Viable Myocardium Scintigraphy with Intravenous Nitroglycerine by Computed Tomography with Tc-99m (MIBI)

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Summary

Background: **The selection of patients with chronic coronary disease for recanalization is based on the detection of the affected myocardium that is potentially viable.**

Objective: **To evaluate the potentially viable ischemic myocardium through single photon emission computed tomography (SPECT) with MIBI after a maximum tolerated dose of I.V. nitroglycerin.**

Methods: **We prospectively investigated by SPECT with Tc-99m (MIBI), from April 2004 to November 2005, 40 patients (mean age: 62 ± 8.9 yrs, 30 men) with coronary obstruction demonstrated angiographically; the myocardium scintigraphy was carried out at rest and after intravenous (I.V.) nitroglycerin, which was started at a dose of 1 ug/kg/min and increased every minute until the systolic blood pressure decreased by 20 mmHg. The decrease in the perfusion of the segments was classified as moderate or severe and compared after the nitroglycerin. The angiographic, hemodynamic and myocardial perfusion variables were analyzed.**

Results: **We analyzed 680 myocardial segments at rest: 538 with a homogenous distribution and 142 with hypoperfusion (54 with moderate and 88 with severe decrease). After the nitroglycerin, there was an increase in the perfusion in 19 (47.5%) of 40 patients and 55 of 142 segments became viable: 33 (61.1%) with moderate and 22 (25%) with severe decrease; both presented a significant increase in the radiotracer distribution ($p < 0.001$, Chi-square).**

Conclusion: **One of the components with Tc-99m is Tc-99m 2-methoxy-isobutyl-isonitrile (MIBI), which, when used with an optimized dose of I.V. nitroglycerin, can increase the radiotracer uptake in areas with moderate and severe hypoperfusion. The results of the present study suggest the increase in the Tc-99m (MIBI) sensitivity by nitroglycerin for the detection of viable myocardium. (Arq Bras Cardiol 2008;91(3):134-141)**

Key words: **Coronary atherosclerosis; myocardial reperfusion; nitroglycerin; myocardial stunning.**

Introduction

In Brazil, cardiovascular diseases represent 26.6% of the total deaths, being the first cause of death when considering only individuals older than 50 years[1]. In recent years, an increase in these patients' survival has been observed, due to the possibility of early and late recanalization through percutaneous coronary intervention, thrombolytic therapy or myocardial revascularization surgery[2]. The appropriate selection of patients with coronary artery disease (CAD) in acute and chronic diagnostic situations for recanalization procedures is based in part on the detection of the affected myocardium extension, although potentially viable, with the objective of reverting the ventricular dysfunction[3].

The main techniques developed for the detection of the viable ischemic myocardium are: positron emission tomography (PET)[4-7], myocardial perfusion scintigraphy with thallium-201[8], Pharmacological Stress Echocardiogram, tissue Doppler[9] and nuclear magnetic resonance.

In recent years, several authors have studied the use of single photon emission computed tomography (SPECT) with MIBI as an alternative for the detection of the viable myocardium[10-12], associated with the use of sublingual or I.V. nitrates, which showed to be a good tracer to demonstrate viability, with the advantage of presenting higher availability and lower cost.

The use of nitrates effectively improves the detection of the viable myocardium through SPECT with MIBI, although no comparative studies, showing the superiority among the techniques used and the different nitrate presentations, have been carried out to date[13-16].

The perfusion and the metabolic tracers have an important role in the detection of viable, hibernating and stunned myocardium. In 1984, Rahimtoola[17] defined the "hibernating myocardium" as a state of extreme regulation in response to chronic and severe ischemia. Under reduced coronary flow conditions, the myocardium reduces its energy consumption

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Manuscript received July 19, 2007; revised received December 01, 2007; accepted December 26, 2007.

to the maximum, directing it to the maintenance of its integrity, at the expense of the reduced contractile function.

It is believed that the decrease in the regional perfusion predisposes to the accumulation of organic phosphate[3], disorders in the uptake of calcium by the myocyte[18,19], local acidosis and accumulation of oxygen-derived free radicals[20]. These factors would be involved in the decrease in the contractile function during chronic severe ischemia and the consequent lower energy consumption.

