

# Adenosine Myocardial Perfusion SPECT with Tc-99m-MIBI in Patients with Obstructive Coronary Artery Disease: Correlation between Quantitative Coronary Angiography and Intravascular Ultrasound Measurements

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## OBJECTIVE

To correlate myocardial perfusion scintigraphy (MPS) with Tc-99m-MIBI and adenosine infusion using quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS).

## METHODS

Seventy patients with coronary artery disease (CAD) referred for myocardial perfusion scintigraphy (MPS) with MIBI and adenosine were studied. Clinical, electrocardiographic (ECG), and scintigraphic findings were correlated with variables of visual and quantitative angiographic analysis, as well as to those of IVUS.

## RESULTS

The mean age of patients was 60.6 years, and 39 were male. Coronary angiography showed percentage of diameter stenosis (% DS) of 49.94% in 105 arteries, 83 of which were re-evaluated by QCA (79%), mean of 44.20%,  $p < 0.05$ . ST-segment depression during adenosine infusion was associated with higher degrees of % DS (55.0% vs. 47.8%),  $p < 0.05$ . Scintigraphic ischemia was correlated with greater cross-sectional area (CSA) of lumen obstruction by IVUS (% CSA). Clinical, ECG, and IVUS findings were considered together and expressed as global ischemic versus non-ischemic responses. Ischemia was associated with lower values of minimal lumen diameter (MLD) and minimal lumen area (MLA) determined by QCA and IVUS.

## CONCLUSION

Tc-99m-MIBI and adenosine myocardial SPECT is correlated with % CSA on IVUS, perfusion images considered. Global results assessment showed association between lumen diameter and area at obstructed sites as determined by QCA and IVUS.

## KEY WORDS

myocardial scintigraphy, coronary artery disease, coronary angiography, myocardial ischemia, technetium-99m-MIBI, clinical decision

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SPECT myocardial perfusion with radiopharmaceuticals (either thallium-201 or Tc-99m-labeled sestamibi) associated with stress testing or pharmacological vasodilation is a well-established and widely accepted method for the diagnosis and risk stratification of coronary artery disease<sup>1-7</sup> (CAD), using coronary angiography as standard. Optimal diagnostic and prognostic values are obtained in the presence of severe coronary lesions, with a decreased level of accuracy of scintigraphic examination in case of lower degrees of obstruction. Likewise, angiogram visual interpretation demonstrates significant inter- and intraobserver variability, and any standard angiographic view may estimate the degree of luminal narrowing incorrectly.

Therefore, this study was designed to correlate Tc-99m-MIBI and adenosine myocardial SPECT in lesions of varying degrees using off-line quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS).

## METHODS

From March 2001 to February 2003, seventy consecutive CAD patients referred for myocardial perfusion imaging (Gated-SPECT) were enrolled in this study. Inclusion criteria were: subjects of both genders older than 30 years; clinical manifestation of stable or controlled unstable angina; silent ischemia demonstrated by previous functional tests; varying degrees of luminal narrowing with single- or multi-vessel disease. Exclusion criteria were: patients with acute myocardial infarction, decompensated heart failure, symptomatic cerebrovascular insufficiency or history of recurrent vascular headache, chronic obstructive pulmonary disease, left bundle branch block, second-degree or higher atrioventricular block (AV), systolic pressure lower than 90 mmHg, history of hypersensitivity to dipyridamole or adenosine, and use of substances such as methylxanthines and caffeine at the day of examination. The study protocol was approved by the Institutional Research Ethics Committee, and all patients signed an informed consent.

*Study flow chart* – Once clinical eligibility was confirmed, standard coronary angiography was reevaluated by the researcher and by two independent observers and, whenever possible, lesions were submitted to an off-line quantitative assessment for the degree of lumen diameter stenosis. Patients were then referred for myocardial scintigraphy associated with adenosine injection, in a two-step procedure carried out on subsequent days. Finally, all data, including available IVUS information, were quantitatively analyzed off-line at the core laboratory.

*Myocardial perfusion scintigraphy (Gated-SPECT) with Tc-99m-MIBI* – Performed following the two-day protocol,<sup>9</sup> with images acquired 30-60 minutes after the pharmacologic stress phase and at rest, 24 hours after the first step. Nitrates were discontinued the day of test; caffeine, methylxanthines or derivatives, for 24 hours<sup>10</sup> and beta-blockers, for 48 hours.

