Vastarel MR: from decades of clinical experience in stable angina to new perspectives

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Abstract

Trimetazidine has been known for years as being an effective, ''patient-friendly'', anti-anginal agent. Recent studies using the modified release formulation (Vastarel MR) have confirmed the efficacy of trimetazidine in stable ischemic heart disease and suggested that it can be beneficial in a number of cardiac conditions.
Trimetazidine has been reported to have a favourable impact on the prognosis of patients surviving an ST-elevation myocardial infarction and to exert a cardioprotective effect in patients undergoing an ischemia-reperfusion sequence, such as patients submitted to PCI or CABG procedures.
However, the most exciting perspectives come from the heart failure area, where a beneficial effect has been reported on quality of life and prognosis.
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Introduction

Cardiovascular disease and chronic congestive heart failure represent major public health concerns that continue to have a poor prognosis [1]. The need to improve the management of myocardial ischemia and heart failure is therefore widely recognized, even though many advances have been made over the past decade.

In recent years, strong evidence has been accumulated implicating altered cardiac energy metabolism in the pathogenesis and progression of ischemic heart disease and of heart failure, and this has focused attention on new pharmacological targets for the better management of these diseases [2].

In myocardial ischemia, most patients are initially prescribed drugs (such as β-blockers, calcium antagonists, and nitrates) that address the hemodynamic imbalance between oxygen supply and demand. However, besides hemodynamic imbalance, ischemia has harmful metabolic consequences that also should be addressed from the outset. These are approached through anti-ischemic metabolic therapy, which acts directly on cardiomyocytes and optimizes energy production, enhancing cardiac efficiency and counteracting the metabolic disturbances caused by ischemia.

The use of metabolic therapies for treating myocardial ischemia began to attract attention in the late 1960s and the 1970s. In 1999 it was clearly

recognized that ''fundamentally, myocardial ischaemia is a metabolic disorder and thus should ideally be treated by metabolic therapy'' [3].

Trimetazidine (Vastarel MR), inhibits 3-ketoacyl coenzyme A thiolase within the cardiomyocytes, which reallocates energy generation from fatty acids to the more efficient oxidation of glucose [4]. By its unique mode of action, trimetazidine increases the amount of energy available for the heart under ischemic conditions by one-third [5]. Today, trimetazidine is the most studied and widely used metabolic anti-ischemic agent.

Trimetazidine in stable angina

The therapeutic effect of trimetazidine in patients with stable angina has been extensively investigated in monotherapy and in association with β-blockers, calcium antagonists, or nitrates [6–8]. The clinical benefits include a reduced number of anginal attacks, increased exercise capacity, and a prolonged ischemic threshold and time to 1-mm ST-segment depression.

A recent meta-analysis, performed on the same methodological basis as that published in the Cochrane library, gathered 2786 patients from 22 randomized, placebo-controlled, simple or double-blind, parallel or crossover design trials conducted with trimetazidine in patients with stable angina [9]. It evaluated the effect on symptoms and exercise response achieved by treatment with trimetazidine, in monotherapy and in combination, in comparison with placebo or classic agents. The results of this meta-analysis showed that the overall treatment effect was statistically significant in favor of trimetazidine for all efficacy criteria, with the following differences between the trimetazidine and placebo groups at the end of treatment:

- a reduction of 1.44 (95% confidence interval [CI] 0.82 to 2.06) in the number of weekly episodes of angina.
- a decrease of 1.29 (95% CI 0.71 to 1.88) in the frequency of use of glyceryl trinitrate per week.
- an increase of 23.31 s (95% CI 2.65 to 43.97 s) in total exercise duration.
- a delay of 33.88 s (95% CI 15.94 to 51.83 s) in the time to 1-mm ST-segment depression.

Trimetazidine, therefore, has today an extensive clinical evidence base demonstrating its efficacy in treating patients with stable angina when it is used either as monotherapy or in combination with other antianginal drugs. Moreover, unlike the hemodynamically acting agents, trimetazidine does not suppress heart rate or blood pressure and is very well tolerated,

providing a particularly well suited solution for fragile coronary patients such as those with diabetes or who are elderly.

