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. Radiomolecule 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 significant 6,9,11,12. Coronary angiography allows the detection of atherosclerotic lesions, whose severity can be estimated through percentage stenosis in the lumen, qualitatively or quantitatively 13-14.

The aim of this work was to compare 201TI Thallium SPECT with different coronary angiographic cutoff values.

METHODS

Data pertaining to 145 patients were tabulated. All patients underwent stress ECG. 201Thallium SPECT and coronary angiography. To assess the cutoff impact, two criteria for coronary angiography diagnosis were used: a) ≥ 50 % and b) ≥ 75 % stenosis, and applied to data from patients and vessels.

RESULT

On a patient basis, 201Thallium SPECT sensitivity, specificity and accuracy were 87 %, 57 % and 81 % with ≥ 50 % cutoff and 93 %, 51 % and 79 % with ≥ 75 % cutoff, respectively (NS). When performing individual vessel analysis, sensitivity, specificity and accuracy were 59 %, 78 % and 68 % for ≥ 50 % cutoff and 70 %, 75 % and 74 % for ≥ 75 % cutoff, respectively (p < 0.029 for specificity). As expected, the severer the stenosis the higher the detection rate. There were 19 patients who had stenosis between 50 % and 74 %. Of these, 21 % had normal stress ECG and 58 % abnormal Thallium 201 SPECT.

Conclusion: 201Thallium SPECT results support the use of ≥ 50 % stenosis cutoff criteria for CAD diagnosis and evaluation. Combined with coronary angiography, myocardial SPECT offers an excellent management strategy to patients.

KEY WORDS: 201Thallium. SPECT. Myocardial perfusion. Coronary stenosis.

SPECT DE PERFUSIÓN MIÓCARDICA CON 201TI MYOCARDIAL SPECT DETECTS SIGNIFICANT CORONARY ARTERY DISEASE BETWEEN 50% AND 75% ANGIOGRAM STENOSES


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Abstract.—Coronary angiography is the “gold standard” for the diagnosis of coronary artery disease (CAD). The aim of this work was to compare 201Thallium SPECT with different coronary angiographic cutoff values.

Methods: Data pertaining to 145 patients were tabulated. All patients underwent stress ECG. 201Thallium SPECT and coronary angiography. To assess the cutoff impact, two criteria for coronary angiography diagnosis were used: a) ≥ 50 % and b) ≥ 75 % stenosis, and applied to data from patients and vessels.

Results: On a patient basis, 201Thallium SPECT sensitivity, specificity and accuracy were 87 %, 57 % and 81 % with ≥ 50 % cutoff and 93 %, 51 % and 79 % with ≥ 75 % cutoff, respectively (NS). When performing individual vessel analysis, sensitivity, specificity and accuracy were 59 %, 78 % and 68 % for ≥ 50 % cutoff and 70 %, 75 % and 74 % for ≥ 75 % cutoff, respectively (p < 0.029 for specificity). As expected, the severer the stenosis the higher the detection rate. There were 19 patients who had stenosis between 50 % and 74 %. Of these, 21 % had normal stress ECG and 58 % abnormal Thallium 201 SPECT.

Conclusion: 201Thallium SPECT results support the use of ≥ 50 % stenosis cutoff criteria for CAD diagnosis and evaluation. Combined with coronary angiography, myocardial SPECT offers an excellent management strategy to patients.

KEY WORDS: 201Thallium. SPECT. Myocardial perfusion. Coronary stenosis.
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.\textsuperscript{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 a 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, beginning 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 rest 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>
<thead>
<tr>
<th>Angiographic Cutoff ≥ 50 %</th>
<th>Angiographic Cutoff ≥ 75 %</th>
<th></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 % (38/94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>74 % (17/23)</td>
<td>76 % (32/42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>43 % (59/136)</td>
<td>51 % (70/136)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>87 % (142/163)</td>
<td>79 % (38/48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>19 % (17/88)</td>
<td>36 % (32/88)</td>
<td>0.018</td>
<td>26 %–47 %</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>Angiographic Cutoff ≥ 50 %</th>
<th>Angiographic Cutoff ≥ 75 %</th>
<th></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></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>57 % (18/28)</td>
<td>51 % (24/47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>81 % (118/145)</td>
<td>79 % (115/145)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>99 % (102/154)</td>
<td>80 % (91/114)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>52 % (16/31)</td>
<td>77 % (24/31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

Thallium-201 SPECT value for individual vessel detection, at 50% and 75% thresholds, are described in Table 3. There was no difference between both thresholds, regarding sensitivity, specificity, accuracy and PPV. However, NPV was higher for LAD and CX at 75% threshold.