*First step* – Included clinical evaluation, continuous monitoring and 13-lead ECG tracings<sup>11</sup>, minute by minute, during 8 minutes, using the Teb Apex 2000 multi-channel recording system (TEB – São Paulo, Brazil), concomitantly with adenosine infused at 140  $\mu\text{g.kg.min}^{-1}$ , over 6 minutes<sup>12</sup>, by intravenous pump (DigiBomb, model DB-03-FAJ, São Paulo, Brazil). A dose of 740 to 814 MegaBequerel (Mebq) of Tc-99m-MIBI was administered at the third minute of adenosine injection, and treadmill walking was added with energy expenditure up to seven metabolic equivalents (METs) after routine controls and IV aminophylline (1 to 2  $\text{mg.kg.min}^{-1}$ ) in case side effects or high-risk ischemia signs persisted. Criteria for ischemic response included ST-segment depression equal to or higher than 1 mm according to established guidelines<sup>13</sup>; pain or associated clinical manifestations suggestive of coronary failure<sup>14-16</sup>. A Millennium VG dual-head gamma camera (GE Medical Systems, Milwaukee, USA) equipped with high-resolution, low-energy parallel-hole collimators was used. Sequential tomographic images were obtained on a 64 x 64 matrix, starting within 60 minutes of Tc-99m-MIBI injection, using the Gated-SPECT technique according to standard methodology<sup>17</sup>.

*Second step* – Performed 24 hours after the first one, without the pharmacological effect of adenosine and using the same imaging sequence and processing<sup>18</sup>.

*Analysis of SPECT perfusion images* - After image reorientation and reconstruction, radiopharmaceutical uptake and wall motion and thickening classification<sup>2,19,20</sup>, interpretation was made by two independent observers, according to the I Guideline for Nuclear Cardiology of the Brazilian Society of Cardiology<sup>10</sup>. Myocardial distribution patterns of the radiopharmaceutical<sup>10</sup> were treated as categorical variables, and only two possibilities were considered: normal uptake *versus* altered uptake and non-ischemic uptake *versus* reversible reduced uptake or suggestive of ischemia. Similarly, quantitative analysis of myocardial left ventricular motion and thickness was classified in normal *versus* altered response, aiming at the association with those variables derived from visual angiography, QCA and IVUS.

*Conventional and quantitative coronary angiography* – Lesions were reevaluated visually, according to degree of obstruction<sup>21,22</sup> ( $\leq 30\%$ ; 30 to 49%; 50 to 69%;  $\geq 70\%$ ; 95% and 100%, respectively), location (ostial, proximal, middle third or distal), using the angiographic definitions of the Bypass Angioplasty Revascularization Investigation trial (BARI). Vessels included left main coronary artery (LM), left anterior descending artery (LAD), diagonal or diagonalis ramus (Dg), left circumflex (Cx), marginal or marginalis ramus (Mg), and right coronary artery (RCA).

Examinations were performed in an H5000<sup>®</sup> catheterization laboratory (Phillips Medical Systems<sup>®</sup>,

Eindhoven, the Netherlands), using standard technique and procedures<sup>24</sup>. As for the quantitative evaluation, the system itself (CMS®, Medis Medical System®, the Netherlands) characterized artery boundaries according to criteria of arterial lumen brightness, with operator interaction. Quantitative variables for off-line analysis included proximal reference diameter (PRD), distal reference diameter (DRD), interpolated reference diameter (IRD) and minimal lumen diameter (MLD), all expressed in millimeters. IRD was adopted as reference diameter (RD) value for the site of obstruction. Percentage of diameter stenosis (% DS) was calculated from the ratio between the difference of RD and minimal lumen diameter divided by reference diameter, according to the following equation:

$$\% \text{ DS} = \frac{\text{RD} - \text{MLD}}{\text{RD}} \times 100$$

Angiographic minimal lumen cross-sectional area (MLA) was estimated from the sum of the square of minimal lumen diameters derived from two orthogonal views (MLD1 and MLD2) adjusted by a correction factor, according to the following formula.

$$\text{MLA} = 0.51 \times (\text{MLD1})^2 + (\text{MLD2})^2$$

Intravascular ultrasound indicated by the patient's referral physician was performed immediately after standard coronary angiography, using the Clear View® system (Boston Scientific®, Boston, USA) and the Ultra® 30-MHz catheter (CVIS®, USA), in accordance with the previously mentioned methodology. Off-line quantitative analysis was performed using a computerized planimetry system (TapeMeasure®, Indec Systems, Inc, California, USA) following standard methodology of the interventional cardiology unit<sup>24</sup>. IVUS quantitative variables used for the association with scintigraphic variables included: a) arterial lumen area, measured at references and at lesion site, characterizing reference lumen area (RLA) and minimal lumen area (MLA), both in square millimeters; b) minimal lumen diameter (MLD), derived from the MLA outline, in millimeters; c) cross-sectional area of lumen obstruction (CSA), according to the following formula:

$$\% \text{ CSA} = \frac{\text{RLA} - \text{MLA}}{\text{RLA}} \times 100$$

Statistical analysis was performed by the SPSS software (SPSS Inc, Chicago, Illinois). Categorical

variables were expressed as absolute frequencies and percentages, and quantitative variables, as means, standard errors, minimum and maximum values. Student's t test was used to compare dichotomous and quantitative variables, by comparing the means, using Pearson's correlation coefficient to assess the relationship between two quantitative variables. Statistical significance level was set at 0.05.

