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ORIGINAL ARTICLE

Effect of trimetazidine on myocardial salvage index in patients with acute ST segment elevation myocardial infarction undergoing primary PCI

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KEYWORDS

Trimetazidine;
Myocardial salvage index;
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Abstract *Introduction:* Acute STEMI is the most serious presentation of CAD. Restoration of the coronary flow facilitates cardiomyocyte salvage and decreases cardiac morbidity and mortality. However, reperfusion may result in paradoxical cardiomyocyte dysfunction, a phenomenon termed reperfusion injury. Trimetazidine is a metabolic anti-ischemic drug which is beneficial in reducing periprocedural myocardial reperfusion injury.

The aim of the work is to study the effect of trimetazidine on myocardial salvage index in patients with acute STEMI who underwent primary PCI.

Methods: Forty patients presented with acute STEMI, underwent primary PCI with injection of an intravenous dose of Tc-99m labeled Sestamibi before primary PCI then first set of SPECT images were taken within 6 h from injection time to assess the initial size of the perfusion defect. Prior to discharge the patients received another dose of Tc-99m labeled Sestamibi and follow up SPECT images were taken to assess the final perfusion defect and to calculate myocardial salvage and myocardial salvage index.

Twenty patients of them received trimetazidine before primary PCI (study group) and the other twenty patients did not receive trimetazidine (control group).

Results: (1) Patients with acute STEMI undergoing primary PCI who received trimetazidine before primary PCI had better myocardial salvage index, however it was statistically non significant. (2) Statistically significant better myocardial salvage index with post procedural TIMI 3 flow than with post procedural TIMI 2 flow among patients who received trimetazidine before primary PCI.

Conclusion: In the presence of post procedural TIMI3 flow trimetazidine is beneficial in improving myocardial salvage index in patients presented with acute STEMI who underwent primary PCI.

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1. Introduction

ST segment elevation myocardial infarction (STEMI) is the most serious presentation of atherosclerotic coronary artery disease carrying the most hazardous consequences and it is caused by occlusion of major coronary artery.[1] Primary

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percutaneous coronary intervention (PCI) is the preferred reperfusion strategy especially when performed by an experienced team within the shortest possible time from first medical contact.[2]

One of the main aims of all treatment modalities in STEMI is mortality reduction, and since the use of mortality as an end point in randomized trials of reperfusion therapy requires increasingly large sample sizes, there has been a growing interest in assessment of infarct size by technetium (Tc)-99m Sestamibi single photon emission computed tomography (SPECT) imaging as a surrogate end point for both early and late mortality.[3] On the basis of the available scientific evidence, SPECT imaging with Tc-99m Sestamibi is the best available measurement tool for infarct size in clinical medicine. Tc-99m Sestamibi scintigraphy is considered a reliable method to assess myocardial salvage (difference between the actual and potential infarct size) achieved by reperfusion therapy.[3] Trimetazidine is a metabolic anti-ischemic drug that exerts its beneficial effects without altering hemodynamic function of the heart.

It acts by optimizing cardiac metabolism by reducing fatty acid oxidation through selective inhibition of mitochondrial 3-ketoacyl coenzyme A thiolase so it decreases ischemic stress and improves cardiac performance and also it showed cytoprotective effect in several models of myocardial infarction.[4] Also trimetazidine is beneficial in reducing peri-procedural myocardial reperfusion injury in elective PCI.[5]

2. Aim of the work

To assess the effect of trimetazidine on myocardial salvage index in patients with STEMI undergoing primary PCI.

3. Patients and methods

This study was conducted on forty patients admitted to the Ain Shams University Hospital by acute STEMI eligible for reperfusion within the period between September 2010 and July 2011.

3.1. Patients

3.1.1. Inclusion criteria

All patients were presented with typical rise and/or fall of cardiac biomarkers of myocardial necrosis with at least one of the following:

(1) New ST segment elevation at the J point in two contiguous leads with cut off points: 0.2 mV in men and 0.15 mV in women in leads V2 and V3 and/or 0.1 mV in other leads.
(2) Any ischemic symptoms such as chest pain, palpitation or dyspnea.[6] Reperfusion therapy was indicated in patients who sought medical advice within 12 h of onset of continuous symptoms, also persistence of ischemic symptoms after 12 h was considered as an indication of reperfusion.

