Trimetazidine on Ischemic Injury and Reperfusion in Coronary Artery Bypass Grafting

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Abstract

Background: The ischemia and reperfusion ischemia is a common physiopathological mechanisms, which has difficult control during Coronary Artery Bypass Grafting (CABG) with cardiopulmonary bypass, the critical moment of which happening by the end of surgery, when there is declamping of aorta and release of hyperoxic radicals causing the injury.

Objective: Evaluate, in a randomized double-blind prospective study, controlled with placebo, the effects of Trimetazidine (Tmz) on ischemic injury and myocardial reperfusion, identifying the change in plasma markers of a myocardial aggression (troponin T and CPK-Mb), and echocardiographic changes of ventricular function.

Methods: We studied 60 patients divided in two groups (placebo and Tmz) with mild ventricular dysfunction at the most, stratified by echocardiography and receiving medication/placebo at a dose of 20 mg/3x/day, starting from 12 to 15 days after pre-operative period up to 5 to 8 days after post-operative period. Troponin T and CPK-Mb were measured preoperatively without medication, 12 to 15 days of medication/placebo taken five minutes after aortic declamping, and at subsequent 12, 24 and 48 hours.

Results: Both Troponin T and CPK-Mb reached highly significant values (p = 0.0001) in the treated group compared to the control group at the four moments analyzed – 5 min, 12h, 24h and 48h. The echocardiographic variables did not show evolutive changes in each group severally considered and when compared among themselves.

Conclusion: Trimetazidine was effective in reducing ischemic injury and reperfusion, had no effect on left ventricular function, and no side effects were observed. (Arq Bras Cardiol 2011; 97(3) : 209-216)

Keywords: Trimetazidine/administration & dosage; myocardial reperfusion; myocardial ischemia; myocardial revascularization.

Introduction

The reperfusion injury is a pathophysiological phenomenon which may happen in general coronary syndromes, such as unstable angina, vasospastic angina, infarction without elevation and myocardial infarction, whether or not followed by thrombolysis or angioplasty procedures, as well as in cardiovascular surgeries and in elective angioplasties[1].

The phenomenon has been drawing the attention of researchers for its evident and significant impacts on clinical cardiology practice, and has facilitated a better understanding of the associated events, particularly after so-called hyperoxic radicals, formed at the end of the cellular oxidative metabolism, which may cause injury after declamping of aorta in cardiac surgery. Hyperoxic radicals cover the superoxide anion (O^{-2}), hydroxyl radical (OH) and the hydrogen peroxide (H^2O^2), which are removed from cells by systems of enzymes with antioxidant functions, generally present in myocardial physiology. These systems of endogenous antioxidant enzymes are responsible for limiting the intracellular accumulation of O^{-2} and H^2O^2 during the normal metabolism, reducing oxidative damage on proteins and lipids[2-4].

To improve myocardial protection during procedures involving reperfusion injury, recently, attention has been drawn to the research of cytoprotective drugs with action on segments of the cellular metabolism, used isolatedly or combined to reduce or prevent damage on the cardiac cell[5,6].

The mechanism of cytoprotective action of Tmz on changes in cardiac metabolism during ischemia paved the way for a therapeutic approach on reperfusion. Its anti-ischemic action helps reduce metabolic damages caused during ischemia by acting on a critical stage of cardiac metabolism, blocking the beta oxidation of fatty acids through the inhibition of long-chain 3 acetyl coenzyme A (thiolase). This anti-ischemic effect results in the increase of glucose oxidation, in addition to glycolysis, resulting in the reduction of protons, elevation of intracellular pH and tissue acidosis, recovery of cardiac efficiency and improvement of production of acetyl coenzyme A. In addition to

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these effects, it limits the accumulation of calcium, inflammation and production of hyperoxic free radicals which occur after reperfusion, without causing hemodynamic changes. Its use in prophylaxis of ventricular dysfunction has also shown a beneficial effect on the "stunned myocardium", clinical translation of the injury on ventricular function after CABG[7-10].

