Metabolic cardiac protection is beneficial in patients undergoing coronary revascularization: is it necessary afterwards?

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Abstract

Coronary revascularization procedures (coronary artery bypass grafting and percutaneous coronary intervention) take their place among the principal approaches to coronary artery disease (CAD) treatment. These procedures not only successfully alleviate the symptoms of the disease, but may also improve outcome in subsets of CAD patients. However, accumulating data suggest the possibility that myocardial injury develops as a response to the restoration of coronary blood flow. This paper describes the potential benefits of trimetazidine as a promising agent for cardiac protection in patients undergoing coronary revascularization. The rationale for long-term treatment with trimetazidine after coronary revascularization procedures is also discussed.

Keywords: coronary artery bypass grafting (CABG); metabolic cardioprotection; percutaneous coronary intervention (PCI); trimetazidine

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Introduction

The history of the use of coronary revascularization procedures – coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI) – extends back half a century. Over this period, the two strategies of coronary revascularization have undergone serious technical advances and take their place among the principal approaches to coronary artery disease (CAD) treatment. Indeed, both CABG and PCI not only successfully alleviate the symptoms of the disease, but can also improve outcome in subsets of CAD patients (ie, those with left main CAD, proximal stenoses of the left anterior descending (LAD) artery or two to three-vessel coronary disease with left ventricular dysfunction) [1].

In recent years, there have been active discussions about the benefits of drug-eluting stents, arterial grafts, off-pump CABG, as well as hybrid operations [2–4]. Moreover, convincing evidence has been obtained in favour of the use of optimal medical treatment in CAD patients, which includes rational combination of intensive lifestyle interventions and pharmacological management [5,6]. In this setting, the choice of the most preferable method (or methods) for the

treatment of CAD patients implies that the maximal benefit is gained from each strategy used, irrespective of whether it is invasive or not. Therefore, the decision-making behind the choice of a particular procedure for coronary revascularization, especially in patients with multivessel disease, necessitates active communication between cardiologists and cardiac surgeons, and other experts, if required. This principal position was highlighted in the European guidelines on myocardial revascularization updated in 2010 [1].

It is interesting that from the beginning of the era of myocardial revascularization in CAD patients, the data began to accumulate about the development of myocardial lesions in response to the restoration of coronary blood flow after an ischemic episode. Myocardial reperfusion injury was described for the first time in 1960 by Jennings et al [7]. The authors observed cell swelling, contracture of myofibrils, disruption of sarcolemma, and the appearance of intramitochondrial calcium phosphate particles in reperfused ischemic canine myocardium. In 1977, Bulkely and Hutchins [8], in a study of myocardium in 58 patients after CABG (all patients died within 1 month after the intervention), reported for the first time the paradox of myocardial lesion development despite successful coronary revascularization. This paradox was called "ischemia-reperfusion injury", and its occurrence and development is profoundly influenced by the formation of reactive oxygen species (such as superoxide anion [$\bullet O_2^-$], hydroxyl radical [•OH] and hydrogen peroxide [H_2O_2]) in response to reperfusion of ischemic myocardium, which leads to cardiomyocyte calcium overload and, eventually, to the injury and death of heart cells.

The development of ischemia-reperfusion injury was shown to be associated with an aggregation and activation of leukocytes, aggregation of platelets, activation of apoptosis, cardiotoxic effect of angiotensin II, and activation of the complement system [9–11]. The above stated disorders can manifest not only as the "no-reflow" phenomenon, microvascular and endothelial dysfunction, myocardium stunning, reperfusion arrhythmias, but also as irreversible myocardial reperfusion injury.

Of note is the fact that periprocedural myocardial injury is not a rare observation. For example, Ioannidis et al [12] have shown that approximately one-third of all elective PCI procedures are associated with severe myocardial injury, which has been linked with higher subsequent mortality. Is it possible to prevent potential cardiomyocyte death occurring at the restoration of coronary blood flow?

Does the administration of trimetazidine represent a promising method of cardioprotection in patients undergoing PCI and CABG?

One of the promising methods for cardioprotection in patients undergoing PCI and CABG is the administration of trimetazidine. Trimetazidine is known to exert its anti-ischemic effect by the selective inhibition of long-chain 3-ketoacyl-CoA thiolase and direct stimulation of pyruvate dehydrogenase, which provides a shift in cardiac energy metabolism from fatty acid oxidation to glucose oxidation. As a result, trimetazidine preserves the necessary ATP level in cardiomyocytes, promotes a decrease in intracellular acidosis and prevents intracellular calcium overload. It reduces the myocardial injury caused by free radicals and, therefore, modulates the inflammatory response and can limit the necrotic area of myocardium. This effect becomes especially useful in the reperfusion period, when because of the restoration of oxidized blood inflow to the previously ischemic areas of myocardium, fatty acid β-oxidation is increasing sharply, and pyruvate (formed from glucose or lactate) oxidation is paradoxically decreasing. Experimental studies have shown that trimetazidine in the settings of ischemia-reperfusion prevents a sharp increase in the permeability of mitochondrial membranes, reduces the activation of neutrophils, as well as decreasing the rate of apoptosis of cardiomyocytes [13–16].