3.1.2. Exclusion criteria

Patients who had one or more of the following were excluded from the study:

(1) Previous AMI.
(2) Patients with contraindication for primary PCI such as high risk bleeding as intracranial hemorrhage.
(3) Patients who were hemodynamically unstable or clinically unfit to be transferred to myocardial perfusion scan laboratory.
(4) Previous CABG surgery.
(5) Re-infarction during CCU admission before acquiring second SPECT image.

Patients were classified into two groups, **group 1** included twenty patients who received 70 mg of **trimetazidine** loading before primary PCI and continued on 70 mg/day in two divided doses till the second SPECT image (study group) and **group 2** included twenty patients who did not receive **trimetazidine** (control group).

3.2. Methods

All patients were subjected to:

3.2.1. Thorough history taking

Full history was taken from all cases as regards:

1- *Personal history*: Age, sex, and detailed risk profile as regards diabetes mellitus, hypertension, dyslipidemia and smoking status.
2- *Past history*: Including past history of AMI or prior history of anginal symptoms or renal impairment.
3- *Family history*: As regards family history of premature CAD (men <55 years of age or women <65 years of age) or occurrence of sudden cardiac death.
4- *Presenting complaint*: Chest pain was analyzed as regards duration prior to admission, associated symptoms, and presence of angina equivalents.

3.2.2. Full clinical examination

Each patient was thoroughly examined

1- *General examination:* With special emphasis on vital data especially arterial blood pressure and heart rate.
2- *Local cardiac examination:* All patients were subjected to full cardiac examination stressing on the presence of mechanical complications and signs of heart failure as: mitral regurgitation, ventricular septal defects, S3 gallop and basal rales.

3.2.3. Twelve lead surface ECG

ECG was done to all patients on admission, immediately post procedure, 90 min after primary PCI and serially every 8 h for the next 24 h, then daily till discharge. ECG machine was used to record standard 12-lead ECGs.

3.2.4. Full Labs

Full labs were carried out for all patients on admission and followed up thereafter with special emphasis on cardiac enzymes (CK and CK-MB), renal profile (serum creatinine, sodium, and potassium) and complete blood count (hemoglobin and platelet count).

3.2.5. Echocardiography

Echocardiographic assessment was done to each patient prior to discharge using a GE vivid five machine to assess ejection fraction, LV dimensions, presence of segmental wall motion abnormality, or mechanical complications.

3.2.6. Primary PCI protocol

All cases were given:

(1) *Acetyl salicylic acid*: All patients were given 300 mg loading of acetyl salicylic acid and kept on 150 mg daily thereafter.
(2) *Clopidogrel*: All patients were given a loading dose of 600 mg clopidogrel prior to procedure, and kept on 75 mg daily thereafter.
(3) *Unfractionated heparin*: All patients were given 10,000 international units (IU) of unfractionated heparin at the beginning of intervention and kept on it till discharge with partial thromboplastin time adjusted to 1.5–2 basal.
(4) *GP IIb/IIIa inhibitor*: Was given at the discretion of treating physician. Then all patients underwent primary PCI after diagnostic coronary angiography, the infarct related artery (IRA) was identified and treated using bare metal stents ± pre-dilatation by balloons according to the discretion of treating physician. After the end of revascularization TIMI flow grading was calculated.[7]

3.2.7. SPECT imaging protocol

The patients were given an intravenous dose of Tc-99m labeled Sestamibi (20–30 mCi) followed by their designated reperfusion therapy via primary intervention then SPECT first set of images were taken within 6 h from the time of injection of the radioactive material to assess the initial size of the perfusion defect prior to reperfusion (myocardium at risk). With semi-quantitative visual analysis and displaying the images using a four dimension (4DM) SPECT, a score was assigned to represent myocardial perfusion.

