Acute oral trimetazidine administration increases resting technetium 99m sestamibi uptake in hibernating myocardium

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Background. **Trimetazidine is an antiischemic drug protecting the myocardium from ischemic damage through the preservation of mitochondrial oxidative metabolism, without any hemodynamic effect. ^{99m}Tc-sestamibi is accumulated by myocytes according to mitochondrial function. As mitochondrial metabolism is thought to be present in hibernating myocardium, the aim of the study was to investigate trimetazidine effects on infarcted and eventually hibernating myocardial areas by means of ^{99m}Tc-sestamibi perfusional scintigraphy, comparing them to postoperative recovery of wall motion.**

Methods and Results. **Twelve patients with previous myocardial infarction underwent 2 perfusion imaging tomographic studies at rest with ^{99m}Tc-sestamibi, receiving placebo or trimetazidine (60 mg orally), and subsequently underwent revascularization procedures. An echocardiographic study was carried out before and >3 months after revascularization. At polar map analysis of placebo scan, infarcted vascular territories (wall motion score index: 2.65 ± 0.31) showed 73.7% ± 10.4% of the territory with activity <2.5 SD from the mean of normals, for a severity (expressed as the sum of the standard deviations below average normal values in all abnormal pixels) of 833.8 ± 345.7. Polar map analysis of the trimetazidine scan showed tracer uptake increased significantly in 11 of them, by 8.2% ± 3.0% ($p < 0.001$) and by 180.3 ± 111.0 SD ($p < 0.001$), respectively. Postoperative wall motion score index improved significantly in 9 of these territories (–0.9 ± 0.4, $p < 0.001$).**

Conclusions. **Trimetazidine-associated increase in ^{99m}Tc-sestamibi uptake in infarcted but viable myocardial areas is probably related to an improvement in mitochondrial oxidative metabolism that is essential to ^{99m}Tc-sestamibi retention. Additionally, coupling trimetazidine administration to ^{99m}Tc-sestamibi perfusional scintigraphy may represent a means of detecting viable myocardium. (J Nucl Cardiol 1998;5:128-33.)**

Key words: hibernating myocardium • myocardial scintigraphy • ^{99m}Tc-sestamibi • trimetazidine

Among recently developed antiischemic drugs, trimetazidine (1-(2,3,4,trimethoxy-benzyl)-piperazine dihydrochloride) (TMZ) is capable of maintaining cellular homeostasis,[1-3] as well as electrical and contractile functional activity, and of limiting cytolysis.[4,5] Such effects take place in the absence of significant changes in myocardial oxygen supply or consumption and were attributed to a protective role played by TMZ on energetic metabolism,[6-8] and to the capability of limiting acidosis and intracellular sodium and calcium accumulation.[2,3] Thus, TMZ could delay the interruption of mitochondrial respiration and the shift to anaerobic glycolysis responsible for the metabolic changes typical of ischemia, actually allowing myocytes to keep on living despite the ischemic insult.

The effects observed in vitro were confirmed in the clinical setting in a model of angina on effort, where acute[9] and chronic[10,11] treatment with TMZ improved exercise tolerance similarly to calcium antagonists[12] and beta-blockers,[13] though in the absence of changes in heart rate, blood pressure, and myocardial contractility.[14]

Although the results reported are extremely interesting, no investigation was carried out using more accurate and effective diagnostic techniques, such as myocardial scintigraphy, that represents the most complete and effective tool to study the pharmacological effects of antiischemic drugs in the clinical setting. Moreover, ^{99m}Tc-

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sestamibi, one of the most widely used tracers for the analysis of myocardial flow and perfusion,[15-18] is suited also for use as a viability tracer.[19-21] It is described to be taken up by the myocytes and concentrated in the mitochondria, depending on functional and metabolic situations, especially when altered oxidative metabolism occurs.[22]

Hibernating myocardium is one of the possible outcomes of myocardial ischemia. It is characterized by the reversibility of abnormal wall motion after reperfusion of a chronically hypoperfused myocardial area.[23-24] From a molecular point of view, it has been hypothesized that a mitochondrial oxidative metabolism, though at very reduced rates, is still present in the hibernating state.[25] Its identification is very important from a clinical point of view, and many methods have been tested, including nitroglycerin administration during ^{99m}Tc-sestamibi scintigraphy[19-20] and low-dose dobutamine echocardiography.[26]

As both TMZ and ^{99m}Tc-sestamibi share the same intracellular target, that is, the mitochondria, we carried out a study aimed at evaluating the changes induced by TMZ on resting myocardial perfusion in infarcted and possibly hibernating zones using perfusional tomography with ^{99m}Tc-sestamibi.