### DISCUSSION

Thallium-201 and Tc-99m agents are being employed 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 standard”, the coronary angiography, which depicts atherosclerotic lesions in the lumen of coronary arteries. In spite of its limitations, it is used as the most convenient 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 significant. To separate normal from abnormal cases and to make decisions as far as revascularization, most researchers use ≥ 50% but others use ≥ 70% or ≥ 75% as thresholds. In a recent work, significant 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 define 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 Thallium-201 results in the same group of patients who had no left main lesions.

Regarding analysis on a patient basis, similar values 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**

DETAILED REGIONAL WALL FINDINGS ON ABNORMAL THALLIUM-201 SPECT OF 11 PATIENTS WITH LESIONS BETWEEN 50% AND 75% ON CORONARY ANGIOGRAPHY

<table>
<thead>
<tr>
<th>Wall</th>
<th>Fixed defect</th>
<th>Reversible defect</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Lateral</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Inferior</td>
<td>1</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Septal</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Apical</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 4**

THALLIUM-201 SPECT IN ALL VESSELS (n=435) FOR TWO DIFFERENT STENOSIS THRESHOLDS

<table>
<thead>
<tr>
<th>Angiographic Cutoff</th>
<th>Angiographic Cutoff</th>
<th>CI Cutoff ≥ 50%</th>
<th>CI Cutoff ≥ 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>59% (130/220)</td>
<td>70% (108/154)</td>
<td>0.029</td>
</tr>
<tr>
<td>Specificity</td>
<td>78% (168/215)</td>
<td>75% (212/281)</td>
<td>ns</td>
</tr>
<tr>
<td>Accuracy</td>
<td>68% (298/435)</td>
<td>74% (320/435)</td>
<td>ns</td>
</tr>
<tr>
<td>PPV</td>
<td>73% (130/177)</td>
<td>61% (108/177)</td>
<td>0.017</td>
</tr>
<tr>
<td>NPV</td>
<td>65% (166/256)</td>
<td>82% (212/258)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.
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 ≥ 50 % or ≥ 70 %, using SPECT and Tc-99m sestamibi. Montz et al, in 144 patients using Tc-Tetrofomisin, found similar sensitivity and accuracy for ≥ 50 % (97 % and 82 %, respectively) and ≥ 75 % (94 % and 87 %, respectively).

As far as individual vessel analysis, it was found that Thallium-201 SPECT, had better sensitivity at ≥ 75 % threshold. It is known that detection of coronary lesions is easier when blood flow impairment is greater. DePascuale et al, using Thallium-201 found that sensitivity of quantitative myocardial perfusion SPECT for individual vessels was 95 % in ≥ 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 ≥ 50 % to 91 % at 45 %). Mahmarian et al, in relation to sensitivity in individual vessels, found no difference between the thresholds of ≥ 50 % and ≥ 70 %. Again relatively high values of sensitivity with ≥ 50 % stenosis were found.

The group of Sacchetti et al 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 ≥ 75 % threshold, but abnormal with ≥ 50 % threshold. As a consequence, Thallium-201 SPECT specificity was lower compared to ≥ 75 % threshold, due to the fact that these patients are more likely to have an abnormal Thallium-201 SPECT, being true positive for ≥ 50 %, but appearing as false positive when using ≥ 75 %.

Table 5

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Angiographic cutoff</th>
<th>Angiographic cutoff</th>
</tr>
</thead>
<tbody>
<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>51.72 %</td>
<td>57.80 %</td>
</tr>
<tr>
<td>Specificity</td>
<td>65 %</td>
<td>82 %</td>
</tr>
<tr>
<td>CI</td>
<td>52.77 %</td>
<td>72.98 %</td>
</tr>
<tr>
<td>Accuracy</td>
<td>63 %</td>
<td>75 %</td>
</tr>
<tr>
<td>CI</td>
<td>(92/145)</td>
<td>(109/145)</td>
</tr>
<tr>
<td>PPV</td>
<td>72 %</td>
<td>77 %</td>
</tr>
<tr>
<td>CI</td>
<td>61.83 %</td>
<td>64.87 %</td>
</tr>
<tr>
<td>CI</td>
<td>(54/74)</td>
<td>(65/80)</td>
</tr>
<tr>
<td>NPV</td>
<td>53 %</td>
<td>76 %</td>
</tr>
<tr>
<td>CI</td>
<td>41.65 %</td>
<td>66.85 %</td>
</tr>
<tr>
<td>CI</td>
<td>(38/71)</td>
<td>(65/85)</td>
</tr>
</tbody>
</table>

All other comparisons: p = NS. *NPV were significantly higher for LAD and CX with ≥ 75 % (p ≤ 0.02).

CI: 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 201TI 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 with 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 no 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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We thank Mr. Rodrigo Villegas and Dr. Héctor Gatica for their statistical assistance and to Ms. Nancy Garces, Medical Technologist at University of Chile, for her important collaboration.

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