This dysfunction can be reverted, total or partially, by improving the regional perfusion or after myocardial recanalization procedures, resulting in the improvement of ventricular fucntion[17].

The term "viable", however, refers strictly to the living myocardium, with no particular impact on the functional state, perfusion or metabolism close to fibrotic regions and many times it impairs the clinical interpretation for the ideal recanalization procedure. The objective of the present study is to use a maximum tolerated dose of I.V. nitroglycerin aiming at attaining the maximum vasodilator effect and verify whether there is an improvement using the radiolabeled tracer (Tc-99m) in areas of hypoperfusion at rest.

Methods

A total of 45 adult individuals, admitted at the Hospital Universitário São Francisco in Braganca Paulista, state of São Paulo, Brazil, in the period of April 2004 to November 2005, were studied prospectively. The studied population comprised 10 women (25.0%) and 30 men (75.0%), with a mean age of 62 ± 8.9 years (maximum 78 yrs and minimum 36 years) (Table 1). The included patients presented: 1. CAD confirmed by the presence of lesions with a degree of obstruction ≥ 60% of the lumen or motility deficit by cardiac catheterism; and 2. Previous history of myocardial infarction or unstable angina. Excluded patients presented: 1. Contraindication to the revascularization procedures; 2. Hypersensitivity to nitroglycerin; 3. Systolic arterial pressure (SAP) < 110 mmHg; 4. Ischemic involvement of right ventricle or right heart failure; and 5. Decrease in the SAP < 20 mmHg during the nitroglycerin infusion. This study was approved by the Ethics Committee in Research of Universidade São Francisco and all patients signed the informed consent form.

A SPECT with MIBI was carried out at rest and repeated after the nitroglycerin infusion in the one-day protocol. The MIBI dose used was 370 to 1,110 Mega Becquerel (MBq). Tc-99m was chosen as it is a tracer that has a low radiation exposition, better image quality in obese patients and women with large mammary glands. The acquisition of sequential tomographic images was carried out in a gamma chamber Starcam 4000i (GE Medial Systems Milwaukee/WI, USA), which had a scintillation detector and a high-resolution and low-energy parallel-hole collimator. The image acquisition was carried out up to 60 minutes after the radiotracer infusion, using the SPECT technique, according to the usual methodology in a 64 x 64 matrix. For the second assessment, the continuous monitoring and 13 lead electrocardiograms, every 5 minutes, using the multichannel monitor system TEB Apex 2000 (TEB-Sao Paulo, Brazil), concomitantly to the administration of the progressive dose of I.V. nitroglycerin, through a continuous infusion pump, with an initial dose of 1 ug/kg/min. The solution used was 50 mg of nitroglycerin (Tridil®) diluted in 500 ml of saline solution (Soluflex®). During the nitroglycerin infusion, the blood pressure was measured every 2 minutes. The MIBI was administered when the SAP decreased by 20 mmHg. The nitroglycerin infusion was interrupted within the first minute after the MIBI infusion. A 17-segment myocardium segmentation model was used, which corresponded to the left ventricle regions[21] (Figure 1). The MIBI uptake in each segment was evaluated quantitatively: 1. Normal uptake; 2. Moderate hypouptake and 3. Severe hypouptake.

The different patterns of segmental uptake that were observed at rest were compared to those obtained during the nitroglycerin infusion (Figure 2). The uptake improvement rates were calculated for the total number of segments with moderate and severe hypouptake at rest and compared by the Chi-square test. The means of the hemodynamic parameters before and after the nitroglycerin infusion were compared by Student's *t* test. The level of significance used was $p < 0.05$.

Results

Forty patients were studies and 5 were excluded: 2 presented initial SAP < 110 mmHg and three did not present a decrease in SAP of at least 20 mmHg, despite the use of high doses of nitroglycerin (12.3 ± 0.5 ug/kg/ min).