METHODS

Patients. We prospectively studied 12 consecutive male patients (mean age 55.3 ± 12.6 years) with previous myocardial infarction localized to the anterior wall in 7 patients, to the inferior wall in 4, and to the posterolateral wall in 1. All patients presented with pathological Q waves on electrocardiogram. No patient with recent (<6 months) myocardial infarction or unstable angina was included. Eight patients presented with angina on effort, and 5 with dyspnea for mild to moderate efforts (class III, according to the New York Heart Association).

Patients underwent biplane left ventriculography and selective coronary angiography in standard orthogonal views. Coronary stenoses were visually evaluated by 2 investigators, and disagreements were resolved by a third physician. Only >70% reductions of internal diameter were considered to be significant. Coronary collateral circulation, when present, was visually graded from 0 to 3 (0 = no visible filling, 1 = filling of side branches only, 2 = partial filling of epicardial segments, 3 = complete filling of epicardial segments).[27]

An echocardiographic study was also carried out in the standard parasternal long and short -axis and apical 2- and 4-chamber view. Images were stored on tape and subsequently visually analyzed by 2 experienced operators who were unaware of other clinical data. In case of disagreement, a consensus between the two was reached. Left ventricular wall was divided into 16 segments, related to the 3 main coronary arteries.[28] Wall motion abnormalities in infarcted areas were identified by comparing segment motion and systolic thickening with that of adjacent segments. Each segment was assigned a semiquantitative score (1 = normokinetic, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic). A wall motion score index was obtained for each infarcted territory.

The patients, in complete pharmacological wash-out, underwent a scintigraphic study at rest after administration of placebo (vitamin B complex, 3 tablets). A second scintigraphic study was carried out 4 days later after oral administration of TMZ (60 mg, i.e., 3 tablets). Written informed consent was obtained from each patient.

Within 3 weeks, all patients underwent successful revascularization procedures (percutaneous coronary angioplasty in 2 cases, coronary artery bypass surgery in 10 cases (mean 3.3 ± 1.3 grafts per patient). Complete revascularization was attempted in all cases, and the left mammary artery was used for grafting left anterior descending artery. During routine follow-up examination >3 months later, a standard echocardiographic study was repeated, and regional wall motion in the infarcted areas compared to that of preoperative study by using the same semiquantitative scoring system.

Myocardial Scintigraphy. Sestamibi was labeled according to standard guidelines. The patients, after overnight fasting and in a blinded fashion, received 3 tablets orally. Blood pressure, heart rate and 12-lead ECG were checked at 30-minute intervals until scan completion during both studies. Two hours after tablet administration, 370 MBq of ^{99m}Tc-sestamibi in 0.5 ml was injected intravenously. Approximately 40 minutes later, a light meal was administered to accelerate hepatic clearance of the tracer. Ninety minutes after injection a computer-interfaced gamma-camera (Starcam 2000, General Electric, IGE Medical System Limited, St. Albans, Herts, England) equipped with a high-sensitivity parallel hole collimator acquired a tomographic scan in 64 × 64 matrix composed of 48 views lasting 20 seconds each, covering 180 degrees, from right anterior oblique to left posterior oblique view.

Each tomographic scan was processed without knowledge of the drug administered. After checking for artefacts due to patient motion, transaxial sections were reconstructed through a back projection algorithm using standard Ramp-Hanning filtering and bidimensional spatial smoothing. No correction for attenuation was used.

The bidimensional reconstruction on the short axis was plotted on a polar map ("bull's-eye" method). The count profile of each study was compared with a gender-matched database of rest ^{99m}Tc-sestamibi studies performed at our institution in 20 subjects free of overt heart diseases at clinical examination, echocardiography and exercise test. Acquisition and processing techniques were the same as used in the present study. The lower limit of the normal activity range for each pixel was set at 2.5 SD below the average value of the normal group and always corresponded to a <70% of the maximum activity value in the image. The quantitative polar map was then divided into territories corresponding to the distribution of the 3 main coronary vessels. The extent of each observed abnormality was expressed as a percentage of the total number of pixels included into the territory. The severity of the defect was expressed as the total number of SD below the average value of the normal file in the pixels included into the defect by using a commercially available software.[29]

Continuous variables are expressed as mean values ± SD. Student's t test for paired data and χ^2-test were used to compare quantitative and qualitative data, respectively. Statistical significance was considered $p < 0.05$.

