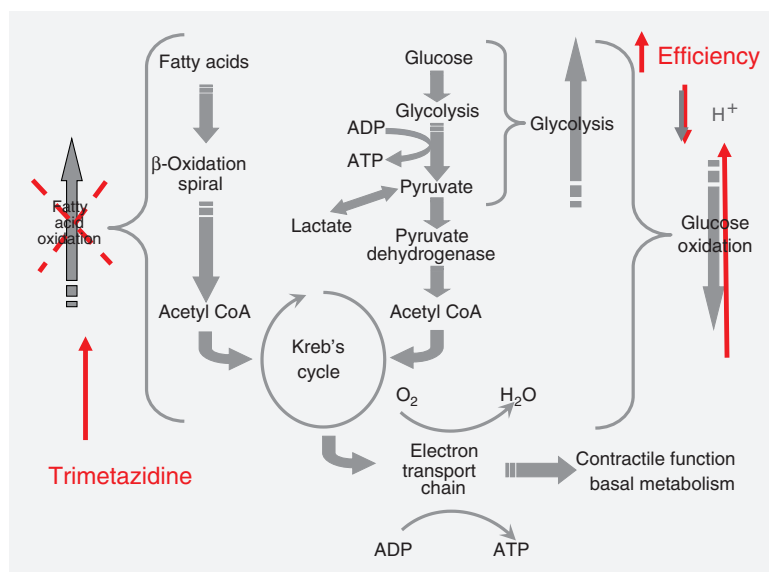


Figure 1. Glucose and fatty acid metabolism in the heart. Trimetazidine inhibits 3-ketoacyl coenzyme A thiolase, which leads to a reduction in fatty acid oxidation and stimulation of glucose oxidation. By shifting metabolism from fatty acid oxidation to glucose oxidation, trimetazidine improves cardiac efficiency. CoA, coenzyme A.

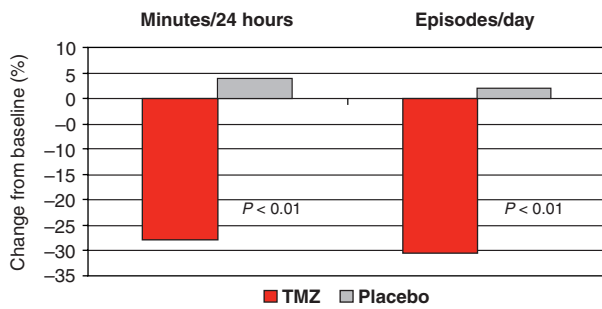


Figure 2. Comparison of the effect of placebo or trimetazidine added to standard anti-anginal therapy on episodes of silent myocardial ischemia and total ischemic burden. TMZ, trimetazidine. (From Marazzi et al [9], with permission.)

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approach to their treatment, given the mechanism of action of these agents, because patients with diabetes exhibit reduced glucose uptake and utilization, and an increased uptake and utilization of FFAs [8] – in short, patients with diabetes are metabolically vulnerable to ischemia. The use of trimetazidine in diabetes has been shown to reduce the incidence of symptomatic and silent ischemia – the total ischemic burden (Figure 2) [9]. These benefits, combined with the evidence that trimetazidine can improve the failing heart in addition to decreasing the symptoms of angina, places metabolic therapy at the centre of the management of ischemia, not the periphery.

The metabolic approach to anti-ischemic protection is gathering both momentum and importance. ■

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