There were no side effects due to the nitroglycerin infusion in all patients. The hemodynamic parameters before and after the infusion are shown in Table 2 and Figure 3. The mean necessary dose of the nitroglycerin infusion was 5.83 ± 2.64 ug/kg/min. A total of 680 segments were analyzed, with 538 being viable, whereas 142 showed hypouptake (54 with moderate hypouptake and 88 with severe hypouptake). We observed an improvement in the radiotracer uptake in 19 (47.5%) of the 40 patients studied. Of the 142 segments with hypouptake, we observed moderate and severe hypouptake in 54 (7.9%) e 88 (12.9%) segments, respectively. Of 142 segments, 55 became viable: 33 (61.1%) with moderate hypouptake and 22 (25.0%) with severe hypouptake at rest ($p < 0.001$) (Figure 4). The angiographic characteristics of the studied patients are shown in Tables 3 and 4. The number of affected coronary arteries and the presence of collateral circulation were not associated with the improvement in the MIBI uptake during the nitroglycerin infusion.

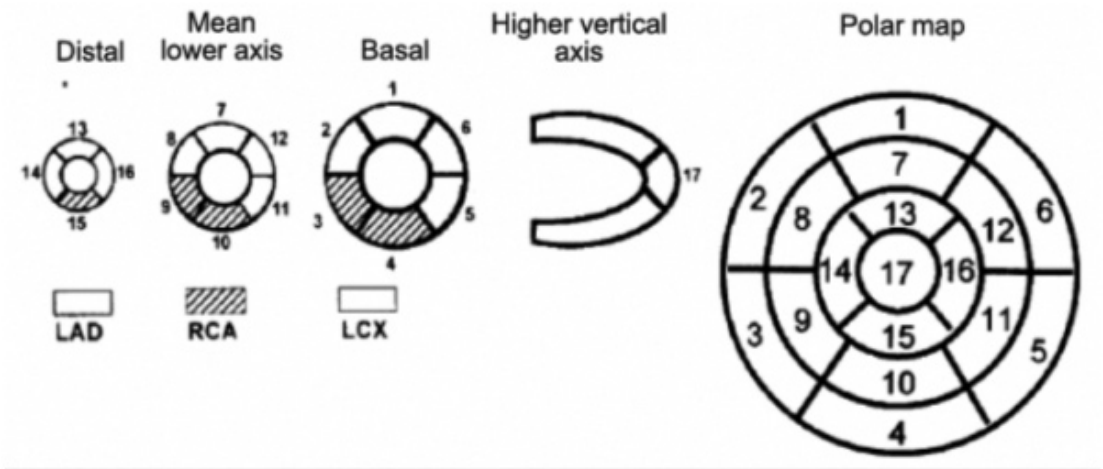
Discussion

The use of SPECT with MIBI to detect viable myocardium in patients with chronic CAD is still debatable. The first clinical trials suggested that the myocardial perfusion images generated by the SPECT with MIBI underestimated the presence of viable myocardium in ischemic areas, when compared to other methods[10,22-23]. In the present study, we demonstrated that the Tc-99m (MIBI), sensitized by a maximum dose of I.V. nitroglycerin, increased the perfusion in several myocardial segments, which were previously hypoperfused, reducing ischemic areas that could be recanalized. Our findings suggest that there are benefits in using a radiotracer sensitized by I.V.

Table 1 – Characteristics of the studied patients.