Table 1. Clinical and angiographic characteristics of the patient group

Patient	Age	Infarct site	Angina	Collateral flow	Coronary stenoses (%) LAD	LCX	RCA	Grafts
1	39	A	+	–	100	70	80	4
2	44	A	+	–	99	75	–	3
3	64	I	–	–	70	95	100	5
4	48	A	–	2	95	–	–	1 PTCA
5	72	PL	+	–	80	85	70	5
6	50	A	+	–	100	–	90	3
7	46	A	–	2	85	70	–	4
8	63	A	+	2	100	–	85	3
9	37	PL	+	–	75	80	–	3
10	66	I	+	1	70	75	100	4
11	70	A	–	3	90	–	–	1 PTCA
12	65	I	+	3	70	70	100	3

A, Anterior wall; *AL*, anterolateral wall; *Ap*, apex; *AS*, anteroseptal wall; *I*, inferior wall; *IL*, inferolateral wall; *LAD*, left anterior descending coronary artery; *LCX*, left circumflex coronary artery; *PL*, posterolateral wall; *PTCA*, coronary angioplasty; *RCA*, right coronary artery.

Table 2. Scintigraphic and echocardiographic results

Patient	Placebo %	Placebo ΣSD	Trimetazidine %	Trimetazidine ΣSD	ΔMIBI %	ΔMIBI ΣSD	WMSI Preop	WMSI Postop	ΔWMSI
1	51	755	42	639	–9	–116	2.3	1.7	–0.6
2	79	952	71	807	–8	–145	2.7	1.9	–0.8
3	68	383	63	299	–5	–84	3.3	3.3	0
4	88	1467	79	994	–9	–473	2.9	1.2	–1.7
5	59	527	48	341	–11	–186	2.3	1.5	–0.8
6	82	1458	67	1320	–15	–158	2.4	1.7	–0.7
7	72	776	79	905	+ 7	+ 129	2.9	2.9	0
8	78	917	72	748	–6	–169	2.8	2.9	0.1
9	71	695	63	428	–8	–267	2.5	1.3	–1.2
10	75	591	67	469	–8	–122	2.7	1.3	–1.4
11	81	944	77	743	–4	–201	2.3	1.9	–0.4
12	80	501	73	419	–7	–82	2.7	1.7	–1.0

ΔMIBI, Change of scintigraphic parameters; *WMSI*, echocardiographic wall motion score index; *ΔWMSI*, change in WMSI; *%*, percentage of pixel composing the vascular territory showing activity below 2.5 SD from the mean of normal subjects; *preop*, preoperative; *postop*, postoperative; *ΣSD*, sum of SD below 2.5 from the mean of normal subjects.

RESULTS

Significant stenoses of 1, 2, or 3 main coronary vessels were detected in 2, 5, and 5 cases, respectively (Tables 1 and 2). Left ventriculography allowed identification of infarct-related artery, as a stenotic vessel always supplying an akinetic or dyskinetic myocardial wall (left anterior descending artery in 7 cases, left circumflex artery in 2 cases, right coronary artery in 3 cases). Average ejection fraction was 37.3% ± 4.5%. Collaterals to infarcted areas were detected in 6 patients, and were graded as 1, 2, and 3 in 1, 3, and 2 cases, respectively.

At echocardiographic study, wall motion abnormalities were detected in all infarcted territories, always affecting >50% of the territory, for an average wall motion score index of 2.65 ± 0.31 in infarcted territories.

No side effects or adverse reactions related to TMZ administration were detected. Both blood pressure and