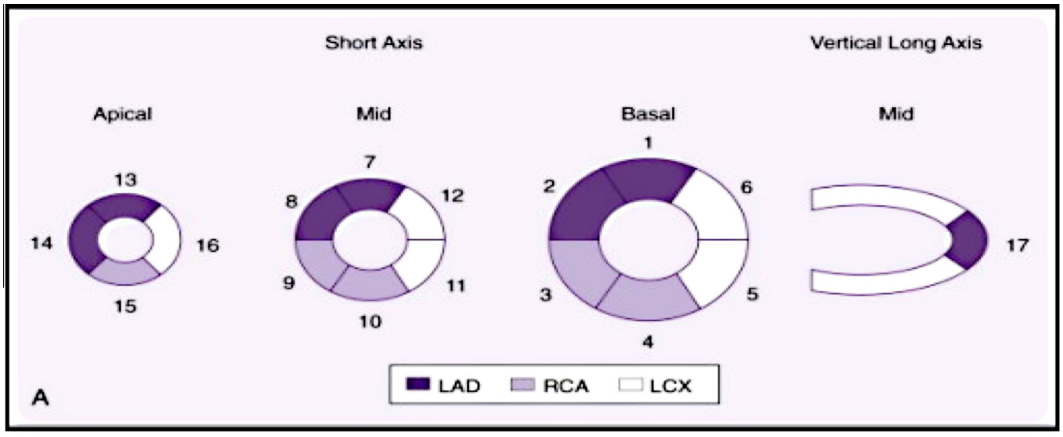
A segmentation model has been standardized for this approach by dividing the myocardium into 17 segments on the basis of three short-axis slices and a representative long-axis slice to depict the apex, see Fig. 1. Perfusion was graded within each segment on a scale of 0–4, with 0 representing normal perfusion and four representing a very severe perfusion defect. Scores for all 17 segments were added to create a summed score representing myocardium at risk.[8] Prior to discharge the patients received another dose of Tc-99m labeled Sestamibi (20–30 mCi) and follow up SPECT images were taken to assess the final perfusion defect and to calculate myocardial salvage. Sum of the 17 segmental scores from the 2nd image represented the final size of infarction. See Figs. 3 and 4. Myocardial salvage is the difference between initial perfusion defect (myocardium at risk) and final perfusion defect (final size of infarction) and myocardial salvage index was obtained from the following equation.

Initial perfusion defect

– Final infarction size/Initial perfusion defect

3.3. Statistical analysis

- Categorical variables were expressed as absolute and relative frequencies (percentage) while continuous variables were presented as mean values ± standard deviation (SD).
- Comparisons were made between the two groups using *t*-test for continuous variables and chi-square test and Pearson correlation coefficient for categorical variables.
- Statistical analysis was performed using SPSS (statistical package version sixteen).



1=basal anterior segment, 2=basal anterior septum, 3= basal posterior septum, 4=basal inferior segment,5=basal posterior segment, 6= basal lateral segment, 7=mid anterior segment, 8=mid anterior septum, 9=mid posterior septum, 10=mid inferior segment,11=mid posterior segment,12=mid lateral segment,13= apical anterior segment, 14=apical anterior septum, 15=apical inferior segment, 16=apical lateral segment,17= apex proper.

Figure 1 Standard segmental myocardial display for semi-quantitative visual analysis in a 17 segment model, with corresponding vascular territory schematic.[8]

Table 1 Comparison between patients who received trimetazidine before primary PCI (**group 1)** and patients who did not receive trimetazidine before primary PCI (**group 2)** as regards age, sex, risk factors for CAD, time to reperfusion, location of myocardial infarction, and the culprit vessel.

Variable		Group 1 $n = 20$	Group 2 $n = 20$	P value
Age in years Mean ± SD		54.7 ± 9.3	57.8 ± 11.8	P = NS
Sex number (%)	Female	3 (15%)	2 (10%)	P = NS
	Male	17 (85%)	18 (90%)	
Hypertension number (%)	+ve	6 (30%)	8 (40%)	P = NS
Diabetes mellitus number (%)	+ve	11 (55%)	9 (45%)	P = NS
Smoking number (%)	+ve	15 (75%)	12 (60%)	P = NS
Family history number (%)	+ve	1 (5%)	2 (10%)	P = NS
Time to reperfusion in hours Mean ± SD		4.95 ± 3.6	4.96 ± 4.3	P = NS
Location of AMI number (%)	Anterior	13 (65%)	11 (55%)	P = NS
	Non anterior	7 (35%)	9 (45%)	
Culprit vessel number (%)	LAD	13 (65%)	11 (55%)	P = NS
	LCX	2 (10%)	2 (10%)	
	RCA	5 (25%)	7 (35%)	

Table 2 Comparison between patients who received trimetazidine before primary PCI (**group 1**) and patients who did not receive trimetazidine before primary PCI (**group 2**) as regards post procedural TIMI flow.