n	sex	age (yrs)	Inactive area at ecg	Motility dysfunction (angiography)	Coronary stenosis > 60%
1	F	68	High lateral	Diffuse	AD, CX, RC
2	M	60	High lateral	Antero-apical	AD
3	M	64	Did not have	Diffuse	AD, CX, RC
4	M	55	Anterior, lateral high, septal	Antero-apical	AD
5	M	73	Antero-septal Inferior	Lateral, antero-apical	AD, CX, RC, Dg
6	F	78	Inferior	Lateral	AD, CX, RC
7	M	67	Anterior, inferior, septal	Antero-apical, Inferior-apical	AD
8	F	54	Anterior, lateral, septal	Diffuse	AD, RC
9	F	51	Antero-septal Inferior	Antero-septal	AD, CX, RC
10	M	78	Anterior, lateral, septal	Did not have	AD, CX
11	M	58	High lateral, septal	Antero-apical	AD, MgL
12	M	53	Did not have	Anterior e apical	RC
13	M	69	Anterior, inferior	Diffuse	AD, CX, RC
14	M	70	High lateral	Ventriculography was not performed	CX
15	F	65	Anterior, septal	Antero-apical	AD
16	M	48	High lateral	Inferior	RC
17	M	69	Anterior, septal	Medium apical anterior, septal	AD
18	M	55	Did not have	Inferior-apical	RC
19	M	61	Inferior	Diffuse	CX, RC
20	M	36	Anterior	Diffuse	AD, CX, RC
21	M	46	Did not have	Inferior	CX, RC
22	F	64	Blockade left branch	Anterior	No lesions > 60%
23	F	60	Anterior, septal	Diffuse	No lesions > 60%
24	M	61	Did not have	Inferior	RC
25	F	57	Did not have	Inferior	RC
26	M	53	Septal	Antero-apical	AD, RC
27	M	73	High lateral	Diffuse	AD, CX, RC
28	M	58	High lateral	Antero-apical	AD, CX
29	M	59	Anterior, lateral, septal	Apical and septal	AD
30	M	73	Did not have	Did not have	AD, RC
31	F	61	Did not have	Lateral	CX
32	F	72	Did not have	Ventriculography was not performed	AD, RC
33	M	69	Anterior, inferior	Apical	AD, RC, MgL
34	M	61	Did not have	Antero-apical and inferior	AD, RC
35	M	58	Did not have	Antero-apical	AD, RC
36	M	71	High lateral	Diffuse	AD, CX, RC
37	M	69	High lateral	Inferior	RC
38	M	62	Inferior	Inferior, severe	RC
39	M	65	Did not have	Septal	AD, MgL, RC
40	M	58	Did not have	Diffuse	AD, MgL, RC

AD - anterior descending artery; CX - circumflex coronary artery; RC - right coronary artery, Dg - diagonal coronary artery; MgL - marginal left coronary artery.



Regions	Distal	Medial	Basal
Anterior	(13)	(7)	(1)
Antero-septal	(14-septal)	(8)	(2)
Inferior-septal		(9)	(3)
Inferior	(15)	(10)	(4)
Inferior-lateral		(11)	(5)
Antero-lateral		(12)	(6)
Lateral	(16)		
Apex	(17)		

VERT-vertical; LAD-Left anterior descending artery; RCA-Right Coronary artery; LCX-Left circumflex artery;

Figure. 1 - Model of myocardial segmentation in 17 segments[21].