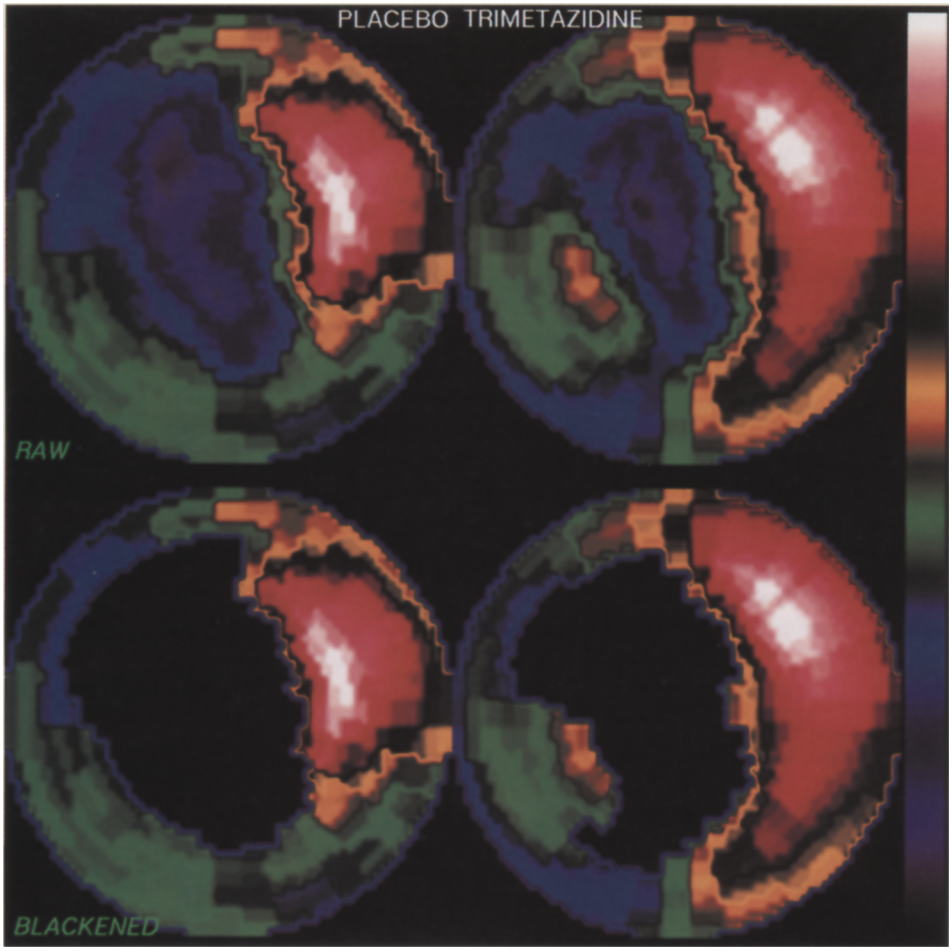

Figure 1. Patient 4. Bull's-eye polar map of placebo *(left)* and trimetazidine *(right)* scans. In the *top row,* raw data are shown; in the *bottom row,* pixels with tracer activity <2.5 SD from normal subjects were blackened. A clear-cut increase in ^{99m}Tc-sestamibi uptake at trimetazidine scan in comparison with placebo is confirmed by the reduction in the size of the blackened area.

heart rate did not show any change between placebo and TMZ study. No ECG changes were detected.

Tomographic scan analysis of infarcted areas detected pixels with activity <2.5 SD from normal subjects at placebo scan in 73.7% ± 10.4% of the vascular territory, showing a severity of 833.8 ± 345.7 SD below normal limits. At TMZ scan, 11 of 12 infarcted territories showed a decrease in the extent of the defect (–8.2% ± 3.0%, $p < 0.001$), as well as in its severity (–180.3 ± 111.0 SD, $p < 0.001$), in comparison to placebo scan (Figure 1). The remaining patient showed an increase in tracer defect extent and severity, in the absence of symptoms and ECG changes. No significant difference was detected by dividing coronary territories according to the presence of collaterals or to the degree of luminal narrowings in coronary arteries.

At postrevascularization echocardiography, the average wall motion score index in the infarcted areas was 1.93 ± 0.69 ($p < 0.001$ vs prerevascularization study). Nine patients (75%) showed an improvement of regional wall motion in the infarcted area (from 2.53 ± 0.22 to 1.58 ± 0.26, $p < 0.001$), and all had shown a significant increase of tracer uptake after TMZ study (by 8.8% ± 2.9%, $p < 0.001$, and by 192.2 ± 118.6 SD, $p < 0.001$, respectively). Of the remaining 3, 1 showed a worsening in wall motion score index and 2 no change at all.

DISCUSSION

TMZ is an interesting antiischemic agent with a unique mechanism of action. Unlike nitrates or calcium antagonists, it does not interfere with coronary blood flow. Unlike beta-blockers, it does not affect heart rate, myocardial contractility, or blood pressure, all maneuvers favorable in decreasing myocardial oxygen demand. Grynberg[30] hypothesized that TMZ can optimize meta-

bolic behavior of the ischemic myocardial cell, thereby allowing it to better use the residual supply in oxygen and substrates. In particular, experimental evidence has shown that in the presence of TMZ ischemic myocytes shift metabolism from fatty acid oxidation toward carbohydrate oxidative pathway.[31] This allows a larger amount of ATP for each mole of oxygen to be produced in comparison with beta-oxidation.

