TI myocardial SPECT detects significant coronary artery disease between 50% and 75% angiogram stenosis

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INTRODUCTION

Perfusion myocardial Single Photon Emission Computed Tomography (SPECT) is a well established procedure for the diagnosis and evaluation of coronary artery disease (CAD). The sensitivity and specificity around 90% and 70% (normalcy rate 89%) respectively, are adequate for clinical practice using either exercise or dipyridamole (DIP)1-10. Radionuclide studies have been classically compared to the coronary angiography as the most accepted, though not perfect, “gold standard” and different cutoff values, between 50% and 75% are being used to define a lesion as significant6,11,12. Coronary angiography allows the detection of atherosclerotic lesions, whose severity can be estimated through percentage stenosis in the lumen, qualitatively or quantitatively13,14.
Our “goal” was to assess how the cutoff variation in the “gold standard”, affects Thallium-201 SPECT perfusion results in the same group of patients. Eventually, choose the one with best performance. We were motivated by the wide spectrum of criteria employed to define significance in coronary angiography in current clinical practice and literature.11,15-19.

MATERIAL AND METHODS

We collected prospectively data from 145 patients referred for CAD diagnosis, who gave their informed consent prior to all nuclear procedures. They were part of cooperative research on the value of Thallium-201 perfusion SPECT for the diagnosis of CAD. This work was approved by the Ethics Committee of the University Hospital. All patients had clinical cardiovascular assessment, coronary angiography, stress electrocardiogram (ECG) and myocardial Thallium-201 SPECT perfusion study. Ninety three percent of patients had less than 90 days between contrast angiography and radionuclide studies and no change in their clinical status during that period. There were 98 (67 %) males, and 47 (33 %) females. The mean age of the whole group was 60 ± 12 years (range: 29-79).

Coronary angiography

Coronary angiography was performed in the standard way, using multiple views, including contrast ventriculography and complete visualization of all coronary vessels. The observer was requested to assess visually, the grade of stenosis in coronary arteries for analysis and comparison to ECG and SPECT perfusion study. In particular, we compared the parameters of SPECT with two different thresholds of luminal diameter. Patients and individual vessels were deemed normal (non significant stenosis) or abnormal (significant stenosis), if below or above 50 % or 75 % cutoff values, respectively. In the whole group of 145 patients, we considered 435 individual vessels, (there were no left main CAD cases).

Stress ECG

Exercise was used in 63 (43 %) patients and DIP in 82 (57 %) cases. In all cases detailed results of the concomitant 12 lead ECG were available. For ECG analysis only, we excluded those tests on patients with left bundle branch block (LBBB), pacemaker or with incomplete signal registration. Exercise ECG was performed with Bruce protocol, recording 12 leads, being endpoints maximal heart rate (≥ 85 % predicted), angina, fatigue or significant ST abnormalities. Thallium-201 was injected 1 min before the end of the test. For pharmacological stress, DIP dose was 0.56 mg/kg infused in 4 minutes; Thallium was injected at min 8 after starting the infusion.

Analysis of ECG was performed only on patient basis due to the difficulties related to define territory involvement.

SPECT myocardial scintigraphy

The SPECT perfusion study was performed with 111 MBq of the tracer injected at peak stress. Acquisition of Thallium-201 SPECT study was started 10 min after injection, using a GE 3200 gamma camera. From right anterior oblique to left posterior oblique views, 32 projections were obtained through 180 degrees, in 64 × 64 matrix. Three to four hours later, the resting SPECT exam was acquired in a similar way. In 15 (10 %) cases, only redistribution images were acquired and in 130 (90 %) reinjection of 37 MBq of Thallium-201 3 hours previous to the resting acquisition was done.