Variable		Group 1 $n = 20$	Group 2 $n = 20$	P value
Post procedural TIMI flow number (%)	TIMI 0	0 (0%)	0 (0%)	P = NS
	TIMI 1	0 (0%)	0 (0%)	
	TIMI 2	8 (40%)	11 (55%)	
	TIMI 3	12 (60%)	9 (45%)	

Table 3 Comparison between patients who received trimetazidine before primary PCI (**group 1**) and patients who did not receive trimetazidine before primary PCI (**group 2**) as regards the initial perfusion defect, the final perfusion defect and the myocardial salvage index.

Variable	Group 1 $n = 20$	Group 2 $n = 20$	P value
Initial perfusion defect Mean ± SD	27 ± 11.1	27.9 ± 12.3	P = NS
Final perfusion defect Mean ± SD	18 ± 9.5	22.15 ± 10.10	P = NS
Myocardial salvage index Mean ± SD	29.71 ± 24.4%	21.43 ± 21.5%	P = NS

- Difference was considered statistically significant at a P value < 0.05 and highly significant at P value < 0.01.

4. Results

According to receiving of trimetazidine patients were divided into two groups:

Study group (1): It included twenty patients who received trimetazidine before primary PCI.

Control group (2): It included twenty patients who did not receive trimetazidine before primary PCI. Both groups were comparable as regards age, sex, risk factors for CAD, time to reperfusion, location of myocardial infarction and the culprit vessel as shown in Table 1.

After the end of primary PCI post procedural TIMI flow grading was done. Although, post procedural TIMI 3 flow was more among the study group (12 vs. 9) yet the difference was not statistically significant as shown in Table 2.

Both groups were compared as regards the initial perfusion defect, the final perfusion defect and the myocardial salvage index. There was no statistically significant difference between both groups with nearly equal initial perfusion defect (27 ± 11.1 vs. 27.9 ± 12.3) and smaller final perfusion defect in **group 1** than in **group 2** (18 ± 9.5 vs. 22.15 ± 10.10) and better myocardial salvage index in **group 1** than in **group 2** (29.71 ± 24.4% vs. 21.43 ± 21.5%). These results are shown in Table 3 and Fig. 2.

An important factor that affects the myocardial salvage index is post procedural TIMI flow. Myocardial salvage index in both groups was correlated with post procedural TIMI flow as shown in Table 4.

Myocardial salvage index was higher in patients with post procedural TIMI 3 flow than in patients with post procedural TIMI 2 flow in both groups with statistically significant difference in **group 1** receiving trimetazidine before primary PCI (38.32 ± 26.6% vs. 16.80 ± 13.88%) and non statistically significant difference in **group 2** who did not receive trimetazidine before primary PCI (28.09 ± 27.95% vs.15.99 ± 13.44%). Initial perfusion defect, final infarction size and myocardial salvage index were compared between the two groups in patients with post procedural TIMI 2 flow, and in patients with post procedural TIMI three flow. There was nearly equal myocardial salvage index in both groups in patients with post procedural TIMI 2 flow but it was slightly higher in **group 1** who

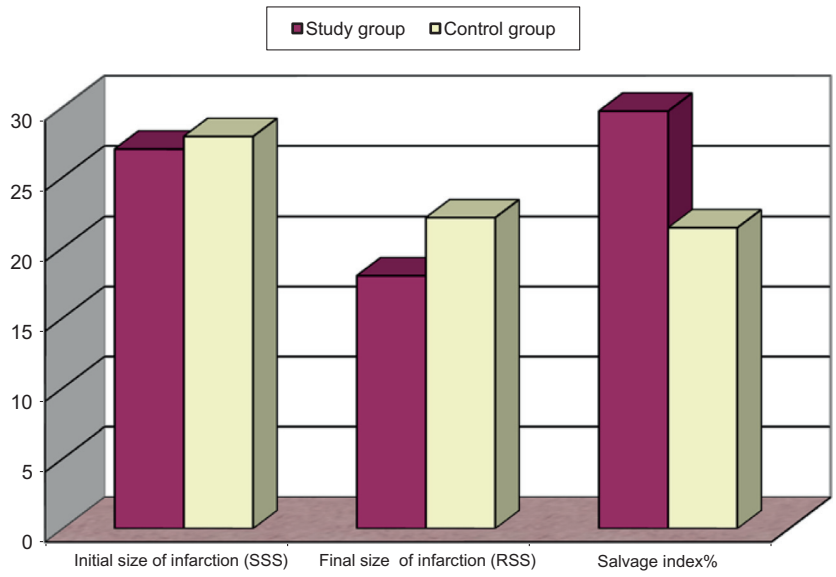


Figure 2 Comparison between both groups as regards initial size of infarction, final size of infarction and myocardial salvage index.