Several randomized clinical trials (RCT) have demonstrated that the administration of trimetazidine before PCI or CABG is associated with more rapid normalization of the ST-segment on the surface ECG, lower levels of oxidative stress markers (lactate, malondialdehyde) and myocardial necrosis markers (troponin, creatine phosphokinase [CPK], creatine phosphokinase myocardial type [CPK-MB]) in the postoperative period.

The first RCT on this issue was a double blind, placebo controlled study performed by Kober et al [17], in which 20 patients with CAD and LAD artery disease received intracoronary trimetazidine solution (6 mg) or placebo during PCI. The authors found that trimetazidine solution, compared to placebo, provides a significantly earlier recovery of ST-segment to the isoelectric

line and in T wave changes during the repeated balloon inflations, without altering hemodynamic parameters.

In another RCT, called LIST [18], patients also received trimetazidine in solution form. This prospective, double blind, placebo controlled study included 94 patients with acute myocardial infarction, who were treated with trimetazidine intramuscularly (40 mg bolus for 2 minutes, and then 60 mg daily in the form of constant infusion for 48 hours) before primary PCI on the infarct-related artery.

That RCT has also shown more rapid resolution of ST-segment change in patients treated with trimetazidine solution compared with placebo.

The results of these two RCT, which used trimetazidine solution, should be considered primarily as the rationale for trimetazidine administration before PCI. However, there are data that demonstrate a positive effect of trimetazidine administered in oral form before PCI.

In the open, controlled RCT of Polonski et al [19], which included 44 patients with one-vessel disease (stenosis >70% in the middle of the LAD artery), trimetazidine was administered from at least day 4 before PCI. The authors found that trimetazidine treatment resulted in a significantly lower ST-segment elevation during PCI. In addition, the mean values of ST-segment elevation during all the balloon inflations were lower in the trimetazidine group (1.66 ± 1.50 mm versus 3.29 ± 1.59 mm in the comparison group; $P = 0.001$). Moreover, trimetazidine significantly increased the time from balloon inflation to angina occurrence (50 ± 26.2 seconds versus 32 ± 15.0 seconds in the comparison group; $P = 0.03$) and, accordingly, decreased the time from balloon deflation to the disappearance of pain (19.3 ± 11.4 seconds versus 40.1 ± 16.8 seconds in the comparison group; $P = 0.001$).

The study of Bonello et al [20] included 206 stable angina patients with one-vessel coronary disease. Half of the patients received trimetazidine in the single loading dose of two tablets daily at 30 minutes before PCI. The primary endpoint was the maximal level of troponin I, which is the marker of irreversible myocardial injury. Troponin I levels were measured before PCI, as well as at 6, 12, 18 and 24 hours after PCI. The trimetazidine intake in a single dose was associated with a significant reduction in the troponin I level, compared to the control group, at all the time points after PCI (mean value and SD: at 6 hours – 4.2 (0.8) versus 1.7 (0.2), $P < 0.001$; at 12 hours – 5.5 (1.5) versus 2.3 (0.4), $P < 0.001$; at 18 hours – 9 (2.3) versus 3 (0.5), $P < 0.001$; and at 24 hours – 3.2 (1.2) versus 1 (0.5), $P < 0.001$).

The results were also positive in studies with trimetazidine administration before CABG.

The double blind, placebo controlled study of Fabiani et al [21] is probably the first study performed in this setting. The participants with scheduled CABG received trimetazidine (60 mg daily) for 3 weeks before surgery. Moreover, the drug was added to the cardioplegic solution (trimetazidine 10^{-6} M). The measurements of malondialdehyde in the blood from the coronary sinus showed that at 20 minutes after the reperfusion was started, the increase in this marker of oxidative stress was significantly lower in the trimetazidine group (from 1.60 ± 0.11 to 1.79 ± 0.2 mmol/L), compared with the placebo group (from 1.17 ± 0.11 to 2.84 ± 0.58 mmol/L). At 4 hours after the operation, circulating myosin was identified in all the CAD patients from the placebo group and in only half of the patients from the trimetazidine group ($P = 0.036$ between groups). These data are consistent with the results of other double blind, placebo controlled studies [22,23], showing that trimetazidine provides a significant (versus placebo) reduction in lactate levels, a reduced requirement for calcium-channel blockers in the period of aortic X-clamp removal, as well as a reduction in the troponin T level.