Standard processing made it possible to obtain short, vertical and horizontal slices, which were interpreted blindly to clinical, ECG or angiographic results, by 2 independent observers, reaching consensus in discrepant cases. All myocardial segments were classified as normal (no perfusion defects), ischemic (reversible perfusion defects) or necrotic (fixed perfusion defects). At the time of image interpretation semi quantitative polar maps of stress, rest and reversibility were also included to classify each segment. Necrotic and ischemic regions were both deemed as indicative of CAD. The analysis considered anterior, septal, lateral, inferior and apical areas, correlated to lesions in the left anterior descending artery (LAD), right coronary artery (RCA) or circumflex artery (CX). In this regard, to correctly match the territory subtended by the corresponding coronary artery, the anatomy variation was taken into account in each patient. The sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated on patients and individual vessels. Student’s t test was employed to compare mean differences and Z test for proportions.
RESULTS

In regard to general clinical data, 52/145 cases (36 %) had history of prior myocardial infarction (MI). They were included because those patients represented a clinical practice sample and they were consecutively studied. In 24/145 patients (16 %) coronary revascularization had been undertaken before to inclusion in our protocol. Coronary angiography was performed within a mean of 27 days (range: 1 to 180), compared to the SPECT study and there were 93 % of cases done within less than 90 days. No cardiac events occurred between the date of both procedures. In 51 % coronary angiography was carried out before myocardial scintigraphy, and in 49 % after the radionuclide study.

When using ≥ 50 % threshold criteria, coronary angiography was considered normal in 28/145 (19 %) cases and abnormal in 117/145 (81 %) patients. There were 47 patients with single vessel disease (1VD), 36 with two vessel disease (2VD) and 34 with three vessel lesions (3VD).

On the other hand when using ≥ 75 % stenosis criteria, the angiogram was considered normal in 47/145 (32 %) cases and abnormal in 98/145 (68 %). With this threshold it was found 55 patients with 1VD, 28 with 2VD and 15 with 3VD.

Setting the angiography cutoff at ≥ 50 % and on a patient basis, stress ECG had 37 % sensitivity, 74 % specificity, 43 % accuracy, 87 % PPV and 19 % NPV. Setting the angiography cutoff at ≥ 75 %, stress ECG had 40 % sensitivity, 76 % specificity, 51 % accuracy, 79 % PPV and 36 % NPV (table 1).

At ≥ 50 % threshold, Thallium-201 SPECT sensitivity, accuracy and NPV by patients, were 87 %, 81 % and 52 %, respectively. These values are significantly greater than those of stress ECG (p < 0.001); PPV were similar, 87 % and 89 % respectively (NS) and the specificity was higher in the stress ECG, 57 % and 74 %, respectively (p < 0.001).

At ≥ 75 % threshold, Thallium-201 SPECT sensitivity, accuracy and NPV by patients, were 93 %, 79 % and 77 %, respectively. These values are significantly greater than those of stress ECG (p < 0.001); PPV were similar, 79 % and 80 % respectively (NS) and the specificity was higher in the stress ECG, 51 % and 76 %, respectively (p < 0.001).

Thallium-201 SPECT parameters in patients with ≥ 75 % threshold, compared with those with ≥ 50 % can be seen in table 2. It was found that sen-

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Angiographic Cutoff ≥ 50 %</th>
<th>Angiographic Cutoff ≥ 75 %</th>
<th>P</th>
<th>CI Cutoff ≥ 50 %</th>
<th>CI Cutoff ≥ 75 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>37 % (42/113)</td>
<td>40 % (36/94)</td>
<td>ns</td>
<td>28 %-47 %</td>
<td>30 %-51 %</td>
</tr>
<tr>
<td>Specificity</td>
<td>74 % (17/23)</td>
<td>76 % (32/42)</td>
<td>m</td>
<td>52 %-90 %</td>
<td>61 %-88 %</td>
</tr>
<tr>
<td>Accuracy</td>
<td>43 % (59/136)</td>
<td>51 % (70/136)</td>
<td>m</td>
<td>75 %-95 %</td>
<td>65 %-89 %</td>
</tr>
<tr>
<td>PPV</td>
<td>87 % (42/48)</td>
<td>79 % (36/48)</td>
<td>m</td>
<td>12 %-29 %</td>
<td>26 %-47 %</td>
</tr>
<tr>
<td>NPV</td>
<td>19 % (17/91)</td>
<td>36 % (32/88)</td>
<td>0.018</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes exercise and dipyridamole cases.
Excludes pacemaker and LBBB cases.
CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Angiographic Cutoff ≥ 50 %</th>
<th>Angiographic Cutoff ≥ 75 %</th>
<th>P</th>
<th>CI Cutoff ≥ 50 %</th>
<th>CI Cutoff ≥ 75 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>87 % (102/117)</td>
<td>93 % (91/98)</td>
<td>m</td>
<td>80 %-93 %</td>
<td>86 %-97 %</td>
</tr>
<tr>
<td>Specificity</td>
<td>57 % (16/28)</td>
<td>51 % (24/47)</td>
<td>m</td>
<td>37 %-75 %</td>
<td>36 %-66 %</td>
</tr>
<tr>
<td>Accuracy</td>
<td>81 % (118/145)</td>
<td>79 % (115/145)</td>
<td>m</td>
<td>82 %-94 %</td>
<td>71 %-87 %</td>
</tr>
<tr>
<td>PPV</td>
<td>99 % (102/103)</td>
<td>80 % (91/114)</td>
<td>m</td>
<td>33 %-70 %</td>
<td>59 %-90 %</td>
</tr>
</tbody>
</table>