The findings of a recent original research paper, furthermore, revealed that the inclusion of the metabolic agent trimetazidine early in the treatment of patients with stable angina may confer a survival benefit [10]. These were the data from a multicenter study that assessed the independent effects, on 6-month predicted mortality risk, of different antianginal agents used in patients with stable angina who went on to survive a myocardial infarction. The study included 353 relatively young (mean age 55 years) patients with stable angina, most of whom (91.5%) had not had a prior myocardial infarction and had previously been receiving at least one antianginal drug (β-blockers, calcium antagonists, nitrates, nicorandil, or trimetazidine) for an average of 2 years. The 6-month postdischarge mortality risk was calculated using a GRACE (Global Registry of Acute Coronary Events) prediction score card and nomogram for each patient. For treatments that included the agents listed, the odds ratios (95% CI) of 6-month all-cause mortality after surviving a myocardial infarction were:

β-adrenoceptor antagonist: 0.63 (0.26 to 1.52; $P = 0.309$)

calcium channel antagonist: 0.76 (0.12 to 2.89; $P = 0.638$)

nitrate: 0.52 (0.26 to 1.05; $P = 0.070$)

nicorandil: 0.62 (0.29 to 1.33; $P = 0.221$)

trimetazidine: 0.36 (0.15 to 0.86; $P = 0.022$).

The results (*Figure 1*) indicated that only those patients receiving antianginal treatment that included trimetazidine before they had a myocardial infarction experienced a significant reduction in mortality risk.

Figure 1. Independent effects, on 6-month predicted mortality risk, of different antianginal agents used in patients with stable angina who went on to survive a myocardial infarction (MI). From Iyengar and Rosano [10], with permission.

Trimetazidine in acute ischemic conditions

Various mechanisms are involved in the development and the progression of ischemia-reperfusion injury, such as increased oxidative stress, endothelial dysfunction, and metabolic disturbances. A better understanding of the changes associated with ischemia and reperfusion is now translating into new cardioprotective strategies that might provide benefits over and above those derived from myocardial reperfusion alone [11]. A strategy involving trimetazidine has also been shown to confer important benefits in patients experiencing acute periods of ischemia when undergoing revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]). The effect of pretreatment with, or concomitantly administered, trimetazidine on ischemic reperfusion injury was first studied some time ago. Trimetazidine was reported to protect the myocardium and improve cardiac function during percutaneous transluminal coronary angioplasty (PTCA), without altering heart rate or systemic or intracoronary pressures [12,13].

More recently, it has been shown that trimetazidine prevents contrast-induced nephropathy in patients undergoing coronary procedures, even in those who are at high risk (patients with chronic renal insufficiency) [14]. An accompanying paper [15] reported the beneficial effects of pretreatment with an acute loading dose of trimetazidine before PTCA. Before intervention, 266 patients with coronary artery disease were randomly assigned to a trimetazidine group or a control group. Troponin Ic concentrations were measured before and 6, 12, 18, and 24 h after PTCA. Post procedural cTnI concentrations were significantly reduced in the trimetazidine-treated group compared with the control group, at all time points: 6 h (4.2 ± 0.8 ng/mL compared with 1.7 ± 0.2 ng/mL; $P < 0.0001$), 12 h (5.5 ± 1.5 ng/mL compared with 2.3 ± 0.4 ng/mL; $P<0.0001$), 18 h (9 ± 2.3 ng/mL compared with 3 ± 0.5 ng/mL; $P<0.0001$), and 24 h (3.2 ± 1.2 ng/mL compared with 1 ± 0.5 ng/mL; $P<0.0001$).

Labrou et al [16] have demonstrated that the administration of trimetazidine to patients before and after PCI minimizes PCI-induced myocardial damage and improves left ventricular function 1 and 3 months after the procedure.

The cardioprotective effect of trimetazidine during coronary artery graft surgery was assessed by treating patients with the drug for 3 weeks before surgery and by including trimetazidine in the cardioplegic solution. Patients pretreated with trimetazidine had better ventricular function ($P = 0.01$) than patients treated with placebo [17]. In another study, patients received trimetazidine 3 weeks before CABG and troponin T concentrations were measured before
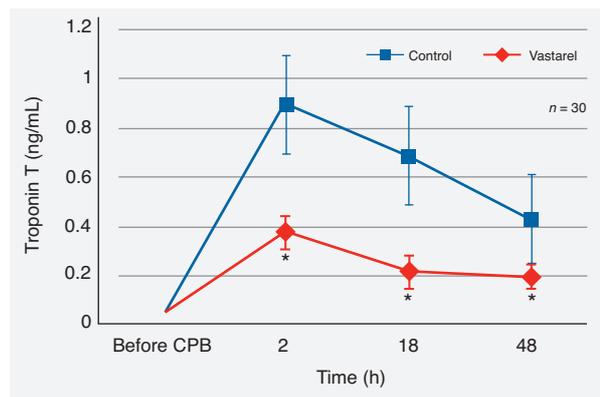

Figure 2. Cardioprotective effect of trimetazidine (Vastarel) during coronary artery graft surgery in patients treated with the drug for 3 weeks before surgery and receiving trimetazidine in the cardioplegic solution. CPB = cardiopulmonary bypass. From Tünerir et al [18], with permission.

and at 12, 24, and 48 h after the procedure, to evaluate myocardial injury. The patients pretreated with trimetazidine exhibited significantly lower troponin T concentrations after completion of surgery and at each postoperative time point (*Figure 2*) [18].