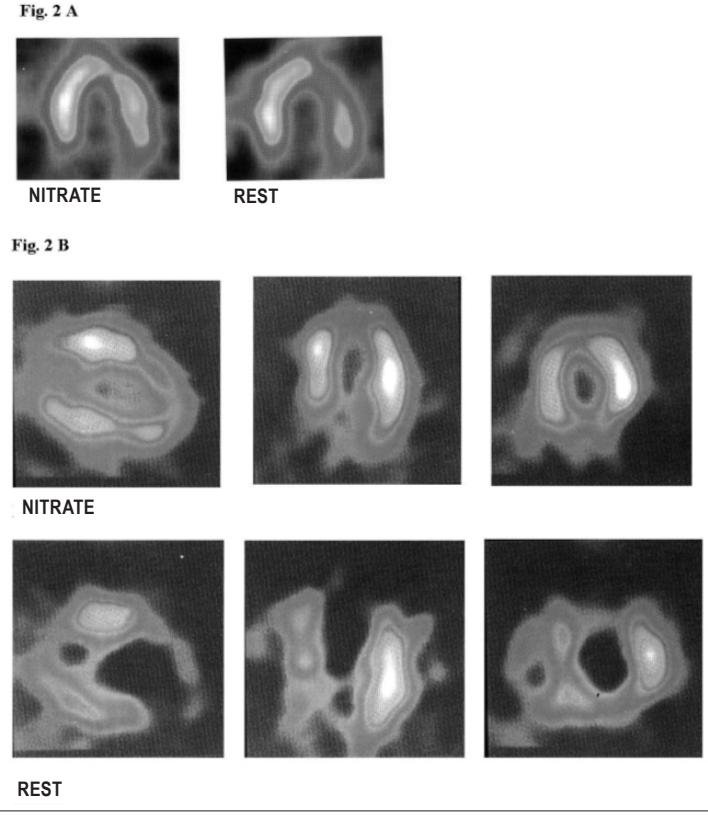


***Figure 2 –** Example of MIBI uptake improvement with nitroglycerin. A - moderate hypouptake; B - severe hypouptake..*

nitroglycerin, due to clear evidence of ischemia reduction.

We tried to administrate a maximum tolerated dose of nitroglycerin limited by the SAP decrease, aiming at the maximum vasodilator effect and observed a better performance in segments with moderate hypouptake in relation to those with severe hypouptake, which is in agreement with previous findings in the literature. Maurea et al[16], when studying the MIBI uptake in patients with CAD, demonstrated that the defects that were reversible with the use of nitrates presented a higher uptake at rest, in comparison with the irreversible defects and that the occurrence of reversibility of the MIBI uptake defects, after the administration of nitroglycerin in their study, was of 71% of the patients. In the present study, we observed a lower rate of reversibility (47.5%), despite the use of the maximum tolerated dose of nitroglycerin; however, this finding can be associated with qualitative analysis of the perfusion used, observer-dependent and probably less accurate than the quantitative analysis used by Maurea and other researchers.

In the present study, there was an uptake improvement in almost 50% of the studied patients and that helped the clinical decision-making, by showing the myocardial segments that could be recanalized. These patients will be re-investigated after the recanalization procedures that they will undergo.

The angiographic characteristics of the studied patients suggest that the benefits of the administration of the maximum tolerated dose of nitroglycerin do not depend on the total number of affected coronary arteries, as well as on the presence of collateral circulation; however, it is possible that this discordance may be due to the presence of collateral circulation that was not detected angiographically. Moreover, the myocardial viability depends mainly on the ischemia period to which the muscular tissue was submitted; it is possible to have collateral circulation for segments with non-viable myocardium, which therefore, will present uptake defects that are irreversible by MIBI, despite the improvement in perfusion promoted by the nitroglycerin.

Studies with 18F-deoxyglucose (18FDG) demonstrated that the MIBI uptake is primarily associated with the regional blood flow and secondarily, with the presence of viable myocardium[10]. When analyzing images generated by PET with 18FDG in patients with chronic CAD, Altehoefer et al[25] observed evidence of metabolic activity in 23% of the segments with MIBI uptake deficit, which suggests the underestimation of the presence of myocardial viability in these segments. Similar findings to our study were observed by Sawada et al[33], who demonstrated the presence of viable myocardium in 53% of the segments with moderate hypouptake at rest

Table 2 – Hemodynamic parameters before and after nitroglycerin infusion

Parameter	Control	Nitroglycerin	p
Heart rate	73.33+-14.00 bpm	79.08+-15.64 bpm	0.0916
Systolic arterial pressure	135.13+-15.20 mmHg	112.31+-16.30 mmHg	<0.001
Diastolic arterial pressure	83.33+-10.60 mmHg	73.85+-12.70 mmHg	<0.001