This study evaluates improvements and protection to reperfused myocardium of trimetazidine (Tmz), used as pretreatment in patients subject to CABG with cardiopulmonary bypass, on ischemic injury and myocardial reperfusion. The effects of Tmz would be evaluated in view of the change in plasma markers of myocardial aggression (Troponin T and CPK-Mb) and echocardiographic changes of ventricular function[11,12].

Methods

Prospective double-blind randomized clinical trial, controlled with placebo and performed between July 2007 and August 2008, at Instituto de Cardiologia Aloysio de Castro, in Rio de Janeiro (RJ-IECAC). Its main objective is to evaluate the significant difference in serum markers of myocardial injury and echocardiographic parameters between the two groups undergoing CABG, the treated group and the placebo group.

The following assumptions for the calculation of sample size were considered: significance level of 5%, the power of statistical test of 80%; and the relatively "large" expected difference in markers between the groups, which is referred to as *effect size*, based on the literature. According to Cohen[13], the number of cases required for each group analyzed is 28 individuals, taking into consideration a maximum loss of 30% over the study. Hence, a sample containing two groups should include 73 patients.

We evaluated clinically 137 coronary artery disease patients with indication of CABG. Out of them, 75 were initially selected upon transthoracic echocardiographic protocol using segmental contraction analysis to classify the ventricular function through calculation of the rate of segmental contraction (ICS) for 17 segments[14]. Patients with moderate and severe dysfunction were excluded, and only those with normal ventricular function (ICS = 1) or with mild systolic dysfunction (ICS = 1.1 to 1.6) remained. The evaluation divided the patients in two subgroups: the one without change in segmental contraction and the one with change in segmental contraction, referred to as SAS group and CAS group, respectively, targeted at analyzing the uniformity between the placebo and Tmz groups. We evaluated patients needing CABG with cardiopulmonary bypass only and who agreed to sign the informed consent.

Out of the 75 selected patients, three have desisted from surgery, two operated at another institution, two were not medicated, four discontinued the medication after 24 hours, and four needed reoperation due to bleeding and eventually died. Therefore, 60 patients actually completed the study with no clinical or surgical complications. These patients have had three or more coronary branches remedied.

The patients underwent three echocardiographic assessments during the research. The first evaluation (D0) was used as criterion for inclusion through ICS, and the subsequent two (D1 and D2), as a follow-up of the study. We also conducted analysis of ventricular function by the Simpson's method with electrocardiographic monitoring, the image moments of which were standardized during systole (at the peak of the electrocardiogram R wave) and diastole (at the end of the electrocardiogram T wave), and by the TEI index (ratio between systole and diastole).

The first echocardiographic assessment (D0) was performed with patients without medication; the following one (D1) on the day of the surgery, being from 12 to 15 days with medication/placebo. The third one (D2), at the discharge from ICU, was on post-operative period, from day three to five, using medication/placebo from 15 to 18 days.

Tmz was given to patients after 1:1 randomization masking, permuted in blocks by Cytools Excel add-in software. The evaluators were unaware of which patients had used drugs or placebo. The statistical studies were also performed blindly with codes referring to drug/placebo broken only after statistical analysis.

Eligible patients received 60 mg of the medication/placebo divided in three daily intakes, starting from at least 12 days and 15 days at the most prior to the surgery; 60 patients receiving drug administration over an interval of five to eight days after the surgical procedure, totaling 20 days of intake of medication/placebo.

All patients underwent elective surgical treatment involving trans-sternal median sternotomy, with the insertion of cannulas into the aorta and a single one for cava, following this sequence. Cardiopulmonary bypass was performed with moderate core hypothermia (32 °C - 34 °C), and the myocardial protection was made by hypothermic blood cardioplegia (4 °C) infused into the aortic root or directly into the coronary sinus. All patients received balanced general venous/inhalation anesthesia in closed circuit with CO_2 absorber (Soda Lime) and mechanical ventilation. Isofluorane with 50% oxygen mixed with nitrous oxide was used as inhalational agent. The following venous drugs were used: the hypnotics etomidate and midazolam, the opioid fentanyl, and the muscle relaxant pancuronium bromide.