*Includes exercise and Dipyridamole cases.
CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.
sitivity, specificity, accuracy, PPV and NPV were similar for both.

Using 75% threshold 19 patients were consid-
ered to have non significant lesions, because they had
stenotic lesions between 50% and 74%. In these pa-
tients, the ECG was abnormal in 4/19 (21%) and
Thallium-201 SPECT in 11/19 (58%). In the 4 ab-
normal cases ECG showed ST depression and angi-
a in 1; angina in another and ECG changes compat-
tible with ischemia in the remaining 2 cases. Detailed
Thallium-201 SPECT results pertaining to the 11 cas-
es can be found in table 3.

Thallium-201 SPECT parameters for 50% and
75% thresholds in all vessels, are shown in
table 4. Sensitivity and NPV were higher at 75%
threshold. Specificity and accuracy were similar for
both thresholds. In this same group, PPV was greater
at 50% threshold.

Thallium-201 SPECT value for individual vessel
detection, at ≥ 50% and at ≥ 75% thresholds, are de-
scribed in table 5. There was no difference between
both thresholds, regarding sensitivity, specificity, ac-
curacy and PPV. However, NPV was higher for LAD
and CX at ≥ 75% threshold.

**DISCUSSION**

Thallium-201 and Tc-99m agents are being em-
ployed as perfusion tracers for myocardial SPECT
scintigraphy. Their value for the diagnosis of
CAD is well known and both are used routinely
worldwide.

The validation of SPECT perfusion imaging has
been based mainly on comparison to a “gold stan-
dard”, the coronary angiography, which depicts ath-
 erosclerotic lesions in the lumen of coronary arteries.
In spite of its limitations, it is used as the most con-
venient and practical available method. Although
there are different ways to interpret the severity of
these lesions, the most used for its simplicity, is the
percentage of stenosis, estimated visually.

In reviewing the literature it was found different
angiographic criteria to define which lesions are sig-
nificant. To separate normal from abnormal cases and
to make decisions as far as revascularization, most re-
searchers use ≥ 50% but others use ≥ 70% or
≥ 75% as thresholds. In a recent work, sig-
nificant CAD has been defined as ≥ 70% diameter
stenosis of ≥ 1 major epicardial artery segment
or ≥ 50% diameter stenosis of the left main coronary
artery. For clinical purposes, other groups, also de-
fine significant lesions as 50% stenosis or more and
severe lesions as 70% stenosis or more.

In this research, we have used thresholds set
to ≥ 50% or ≥ 75% comparing the SPECT Thalli-
um-201 results in the same group of patients who had
no left main lesions.