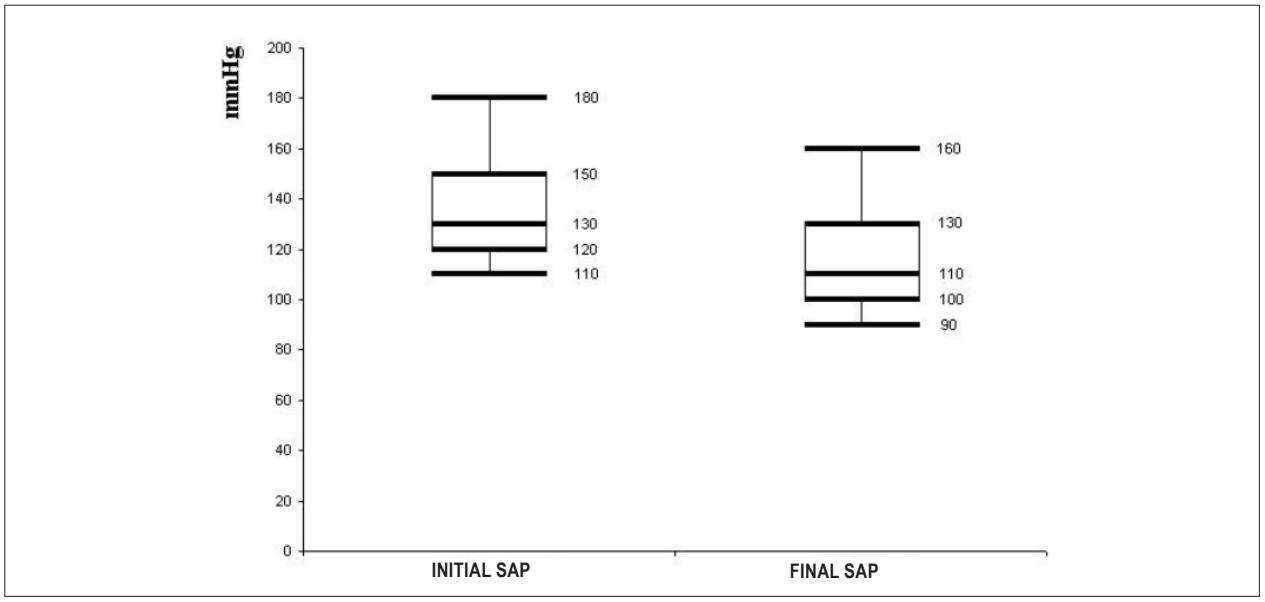


Figure 3 – Box Plot of the initial and final blood pressure during the progressive infusion of nitroglycerin (maximum, 75 percentile, median, 25 percentile and minimum).

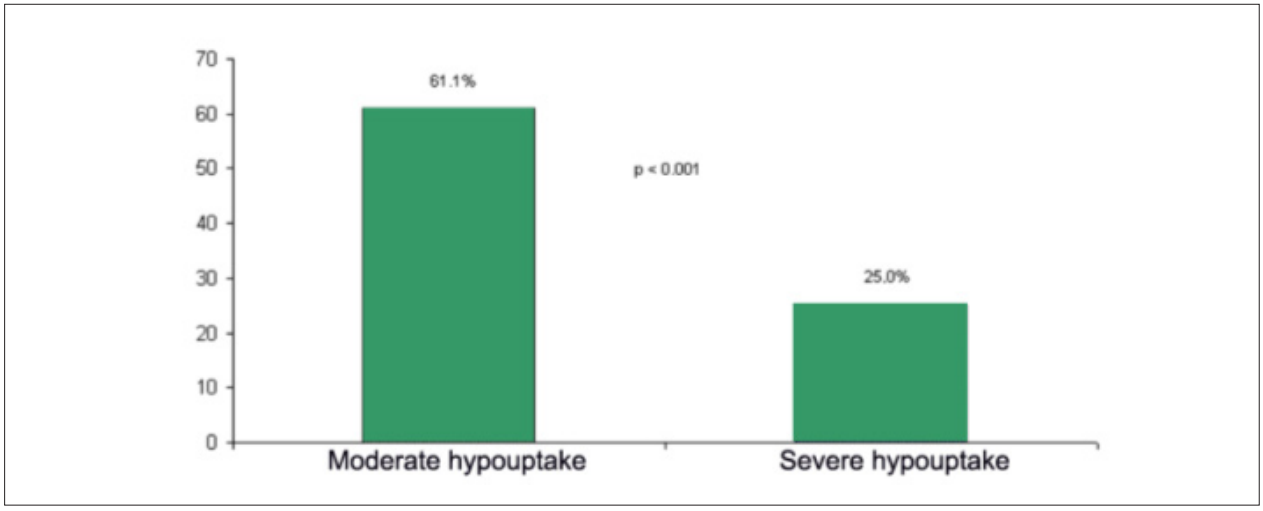


Figure 4 – Improvement in the MIBI uptake after maximum tolerated dose of IV nitroglycerin.

and 46% of the segments with severe hypouptake. However, recent data demonstrated that the quantitative analysis of SPECT with MIBI reduces this discordance when compared to images generated with thallium-201[8,32]. Little difference was observed between images obtained by SPECT with MIBI and PET in segments with severe hypouptake[11,32].

