Indication of Myocardial Perfusion Scintigraphy for Coronary Artery Disease Detection Based on Clinical-Epidemiological and Treadmill Test Evidence

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Objective: To establish when the myocardial perfusion scintigraphy (MPS) should be performed based on well-defined information obtained from treadmill test results and clinical-epidemiological parameters for coronary artery disease (CAD).

Methods: 2,100 patients who underwent MPS were classified according to the results of scintigraphy, the Duke score and a clinical-epidemiological score based on Framingham study. The patients with positive results on MPS were followed to define whether the results were true positives. Receiver operating characteristic (ROC) curves were used to establish the efficiency and the best Duke and clinical-epidemiological scores to define patients that should be submitted to scintigraphy.

Results: It was observed that the MPS use restriction in patients with Duke score below 7.5 and/or clinical-epidemiological score above 4 could decrease the utilization of this method by 50% without exposing the patients to a significant misdiagnosis risk.

Conclusion: The utilization of the Duke score and a clinical-epidemiological score to classify the patients expressively decreased the number of unnecessarily requested scintigraphies.

Key words: Coronary artery disease, perfusion scintigraphy, treadmill, epidemiology, Duke score.

In recent years, expenses with healthcare assistance, for patients as well as healthcare providers (health insurance suppliers and companies and governmental organs) have progressively increased[1,2]. Part of this increase of expenses is due to the large amount of technological resources utilized in diagnostic and therapeutic processes[3]. This increasing problem, which has for long generated debate in developed countries, is even more worrying in developing countries, such as Brazil, whose entire available financial resources for healthcare expenditure is lower, and for which the wasting of such resources will generate further problems. Therefore, if the discussion about how to rationalize the use of diagnostic and therapeutic resources has become constant in developed countries, it is important that this discussion be even more intense in countries such as Brazil, as the rampant use of these resources will bring consequences that will be even more significant for such countries.

Coronary Artery Disease (CAD) is one of the main causes of mortality and morbidity in the world[4]. Its diagnosis is important, in order to establish the necessary treatment and prevent the consequences of the disease. Nevertheless, the diagnosis of this pathology has become very complex due to the multiple exams that can be performed, the imperfections that are inherent to every diagnostic method, and the difficulty to integrate the results of such procedures, not only among them but also with further evidence from the analysis of epidemiological factors and the patient's clinical history.

Due to the high prevalence and incidence of this disease, the amount of resources spent in its diagnosis is quite large. It is estimated that more than a million patients were submitted to coronary angiography in 1993 in the USA, which will increase to 3 million in 2010[5]. According to data published at the ACC/AHA Guidelines for Exercise Testing (guidelines published by the American College of Cardiology/American Heart Association about the protocol for treadmill test)[6] only in the year 1996, MEDICARE was responsible for the payment of approximately 875,000 simple treadmill tests, 889,000 myocardial perfusion scintigraphies, 213,000 stress echocardiograms, and 728,000 coronary angiographies. Thus, if one considers the large number of procedures performed, the complexity of the analysis of such procedures and the difficulty to integrate the results obtained, the potential waste of resources that can take place in an attempt to diagnose CAD can be perceived. In addition to the waste of resources, when these are used inadequately, it is important to remember that, due to the fact that the accuracy of most diagnostic methods utilized for CAD is not perfect, i.e., the method specificity as well as its sensitivity are not 100% guaranteed, the diagnostic performance will depend not only on these two factors, but also on the pre-test probability of the disease[7]. Therefore, the positive predictive value of a test with specificity < 100% in a population with low prevalence of the disease can be so low that its utilization will not be justified.

Thus, when an expensive diagnostic exam is utilized in a population with a low probability of the disease, resources are being wasted, as it is known, beforehand, that the great majority of patients do not have the disease; there is a chance that patients without the disease, but who had false-positive results, will be referred to further unnecessary

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exams or procedures that can include invasive ones, which, in addition to generating more expenses, can also be the cause of morbidity or mortality. In an attempt to decrease such problems, the Cardiology Societies and research groups have strived to produce guidelines and diagnostic algorithms, with the aim of helping doctors decide upon requesting several exams, interpreting them and integrating the results obtained, as well as establishing a "hierarchy" for these requests, with the objective of defining the diagnosis from simpler and more affordable techniques (such as the clinical-epidemiological history and physical examination) and progressively increase the complexity and costs involved, as they are justified, by the pre-test probability of the disease.

Several research groups have published studies proposing algorithms aimed at establishing the best diagnostic strategy for CAD[8-12].