The findings of a very recent double-blind, parallel-controlled, randomized trial confirmed the previous demonstration of the beneficial effects of trimetazidine in protecting the myocardium during cardioplegic arrest in open heart surgery [19]. Treatment with trimetazidine was started 2 weeks before the operation. Several biochemical markers – creatine kinase (CK), CK isoenzyme MB (CK-MB), troponin T, myoglobin, and calculation of lactate extraction – were used to detect myocardial injury and hence the degree of myocardial protection afforded by trimetazidine. The results showed that postoperative concentrations of all these markers of myocardial injury were significantly lower in the trimetazidine group than in the control group ($P < 0.05$).

In all the above studies, whether given before, during, or after intervention, trimetazidine consistently showed marked anti-ischemic properties, which translate into important cardioprotective benefits.

Trimetazidine: therapeutic potential for the treatment of ischemic heart failure

Available evidence suggests that heart failure represents a state of cardiac energy starvation – ''an engine out of fuel'' [20]. This is why the optimization of cardiac energetics by selective inhibition of myocardial fatty acid oxidation may be effective in the early stages of heart failure and might slow down the progression of heart failure and improve cardiac function [21].

Trimetazidine, as an anti-ischemic agent, has also been studied in the more severe stages of ischemic heart disease such as heart failure, predominantly of

ischemic origin. The first report of the beneficial effect of trimetazidine on left ventricular function and of a reduction in the symptoms of patients with ischemic heart failure was published as early as 1989 [22], and other clinical trials confirming these beneficial effects have been completed since then [23,24].

The addition of trimetazidine to conventional medication in long-term treatment has been shown to preserve left ventricular ejection fraction (LVEF) in patients with ischemic dilated cardiomyopathy [25]. The results from a 48-month follow-up of these patients were subsequently reported [26]. The distribution of patients in the New York Heart Association functional classification and their exercise capacity (6-min walk test) significantly improved with trimetazidine. Furthermore, two studies conducted with trimetazidine have provided preliminary findings on its potential beneficial prognostic effects in patients with coronary heart disease presenting with severe conditions such as altered cardiac function. More particularly, in 2005, El Kady et al [27] showed that trimetazidine substantially increased the survival rate (92%, compared with 62% in the placebo group) in 200 patients with left ventricular dysfunction and severe multivessel coronary disease at 2-year follow-up. Later on, Di Napoli et al [26] also showed, in 62 similar patients, that trimetazidine significantly reduced all-cause mortality (by 56%) and admission to hospital for heart failure by (47%).

The positive effects of trimetazidine treatment on cardiac function have also been evaluated in patients with non ischemic cardiomyopathy. A paper published in 2008 [28] reported that trimetazidine was found to improve left ventricular function in patients with chronic heart failure caused by non ischemic dilated cardiomyopathy, and a new study published in 2009 assessed the effects of trimetazidine on cardiac function using myocardial tissue Doppler imaging in patients with heart failure of ischemic or non ischemic origin [29]. In this latter study, trimetazidine or placebo was given to 87 patients with heart failure who were receiving ''optimal'' heart failure therapy for 3 months. In those treated with trimetazidine, the increase in LVEF was significantly greater than that in the placebo group ($9.1 \pm 4.2\%$ compared with $2.5 \pm 1.4\%$; $P < 0.001$). Similar results were observed with the increase in left ventricular and right ventricular myocardial velocities ($P < 0.001$).

Conclusion

Most pharmacological treatments of myocardial ischemia act on hemodynamic parameters of myocardial ischemia, by increasing oxygen supply (calcium antagonists, nitrates) or decreasing oxygen demand (β-adrenergic receptor antagonists), or both.

However, it is now obvious that there is still a need for other antianginal and anti-ischemic drugs as new options for both initial and subsequent management of these diseases. Scrutinizing the altered energy metabolism during myocardial ischemia helps toward better understanding of a more comprehensive anti-ischemic approach, including metabolic optimization, which seems to be ''the missing component of the optimal treatment strategy''.

Improvement in cardiac energy metabolism during cardiac ischemia, confirmed as achievable with trimetazidine, is an established therapeutic option for relieving the symptoms of stable angina, but also shows beneficial effects on cardiac function and a possible positive influence on prognosis. ■

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