## RESULTS

Sample consisted of 39 (55.7%) men and 31 (44.3%) women, mean age 60.6 years (SD = 9.43). Mean number of risk factor was 2.69 (SD = 1.11) per patient, notably arterial hypertension in 74.3%, diabetes in 30%, previous myocardial infarction in 25.7%, and percutaneous coronary intervention in 15.7%. Patients were clinically stable on the day of pharmacological test, and the interval between coronary angiography and scintigraphy was 2.48 (SD = 2.97) months.

Angiograms were reviewed aiming at off-line quantitative analysis and obtaining data to be compared with scintigraphic variables results. A hundred and five coronary lesions were reevaluated. The number of affected vessels is described in Table I.

**Table I – Distribution of coronary artery disease according to the number of affected vessels per patient**

Nº of vessels	n	%	% accumulated
1	43	61.4	61.4
2	20	28.6	90.0
≥ 3	7	10.0	100.0
Total	70	100.0	

*n = number of patients; % = percentage*

The artery most frequently affected in patients with one-, two- and three-vessel disease was the left anterior descending (LAD) in 25 patients (58.1%), 14 patients (70.0%), and 6 patients (85.7%) respectively, followed by the right coronary artery (RCA) in 14 patients (32.5%), 7 patients (35%) and 5 patients (71.4%), and the left circumflex (Cx) in 3 patients (7%), 8 patients (40%) and 6 patients (85.7%). Collateral circulation was present in 6 patients (8.6%); in three (50%) of them it was intracoronary and intercoronary in the other 3 (50%); grade I/II in 4 (66.6%), and grade III in 2 (33.3%). In 5 patients (83.3%) this collateral circulation was related to the occluded arteries and in 1 patient (16.6%) to an intermediate lesion. Mean values of diameter stenosis percentage was 49.94% (SD 12.65).

Pre-scintigraphy quantitative coronary angiography – The procedure was completed in 83 (79.0%) of the 105 arteries submitted to off-line evaluation, and mean percentage of diameter stenosis was 44.20% (SD 10.37) (Table II).

**Table II – Results of the variables obtained by off-line quantitative coronary angiography**

Variables	n	Mean	DP	Variation	
% DS	83	44.19	10.37	14.00	74.00
PRD	79	2.78	0.54	1.58	5.05
DRD	82	2.65	0.53	1.36	4.74
MRD	73	2.99	0.52	1.90	4.42
MLD	82	1.53	0.40	0.69	2.93
MLD1	66	1.61	0.40	0.79	2.75
IRD	80	2.72	0.53	1.40	4.80
Area	66	4.08	2.12	0.92	11.41

*% DS = percentage of diameter stenosis; PRD, DRD, and MRD = proximal, distal and maximal reference diameters; MLD, MLD1 = minimal lumen diameter, at the site of greatest obstruction, obtained in different orthogonal views. IRD = interpolated reference diameter; Area = cross-sectional area, at the site of greatest obstruction, calculated in mm<sup>2</sup>; n = number of arteries; SD = standard deviation; Variation = minimum and maximum values. Diameters measured in mm*

Intravascular ultrasound – Forty-six arteries (43.8%) were studied, one per patient; mean minimal lumen area (MLA) was 2.92 mm<sup>2</sup> (SD 1.54), mean minimal lumen diameter (MLD) was 1.68 mm (SD 0.43), and mean cross-sectional area of lumen obstruction (% CSA) was 61.20% (SD 14.31) (Table III).

**Table III – Quantitative variables obtained by IVUS**

Variables	n	Mean	SD	Minimum	Maximum
RLA Px *	40	7.01	3.00	2.80	17.40
MLA	46	2.92	1.54	0.96	7.30
MLD	46	1.68	0.43	0.99	2.70
RLA Dx *	46	7.11	3.31	2.90	17.00
% Area obstruction	40	61.20	14.31	36.40	81.62

*RLA Px = proximal reference lumen area, in mm<sup>2</sup>; MLA = minimal lumen area at the site of greatest obstruction, in mm<sup>2</sup>; MLD = minimal lumen diameter at lesion site, in mm; RLA Dx = distal reference lumen area, in mm<sup>2</sup>; \* Calculated at non-ostial lesions*

Resting electrocardiogram – Up to three diagnoses were considered per patient, and normal morphology was found in 36 patients (51.4%), borderline PR interval ( $\geq$  200 ms) in 7 (10%), atrial fibrillation in 1 (1.4%), anterior myocardial infarction in 4 (5.7%), inferior in 3 (4.2%) and intraventricular conduction disturbance in 6 (8.4%).

Clinical manifestations – Sixty-seven patients (95.7%) had side effects related to adenosine injection, and chest pressure or chest pain experienced by 37 patients (52.9%) during the pharmacological test was not associated with diameter stenosis percentage by visual angiography, nor with minimal lumen diameters and areas established by QCA and IVUS ( $p > 0.05$ ).

Ischemic response – Of 68 patients (97.1%) with adequate records for analysis, 21 (30.9%) had ischemic response and 47 (69.1%), no ST-segment depression during adenosine injection. Comparing the presence versus absence of ST-segment changes on the 12-

lead ECG, a difference between mean percentage of stenosis was noted (55% SD 15.6 vs. 47.8% SD 12.2 respectively,  $p < 0.05$ ).

