

## Efficacy of preoperative trimetazidine for preventing myocardial injury in patients undergoing off-pump coronary artery bypass grafting

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### ABSTRACT

**Objective.** Off-pump coronary artery bypass grafting (CABG) with median sternotomy have been shown to be beneficial and associated with reduced myocardial injury. However, there is still a risk for ischemic myocardial injury that results from the normothermic and metabolically active myocardium during the occlusion of the target coronary artery. We aimed to evaluate the efficacy of trimetazidine in prevention of myocardial tissue injury in patients undergoing off-pump CABG by measuring serum levels of cardiac troponin I (cTnI).

**Methods.** Thirty patients undergoing first-time elective off-pump CABG were randomly assigned to two groups: 15 patients received trimetazidine 60 mg orally per day (trimetazidine group) for three weeks and 15 patients received placebo (control group). As a parameter of myocardial injury, we measured cTnI levels. Blood samples were taken sequentially from the patients before surgery (t1), 30 minutes after the last distal anastomosis (t2), at postoperative 12<sup>th</sup> hour (t3) and at postoperative 24<sup>th</sup> hour (t4). cTnI measurements were made by direct chemiluminometric technology. **Results.** Baseline and operative characteristics of patients are similar. All preoperative serum cTnI concentrations were within the normal range and rose with the beginning of the operation which reached to its peak value at t3 in the control group and t4 in trimetazidine group. When the increase in the serum cTnI concentrations of trimetazidine group and control group were compared there was a slight numerical increase in cTnI levels in all measurements after reperfusion but reached to statistical significance only at t3 (mean: 0.40 ng/ml; mean rank: 12.20; range: 0.05-1.66 vs. mean: 0.20 ng/ml; mean rank: 18.80; range: 0.11-0.30;  $p=0.041$ ). **Conclusion.** Preoperative treatment with trimetazidine might reduce postoperative myocardial injury in patients undergoing first time isolated off-pump CABG, but larger randomized placebo controlled trials are still for recommendation of routine pretreatment with trimetazidine.

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## Introduction

Metabolic treatment with trimetazidine has been suggested to be effective in patients undergoing cardiac surgery by reducing the risk of ischemia reperfusion injury and risk of recurrent angina and improving the patients' postoperative condition. There are several studies concerning about myocardial protective effects of trimetazidine either used preoperatively or as an addition to the cardioplegic solution in patients undergoing cardiac surgery with cardiopulmonary bypass [1].

Coronary artery bypass grafting (CABG) by the help of cardiopulmonary bypass and global cardiac arrest is effective, safe and has an acceptable mortality rate but still there is risk of morbidity and ischemic myocardial injury. Although these adverse effects of cardiopulmonary bypass are mostly reversible avoiding the use of cardiopulmonary bypass either by minimally invasive CABG or off pump CABG with median sternotomy has been shown to be beneficial and to be associated with reduced myocardial injury [2-5]. Off-pump CABG is performed on beating heart without the use of cardiopulmonary bypass and global cardiac arrest. However there is still a risk of ischemic myocardial injury that results from normothermic and metabolically active myocardium during the occlusion of the target coronary artery. In the present study we aimed to evaluate the efficacy of preoperative trimetazidine in the prevention of myocardial tissue injury in patients undergoing offpump CABG by measuring serum levels of cardiac troponin I (cTnI).

## Methods

### *Patients*

After approval of the local ethics committee written informed consent was obtained from every patient. Thirty patients undergoing first time elective off-pump CABG were randomly assigned into two groups: 15 patients received 3 times 20 mg/day trimetazidine preoperatively (trimetazidine group) and 15 patients received placebo (control group). Because of the its optimal dose and optimal time period of pretreatment, during the 3 weeks preoperatively, patients received trimetazidine orally 3 times 20 mg/day [1, 5, 6]. The exclusion criteria were the presence of unstable angina, acute myocardial infarction of less than one month duration, chronic renal insufficiency, ejection

fraction of less than 40%, and concomitant valvular disease or skeletal muscle disease. In addition, patients with electrocardiographically confirmed myocardial infarction in the immediate postoperative period and showing significant increases in cardiac enzymes were also excluded. This design was chosen in order to explore the efficacy of trimetazidine only on the myocardial injury occurring due to the procedure not from the perioperative myocardial infarction which may have a serious impact on the results in a small patient group.