Is the continuation of trimetazidine treatment still needed after coronary revascularization procedures?

Actually, yes, especially if a CAD patient after the coronary revascularization procedure still experiences angina or has left ventricular systolic dysfunction. The subgroup analysis of the TRIMPOL II study [24] has shown that the addition of trimetazidine, to the therapy of 94 patients who had already undergone PCI or CABG and still experienced angina attacks, resulted in a significant increase in time to 1 mm ST-segment depression, total exercise time, time to angina onset, and total work.

Another example of a positive answer to the above question is the results of the placebo controlled RCT performed by Labrou et al [25]. The study aimed to assess the efficacy of trimetazidine in the prevention

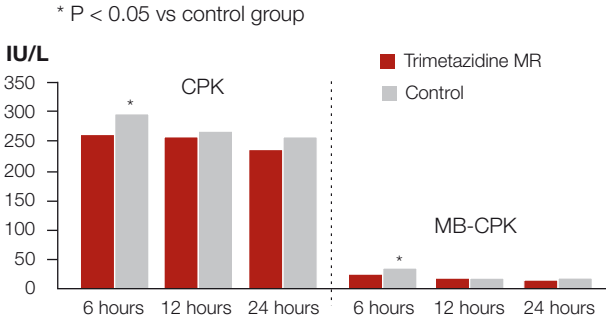
of myocardial injury after PCI, as well as its influence on left ventricular systolic function at 1 and 3 months after the procedure. Compared with placebo, trimetazidine treatment resulted in a significantly greater reduction in troponin I and CPK-MB levels. In particular, at 48 hours after the procedure, the increased troponin I level was found in 15% of patients treated with trimetazidine and 32% of patients who received placebo. At 24 hours after PCI, the increased CPK-MB level (>5 ng/mL) was observed in 22% of patients from the trimetazidine group and 40% of patients from the placebo group.

It is worth mentioning that further intake of trimetazidine resulted in a significant improvement in the regional contractility of left ventricular myocardium, a significant decrease in the number of cases with left ventricular ejection fraction (LVEF) reduction less than 50%. Moreover, trimetazidine therapy was also associated with a significant improvement of the LVEF, compared with placebo, at 1 and 3 months of follow-up.

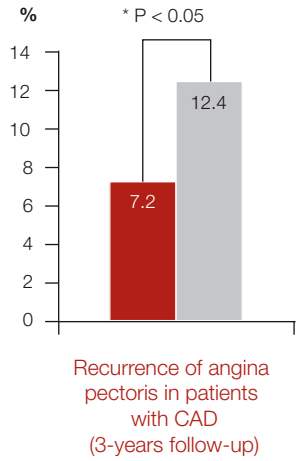
According to the results of an open prospective randomized study [26], which included 306 patients with multivessel CAD and stable angina (2.9 ± 0.2 Canadian Cardiac Society), heart failure (2.2 ± 0.1 New York Heart Association), left ventricular aneurysm (12% of patients) who were undergoing CABG, the administration of trimetazidine MR at a dose of 70 mg/day for 2 weeks before CABG resulted in a lower CPK-MB level in the early postoperative period, less frequent development of hemodynamically significant cardiac rhythm disorders and intraoperative myocardial infarction. It is noteworthy that further administration of the drug for 3 years led to a significantly higher exercise tolerance and a more pronounced increase in LVEF. Repeated angina pectoris was observed in 12.4% of patients in the reference group and in 7.2% of patients with CAD receiving treatment with trimetazidine MR (Figs 1–3).

LVEF in the group of patients receiving trimetazidine MR increased by 15.3% (from 50.3 ± 1.6% to 52.8 ± 1.1% by the end of the first month, and to 56 ± 0.9% by the end of the follow-up period). In the control group, the changes in this parameter were less significant and accounted for 1.5% (from 51.5 ± 2.1% to 53.5 ± 0.2% by the end of the first month, and to 52.3 ± 1.5% by the end of the observation period).

Another open prospective randomized study [27] showed that the prescription of trimetazidine MR at a



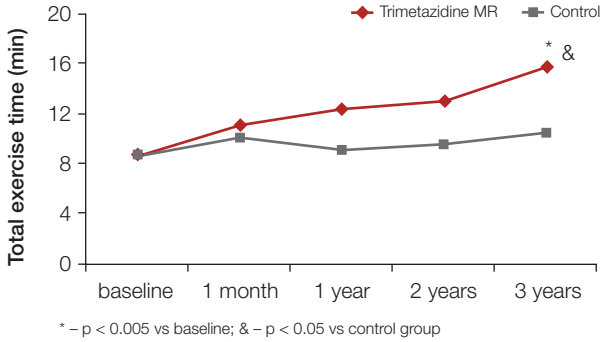
CPK and MB-CPK levels in early postoperative period