To determine the reperfusion injury, creatine kinase-Mb fraction and Troponin T were administered as markers in the following intervals: preoperatively, without the use of drugs; five minutes after aortic declamping, after 12 to 15 days of treatment; and 12, 24 and 48 hours after surgery, with patients using this interval as medication/placebo from 15 to 18 days. Blood samples used were obtained with direct atrial collection in aortic declamping and subsequently in catheter placed in the right atrium. CPK-Mb was analyzed by Olympus AU 400, with modified Szasz' method, and Troponin T, by means of the quantitative immune method with optical reading through a cardiac reader[11,15].

Statistical analyses were performed on software SAS 6.04 (SAS Institute, Inc., Cary, NC) using the following methods: for comparing numerical variables between the two groups, the Student's T-test or Mann-Whitney test was used. The Chi-square test (χ^2) or the Fisher's exact test was used in the comparison of categorical variables between

groups. To analyze the behavior of variables over the time per treatment group, we performed analysis of variance (ANOVA) for repeated measures. Bonferroni's multiple comparison test was used to identify moments different among themselves and between groups.

The study was approved by the Ethics Committee of IECAC-RJ. The participants signed a consent form and were followed until hospital discharge.

The drug and research materials were defrayed by the author. The randomization, blinding and the use of the software were supported by Farmacopa Ltda.

Results

General profile of the sample

Table 1 shows the general profile of 60 patients who completed the clinical trial, comparing the placebo or control groups and those treated with trimetazidine, referred to as Tmz group and a placebo group, respectively.

SD - standard deviation; SAH - hypertension; MI - myocardial infarction; RF - renal failure; EF - ejection fraction; ICS - rate of segmental contraction (mild ventricular dysfunction <1.60).

* Student's T-test for independent samples; † Mann-Whitney test.

Table 2 compares the medication used by the patients at the time of inclusion in the study until the surgery, which was administered again after discharge from the Intensive Care Unit (ICU). Data reveals no significant difference between the two groups. This uniformity especially evinces that the effect of TMZ observed in the treated group was not influenced by any medication previously used.

Comparing the echocardiographic variables of ventricular function by three methods jointly (ICS, Simpson and Tei), we observed homogeneity among the treated group and the placebo group with regard to patients with normal ventricle (ICS = 1) and ventricle with mild dysfunction (ICS = 1.1 to 1.6). For the purposes of comparing the uniformity of ventricular function, patients were divided, as shown in table 3, in a group without change to segmental contraction (SAS) and the other with change to segmental contraction (CAS), showing no significant difference of ventricle systolic function between the groups.

Analysis of surgical variables

Table 4 shows the overall uniformity of the surgical procedure, performed by five different teams, including variables with high prognostic value as the time of anoxia, followed by time of cardiopulmonary bypass, volume of cardioplegia solution, number of anastomoses and average stay at the ICU. This check examines the two groups in very similar surgical conditions.

Analysis of echocardiographic variables

By evaluating the echocardiographic measurements between the two groups jointly, we found no significant difference in ejection fraction by Simpson's method, Tei index, and the rate of segmental contraction. We observed, as shown in Table 5, that, between each group, at each moment, and in the interaction between groups over the time, there was no significant difference. No significant difference of the ventricular function was found between the groups over pre-operative period with no drug (D0), on the day of the surgery after 12 to 15 days of medication/placebo (D1), and on the discharge of post-operative period with 15 to 18 days of medication/placebo (D2). These groups, in fact, had homogeneous distribution when analyzed as subgroups CAS and SAS (table 3).