Experimental investigations showed that TMZ can directly affect mitochondrial function. Demaison et al.[31] observed that pretreatment with TMZ preserved myocytes exposed to hypoxic and ischemic conditions from electromechanical and arrhythmic changes typical of ischemia through a marked inhibition of beta-oxidation in absence of changes in lipid metabolism. Noble et al.[32] showed that pretreatment with TMZ significantly reduced the size of infarcted area in a rabbit experimental model, whereas Kay et al.[33] observed a marked protective effect of TMZ on asystolic rat heart induced by cardioplegia, due to the protection of mitochondrial respiration and the increase of NADH concentration.

The diagnosis of hibernation is clinically relevant because of its therapeutical implications, as the reduced global and regional function secondary to hibernation will improve after revascularization with an improvement of prognosis.[34] We believe this study was the first to use perfusional scintigraphy in the assessment of metabolic effects of TMZ on infarcted and eventually hibernating myocardium. We observed a significant increase of ^{99m}Tc-sestamibi uptake in infarcted areas after TMZ in comparison to placebo. Such a behavior has at present no demonstrated explanation, especially in the absence of a direct measurement of oxygen consumption, nor of coronary blood flow. However, it is at least conceivable that during TMZ administration an increase in mitochondrial oxidative metabolism occurred that was responsible for the larger amount of ^{99m}Tc-sestamibi uptake processes. These data would confirm the mechanism of action hypothesized for the drug itself as well as the uptake and concentration patterns of ^{99m}Tc-sestamibi.

Nitroglycerin infusion coupled to ^{99m}Tc-sestamibi scan is used to detect viable myocardium,[19,20] where the increase of local tracer supply is possible through the dilatation of collaterals and/or eccentric stenoses as well as a decrease in left ventricular end-diastolic pressure. Conversely, TMZ exerts no significant hemodynamic effect. Therefore, it should not increase the amount of ^{99m}Tc-sestamibi available to myocytes in comparison to basal conditions. Rather, it may act on mechanisms controlling ^{99m}Tc-sestamibi cellular uptake without changes in actual coronary flow. It is known that ^{99m}Tc-sestamibi passively enters cell membrane due to its lipophilicity and surface charge distribution.[35] In this way it is concentrated into cytosol up to 5:1, whereas mitochondria concentrate it further, up to 300:1. Such a process takes place through intermediate metabolism of energetic substrates, which allows the supply of reducing equivalents to cytochromes of mitochondrial electron chain. Negative potentials produced by mitochondrial internal matrix membrane through proton transport outside the internal matrix supply the bioenergetic support for ^{99m}Tc-sestamibi retainment.[36]

It is hypothesized that hibernating myocardium decreases its functional needs by reducing mitochondrial oxidative metabolism to match the critical reduction in coronary flow. However, it is conceivable that a metabolic reserve, though extremely reduced, does still exist, allowing hibernating myocytes to resist further decreases of coronary flow due to increases in subendocardial tension, contractility, or heart rate. TMZ might exploit this reserve by increasing mitochondrial oxidative metabolism, thus allowing an increased amount of cytoplasmic ^{99m}Tc-sestamibi to be taken up and concentrated in the mitochondria in comparison with placebo scan. It is impossible to tell from the present study whether such improvement also carries out an improvement in contractility because regional wall motion was not monitored during the time period of efficacy of acute TMZ administration. It is nevertheless conceivable that restoration of regional wall motion in a large, previously akinetic area would affect to some extent blood pressure and heart rate. Conversely, no change in hemodynamic parameters was detected.

Recent hypotheses point to a major role played by endothelial cells and by locally secreted substances during different metabolic states, such as ischemia, reperfusion, and stunned and hibernating myocardium.[37] We cannot rule out the possibility that the improvement induced by TMZ may modulate endothelium-derived factors regulating local blood flow in spite of the lack of direct hemodynamic effects of TMZ.

It is still unclear how TMZ can interact with mitochondria to stimulate oxidative phosphorylation and how it can be possible at relatively reduced concentrations because of the low coronary flow supplying hibernating zones. Additionally, to the best of our knowledge no data are available regarding the effects of TMZ on experimental models of low-flow myocardial ischemia.

In view of our data, a diagnostic use for TMZ in infarcted patients is possible to assess myocardial viability, by coupling it to ^{99m}Tc-sestamibi scintigraphy. Further investigations are warranted on larger patient groups to confirm our results. Future research should address the issue of identifying even more selective molecules, possibly labeled with radioactive tracers, to study the molecular basis of the pathophysiological phe-

nomena clinically known as stunned and hibernating myocardium.

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