In spite of the work developed by these groups attempting to organize the diagnostic strategies of coronary artery disease, the information available has been sub-utilized by a large number of physicians, due to the difficulty to define objective criteria that can suggest the need to progress in the proposed diagnostic algorithms.

One of the main non-invasive methods for the detection of obstructive coronary disease and that is present in most of the proposed algorithms is the myocardial perfusion scintigraphy. However, this is an expensive diagnostic method and must be utilized when the analysis of the clinical-epidemiological factors and results of the treadmill test do not significantly decrease the probability of obstructive coronary disease[8-12]. Therefore, it is important to define objective criteria, based on the analysis of clinical-epidemiological factors as well as the results of the treadmill test, which can be used to indicate the necessity of performing a myocardial perfusion scintigraphy.

The aim of this study is to evaluate when myocardial perfusion scintigraphy exams must be carried out, based on the information obtained from the treadmill test and the analysis of clinical-epidemiological factors for coronary disease.

Methods

A group of 2,100 patients, referred for diagnostic assessment of obstructive coronary disease, was studied through treadmill test and myocardial perfusion scintigraphy results, from August 200 to July 2003. This group represented around 33% of the approximate 6,400 patients that underwent myocardial perfusion scintigraphy associated to the treadmill test or pharmacological stimulation test with dipiridamol, during the aforementioned period.

Patients who presented established diagnosis of coronary artery disease, such as myocardial infarction, cardiac revascularization, angioplasty and coronary angiography with a diagnosis of obstruction, were excluded from the study. Patients with alterations at the electrocardiogram at rest that suggested a previous infarction were also excluded.

All patients in the study group underwent myocardial scintigraphy by means of physical stress, and reached at least 85% of the maximum cardiac frequency expected for age during the treadmill test. Patients who presented confounding factors at the treadmill test such as pacemaker use, left bundle branch block, persistent atrial fibrillation, complex ventricular arrhythmia, Wolf-Parkinson-White, or any other electrocardiographic pattern that can alter the accuracy of the test were also excluded.

Of these 2,100 patients, 86 presented myocardial perfusion scintigraphy results that were interpreted as being abnormal.

The follow-up control of 84 of the 86 patients with scintigraphy results considered abnormal was carried out, and the remaining two could not be contacted despite several attempts by phone.

Thirty-seven (44%) of these patients presented minor events during follow-up (myocardial revascularization surgery or angioplasty), and two of them also presented major events (infarction). The remaining 47 patients did not present events during follow-up.

The mean time between the exam and follow-up was 20 months, with a range of 9 to 40 months for patients who did not present events and 1 to 30 months for those who did.

The clinical-epidemiological variables used in the analysis were: age, gender, arterial pressure, cholesterol levels, diabetes, smoking and the presence of precordial pain and its characteristics.

The epidemiological parameters were chosen based on the "Statement of Healthcare Professional from the American Heart Association and the American College of Cardiology"[13], which is based on the data of Framingham's study.

The information about age, gender and the presence of risk factors (diabetes, smoking and precordial pain) were obtained from the clinical assessment that preceded the treadmill test.

The information on the cholesterol levels were obtained from the patient's electronic medical file and total cholesterol as well as HDL-cholesterol levels were considered. Arterial blood pressure was measured before the treadmill test with the patient on the orthostatic position.

These parameters were joined using a variation of the score established at the "Statement of Healthcare Professional from the American Heart Association and the American College of Cardiology"[13] for the classification of cardiovascular pathology risk.

The modification of the initial score was carried out with the objective of integrating the precordial pain criteria to the score, as well as adjusting it to our population.

This adjustment was based on the analysis of the impact that the aforementioned risk factors have on the diagnosis of our patients.

In a previous study, presented at the V Ibero-American Symposium of Nuclear Cardiology[14], a retrospective analysis on the frequency of myocardial perfusion scintigraphy with different degrees of alteration was carried out in a group of 3,805 consecutive patients. Using the Chi-square test, the association between alterations at the scintigraphy and some risk factors for coronary disease was analyzed (Tab. 1).

It was observed that diabetes and typical pain are associated with a significant increase in the frequency of alterations at the myocardial perfusion scintigraphy. Dyslipidemia is associated

to a slight increase in the frequency of scintigraphy alterations. It appears that smoking, systemic arterial hypertension and family history are not associated with the increased frequency of alterations in myocardial perfusion.

Based on this previous study, the adaptation of the scores obtained through the analysis of the Statement of Healthcare Professional from the American Heart Association and the American College of Cardiology[13] was carried out, resulting in the values shown in Table 2, ranging from –8 to +26.

