Evaluation of the effect of trimetazidine on Tc–99m methoxyisobutyl isonitrile gated scintigraphy in patients with coronary artery ectasia

Berna Okudan, *MD,* ***Feride M. Ozbek,*** *MD,* ***Abdullah Dogan,*** *MD,* ***Begum Ozturk,*** *MD,* ***Mustafa Yildiz,*** *MD.*

ABSTRACT

Objective: Coronary artery ectasia (CAE) is the abnormal dilatation of a segment of the coronary artery to a diameter of at least 1.5 times that of normal adjacent segments. Symptoms are variable, and its prognosis and treatment modalities are unclear. The aim of this study is to evaluate the effect of trimetazidine (TMZ) on ischemic left ventricular function by rest-stress Tc-99m methoxyisobutyl isonitrile (Tc-99m MIBI) myocardial scintigraphy in symptomatic patients with CAE.

Methods: We included patients with ectasia admitted to our Cardiology Department, Turkey, between 2003 and 2004 in this study. All patients underwent coronary angiography and diagnosed with CAE, before and 4 weeks after TMZ administration. Seventeen patients (9 men, 8 women) underwent gated single-proton emission tomographic (SPECT) using Tc-99m MIBI. We performed quantitative global and regional ventricular functional analysis using quantitative gated SPECT software.

Results: The global ejection fraction increased from 59.9%±8.9% to 62.6%±8.3% after therapy (p=0.033). In addition, the end systolic volume and the end diastolic volume decreased after therapy (101.7±23.5 ml to 95.1±22.9 ml, p=0.002; from 41.1±14.3 to 36.4±13.6, p=002). In all segments, we observed significant post-therapy increases in relative tracer uptake. Percentage of MIBI uptake was 71.2±15.3 at baseline stress and 73.2±15 post-TMZ (p=0.001). As global function parameters, the total wall motion normal areas changed significantly (67-74% p=0.01) after therapy, but the total wall thickness did not changed significantly(49-45%, p=0.21).

Conclusion: The results of this study demonstrate that TMZ improves myocardial function by rest-stress Tc-99m MIBI gated SPECT during stress-induced ischemia in patients with CAE. Also, the outcomes revealed improvement in functional parameters, and percentage of MIBI uptake post TMZ administration. We can use this procedure to monitor the effect of TMZ in CAE patients.

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Coronary artery ectasia (CAE) is the abnormal dilatation of a segment of the coronary artery to a diameter of at least 1.5 times that of normal adjacent segments.[1] It is a well recognized, albeit rare, finding at cardiac catheterization. Clinical symptoms vary and include stable angina pectoris, unstable angina pectoris, and atypical chest pain. Additionally, myocardial infarction may occur in the absence of significant coronary artery stenosis.[2] The prognosis and best form of treatment are also

From the Department of Nuclear Medicine (Okudan, Ozbek, Yildiz) and the Department of Cardiology (Dogan, Ozturk), School of Medicine, Suleyman Demirel University, Istanbul, *Turkey*.

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Address correspondence and reprint request to: Dr. Berna Okudan, Assistant Professor, Istek Lojmanlari 19 Mayis Mah. Hilmipasa Cad, Uzay Sokak No. 10/7 Kozyatagi, Kadikoy, Istanbul, *Turkey*. Tel. +90 (532) 3649024. Fax. +90 (216) 4163335. E-mail: okudanb@yahoo.com

unclear. Trimetazidine (TMZ) has been reported to exert anti-ischemic properties without affecting myocardial oxygen consumption, and blood supply.[3,4] Dogan et al,[5] showed that TMZ can relieve exercise-induced angina and improve exercise performance in patients with CAE. But they used only electrocardiographic measurement in the estimation of the result of TMZ and did not evaluate any functional parameters. Electrocardiography gated SPECT myocardial perfusion scintigraphy with technetium-99m (Tc-99m) labeled agents provides the opportunity to assess regional myocardial perfusion, and global functional data simultaneously at stress and rest.[6,7] There is no evidence indicating that the effect of TMZ on myocardial perfusion and functional parameters with Tc-99m methoxyisobutyl isonitrile (Tc-99m MIBI) gated myocardial perfusion scintigraphy is useful in patients with isolated CAE. Therefore, we evaluated the effects of the oral administration of TMZ on ischemic left ventricular dysfunction by rest-stress Tc-99m MIBI myocardial scintigraphy in symptomatic patients with CAE.

Methods.