### *Surgical Technique*

After a median sternotomy and harvesting the bypass grafts, heparin (150 U/kg) was administered. The Octopus Tissue Stabilizer (Octopus 28400, Medtronic, Cardiac Surgical Products, MI, USA) was used for the stabilization of the target coronary artery. First, the proximal anastomosis of the vein grafts was constructed by the help of a partially occluding aortic-side clamp. In all the cases, the left anterior descending artery was the first coronary artery to be revascularized. The target coronary artery was stabilized and occluded proximally with the help of a bulldog clamp and then the distal anastomosis was performed. No coronary shunts were used during the distal anastomosis. Heparin was antagonized with protamin sulphate until the activated clotting time decreased below 200 seconds.

### *Blood Sampling*

As a parameter of myocardial injury, we measured cTnI levels. Blood samples were taken sequentially from the patients before surgery (t1), 30 minutes after the last distal anastomosis (t2), at postoperative 12<sup>th</sup> hour (t3) and at postoperative 24<sup>th</sup> hour (t4). cTnI measurements were made by direct chemiluminometric technology (Automated Chemiluminescence System: ACS-180, Chicron Diagnostics, East Walpole, MA, USA). The ACS system detects free cTnI in addition to the complex forms.

### *Statistical Analysis*

Statistical analyses were performed using the SPSS statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean  $\pm$  standard deviation. Analyses were made with Mann-Whitney U, chi-square, and Fischer's exact tests. Because of the small no patients involved in the study and the cTnI levels are not normally distributed Mann-

**Table 1.** Baseline and operative characteristics of patients

	Trimetazidine Group (n=15)	Control Group (n=15)	<i>P</i>
Age (mean)	59.6 ± 9.5	56.9 ± 9	.325
Gender (male/female)	10/5	11/4	.500
Prior myocardial infarction	7 (46.7)	7 (46.7)	1
Ejection fraction	52.1±8.5	50.8 ± 8.2	.595
Presence of hypertension	6 (40)	6 (40%)	1
Presence of diabetes Mellitus	5 (33.3)	3 (20)	.341
Chronic obstructive pulmonary disease	3 (20)	4 (26.7)	.500
Use of left internal mammary artery	15 (100)	14 (93.3)	.500
Number of vessels grafted (range)	2.4 ±0.7(1-3)	2.2 ± 0.7 (1-3)	.512
Ischemic time (minutes)	25.7± 9.1	23.9 ± 9	.653

Data are presented mean±standard deviation or number (%).

Whitney U-test was used for comparison of changes in levels of cTnI between the two groups, mean rank and range values are presented for description. A *p* value of less than 0.05 was considered to indicate statistical significance.

## Results

Baseline and operative characteristics of patients are shown in Table 1. There were no mortalities in both groups. Mean ischemic time was 25.7±9.1 minutes in trimetazidine group and 23.9±9 minutes in the control group. There were no peroperative myocardial infarction in both groups. All preoperative serum cTnI levels were within the normal range and rose with the beginning of the operation which reached to its peak value at t3 in the control group and t4 in the trimetazidine group (Table 2). When increase in the serum cTnI levels of trimetazidine group and control

group were compared, there was a slight numerical increase in cTnI levels in all measurements after reperfusion but reached to statistical significance only at t3 when control group was compared with trimetazidine group (mean 0.40 ng/ml; mean rank 12.20; range .05-1.66 vs. mean 0.20 ng/ml; mean rank 18.80; range .11-.30 ; *p*=0.041). The cTnI levels was higher in the control group at t4 but it did not reach to a statistical significance (mean: 0.39 ng/ml; mean rank: 12.40; range: 0.02-3.25 vs mean: 0.31 ng/ml; mean rank: 18.60; range: 0.30-0.34; *p*=0.056) Table 2.

## Discussion

Trimetazidine has been shown to reduce myocardial injury during conventional CABG [1, 6- 8]. Trimetazidine selectively inhibits the last enzyme (3-ketoacyl coenzyme A thiolase) participating in the betaoxidation of free fatty acids. which leads to the

**Table 2.** Measurements of cTnI in both groups

	Control Group Mean (ng/ml); mean rank; range	Trimetazidine Group Mean (ng/ml); mean rank; range	<i>P</i> <sup>‡</sup>
t1	0.07; 15.10; 0.01-0.23	0.05; 15.90; 0.01-0.07	0.806
t2	0.34; 15.20; 0.02-1.57	0.20; 15.80; 0.08-0.30	0.870
t3	0.40; 12.20; 0.05-1.66	0.20; 18.80; 0.11-0.30	<b>0.041</b>
t4	0.39; 12.40; 0.02-3.25	0.31; 18.60; 0.30-0.34	0.056