Recurrence of angina pectoris in patients with CAD (3-years follow-up)

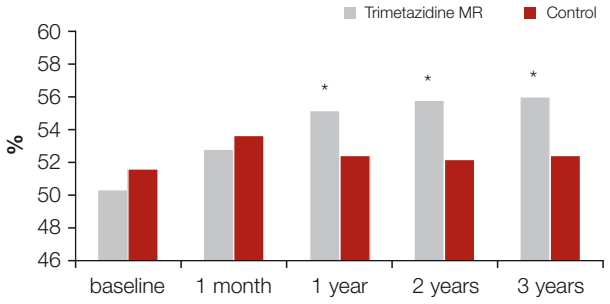
Fig. 1 *Creatine phosphokinase (CPK) and creatine phosphokinase myocardial type (CPK-MB) levels in the early postoperative period. Recurrence of angina in coronary artery disease (CAD) patients after 3 years of follow-up. Significant differences between the compared groups of patients in terms of CPK and CPK-MB levels were noted 6 hours after surgery. Therefore, in the group of patients receiving trimetazidine MR, the CPK and CPK-MB levels were 260.7 ± 10.3 and 23.9 ± 1.26 IU/L, respectively, whereas in the control group they were higher and accounted for 295.1 ± 20.1 (P < 0.05) and 35.2 ± 1.2 IU/L (P < 0.05), respectively. During 3 years of follow-up, the recurrence of angina was noted in 11 (7.2%) patients from the trimetazidine MR group and 19 (12.4%) patients from the control group (P < 0.05).*

dose of 70 mg/day for 2 weeks before PCI in 214 patients with multivessel CAD, stable angina (2.7 ± 0.2 Canadian Cardiac Society) and heart failure (2.0 ± 0.1 New York Heart Association) followed by the administration of the drug for 3 years, provided a significant improvement in left ventricular systolic function and exercise tolerance. Arrhythmias as well as episodes of silent myocardial ischemia were found to be less frequent in the trimetazidine MR group, compared to the control group. The rates of hospitalization for acute coronary syndromes were 4.7% in the trimetazidine MR group and 7.5% in the control group



* – p < 0.005 vs baseline; & – p < 0.05 vs control group

Fig. 2 *Exercise stress testing during long-term trimetazidine MR therapy. A marked increase in the duration of stress test in coronary artery disease patients was noted only in the group of patients who received trimetazidine MR (from 8.7 ± 0.03 to 15.8 ± 0.04 minutes, P < 0.05). In the control group, the changes of this parameter were not significant.*



* p < 0.05 vs. baseline.

Fig. 3 *Left ventricular ejection fraction during long-term therapy with trimetazidine MR.*

($P < 0.05$). The rates of repeat coronary revascularization were 9.3% in the trimetazidine MR group and 14.0% in the control group ($P < 0.05$) (Fig. 4).

Conclusion

At the present time, the pharmacological modulation of fatty acid oxidation is considered a promising option for the treatment of patients with chronic heart failure, including diastolic heart failure, especially in elderly patients and women [28]. According to the meta-analysis of Gao et al [29], which included 17 trials with pooled data for 955 patients with heart failure, trimetazidine improved systolic function and clinical symptoms. Moreover, these improvements associated with trimetazidine treatment may result in reduced all-cause mortality, fewer cardiovascular events and hospitalizations after long-term treatment. Indeed, large scale, prospectively designed, randomized, double blind trials are still required to clarify the role of tri-

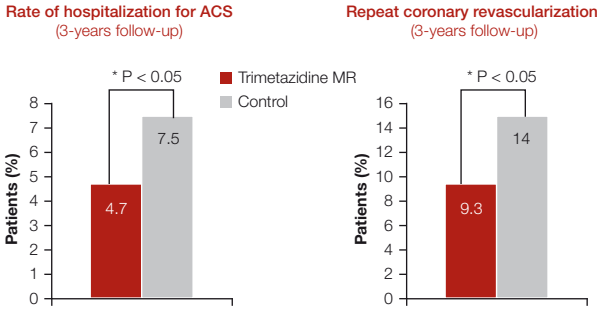


Fig. 4 *The rates of hospitalization for acute coronary syndromes and repeat coronary revascularization after 3 years of follow-up. ACS, acute coronary syndromes; PCI, percutaneous coronary intervention.*

metazidine in patients undergoing coronary revascularization. First, the most optimal timing and route of trimetazidine administration after the intervention needs to be identified. Also a question remains about the duration of trimetazidine therapy after PCI or CABG. It seems to be completely clear that in the case of CAD patients with persistent angina symptoms or the presence of left ventricular systolic dysfunction, trimetazidine administration will provide additional benefits allowing us to expect a reduction in the risk of adverse cardiac events. •

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