Qualitative analysis of perfusion images – Findings of normal uptake in 34 patients (48.6%) and changes in uptake of any nature in 35 (50%) were different relative to % CSA obtained by IVUS, mean 50.4% (SD 19.4) and 61.9% (SD 12.6), respectively ( $p < 0.05$ ). The other variables did not differ by Student's t test ( $p > 0.05$ ). As to presence of ischemia, there was also an association between reversible reduced uptake by myocardial scintigraphy, and IVUS determined higher mean of % CSA values. Means and standard deviations were 50.6% (SD 18.1) for non-ischemic results on myocardial perfusion scintigraphy and 63.7% (SD 12.6) for ischemic results. (figs. 1 e 2).

Wall motion and thickening – No abnormal wall motion was associated with higher degrees of arterial lumen obstruction ( $p > 0.05$ ). However, qualitative evaluation of wall thickening showed a significant difference in mean comparison relative to %CSA by IVUS. Means were 45.2% (SD 30.3) for normal responses and 62.1% (SD 16.4) for any thickness change ( $P < 0.05$ ).

Overall results of myocardial scintigraphy associated with adenosine – Taking into account all clinical and electrocardiographic responses, as well as scintigraphic results, a dichotomous variable was created to express altered versus normal results and another for ischemic versus non-ischemic results. Significant difference was found when MLA means by IVUS were compared, relative to altered (2.81 mm<sup>2</sup> SD 1.40) versus normal results (4.08 mm<sup>2</sup> DP 1.89). Additionally, MLD and MLA mean values by QCA were 1.49 mm (SD 0.34) and 3.74 mm<sup>2</sup> (SD 1.78) for ischemic tests, and 1.71 mm (SD 0.49) and 5.00 mm<sup>2</sup> (DP 2.65), respectively, for non-ischemic tests, with  $p < 0.05$ . Likewise, overall ischemic results were associated with lower MLA and MLD mean values by IVUS ( $p < 0.05$ ). MLD and MLA were 1.63 mm (SD 0.38) and 2.74 mm<sup>2</sup> (SD 1.38), respectively, for ischemic tests and 1.97 mm (SD 0.50) and 4.01 mm<sup>2</sup> (SD 1.79) for non-ischemic tests ( $p < 0.05$ ). These findings are described in figures 3, 4, 5, and 6.

## DISCUSSION

Thirty percent of the patients (21) had diabetes and 44% were female, which by itself added complexity to the population<sup>27</sup>. These facts plus the distribution of other risk factors, more prevalent in patients with coronary artery disease, might have affected scintigraphic precision, because decompensated diabetics would not show an adequate hyperemic response to adenosine in the presence of decreased levels of insulin, possibly limiting test accuracy<sup>28</sup>, in addition to higher occurrence of attenuation defects on scintigraphic images in women because of large breasts<sup>29</sup>. In an attempt to reduce such

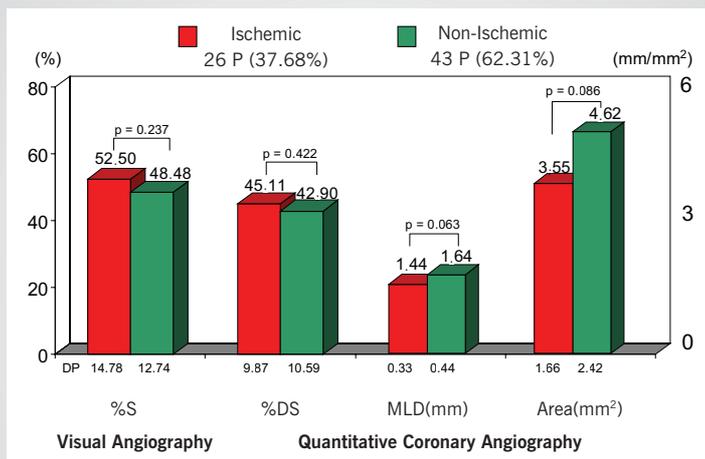


Fig. 1 – Perfusion imaging results, considering possible changes suggestive of ischemia and absence of transient reduced uptake. Comparison of variable means measured by angiographic visual and quantitative analysis. % S and % DS – Percentage of diameter stenosis by angiographic visual and quantitative analysis; MLD – minimal lumen diameter

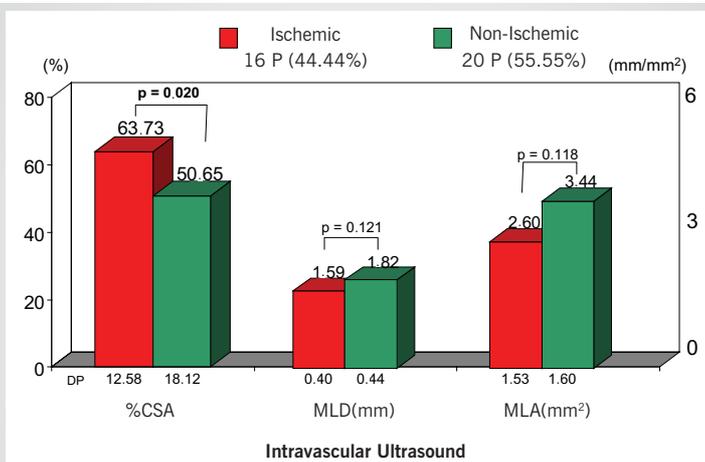


Fig. 2 – Perfusion imaging results, considering possible ischemic changes and absence of transient reduced uptake. Comparison of variable means measured by IVUS; % CSA - cross-sectional lumen area at the site of greatest stenosis; MLD – minimal lumen diameter; MLA – minimal lumen area