Table 1 – General profile of the sample according to the group (Tmz and Placebo)

Variable	TMZ Group (n = 30)			Placebo Group (n = 30)			p valor
	n	average ± SD	%	n	average ± SD	%	
Male gender	19	-	63.3	24	-	80.0	0.15*
Age (years)	-	59.8 ± 8.1	-	-	61.2 ± 6.7	-	0.46
Three-vessel disease	21	-	70.0	19	-	63.3	0.58
Diabetes mellitus	7	-	23.3	2	-	6.7	0.073
SAH	21	-	70.0	18	-	60.0	0.41
Previous MI	5	-	16.7	9	-	30.0	0.22
Obesity	3	-	10.0	2	-	6.7	0.50
Smoking	19	-	63.3	13	-	43.3	0.12
Simpson EF	-	59.9 ± 8.2	-	-	63.5 ± 7.6	-	0.084*
ICS	-	1.1 ± 0.15	-	-	1.05 ± 0.08	-	0.19†
TEI	-	0.36 ± 0.10	-	-	0.36 ± 0.09	-	0.82*

*SD - standard deviation; SAH - hypertension; MI - myocardial infarction; RF - renal failure; EF - ejection fraction; ICS - rate of segmental contraction (mild ventricular dysfunction <1.60); * Student's T-test for independent samples; † Mann-Whitney test.*

Table 2 – General description of medication according to group (Placebo and Tmz)

Variable	Placebo Group (n = 30)		Tmz Group (n = 30)		p value*
	n	%	n	%	
BBLOQ	24	80.0	26	86.7	0.48
ACEI	11	36.7	13	43.3	0.59
RAB	2	6.7	3	10.0	0.50
Nitrate	30	100	30	100	NS
Anti reagent	29	96.7	30	100	0.50
Statin	25	83.3	28	93.3	0.21
Diltiazem	4	13.3	2	6.7	0.33
Diuretic	5	16.7	6	20.0	0.73
Hypoglycemic agent	4	13.3	5	16.7	0.71

χ2 test or Fisher's exact test. NS - not significant because exactly equal; BBLOQ - beta blocker; ACEI - angiotensin-converting enzyme inhibitor; RAB - renin-angiotensin system blocker.

Table 3 – Analysis of baseline variables by the rate of segmental contraction in Placebo and Tmz groups

Variable	Categoria	Placebo Group (n = 30)		Tmz Group (n = 30)		p value
		n	%	n	%	
Subgroup	SAS	17	56.7	14	46.7	0.43
	CAS	13	43.3	16	53.3	
Gender	Male	24	80.0	19	63.3	0.15

SAS - no change in segmental contraction; CAS - change in segmental contraction.

Analysis of enzyme markers

In the analysis of enzymatic measurements per group, the levels of Troponin T (chart 1) and CPK-Mb (chart 2) were significantly lower in the Tmz group compared to Placebo group ($p = 0.0001$). The same happened between groups relating to the evolution of these markers when analyzed over the time ($p = 0.0001$). These lower levels of markers show a higher protection to myocardium and, thus, to cardiac cell.

Discussion

The reperfusion injury may have as functional ventricle manifestation the so-called "stunned myocardium". Described by Bolli and Marban[16], it is basically a post-ischemic event characterized by transient depression of the function of the myocardium affected by reperfusion, which is usually rescued before an irreversible damage occurs. This damage is avoided if ischemia is transient, post-ischemic ventricular dysfunction is reversible over time, and if the myocardium receives a regular or quasi-regular flow after the ischemic episode17[17].

The sixty patients studied, with coronary artery disease, two-vessel and three-vessel lesions and normal or slightly compromised ventricular function, were evaluated using three echocardiographic methods following a prospective protocol aimed to examine the effects of trimetazidine in protecting cardiac cell and ventricular systolic function against aggression after CABG reperfusion. The recommended dosage of the drug administered was 60 mg of active principle, and the time of use until surgery was 12 days at least, following the mechanism of bioavailability, as observed in other trials[4,18].