Patient selection. Patients with coronary ectasia with wall motion (WM) abnormalities who were admitted to our Cardiology Department, Suleyman Demirel University, Turkey between 2003 and 2004 were included in this study. This study included 19 consecutive patients with angiographically documented isolated CAE and left ventricle WM abnormalities. Isolated CAE was considered to be present if there was coronary ectasia in any of 3 major epicardial coronary arteries without any luminal narrowing. Two patients were excluded from the study due to non-compliance. The remaining 17 (9 males, 8 females; mean age 55.76±11.76 years) patients consisted the main study group. Of these, one patient had one-vessel ectasia disease, 11 had 2-vessel ectasia disease, and 5 had 3-vessel ectasia disease. Four patients (3 males, 1 female) had a previous myocardial infarction all of them had an inferior myocardial infarction **(Table 1).** Exclusion criteria were as follows; ectasia patients with known inflammatory or connective tissue diseases, significant valvular disease (aortic and mitral regurgitation >2^{O}, severe aortic stenosis), diabetes mellitus, hypertrophic cardiomyopathy, ventricular hypertrophy by echocardiography, and obstructive pulmonary disease. The patients underwent rest and stress Tc-99m MIBI SPECT 2 times. All medications were discontinued at least one week before the study and discontinued to the therapy during one month. All medications were discontinued at least one week before the first scintigraphic study and discontinued to the therapy during one month. Also, administration of all medications were stopped at least 48 hours before the second scintigraphic examination except TMZ, antiplatelets antiaggregants and anti-coagulants. TMZ was administered three times daily for 4 weeks (20 mg 3 times).

Radionuclide imaging. The rest and stress studies were performed in a one-day protocol, using 0.11 mCi/kg Tc-99m MIBI, and 0.31 mCi/ kg at rest and at stress. All of the patients underwent symptom limited exercise on a treadmill. Exercise was continued for one minute after injection. The scintigraphic data were acquired in continuous SPET over 180° elliptical rotation from the 45° right anterior oblique position with a dual-head gamma camera (Siemens E-CAM), using a low energy high-resolution collimator and zoom factor of 1.45. Sixty-four projections were obtained in a 128 x 128 matrix. The acquisition time was 20 or 30 seconds per projection.

Image processing. Tomographic reconstruction and calculation of short axis slice images were performed using Siemens software. A 2-dimensional Butterworth pre-reconstruction filter was used with critical frequency of 0.35, order 5. For each patient, the same sets of short axis slices were then processed with the automatic software packages 4D-MSPECT (University of Michigan). The software packages define apex and base and generate polar maps. In 4D-MSPECT, it is possible to change the automatically chosen apex and base slices. The operators used this possibility when necessary. Polar maps were created as described and normalized to 100% peak activity.[8,9,10,11] Both rest and stress studies were processed using the 17- segment model for scoring. In addition, percentage of MIBI uptakes was obtained by using 9 segment polar maps. The segments were automatically scored regarding radiotracer uptake, using a 5-point scoring system (0=normal, 1=equivocal, 2=moderately reduced, 3=severely reduced, and 4=absent). The summed stress score (SSS) and summed rest score (SRS) were automatically calculated for each patient by each software package. Both SSS and SRS values were generated based on comparisons with normal limits databases. The database was used best corresponded to a one-day Tc-99m MIBI protocol. The 4D- MSPECT software generated scores based on the normal file from one-day Tc-99m-sestamibi protocols, non-corrected (attenuation), and gender-matched cases. Polar maps of regional perfusion, WM, and wall thickness (WT) were generated. Regional perfusion (tracer uptake), was expressed as the percentage of maximal myocardial counts on non-gated images. For regional functional analysis, the myocardium was divided into 9 segments each, and analyzed quantitatively on the basis of each functional polar map **(Figure 1)**. For global functional analysis, total WM and WT were calculated by summing all 17 segmental values. The semi-automatic 4D-MSPECT software processes data on the basis of a 2-dimensional gradient image,

Table 1 - Clinical characteristic of the patients (n=17).