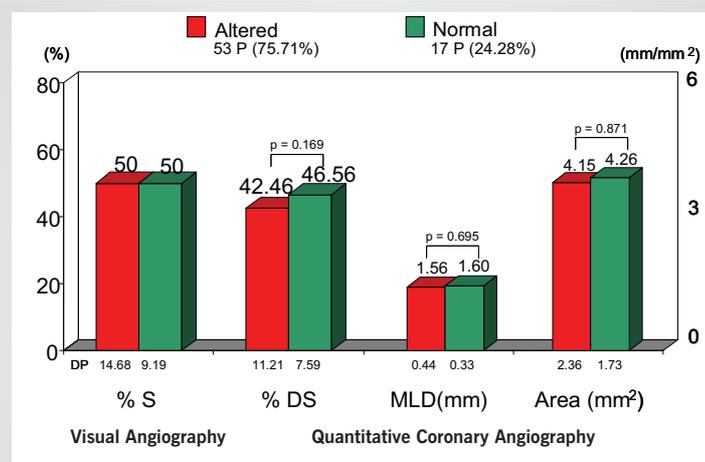


Fig. 3 – Overall results categorized in altered and normal responses. Comparison of variable means by angiographic visual and quantitative analysis. % S and % DS - Percentage of diameter stenosis by angiographic visual and quantitative analysis; MLD – minimal lumen diameter

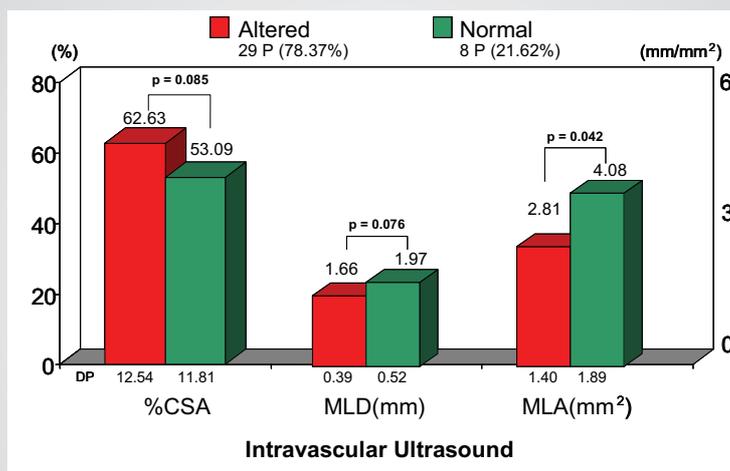


Fig. 4 – Overall results categorized in altered and normal responses. Comparison of variable means measured by IVUS. %CSA – cross-sectional lumen area at the site of greatest stenosis; MLD – minimal lumen diameter; MLA – minimal lumen area

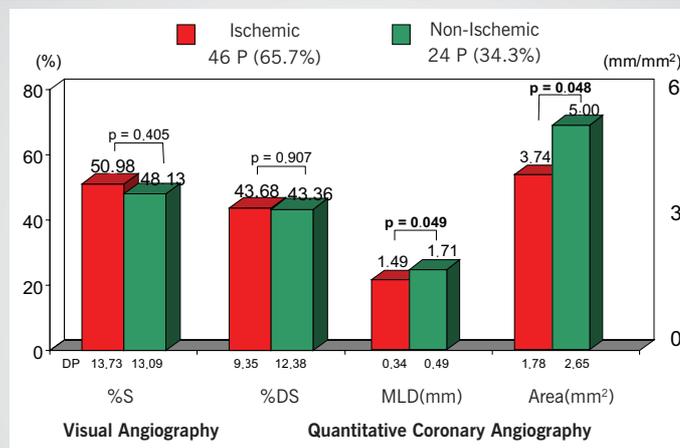


Fig. 5 – Overall results considering combined analysis of clinical manifestations, electrocardiographic responses, and scintigraphic images, categorized in ischemic and non-ischemic responses. Comparison of variable means measured by angiographic visual and quantitative analysis. %S and %DS – Percentage of diameter stenosis by angiographic visual and quantitative analysis; MLD – minimal lumen diameter; Area – cross-sectional lumen area by QCA at the site of greatest obstruction