The treadmill test (TT) was performed according to Bruce, modified Bruce, and Ellestad protocols; Duke score was used for test classification. The one-day protocol with Sestamibi-[Tc-99m] (MIBI), at resting and peak exercise phases was utilized for the acquisition of tomographic images (Single Photon Emission Tomography - SPECT) of myocardial perfusion. Images at rest were acquired 30 min after the injection of 370 MBq (10 mCi) of MIBI. The stress phase was performed 4 hours after the rest phase. Cardiac stress was induced by programmed exercise on a treadmill, using one of the following aforementioned protocols: Bruce, modified Bruce, or Ellestad. During the exercise peak, or when the patient presented exercise-limiting symptoms, 1.11 Gbq (30 mCi) of MIBI were injected i.v. The images were acquired 45 to 60 min after the injection, with and without attenuation correction. The stress images were acquired in synchrony with the patient's electrocardiogram (Gated technique), which allows the simultaneous assessment of the left ventricle motility at this exam phase.

In cases where the perfusion defect was debatable (suspected attenuation artifacts), the nuclear physicians also analyzed the images with attenuation corrections and the images that represented the myocardial motility, in order to increase the diagnosis specificity. ROC (Receiver Operating Characteristic) curves were used to select the values of Duke and clinical-epidemiological scores that should be used to define whether the patient had to be submitted to scintigraphy. The statistical software SPSS® was used to calculate the areas under the curve and their confidence intervals, and define the sensitivity and specificity of each score value. In this study, the fixed and/or transient perfusion defects established by the visual analysis of the nuclear doctors and who presented events during follow-up were considered to be positive (37 patients).

Results

The distribution of the scintigraphy results in relation to the clinical-epidemiological and Duke scores is shown in the dispersion diagram presented in Figure 1. The developed clinical-epidemiological score presents an area below the ROC curve of 0.84 (95% CI: 0.78-0.90) (Fig. 2). The specificity and sensitivity levels for some clinical-epidemiological score values are shown in Table 3. Duke score presents an area below the ROC curve of 0.85 (95% CI: 0.81-0.90) (Fig. 3). The specificity and sensitivity levels for some Duke score values are shown in Table 4. The Duke score performance in those patients with higher probability of presenting coronary disease after the clinical-epidemiological evaluation was also assessed, i.e., the Duke analysis was restricted for those patients that presented clinical-epidemiological score > 4 (Tab. 3). For this population, Duke score presents an area below the ROC curve of 0.84 (95% CI: 0.79-0.89) (Fig. 4). The specificity and sensitivity levels for some Duke score values in a population with a clinical-epidemiological score > 4 are shown in Table 5.

Discussion

The initial analysis of the patients evaluated in this study show the importance of creating effective mechanisms to define when a myocardial perfusion scintigraphy must be requested. Of the 2,100 patients studied in this work, only 86 (4%) presented alterations at the myocardial perfusion scintigraphy, and of the latter, only 37 presented coronary disease that was confirmed during follow-up. Thus, if one considers the cost of a myocardial

Risk factor	NP	SD	MD	AD	p
NO SAH	80.7%	9.7%	3.8%	5.7%	
SAH	76.3%	10.5%	5.2%	7.9%	p=0.28
NO DIAB	81.0%	9.1%	4.1%	5.8%	
DIAB	62.4%	16.8%	7.0%	13.8%	p<0.001
NO SMO	78.5%	10.3%	4.5%	6.6%	
SMO	79.8%	9.0%	4.0%	7.2%	p=0.64
NO DYSL	81.2%	9.2%	3.9%	5.7%	
DYSL	75.3%	11.3%	5.3%	8.1%	p<0.001
NO FH	78.0%	10.0%	4.8%	7.1%	
FH	79.4%	10.1%	4.1%	6.3%	p=0.87
NO TIP	81.0%	9.9%	3.9%	5.2%	
TIP	54.7%	14.5%	12.6%	18.2%	p<0.001

SAH- *systemic arterial hypertension;* DIAB- *diabetes;* SMO- *smoker;* DYSL- *dyslipidemia;* FH- *family history;* TIP- *typical pain;* NP- *normal perfusion;* SD- *slight perfusional defect;* MD- *moderate perfusional defect;* AD- *accentuated perfusional defect.*

Table 1 - Incidence of perfusion defects at the scintigraphy in patients with and without risk factors for obstructive coronary disease