Table 4 Correlation between post procedural TIMI flow and myocardial salvage index in both groups.

Variable	TIMI 2 (%)	TIMI 3 (%)	*P* value
Myocardial salvage index in **group 1** Mean ± SD	16.80 ± 13.9	38.32 ± 26.6	$P < 0.05$
Myocardial salvage index in **group 2** Mean ± SD	16 ± 13.44	28.09 ± 28	P = NS

received trimetazidine before primary PCI than **group 2** who did not receive trimetazidine before primary PCI (16.80 ± 13.9 vs. 15.99 ± 13.44) as shown in Table 5.

Among patients with post procedural TIMI 3 flow in spite of larger initial perfusion defect (28.5 ± 12.2 vs. 25.11 ± 15.4) the final size of infarction was smaller (16.25 ± 9.6 vs. 17.44 ± 11.5) and myocardial salvage index was higher (38.32 ± 26.6 vs. 28.09 ± 27.9) in **group 1** who received trimetazidine before primary PCI than **group 2** who did not receive trimetazidine before primary PCI yet it was not statistically significant as shown in Table 6.

5. Discussion

The primary goal in the management of acute STEMI is to start reperfusion therapy as early as possible whether mechanical or pharmacological reperfusion.[2] Primary PCI according to the ESC guidelines is the preferred treatment if performed by an experienced team within 90 min of first medical contact (FMC) or in patients presented by cardiogenic shock and those with contraindications to fibrinolytic therapy irrespective of time delay.[2] Compared with fibrinolytic therapy, primary PCI had shown more effective restoration of patency, less re-occlusion, less bleeding complications, improved residual LV function and better clinical outcome.[9]

Maintenance of myocardial viability is the goal of reperfusion therapy during AMI. Myocardial salvage, defined as the amount of myocardium that was jeopardized by a coronary occlusion but spared from infarction and can be used to compare different treatment options so that strategies that show a benefit in salvage could be implemented in clinical practice.[10]

Restoration of the coronary flow facilitates cardiomyocyte salvage and decreases cardiac morbidity and mortality. However, reperfusion may result in paradoxical cardiomyocyte dysfunction, a phenomenon termed "reperfusion injury" and this is observed in all modalities of reperfusion including thrombolysis, PCI, CABG, and cardiac transplantation.[20]

Trimetazidine is a metabolic anti-ischemic drug which is beneficial in reducing peri-procedural myocardial reperfusion injury in elective PCI.[5]

5.1. Effect of trimetazidine on myocardial salvage

In the present study myocardial salvage was better in the group who received trimetazidine before primary PCI yet it was not statistically significant. This finding agrees with *Steg and his colleagues in 2001* who carried out a study on 94 patients with AMI who were randomized to receive trimetazidine (40 mg bolus followed by 60 mg/day intravenously for 48 h) or placebo, starting before re-canalization of the infarct vessel by primary angioplasty and it reported that blinded ST segment analysis showed that despite higher initial ST deviation from baseline in the trimetazidine group there was an earlier and more marked return toward baseline within the first 6 h than in the placebo group. There was a trend toward less frequent exacerbation of ST deviation at the time of re-canalization in the trimetazidine group. There was no difference in LV wall motion at day 14, or in enzymatic infarct size.[11] This was concordant too with *Dong and his colleagues in 2007* who studied the effect of trimetazidine as an adjunctive treatment to reperfusion therapy in AMI. Sixty patients with AMI were randomized to receive trimetazidine (a loading dose of 60 mg followed by 20 mg 3 times daily) for 2 weeks or to be controls. The