Transthoracic echocardiography was used to analyze left ventricular function by methods considered accurate to measure the ejection fraction[12,14]. TEI index was the additional method, targeting at a noninvasive manner of pursuing ventricular performance evidence[19].

No significant difference between the studied groups was found by the analysis of results using the curve of ejection

Table 4 – Analysis of surgical variables according to the group (Placebo and Tmz)

Variable	Group*	n	Average	SD	Median	Minimum	Maximum	p value
Age	1	30	61.2	6.7	62	46	72	0.46
	2	30	59.8	8.1	58.5	47	80	
Anoxia time	1	30	63.1	26.1	55	30	156	0.29
	2	30	65.9	20.8	60	34	120	
CPB time	1	30	81.6	27.2	78.5	45	179	0.95
	2	30	78.6	22.0	79.5	40	130	
Cardioplegia volume	1	30	338.3	171.6	250.0	200	750	0.76
	2	30	325.7	120.1	300.0	200	600	
Number of bridges	1	30	3.03	0.67	3.0	2	4	0.43
	2	30	2.90	0.66	3.0	2	4	
Hours at the ICU	1	30	76.8	13.1	72	60	120	0.76
	2	30	74.8	8.7	72	60	96	

**: 1 - Placebo group, and 2 - Tmz group; CPB - cardiopulmonary bypass; SD - standard deviation.*

fraction in any of the three methods used. This fact may be related to a limitation of the method since the variation in ventricular function may occur immediately after the aortic declamping, characterizing myocardial stunning of reperfusion.

Regarding the tests which assess ventricular function through invasive and noninvasive measures using CABG on a continuous basis, there was improvement in ventricular function by administering Tmz[7,20-22]. It is worth to underscore, however, that the evaluation interval between the first echocardiogram and the last was 48 hours at least, and, thus, only the most persistent changes to ventricular function could be checked, and this reduced the probabilities of detection of stunned myocardium.

Table 5 – Comparative analysis of echocardiographic variables between Placebo and Tmz groups

Variable	Components (p value *)		
	Group (Placebo and Tmz)	Time (D0, D1 and D2)	Interaction (group*time)
Simpson EF	0.30	0.16	0.10
Tei	0.61	0.63	0.28
ICS	0.11	0.91	0.53

** - ANOVA for repeated measures; D0 - pre-operative period without trimetazidine; D1 - surgery day; D2 - discharge of post-operative period.*

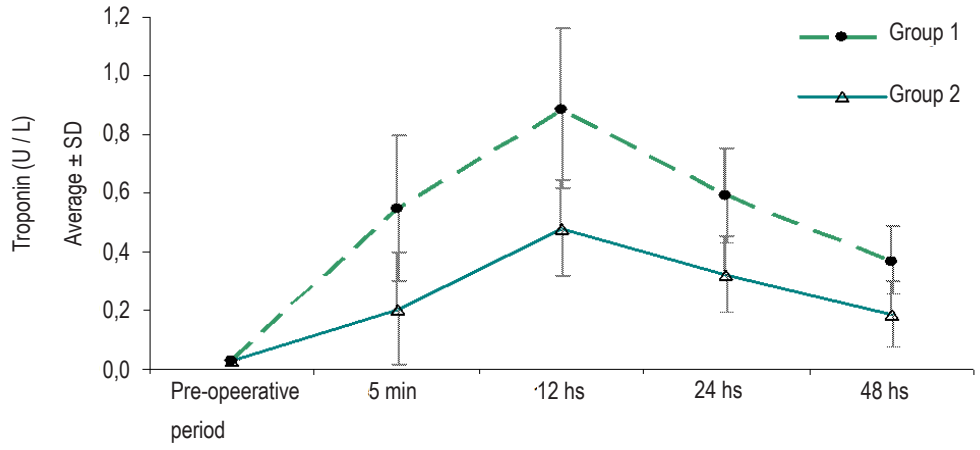

Chart 1 - *Serum values of Troponin T over the time according to treatment group: Group 1; Placebo and Group 2 Trimetazidine.*