		Risk points	
Risk factors		**Male**	**Female**
Age (yrs)	<34	-2	-6
	35-39	-1	-3
	40-44	1	-1
	45-49	2	1
	50-54	2	1
	55-59	3	2
	60-64	3	2
	65-69	3	2
	>70	4	4
Total cholesterol (mg/dl)	<169	-1	-1
	169-199	1	0
	200-239	1	1
	240-279	2	1
	>279	2	2
HDL cholesterol (mg/dl)	<35	3	2
	35-44	1	1
	45-49	1	1
	50-59	0	0
	>59	0	0
Systolic pressure (mmHg)	<120	0	-1
	120-129	0	0
	130-139	1	1
	140-159	2	1
	>160	3	3
Diabetes	No	0	0
	Yes	4	6
Smoker	No	0	0
	Yes	2	2
Precordial Pain	No	0	0
	Atypical	0	0
	Typical	8	6

Table 2 - Clinical-epidemiological scores adapted to our population

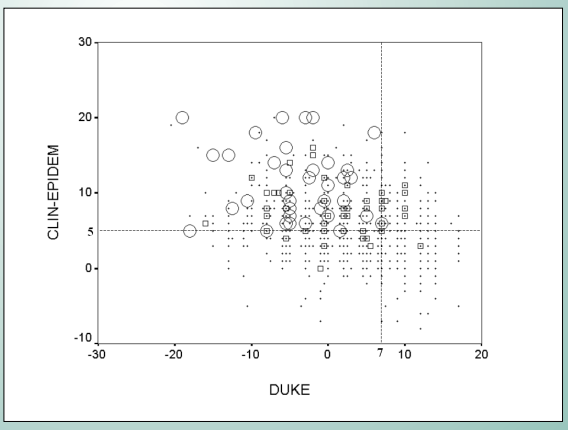

Fig. 1 *- Dispersion diagram showing the distribution of scintigraphy results regarding the clinical-epidemiological scores (Y axis) and Duke score (X axis). The altered scintigraphies that presented events during the follow-up are represented by circumferences. The altered scintigraphies that did not present events are represented by squares. The dots represent normal scintigraphies. The dotted lines limit the score levels beyond which no altered scintigraphies that presented events during follow-up were observed.*

CE Score	Sensitivity	Specificity
3.5	1.00	0.23
4.5	1.00	0.37
5.5	0.92	0.52
6.5	0.81	0.65
7.5	0.70	0.77
8.5	0.62	0.85
9.5	0.51	0.91
10.5	0.49	0.93
11.5	0.46	0.95
12.5	0.38	0.97
13.5	0.30	0.98
14.5	0.24	0.99
15.5	0.19	0.99
16.5	0.16	0.99
17.5	0.16	1.00
18.5	0.11	1.00
19.5	0.11	1.00
21	0.00	1.00

Table 3 - Sensitivity and specificity levels of the different clinical-epidemiological (CE) score for the indication of true positive scintigraphies Tabela 3 - Valores de sensibilidade e especificidade dos diferentes valores de escore clínico-epidemiológico (CE) para a indicação de cintilografias verdadeiras positivas

perfusion scintigraphy (around R$1,000 reais or 440 US dollars), the detection of patients with altered scintigraphy results who presented events at the follow-up will cost more than R$ 50,000 reais (approximately 21,000 US dollars). When we evaluate the dispersion diagram shown in Figure 1, it is clear that patients with high Duke scores or low clinical-epidemiological scores rarely present positive scintigraphy, and the performance of this exam is little indicated. If the patients who presented clinical-epidemiological score < 5 were excluded from the coronary disease investigation, around 35% of them would not be submitted to the myocardial perfusion scintigraphy or even the treadmill test; such procedures would have been

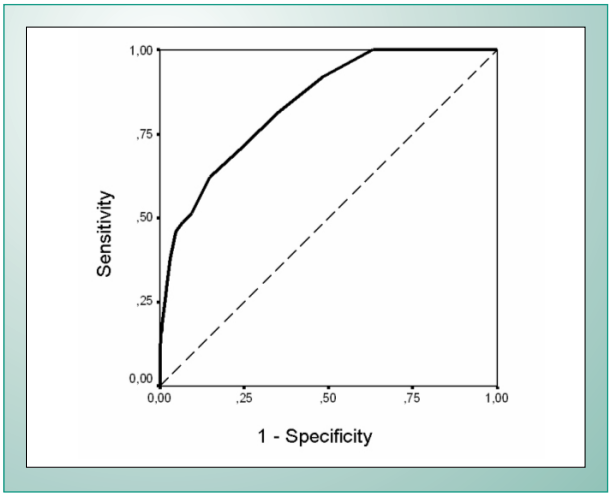

Fig. 2 - *ROC curve showing sensitivity versus "1 – specificity" of the different values of the clinical-epidemiological score for the detection of patients with altered scintigraphy and who presented event during follow-up.*