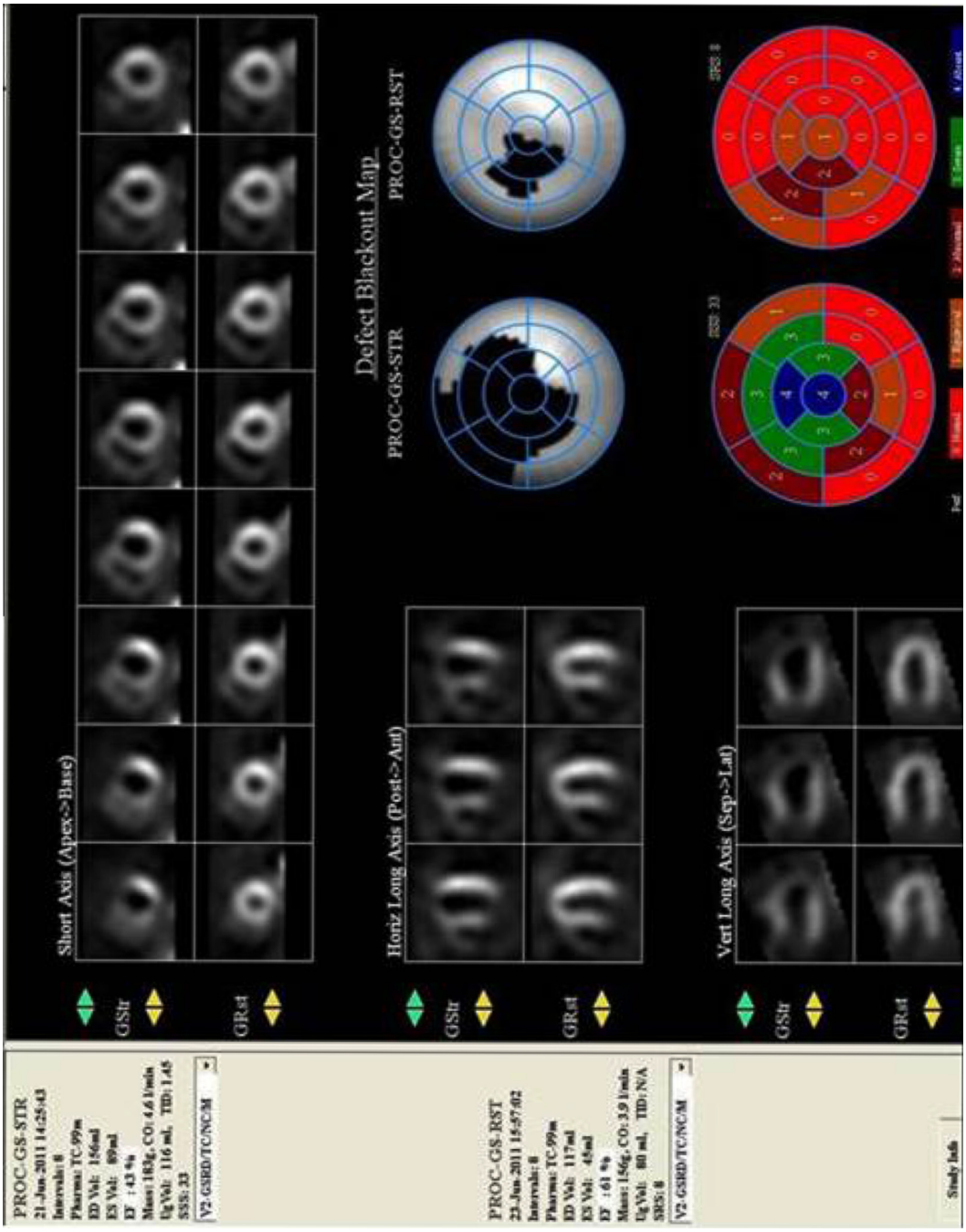


Figure 3 Calculation of the initial and final size of infarction in patient number "16" in the study group.

loading dose was started early before the reperfusion therapy. Patients received intermittent ST segment monitoring to assess the resolution of ST segment deviation one hour after reperfusion therapy. In-hospital and 3-months major adverse cardiac events were recorded. Blinded ST segment analysis showed that there was a more marked return toward baseline one hour after reperfusion therapy in the trimetazidine group, than in the control group [change (7.14 ± 3.50) vs. (3.79 ± 1.32) mm, $P = 0.041$].[12]

There were also several studies that support the cardio-protective effect of trimetazidine during PCI procedure such as *Poloński and his colleagues in 2002* who studied the effect of pre-treatment with trimetazidine on the degree of ischemia during PTCA. Overall 44 patients with one-vessel coronary artery stenosis (>70%) in the med LAD artery were included. One group was pretreated with oral trimetazidine. The other group was the control. The mean ST segment elevation during all balloon inflations was significantly lower in the trimetazidine group than in the control group (−1.66 ± 1.50 vs. 3.29 ± 1.59 mm, $P = 0.001$). Maximal ST segment elevations and mean ST elevation values during sequential balloon inflations were also significantly lower with trimetazidine ($P = 0.018$), and they suggested that trimetazidine administered a few days before PTCA appears to be a cardio-protective agent for the prevention of myocardial ischemia.[13]