Gender	Age (years)	Site of previous myocardial infarction	Coronary artery ectasia Left anterior descending	Left circumflex	Right coronary artery
Female	74	-	Proximal coronary ectasia	Proximal, middle coronary ectasia	Coronary ectasia
Female	72	Inferior	Proximal coronary ectasia	Coronary ectasia	-
Female	48	-	Coronary ectasia	Coronary ectasia	-
Male	59	-	-	-	Coronary ectasia
Male	56	-	Proximal coronary ectasia	-	Coronary ectasia
Male	40	-	Coronary ectasia	Coronary ectasia	-
Female	42	-	Proximal coronary ectasia	Proximal, middle coronary ectasia	-
Female	55	-	Proximal, middle coronary ectasia	-	Coronary ectasia
Male	66	-	Proximal, middle coronary ectasia	-	Coronary ectasia
Male	47	Inferior	Coronary ectasia	Coronary ectasia	Coronary ectasia
Male	50	-	Proximal, middle coronary ectasia	Coronary ectasia	Coronary ectasia
Female	65	-	Coronary ectasia	Coronary ectasia	Coronary ectasia
Male	51	-	Coronary ectasia	Coronary ectasia	-
Female	63	-	Proximal, middle coronary ectasia	-	Coronary ectasia
Male	32	Inferior	Coronary ectasia	Coronary ectasia	Coronary ectasia
Female	68	-	Coronary ectasia	Proximal coronary ectasia	-
Male	60	Inferior	Proximal coronary ectasia	-	Coronary ectasia

Table 2 - Hemodynamic data and gated Tc-99m methoxyisobutyl isonitrile myocardial scintigraphy parameters at baseline and post trimetazidine therapy.

Parameters	Baseline	Post-trimetazidine	*P*-value
Heart rate (beat per min^{-1})	79 ± 14	79 ± 10	0.70
Systolic blood pressure (mm Hg)	135 ± 17	123 ± 17	0.01
Diastolic blood pressure (mm Hg)	84 ± 14	80 ± 13	0.30
Left ventricle ejection fraction (%)	59.9 ± 8.9	62.6 ± 8.3	0.03
Left ventricle end systolic volume (ml)	41.1 ± 14.3	36.4 ± 13.6	0.02
Left ventricle end diastolic volume (ml)	101.7 ± 23.5	95.1 ± 22.9	0.02
Myocardial uptake (in stress %)	71.2 ± 15.3	73.2 ± 15	0.00
Left ventricle hypoperfused segments (%)	106 (37)	89 (30)	0.001
Left ventricle wall motion normal scores (%)	194 (67)	215 (74)	0.01

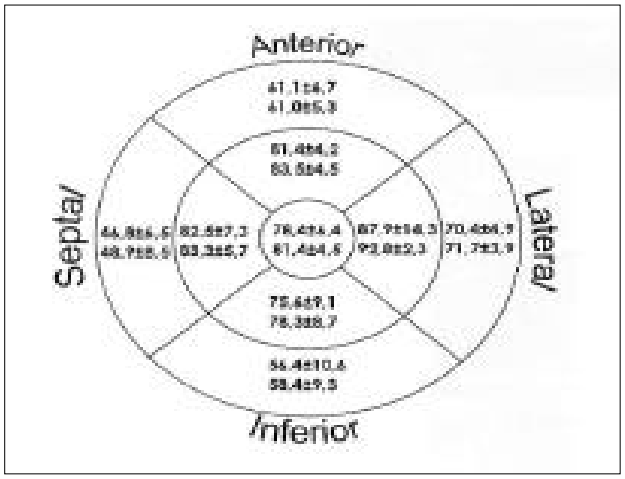

Figure 1 - Change in segmental relative tracer uptake (percentage, mean ± SD) before and after trimetazidine (TMZ). In each segment, top values are pre-therapy uptake and bottom values are post-TMZ.

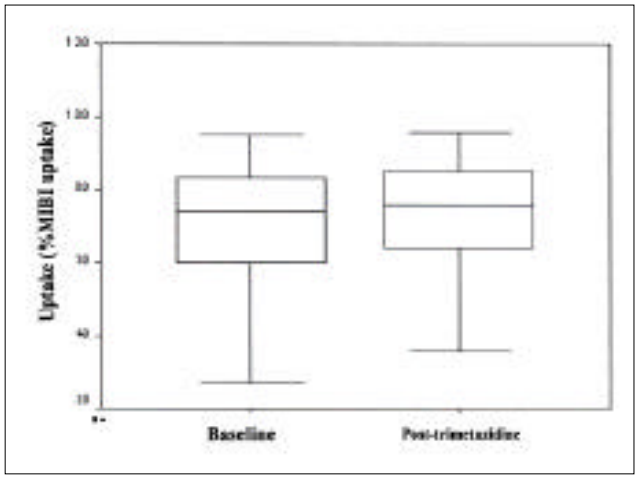

Figure 2 - Tc-99m percentage of methoxyisobutyl isonitrile uptake in myocardium before and after trimetazidine administration.

from which the initial estimates of the ventricle are made.[8,9,10,11]

Statistical analysis was carried out using SPSS 9.5 (SPSS Inc.) software. The data are shown as mean±SD. The mean values of functional parameters were tested for significance using a Wilcoxan-Rank pre and post-TMZ administration as well as Spearman correlation coefficients, $p<0.05$ was accepted as significant.