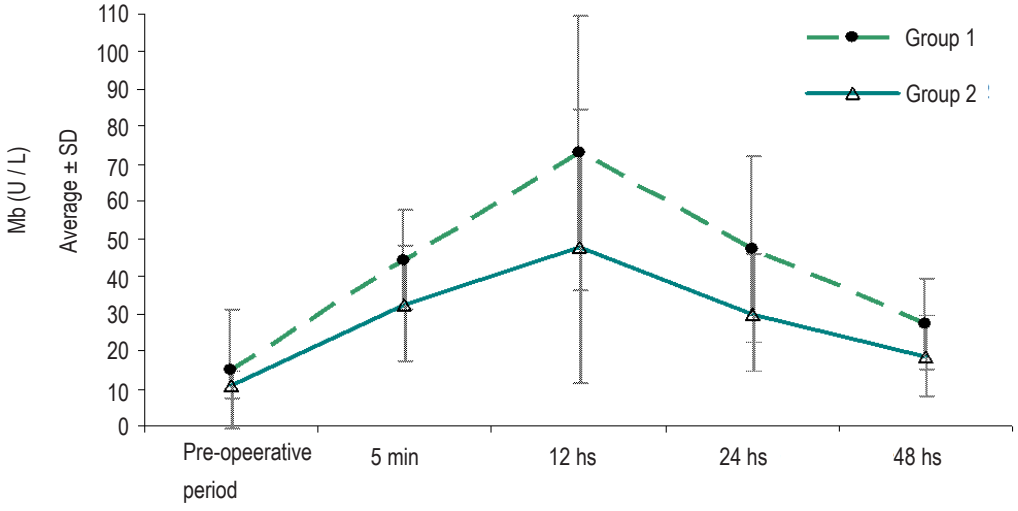

Chart 2 – *Creatine kinase-MB over time according to treatment group: Group 1 Placebo and Group 2 Trimetazidine.*

In invasive studies, the impairment of ventricular function was assessed at the end of surgery for acute injury, i.e., at the time of declamping of the aorta, directly evidencing the improvement of Tmz[7,20]. Lopatin and Dronova[22] analyzed, over a period of three years, patients subject to CABG, half receiving Tmz and half receiving placebo. The authors evaluated the reperfusion injury with cardiac enzyme postoperatively, and, throughout the follow-up, performed periodic evaluations of ventricular function by echocardiography and by exercise tolerance test. As an immediate result of the pre-treatment, they observed a decrease in the values of cardiac enzymes in the treated group compared to the placebo group. In long term, there was difference in clinical parameters between the groups, demonstrated by the improvement of functional class, ejection fraction and exercise tolerance in the treated group.

Although Tmz is formally indicated for treating stable angina associated or not to usual drugs, as it presents low interaction and low prevalence of adverse effects, it also does not alter hemodynamic variables (heart rate and blood pressure) and is safe when combined with nitrates and beta blockers. In national and international guidelines, the drug has degree of recommendation II and level of evidence b. Nonetheless, in this trial, we used the drug preventively with the objective of reducing the effects of reperfusion injury by hyperoxic radicals released in CABG[23].

Trials using Tmz with different designs primarily connected to medical treatment and which used echocardiography to determine the ventricular performance, with methods similar to those used in this study, such as the evaluation of ejection fraction of left ventricular end-systolic volume, end-diastolic volume[21], ejection fraction by the Simpson's method, 16-segment contraction score[24], and evaluation of ventricular function by means of dobutamine stress echocardiogram[25,26], showed that, in most of these scenarios, Tmz brought clinical benefits evidenced by the improvement in functional class and echocardiographic parameters of ventricular function.

Regarding the dosage levels of CPK-Mb and Troponin T, the values were significantly lower in the group undergoing pre-treatment with Tmz compared the placebo group ($p = 0.001$), suggesting a reduction of the aggression by reperfusion on the myocardium.