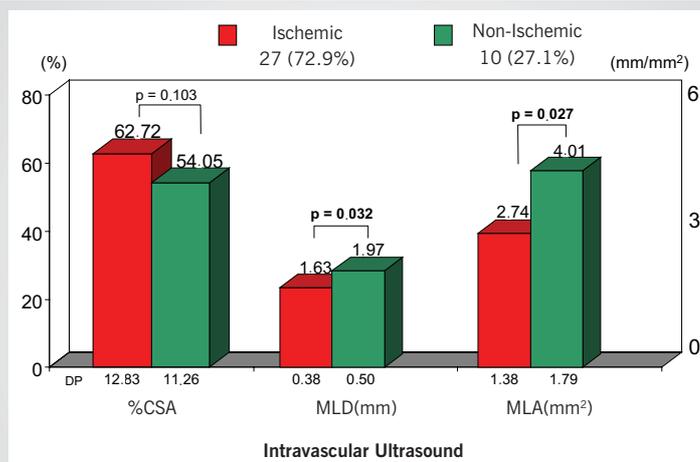


Fig. 6 – Overall results considering combined analysis of clinical manifestations, electrocardiographic responses, and scintigraphic images, categorized in ischemic and non-ischemic responses. Comparison of variable means by IVUS. %CSA – cross-sectional lumen area at the site of greatest stenosis; MLD – minimal lumen diameter; MLA – minimal lumen area

limitations, improve final image quality and decrease persistent clinical manifestations, patients underwent treadmill walking with low energy expenditure after adenosine administration, contrary to information found in literature, where treadmill walking was added during adenosine injection<sup>30-32</sup>.

With respect to ongoing medication, it is worth noting the recommendation for beta-blocker and nitrate discontinuation, which is not included in national<sup>10</sup> or foreign guidelines<sup>33</sup>. We believe that discontinuation of beta-blockers and nitrates for at least 24 to 48 hours is desirable, because pharmacological stimulation is followed by a slight yet significant increase in double product<sup>34</sup>, which could be limited in the presence of the drug, in addition to the negative dromotropic effects of adenosine on the atrioventricular node, already present during beta-blocker therapy. Orientation towards vasodilator discontinuation on the day of the test was also important to reduce false-negative results and allow an accurate estimate of myocardial areas at risk, usually underestimated in patients with chronic use of vasodilators<sup>35,36</sup>.

Chest pain and electrocardiographic ischemic changes during pharmacological stimulation - The high prevalence of side effects exceeded that of the series published in the literature (only 4.5% asymptomatic)<sup>37</sup>, with female and younger patients predominance, as in the series of Thomas et al<sup>32</sup>. In this initial experience, difficulty in characterizing chest pain, discomfort or pressure, present in 53% of the cases, was evident. In our series, 24% of chest discomfort, pressure or pain was radiated to the anterior cervical region, which added to the thoracic location, amounted to 77%. Overall, little association is found between this side effect and coronary failure, with low specificity, because normal volunteers also experience pain during intravenous drug infusion. A dose-effect relationship between adenosine and chest pain has been described<sup>38</sup>, suggesting that this substance causes chest pain during myocardial ischemia episodes, by direct stimulation of cardiac A1-receptors<sup>39</sup>.

Coincidentally, no association was made between pain manifestation during adenosine injection and higher degrees of stenosis of minimal lumen diameter or lower mean values of lumen area at the sites of greatest obstruction, or even of the cross-sectional area of lumen obstruction. Ischemic changes in ST-segment morphology observed in 21 patients (31%), the frequency of which was higher than those reported in classic studies (ranging from 8% to 25%), were associated with greater degrees of diameter stenosis percentage by visual analysis of angiographic images.

Analysis of scintigraphic images and overall results of the test - In the studied population, it became clear the great challenge faced by experts regarding decision making, since angiography by itself was inadequate to evaluating the functional impact of these lesions, ranging from 30 to 70%<sup>40,41</sup> and requiring further information from

invasive and non-invasive studies capable of estimating or measuring coronary flow reserve (CFR) under maximal hyperemia<sup>42,43</sup>.

Based on diagnostic and prognostic data provided by scintigraphic studies, established and related to each other, we decided to correlate Tc-99m-MIBI with adenosine injection with new patterns of comparison that would add value to standard angiography, allowing adequate functional correlation in evaluating ischemic phenomena.

We added, therefore, off-line quantitative analysis to the visual analysis of angiographic images, using established variables to characterize coronary obstruction, such as minimal lumen diameter and percentage of diameter stenosis<sup>44</sup>. Despite knowing that coronary artery diameter quantification failed to elucidate the relationship between stenosis severity and impact on the coronary flow<sup>45</sup>, a condition assessed by myocardial scintigraphy in the indirect estimation of coronary flow reserve<sup>46</sup>, the significance of measurements obtained by quantitative angiography was accepted as predictive of late events<sup>47,48</sup>. In the same way, coronary stenosis evaluation based on information provided by angiography and intracoronary Doppler, in patients with single-vessel disease assessed by exercise stress testing, showed, through logistic regression analysis, that percentage of diameter stenosis or MLD and coronary flow velocity reserve were predictive variables for exercise test results<sup>49</sup>.