<sup>‡</sup>: Mann-Whitney U test; cTnI levels measured (t1: before surgery, t2: 30 minutes after the last distal anastomosis, t3: postoperative 12<sup>th</sup> hour, t4: postoperative 24<sup>th</sup> hour)

inhibition of free fatty acid oxidation and an increase in glucose oxidation. Trimetazidine reduces the formation of free oxygen radicals, inhibits neutrophil infiltration and also limits the accumulation of sodium and calcium in the cytoplasm of cardiomyocytes [7]. There are several reports suggesting that the restoration of ischemia impaired mitochondrial function is affected by trimetazidine and the sites of trimetazidine binding to the mitochondrial membrane have been identified, that confirms the anti-ischemic property of the drug. The inhibition of apoptosis in cardiomyocytes is another possible mechanism of trimetazidine [6, 7]. Argaud *et al.* [9] confirmed these findings in their study in which they showed that administering trimetazidine 10 min before ischemia significantly protects the myocardium from ischemia reperfusion injury, including inhibition of apoptosis in the cardiomyocytes. Ruixing *et al.* [10] obtained similar results in a rabbit model experimental study. cTnI is a structural peptide in cardiac myocytes and is a well documented marker of myocardial injury even in patients with uneventful recovery [3, 11, 12]. On-pump CABG causes higher release of serum markers of myocardial injury that might be due to inadequate perfusion of subendocardium and remaining ischemic areas that could not be grafted, unexpected aortic regurgitation and due to reperfusion (whose consequences are not well known) through the bypass grafts after unclamping or direct trauma to myocardium [12, 13]. Although off-pump CABG has been shown to be associated with lesser myocardial injury in terms of biochemical blood markers there is still a potential risk of ischemic myocardial tissue damage due to normothermic, metabolically active myocardium during the occlusion of the target coronary artery [2, 3, 14].

The present study shows that the amount of myocardial injury might be lesser in patients undergoing off-pump CABG and received 60 mg trimetazidine preoperatively than those did not receive. This is expressed by lower release of cTnI. This finding leads to a suggestion that myocardial injury that occurs due to the regional normothermic warm ischemia and ischemia reperfusion injury because of the target coronary artery occlusion during off-pump CABG might be reduced by prophylactic trimetazidine medication.

Our findings about reducing the myocardial tissue injury with the usage of trimetazidine was supported by several studies which were consisted of patients

undergoing on-pump conventional CABG [1, 8]. Somewhat the cTnI levels in our study were higher than some previous reports, which may be related to different assay technology and kits used [2]. ACS method applied in our study detects free cTnI in addition to complex forms. Similar cTnI levels were reported by Kilger *et al.* [14] who used a fluorogenic sandwich enzyme immunoassay method and by Wan *et al.* [15] who used the same method in our study. Several studies showed that the increase in cardiac specific serum markers of myocardial injury during coronary procedures especially cTnI may be used as an indicator of the efficiency of cardio protective procedures [12, 16]. Without cellular necrosis reversible myocardial ischemia can cause functional disintegration of the myocardial cell membranes and consecutive release of cytosolic molecules [14]. The present study showed that this release of cytosolic molecules leaking from reversibly injured myocytes is significantly lower in patients undergoing off-pump CABG and receive trimetazidine than those who did not.

The main drawbacks of our study are limited no of patients enrolled in our study and disadvantage of showing early graft patency by angiography. Our findings might be influenced by the small number of patients included in the present study. Slightly numerical increase in the cTnI concentrations might reach to a statistical significance in all reperfusion measurements in a larger group. Besides we showed a statistically significant increase in cTnI concentrations of the control group when compared with trimetazidine group at 12<sup>th</sup> hour after the reperfusion.

## Conclusions

On the basis of available studies and our study we can say that metabolic treatment with trimetazidine might be effective in patients subjected to CABG by reducing the risk of ischemia reperfusion injury in terms of biochemical blood marker cTnI. However, there are only a few studies so far, and a very small number of patients are included in most of the studies. Therefore this therapy cannot be recommended until large, randomized, preferably multicentre trials are performed. On the other hand, trimetazidine can obviously be considered as an additional pretreatment in patients subjected to CABG.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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