Results. Trimetazidine administration did not induce significant changes in heart rate, diastolic blood pressure, or electrocardiographic findings, but systolic blood pressure slightly decreased ($p=0.015$) **(Table 1)**. At baseline stress, 106 segments (37% of the total) showed reduced MIBI uptake. Contrary to this, after therapy 89 segments (30% of the total segments) showed reduced uptake ($p=0.001$). Significant post-therapy increases in relative tracer uptake were observed in all segments. Percentage of MIBI uptake was 71.2±15.3 at baseline stress and 73.2±15 post-TMZ ($p=0.001$) (**Table 2**). Segmental relative tracer uptakes before and after therapy are shown in **Figures 1 & 2**. However, at baseline rest and post- TMZ radiotracer uptake (percentage of MIBI uptake) was 72.5±14.1 and 72.9±13.8, ($p=0.161$). In all patients, the segmental analyses revealed a significant change in the segmental perfusion scores after therapy in stress data ($p=0.001$). Contrarily, segmental perfusion scores did not change at rest after therapy. In regional analysis of perfusion score of myocardium, a significant increase was shown especially in the apical lateral, and inferior walls at stress data ($p=0.03$, $p=0.004$). With the global functional parameters, global ejection fraction slightly increased from 59.9%±8.9% to 62.6%±8.3%, pre-therapy to post-therapy, this change was statistically significant ($p=0.033$). Besides, end systolic volume (ESV), and end diastolic volume (EDV) decreased after therapy (101.7±23.5 ml to 95.1±22.9 ml, $p=0.002$; from 41.1±14.3 to 36.4±13.6, $p=002$,) at stress. Also, summed stress score (SSS) in gated stress and rest were decreased from 7.2±6.6 to 6.6±5.7 and from 8.05±7.98 to 5.81±5.99 but it was not statistically significant ($p=0.14$). Transient ischemic dilatation (TID) index was not changed (0.9±0.007 versus 0.9±0.009) ($p=0.55$). The relationship between perfusion and WM was stronger than that between perfusion and WT, and a significant correlation between percentage of MIBI uptake and perfusion scores was observed after therapy at both stress and rest ($p=0.004$ r=0.47 $p=0.030$, r=0.40. The total WM normal areas changed significantly (67-74% $p=0.000$) after therapy, but the total wall thickness did not changed significantly(49-45%, $p=0.21$).

Discussion. The present study shows that TMZ therapy improves left ventricular systolic function of myocardium in patients with CAE. This drug also improves the percentage of MIBI uptake in myocardium in patients with CAE especially in stress without the changes in hemodynamics. Thereby TMZ relieves exercise induced ischemia. Trimetazidine is representative of a new group of metabolic agents with a myocardial anti-ischemic effect achieved independently of changes in the oxygen supply-to-demand-ratio.[12] Unlike other classical anti-ischemic drugs, TMZ neither reduces oxygen consumption nor increases oxygen supply and, as a consequence, no significant changes were observed in heart rate or blood pressure.[12] The anti-ischemic effect of TMZ is obtained at a cellular level by shifting the energy substrate preference from fatty acid oxidation to glucose oxidation, secondary to selective inhibition of 3-ketoacylCoA thiolase (3-KAT).[13] As more adenosine tri-phosphate is produced per oxygen consumed when glycogen is a substrate, compared with fatty acids, and less oxygen is required for a given amount of work.[14] Due to the preferential promotion of glucose, and pyruvate oxidation, TMZ improves the activity of the sodium-potassium ATP'ase and the calcium uptake pump of the sarcoplasmic reticulum, that are responsible for the left ventricular systolic depolarization, and diastolic relaxation. Trimeta-zidine was shown to have a cardioprotective effect during myocardial ischemia due to a more rapid restoration of the phosphorylation processes, protection of cardiac cells against the accumulation of hydrogen ions, and prevention of the intracellular accumulation of sodium and calcium ions.[14,15]