Using serological markers of myocardial injury in recent decades, serum levels of these enzymes were found to be safe instruments safe to exclude or diagnose myocardial damage. Troponin T, a myofibrillar protein present in the contractile apparatus has shown good accuracy due to its high sensitivity when evaluating small damages to the myocardium[27,28].

Over the time, biomarkers have been used as criteria to facilitate the accurate identification of myocardial injury at post-operative period[29-31]. Troponin t, troponin I and CPK-Mb have been useful to define reperfusion injury, and also associated with other findings, such as electrocardiographic and echocardiographic changes[15,32].

Comparing the results of this test with other methods which used similar methodology[7,20] measuring CPK-Mb, myoglobin and troponin in patients undergoing CABG with cardiopulmonary bypass, one may observe that the pre-treatment with the drug has similar cardioprotective effect, which may be ascertained measuring values of the reduced serum markers in the group treated with Tmz.

When the focus is on CABG-related myocardial protection, some authors in retrospective studies, as Klatte et al[33] in of the phases of the multicenter study of GUARDIAN, suggest that patients who progressed to higher levels of CPK-Mb isoenzyme, with and without relationship with the emergence of new Q waves with necrosis characteristics in electrocardiogram, had higher mortality in the immediate and late post-operative period, with interval of six months.

Costa et al[34], in ARTS multicenter study, also show that higher levels of CPK-Mb in the post-operative period of CABG increase mortality. Isoenzyme values that reach five times the baseline increase mortality by around 5% in thirty days, and 10% in one year.

Baggish et al[35], analyzing the levels of Troponin T in patients subject to cardiac surgery, concluded that the level of Troponin T greater or equal to 1.58 ng/mL would be a strong predictor of prolonged ICU stay. It is worth to note that, in this study, none of the patients reached this value of Troponin, both in the placebo group and in the treated group, and the average ICU stay was similar for both.

Lehrke et al[36], studying the levels of Troponin T, found that values higher than or equal to 0.46 ng/mL 48 h after surgery, revealed that to be a good long-term predictor of cardiac mortality, mainly in patients with time of anoxia higher than 65 minutes. Compared with this study, we may suggest that the use of Tmz associated with a shorter duration of anoxia could have an impact on long-term mortality, whereas, in the placebo group, some patients had values of Troponin T higher than 0.46 in 48 hours, and the time of anoxia surpassed 65 minutes. However, in the treated group, although some patients have reached an aortic clamping time higher than 65 minutes, the dose of troponin levels remained lower than the amount described in the author's paper.

Other experimental studies and clinical trials in this field have shown that Tmz has a direct anti-ischemic effect, limiting calcium accumulation and acidosis, inflammation and the production of hyperoxic radicals after reperfusion[4,18,37] and, more recently, in the mitochondrial protection against oxidative stress damage[38]. Maridonneau-Parini and Harley[39] reported that Tmz protects the cell membrane against the aggression and damage after the release of hyperoxic free radicals. Iskesen et al[4,40] demonstrated that the drug reduces levels of malondialdehyde, product of the lipid peroxidation of fatty acids and oxidative degradation of the cell membrane.

The changes in cellular protection shown by the referred tests reflect the effects of Tmz in myocardial cell protection involving the function of mitochondria, providing to clinical practice positive results relating to the improvement of cardiac function demonstrated in functional assessments performed by several methods.

Conclusions

Based on this analysis, we conclude that the use of trimetazidine administered as a pretreatment for patients with coronary artery disease without impairment of left

ventricular function or mild dysfunction, subject to CABG with cardiopulmonary bypass, provides evidence of significant reduction in aggression to the cardiac cell demonstrated by serum markers of injury, CPK-Mb and Troponin T. We also found that, among the groups studied, there were no evolutionary echocardiographic changes in left ventricular systolic function examined over 48 hours of post-operative period.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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