Table 3 – Total of affected coronary arteries (stenosis > 60%) and MIBI uptake improvement after the maximum tolerated dose of nitroglycerin.

Total Coronaries	Group 1	Group 2	Similarity*
Up to one	8	9	A
2	5	6	A
3 or more	6	6	A

** Chi-square, identical letters indicate similarity with a level of significance of 0.05; Group 1: Patients with uptake defects that improved with nitroglycerin; Group 2: Patients with uptake defects that did not improve with nitroglycerin*

Table 4 – Presence of angiographically detectable collateral circulation and MIBI uptake improvement after maximum tolerated dose of nitroglycerin

Presence of collateral circulation	Group 1	Group 2
yes	7	5
no	12	16
total	19	21

Chi-square; P = 0.369; Group 1 - Patients with uptake defects that improved with nitroglycerin; Group 2 - Patients with uptake defects that did not improve with nitroglycerin.

It was also demonstrated that SPECT with MIBI presents good capacity to predict the functional recovery of asynergic segments after myocardial revascularization[8,34]. Udelson et al[8] recently demonstrated that the quantitative analysis of the SPECT with MIBI and of the images generated with thallium at rest can equally differentiate the viable myocardium from the non-viable one and predict the reversibility of the regional motility abnormalities after the myocardial revascularization; these findings were also observed by us in some re-evaluated patients.

Furthermore, the late MIBI uptake can increase the identification of the viable myocardium, as recently suggested by clinical and experimental studies[32,35].

As the administration of nitrates can increase the regional blood flow in areas of ischemic myocardium[36-41], it was hypothesized that this pharmacological effect could promote the MIBI uptake in severely hypoperfused areas and increase the capacity of the test in detecting viable ischemic myocardium, a fact that we fully agree with, after our initial results. Several studies have demonstrated that the concomitant use of nitrates increase the capacity of detection of viable myocardium by the SPECT with MIBI[39] and other radiotracers, such as thallium-210[40] and Tc-99m teboroxime[41] in patients with CAD; however, the authors used several administration protocols and nitrate preparations, with no standardization of the technique based on comparative studies. The best performance of the nitrate observed in our study occurred in segments with moderate hypouptake and it was in agreement with previous findings in the literature, although we also observed viable segments with severe hypouptake at rest, at lower proportions.

The present study describes a technical possibility to use nitrates, with the objective of improving the detection of viable myocardium in patients with CAD in the absence of comparative studies, demonstrating the superiority among the different techniques that use nitrate for such purpose.

We believe that patients with CAD and fixed uptake defects at rest can receive a maximum tolerated dose of I.V. nitroglycerin as described in this study, with the objective of improving the detection of viable myocardium by SPECT with MIBI.

Some limitations must be considered. In the present study, the population had only 25% of women, the analysis of severity and reversibility of segmental hypouptake was carried out qualitatively and there has been no long-term follow-up after the revascularization to evaluate the improvement in the myocardial contractile function.

Although our results suggest an increase in the detection of viable ischemic myocardium by MIBI after the administration of I.V. nitroglycerin at a maximum tolerated dose, they need to be confirmed in larger series, with a more balanced proportion between the genders, preferably using a quantitative analysis methodology of the intensity of MIBI uptake defects and early as well as late follow-up of the patients submitted to recanalization procedures.

Conclusion

The results of the present study suggest an improvement in the sensitivity of SPECT with MIBI to detect viable myocardium, when associated to the maximum tolerated dose of intravenous nitroglycerin, showing that Tc-99m is a good marker for this purpose.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any graduation program.

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