Regarding analysis on a patient basis, similar val-
ues of sensitivity, specificity and accuracy were
found. Mahmarian et al, using quantitative SPECT,
compared ≥ 50% threshold to ≥ 70% and found
87% and 93% sensitivity in patients respectively (a
mild but statistically significant difference). Accura-

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**Table 3**

<table>
<thead>
<tr>
<th>Wall</th>
<th>Perfusion</th>
<th>Wall Findings on Abnormal Thallium-201 SPECT of 11 Patients with Lesions Between 50% and 75% on Coronary Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>Fixed defect</td>
<td>2</td>
</tr>
<tr>
<td>Lateral</td>
<td>Reversible defect</td>
<td>1</td>
</tr>
<tr>
<td>Inferior</td>
<td>Fixed defect</td>
<td>1</td>
</tr>
<tr>
<td>Septal</td>
<td>Reversible defect</td>
<td>2</td>
</tr>
<tr>
<td>Apical</td>
<td>Fixed defect</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 4**

<table>
<thead>
<tr>
<th></th>
<th>Angiographic Cutoff ≥ 50%</th>
<th>Angiographic Cutoff ≥ 75%</th>
<th>Categorical Cutoff ≥ 50%</th>
<th>Categorical Cutoff ≥ 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>59 % (130/220)</td>
<td>70 % (100/154)</td>
<td>0.029</td>
<td>52 %–66 %</td>
</tr>
<tr>
<td>Specificity</td>
<td>78 % (166/215)</td>
<td>75 % (212/281)</td>
<td>ns</td>
<td>72 %–83 %</td>
</tr>
<tr>
<td>Accuracy</td>
<td>68 % (298/435)</td>
<td>74 % (320/435)</td>
<td>ns</td>
<td>70 %–80 %</td>
</tr>
<tr>
<td>PPV</td>
<td>73 % (130/177)</td>
<td>61 % (100/166)</td>
<td>0.017</td>
<td>66 %–80 %</td>
</tr>
<tr>
<td>NPV</td>
<td>65 % (166/258)</td>
<td>82 % (212/258)</td>
<td>0.0001</td>
<td>59 %–71 %</td>
</tr>
</tbody>
</table>

CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

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cy for detecting CAD patients was similar, 87 % and 91 % respectively. In the work of Hambye et al, accuracy did not change using coronary stenosis thresholds set at \( \geq 50 \% \) or \( \geq 70 \% \), using SPECT and Tc-99m sestamibi.

Montz et al, in 144 patients using \( 99mTc \)-Tetrofosmin, found similar sensitivity and accuracy for \( \geq 50 \% \) (97 % and 82 %, respectively) and \( \geq 75 \% \) (94 % and 87 %, respectively).

As far as individual vessel analysis, it was found that Thallium-201 SPECT, had better sensitivity at \( \geq 75 \% \) threshold. It is known that detection of coronary lesions is easier when blood flow impairment is greater\(^{28,29}\). DePascuale et al, using Thallium-201 found that sensitivity of quantitative myocardial perfusion SPECT for individual vessels was 95 % in \( \geq 50 \% \) stenosis threshold, very similar to 94 % when the threshold was set at 45 %. He also suggested that specificity improved when lowering the threshold (from 74 % at \( \geq 50 \% \) to 91 % at 45 %)\(^1\). Mahmarian et al\(^1\), in relation to sensitivity in individual vessels, found no difference between the thresholds of \( \geq 50 \% \) and \( \geq 70 \% \). Again relatively high values of sensitivity with \( \geq 50 \% \) stenosis were found.

The group of Sacchetti et al\(^{22}\) studied Tc-99m tetrofosmin performance in 80 patients, 13 of them without significant stenosis (\( < 50 \% \)). They analyzed individual vessels considering the location of the abnormality; severe stenosis was defined as \( > 75 \% \) proximally or \( > 90 \% \) distally. Sensitivity with \( > 75 \% \) was 80 % and 64 % with \( > 50 \% \) stenosis. On the other hand specificity was 64 % and 66 %, respectively. These values are similar to the ones presented in this report. In our research it is of note, that 19 patients with \( 50 \%-74 \% \) lesions were deemed without significant lesions when using \( \geq 75 \% \) threshold, but abnormal with \( \geq 50 \% \) threshold. As a consequence, Thallium-201 SPECT specificity was lower when compared to \( \geq 75 \% \) threshold, due to the fact that these patients are more likely to have an abnormal Thallium-201 SPECT, being true positive for \( \geq 50 \% \), but appearing as false positive when using \( \geq 75 \% \). On the other hand, a significant number cases in this group, had abnormal stress ECG (21 %) and more importantly, abnormal Thallium-201 SPECT scintigraphy (58 %).