Detection of clinical, electrocardiographic, and scintigraphic ischemia was considered relevant in our study, identified either singly or grouply, since it is an important determinant of coronary events. At first, a trend was observed towards associating images with reversible reduced uptake in 26 patients (37.68%) and lower mean values for MLD and MLA by QCA, comparing the 43 non-ischemic patients (62.31%) (MLD = 1.44 mm vs. 1.64 mm,  $p=0.063$  and MLA = 3.55 mm<sup>2</sup> vs. 4.62 mm<sup>2</sup>,  $p=0.086$ , respectively). Failure to obtain more statistically significant difference was attributed to the very characteristics of our population, presenting mostly intermediate lesions and % SD around 44% on QCA. Likewise, the analysis of % CSA at the site of greatest obstruction by the same method yielded the mean of 4.08 mm<sup>2</sup> (DP 2,12) in 66 arteries, showing normal response of coronary flow reserve (CRF) when isolated arterial lesions were evaluated<sup>50</sup>.

In the study by Harrison et al<sup>50</sup>, a significant correlation was found between proximal lesions of the anterior descending artery and minimal lumen area higher than 3.5 mm<sup>2</sup> measured by QCA plus normal CFR. Taking into account patients diagnosed as having localized disease, we found lower mean values for MLA calculated by QCA for images showing decreased uptake suggestive of ischemia, compared with scintigraphies showing absence of ischemia (3.55 mm<sup>2</sup> vs. 4.62 mm<sup>2</sup>,  $p=0.086$ ). It stood to reason, therefore, that the less-than-perfect

diagnostic performance of the test was associated with borderline anatomic data between normal and abnormal functional response translated by CFR, which was closely related to myocardial perfusion scintigraphy results, both at rest and under maximal hyperemic stimulation by pharmacological vasodilation. When chest pain and ST-segment depression were added to scintigraphic results, creating a dichotomous variable to express overall ischemic *versus* non-ischemic results, a better discriminatory capacity was found, with association of lower MLD and MLA means measured by QCA for the ischemic tests in 46 patients, as compared to those tests showing non-ischemic overall results in 24 patients (1.49 mm and 3.74 mm<sup>2</sup> vs. 1.71 mm e 5.00 mm<sup>2</sup>, respectively,  $p < 0.05$ ).

When myocardial scintigraphy and IVUS findings were compared<sup>51</sup>, the latter being used in this study for further evaluation of intermediate coronary lesions severity according to recently published Guidelines<sup>51</sup>, isolated results of perfusion and thickening images, expressed as dichotomous variables, were found to be significantly associated with cross-sectional area of lumen obstruction (% CSA) only, when compared to any changes in perfusion *versus* normal uptake (63.73% vs. 50.65%,  $p = 0.020$ ), or to any changes in thickening *versus* normal thickening (62.08% vs. 45.18%,  $p = 0.047$ ). Such behavior is directly associated with changes of coronary flow reserve, triggered by moderate diameter stenosis yet corresponding to approximately 75% of the cross-sectional lumen area.

Studies performed after the classic demonstrations by Gould, Wilson et al<sup>52</sup> showed that CFR, measured using intracoronary Doppler catheters, was optimally correlated with cross-sectional area of stenosis, and that lesions less than 70% in area and diameter stenosis lower than 50% were associated with CFR greater than 3.5, data similar to that obtained in animal studies. Using these variables as discriminants for functional changes associated with hyperemia documented by scintigraphy, it called the attention the mean value approaching 60% for % CSA in those patients who underwent IVUS, somewhat corroborating the findings of regular sensitivity and low specificity<sup>53</sup>. Also emphasizing the clear and obvious discrepancy between anatomical and functional findings, and recognizing the limitations imposed by angiography in defining lesions and how they affect coronary flow changes, myocardial perfusion scintigraphy has been used as a comparative method of invasive and non-invasive assessment of coronary flow reserve<sup>42,54</sup> regarding anatomic variables obtained by IVUS and data derived from intracoronary Doppler studies<sup>55</sup>.

Worth noting in this context is the interesting study by Nishioka et al<sup>56</sup>, validating three indexes of stenosis derived from IVUS, as well as a minimal lumen area of 4 mm<sup>2</sup>, as criteria for significant coronary narrowing using stress myocardial scintigraphy as benchmark.

Both the simplicity and high level of accuracy of MLA must be emphasized in the discriminatory value above mentioned, already established as predictive of late events and related to the determination of coronary flow reserve before and after percutaneous coronary intervention<sup>57</sup>. On the other hand, diagnostic performance of scintigraphy, when only images were analyzed, showed regular sensitivity and optimal negative predictive value (NPV), but restricted specificity when the discriminatory limit of 70% was chosen for stenosis area percentage, whether in comparing mean values relative to any change in uptake *versus* normal uptake (Sensitivity = 75%; NPV = 86%; Specificity = 55%) or in changes suggestive of ischemia *versus* non-ischemic uptake (Sensitivity = 75%; NPV = 88%; Specificity = 64%). These indexes must also be understood in the context of the lesions that comprised our evaluated sample.