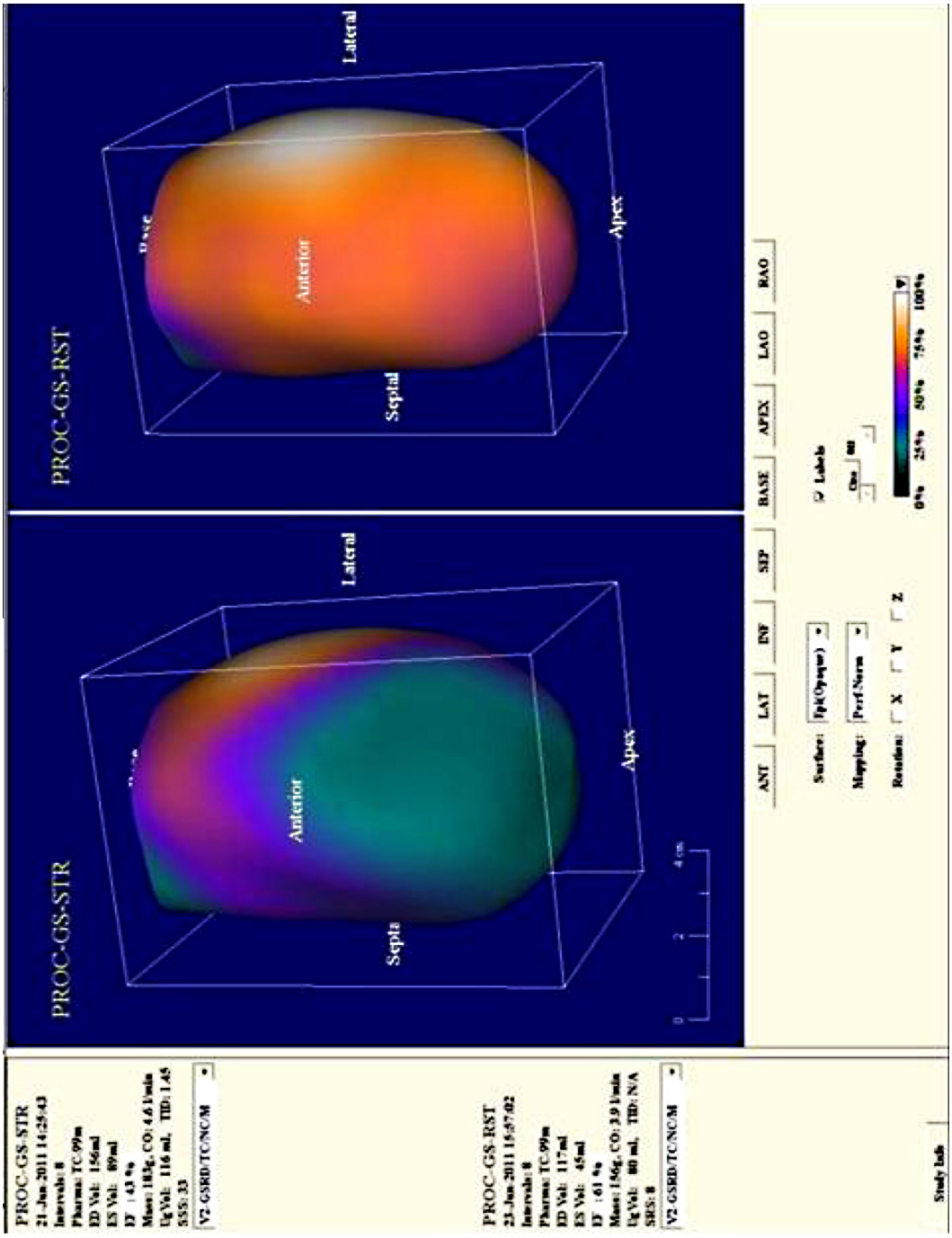


Figure 4 The four DM SPECT images of patient number "16" in the study group before and after reperfusion.