According to Chauveau et al\(^{30}\) and in agreement with our results, evaluation of the functional significance of intermediate coronary narrowing (40 % to 70 % diameter stenosis) is important for clinical decision making and risk stratification. They selectively evaluated severity during cardiac catheterization in PTCO cohort using coronary flow velocity reserve. They performed percutaneous transluminal coronary

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Table 5: THALLIUM-201 SPECT ACCORDING TO INDIVIDUAL CORONARY VESSELS

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Angiographic cutoff</th>
<th>Angiographic cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \geq 50 % )</td>
<td>( \geq 75 % )</td>
</tr>
<tr>
<td></td>
<td>LAD</td>
<td>RCA</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>62 %</td>
<td>70 %</td>
</tr>
<tr>
<td>CI</td>
<td>(54/87)</td>
<td>(46/66)</td>
</tr>
<tr>
<td>Specificity</td>
<td>65 %</td>
<td>82 %</td>
</tr>
<tr>
<td>CI</td>
<td>(92/145)</td>
<td>(109/145)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>63 %</td>
<td>75 %</td>
</tr>
<tr>
<td>CI</td>
<td>(54/74)</td>
<td>(46/80)</td>
</tr>
<tr>
<td>NPV</td>
<td>53 %</td>
<td>76 %</td>
</tr>
<tr>
<td>CI</td>
<td>(38/71)</td>
<td>(65/85)</td>
</tr>
</tbody>
</table>

All other comparisons: \( p = NS \).

\( ^{a} \) NPV were significantly higher for LAD and CX with \( \geq 75 \% \) (\( p \leq 0.02 \)).

Cl: Confidence Interval; LAD: left anterior descending artery; RCA: right coronary artery; CX: left circumflex artery; PPV: positive predictive value; NPV: negative predictive value.
angioplasty only if the SPECT perfusion study showed reversible defects or the coronary flow velocity reserve was below 2.

In addition, all these results are in agreement and supported by the important work of Gould; he employed DIP in dogs, demonstrated that it was possible to detect ischemia with N-13 ammonia and positron emission tomography (PET) with 47% or greater stenosis. This statement is also concordant in part with the findings of a recent report by Blumenthal et al. They studied with 201Tl a high-risk asymptomatic population, (siblings of CAD patients) and exercise scintigraphy identified predominantly mild coronary atherosclerosis, with mean stenosis lesion in arteries feeding defects of only 43±31 %, and 68% of such stenosis were < 50 %. However, in 71 % of all defects, the location matched arteries with the most severe stenosis. They concluded that perfusion defects may be caused by coronary vasomotor dysfunction in addition to atherosclerotic plaque.

Strengths of the study

The investigation was performed on thallium-201 SPECT, a frequently employed tracer for CAD diagnosis. Nevertheless, this information could be applied to Tc-99m tracers as well.

There was no selection of patients in this protocol and they were included prospectively from the clinical practice, including previous MI, prior revascularization, etc. In this way the data represents a sample of patients similar to everyday nuclear cardiology practice.

Limitations of the study

The presence of previous MI could increase CAD sensitivity but the analysis was directed to the same group of patients comparing only different parameters of the same method. Sacchetti et al. separated MI regions for the same analysis with tetrofosmin and their diagnostic values did not change. We did not use digital angiography with quantitative stenosis analysis, but this method is not widely available and not applied in clinical practice.

Clinical implications and conclusions

Based on the arguments given above and the valuable functional data pertaining to myocardial perfusion imaging, it seems reasonable to consider the use of ≥ 50% threshold jointly with angiography for CAD diagnosis and assessment in clinical practice. This threshold has similar accuracy when compared to the currently used higher values of ≥ 75 %, with Thallium-201. This may alter the clinical and therapeutic approach for a relatively important number of patients, who otherwise would be deemed bearing non significant coronary lesions.

In clinical practice, if coronary angiography shows a lesion around 50 %, it is essential to perform a perfusion SPECT to establish the presence of myocardial ischemia. If the study depicts significant ischemia, then revascularization would be pathophysiologically justified. The prognosis is different when the presence of ventricular ischemia has been demonstrated with noninvasive procedures.

ACKNOWLEDGEMENTS

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