Based on these findings, we also attempted to correlate the overall results of the test to some ultrasound variables, similar to what we did with QCA. Once pain manifestation and electrocardiographic changes were added to perfusion imaging findings and overall results were categorized as altered or normal, different mean values were found for MLA on IVUS. Altered tests were correlated with MLA values of 2.81 mm<sup>2</sup> (SD 1.40), whereas normal results were correlated with values of 4.08 mm<sup>2</sup> (DP 1.89),  $p < 0.05$ . A trend towards different means for altered and normal results was also observed, for MLD and %CSA alike, both measured by IVUS ( $p = 0.076$  and  $p = 0.085$ , respectively). When overall ischemic *versus* non-ischemic results were used, persistent reduced uptake excluded from the analysis, an association of ischemic tests with lower MLD and MLA measured by IVUS was found, compared to non-ischemic tests (1.63 mm and 2.74 mm<sup>2</sup> x 1,97 mm and 4.01 mm<sup>2</sup>,  $p < 0.05$ ). It became obvious that the addition of clinical and ECG data to the images increased the correlation between presence of ischemia and values of those quantitative variables that translated into higher anatomic severity of lesions.

Radiopharmaceutical uptake is proportional to perfusion and myocardial viability, with a linear association between intravenous dose per gram of myocardium and coronary blood flow per minute. Myocardial areas with different flow due to obstructive lesions and thus heterogeneous uptake, under maximal hyperemia, justify the genesis of perfusion defects by scintigraphy. Nevertheless, the phenomenon of roll-off, that is, the loss of linear elevation in isotope uptake due to increases in coronary flow exceeding 2.5 times baseline values, with a consequent drop in myocardial extraction of Tc-99m-MIBI from the blood, should not be disregarded<sup>58,59</sup>. If one artery with no significant lesions and at maximal adenosine-induced vasodilation reaches coronary flows around 4.0 to 5.0 ml.min.gr<sup>-1</sup> but linear radioisotope uptake only up to 2.5 to 3.0 ml.min.gr<sup>-1</sup> and another artery with intermediate lesion routinely increases flow two or three times baseline values or 2,5 ml.min.gr<sup>-1</sup>, it can be concluded that both arteries

may produce scintigraphic images with imperceptible differences or approximate uptake when the corresponding regions are compared. Practical implication seems to be the limitation of the test in detecting lesions with 30% to 60% stenosis, a range that coincides with mean values of diameter stenosis percentage of our sample and with wide confidence intervals, thus reducing method previsibility.

*Collateral circulation* – It must be taken into account that coronary lesion is only one of the determinants of changes in coronary flow reserve under maximal hyperemia. Coronary collateral circulation and capillary network also play a key role in the genesis of reversible perfusion defects on scintigraphy induced by stress testing<sup>60</sup>. During stress, collateral vessels are usually insufficient for an adequate response to coronary flow increase associated to higher demands, resulting in frequent appearance of uptake defects. In pharmacological tests, participation of collaterals is mostly related to induction of the steal phenomenon that contributes to trigger myocardial ischemia, in addition to the non-homogeneous uptake of the radiopharmaceutical in areas affected or not with coronary lesion. Also worthy of attention in the studied sample was the presence of collateral circulation in only 6 patients (8.6%), in 5 of them (83.3%) this circulation was related to the occluded arteries and in only one (16.6%), to the intermediate lesion. Considering pharmacological vasodilation, such an angiographic profile may certainly have contributed to further limit detection of ischemia by the method.

Accuracy determination and risk stratification – For more than a decade now myocardial perfusion scintigraphy has been used for risk assessment of subjects with suspected or known coronary artery disease, as well as for the development of strategies for clinical management<sup>3,61</sup>. Therefore, diagnostic definition should

not be separated from risk stratification, because death rate of patients with ischemic scintigraphy of low risk is around 1% per year<sup>62</sup>. The decision to categorize results in dichotomous responses (normal *versus* altered or ischemic *versus* non-ischemic results) limited overall risk assessment, considering the severity of the disease and its influence on ventricular function, which were not evaluated in the present study. Moreover, this did not allow the association of changes in uptake on scintigraphic images with the respective areas of arterial distribution and, thus, failed to define accuracy regarding affected vessels. However, the use of a new method with limited series, heterogeneous clinical characteristics and moderate complexity was somewhat justified. Additionally, limitations related to image acquisition and processing, such as presence of artifacts from background radiation (liver) may have contributed to a potential decrease in method specificity, because observers had no information on previous clinical and angiographic data. Neither prone imaging nor attenuation correction software was used to reduce these interferences.

In conclusion, we believe that this study offers additional useful information for the decision-making process, as provided by association of scintigraphy with invasive methods that, based on anatomic variables, allow functional expression of the disease to be estimated, especially in subgroups of patients with lesions mostly of intermediate severity. Regarding this aspect, myocardial scintigraphy, analyzed from the addition of clinical and electrocardiographic responses to image results, estimates, with good sensitivity but limited specificity, coronary flow reserve under maximal hyperemia, supported now by new methods for comparison.

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