This could be explained by the effect of trimetazidine on mediators of reperfusion injury as trimetazidine decreases fatty acid oxidation and stimulates glucose utilization, restoring coupling between glycolysis and carbohydrate oxidation, and leads to ATP production with less oxygen consumption and by stimulating membrane phospholipid turnover during ischemia and reperfusion, trimetazidine also redirects fatty acids toward phospholipids.[14] This is also supported by *Williams and his colleagues in 1993* who reported that trimetazidine inhibits neutrophil accumulation without adverse effects on vascular permeability and protects myocardial cells from reperfusion injury, attenuates intracellular acidosis during ischemia, and accelerates restoration of phosphorylation at reperfusion.[15]

It agrees too with Bonello and his colleagues in 2007 who studied the beneficial effect of trimetazidine in preventing ischemia–reperfusion injury by inhibiting mitochondrial ATP opening, which represents a crucial event in cardiomyocyte death following ischemia reperfusion.[5]

It also goes with Kuralay and his colleagues in 2006 who reported in their study that patients receiving trimetazidine orally 3 days prior to PTCA had significantly decreased level of C reactive protein, tumor necrosis factor (TNF) α and nitric

Table 5 Comparison of initial perfusion defect, final infarction size and myocardial salvage index between the two groups in patients with post procedural TIMI 2 flow.

Variable	Group 1	Group 2	*P* value
Initial perfusion defect Mean ± SD	24.75 ± 9.29	30.18 ± 9.2	*P* = NS
Final infarction size Mean ± SD	20.62 ± 9.50	26 ± 9.34	
Myocardial salvage index Mean ± SD	16.80 ± 13.9%	15.99 ± 13.44%	

Table 6 Comparison of initial perfusion defect, final infarction size and myocardial salvage index between the two groups in patients with post procedural TIMI 3 flow.

	Group 1	Group 2	*P* value
Initial perfusion defect Mean ± SD	28.5 ± 12.2	25.11 ± 15.4	*P* = NS
Final infarction size Mean ± SD	16.25 ± 9.6	17.44 ± 11.5	
Salvage index Mean ± SD	38.32 ± 26.6	28.09 ± 27.9	

oxide during initial 48 h after PTCA and it is known that PTCA triggers systemic inflammatory response by inducing ischemia reperfusion cycle through repeated balloon inflation which can be followed by tissue injury and impaired anti-oxidant status.[16]

5.2. Myocardial salvage and TIMI flow

An important factor that affects myocardial salvage is the TIMI flow. In the current work myocardial salvage index was higher in both groups in patients with post procedural TIMI 3 flow than in those with TIMI 2 flow. Among patients with post procedural TIMI 3 flow better myocardial salvage index was recorded in **group 1** who received trimetazidine yet it was not statistically significant and among patients with post procedural TIMI 2 flow there was almost equal myocardial salvage index and these data are supported by *Ndrepepa and his colleagues in 2010* as they reported that restoration of suboptimal epicardial flow (TIMI grade $\leqslant$2) denotes increased segmental coronary resistance due to severe vascular obstruction and is associated with extensive myocardial necrosis, reduced myocardial salvage with primary PCI, negative LV remodeling and increased mortality.[17] Only patients with TIMI 3 flow were defined as having successful reperfusion, only TIMI 3 flow was associated with improved mortality and clinical outcome with TIMI 2 flow was comparable to TIMI 0 or 1 flow.[18]

Restoration of an optimal epicardial flow is a prerequisite for restoration of normal reperfusion at the microcirculation level and the latter is a precondition for unimpeded blood flow in the epicardial coronary system and none of the patients with restoration of the suboptimal epicardial flow (TIMI grade $\leqslant$2) had optimal flow at the microcirculation level of myocardial blush grade 3 (MBG3), even those with TIMI 3 flow may have a suboptimal myocardial reperfusion at microcirculation level.[19] A final important point to note is that the effect of TIMI flow on myocardial salvage index was very obvious in the group who received trimetazidine before primary PCI with statistically significant high myocardial salvage index in patients with post procedural TIMI 3 flow than those with post procedural TIMI 2 flow that could be explained by the fact that in the presence of optimal epicardial flow and better perfusion on microcirculation level trimetazidine can exert its cytoprotective effect on the myocytes with resultant better myocardial salvage index.

6. Conclusion

Successful reperfusion with primary PCI with restoration of myocardial blood flow as evident by post procedural TIMI 3 flow, trimetazidine on top of this important factor may be beneficial in minimizing final infarction size and improving myocardial salvage index in patients presented with acute STEMI who underwent primary PCI.

7. Limitations of the study

Our findings are based on a single-center study with a relatively small sample size of the cohort. Multicenter studies employing the same protocol and examining a larger number of patients are further needed.

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