Gated SPECT myocardial perfusion scintigraphy supplies reliable information on regional perfusion at stress and rest as well as providing data on left ventricular function.[6,7] In this study the improvement of left ventricular ESV, EDV, and WM scores obtained by gated SPECT, suggests that the experimental evidence of an improvement of sarcoplasmic calcium pump does translate into an effect on myocardial function. The results of our study are in agreement with previous studies.[16,17] Ciavolella et al,[16] studied hibernating myocardium at rest and indicated that TMZ-associated increase in Tc-99m MIBI uptake in infarcted but viable myocardial areas was probably related to an improvement in mitochondrial oxidative meta-bolism that was essential retention. Spadafora et al,[17] studied Tc-99m tetrofosmin myocardial scintigraphy in patients with coronary artery disease, and suggested that TMZ administration may increase myocardial uptake of tetrofosmin in hypoperfused regions at rest, based on its metabolic effect. In addition, they indicated the accumulation of tetrofosmin by mitochondria is related to their ability to transduce metabolic energy into electronegative membrane potential. Also,

cardiac uptake of Tc-99m MIBI is dependent on coronary blood flow. Although, Ciavolella et al,[16] established myocardial uptake increase in resting perfusion, we found that TMZ administration did not change resting Tc-99m MIBI uptake. This could be attributed to the different experimental conditions; their study was carried out in patients with hibernating myocardium, but ours was in patients with CAE. Moreover, in this study we found out that WM scores improved with TMZ administration: however, in both other studies myocardial WM was not evaluated.

In the literature, there are growing numbers of studies suggesting that ectasia is not a benign condition. Bove and Vliestra,[18] showed that ectatic arteries were prone to spasm, despite the fact that vascular damage and endothelial dysfunction were seen on histology. Suzuki et al,[19] reported that the actual narrowing usually occurred in the areas adjacent to the ectatic portion of the artery. There have been reports of thrombosis, and dissection occurring in ectatic vessels. Kruger et al,[20] indicated exercise- induced myocardial ischemia in patients with isolated ectasia as measured by coronary sinus lactate studies. Papadakis et al,[21] demonstrated that slow coronary flow happened in ectatic coronary vessels. Therefore, they suggested that diminished coronary flow velocity was admitted as a possible mechanism for ischemia. Some hypotheses point to a major role played by coronary artery atherosclerosis during developing CAE.[22] It seems to be a distinctive form caused by the action of different risk factors based on a genetic predisposition.[23] This would cause an initial endothelial damage activating a series of inflammatory mediators that start degeneration of the medial layer of the vessel. These structural alterations, together with the action of nitric oxide and other vasodilators, lead to a dilation of the coronary artery: an extreme form of positive remodeling.[24] How TMZ affects the myocardium in CAE is still unclear. Stanley et al,[25] pointed to hypotheses that a major role is played by inhibition of the enzymes of fatty acid ß-oxidation. The rate of fatty acid oxidation by the heart is mainly controlled by the concentration of free fatty acids in the plasma, the transport of long-chain fatty-acylcarnitine into the mitochondria, and the activity of the enzymes of fatty acid ß-oxidation.[25] Pharmacological inhibitors of fatty acid oxidation are targeted at lowering plasma fatty acid concentration through inhibition of lipolysis in fat cells (as with nicotinic acid), inhibition of fatty acyl transport into the mitochondria or inhibition of the enzymes of fatty acid ß-oxidation such as TMZ.[26] Blardi et al,[27] indicated that several properties of TMZ could be related to adenosine. They described significant increase of plasma adenosine levels after TMZ administration. In our study, we show the effect of TMZ only in stress data, therefore hypothesized that this effect could be related with adenosine, and we cannot rule out the possibility that the improvement induced by TMZ may modulate endothelium derived factors regulating local blood flow. The results of this study, demonstrate that TMZ improves myocardial function by rest-stress Tc-99m MIBI gated SPECT during stress-induced ischemia in patients with CAE. Also, the outcomes reveal improvement in functional parameters, and percentage of MIBI uptake post TMZ administration. For this reason, this procedure can be used to monitor the effect of TMZ in CAE patients.

Our study is one of the largest series reported in gated SPECT literature in patients with CAE post-TMZ administration. However, in order to increase statistical value of the tests used to detect functional variables associated with the presence of CAE, further studies are needed to determine long-term prognosis of this relatively rare but significant illness in larger series of patients.

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