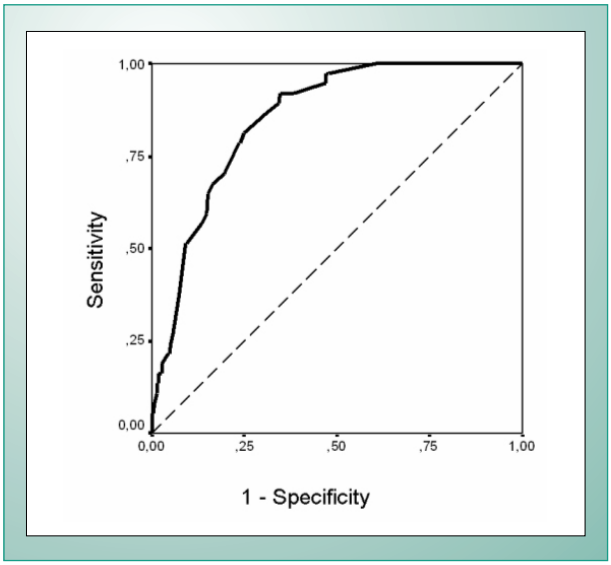

Fig. 3 - *ROC curve showing sensitivity versus "1 – specificity" of the different values of Duke score for the detection of patients with altered scintigraphy who presented event during the follow-up.*

predominantly unnecessary, as none of the patients considered to be positive presented a clinical-epidemiological score below this value (100% sensitivity at Table 3) and around 35% of the patients considered negative have a score below this value (37% specificity in Table 3). Even if more conservative criteria were used to exclude the patients with clinical-epidemiological score < 4, around 25% of them could do without the exam (23% specificity in Table 3). The same can be said of patients who present Duke score > 7.

If the investigation for obstructive coronary disease were called off in patients with Duke score above this value, the procedure would be prevented in 35% of them, with a minimal risk of not investigating patients with significant coronary disease; this is confirmed in Table 4, which shows that none of the patients considered to be positive presented a Duke

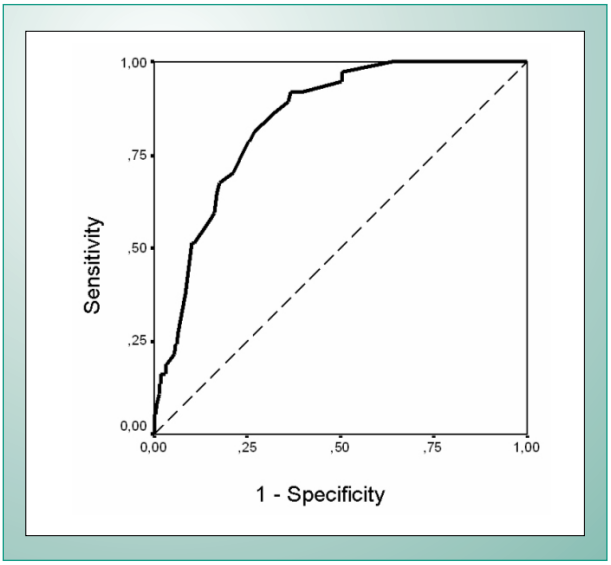

Fig. 4 - *ROC curve showing sensitivity versus "1 – specificity" of the different values of Duke score for the detection of patients with altered scintigraphy who presented event during follow-up in a population that presents a clinical-epidemiological score >4.*

score > 7 (100% sensitivity in Table 4) and that around 35% of the negative exams presented a clinical-epidemiological score above this value (36% specificity in Table 4).

Thus, the development of a clinical-epidemiological score based on Framingham and the analysis of its performance using a ROC curve allows the physician to estimate the appropriateness of proceeding with the patient's investigation and the risks of not performing such investigation. As mentioned before, patients with a clinical-epidemiological score < 5 have a low risk of presenting scintigraphy alterations and events, and so, the physician can choose to stop the investigation and re-evaluate such patients at a later date. Patients with a score above this value have a higher risk of presenting obstructive coronary disease and the physician must strive to proceed with the investigation, as much as possible. When the resources are limited, the physician can choose a score with a slightly lower sensitivity, but with a higher specificity, being aware that some diagnostic loss will occur. By using a score > 6, for instance, the sensitivity will be between 75% and 85%, and the specificity will be around 65% (Tab. 3). When the physician decides to carry on the investigation, it might be worth to submit the patient to the treadmill test, as, in comparison to other non-invasive exams, this is the least expensive and the simplest one to be performed. According to data published at the ACC/AHA Guidelines for Exercise Testing[6] based on MEDICARE information, the cost of a treadmill test is around 20% of that of a myocardial perfusion scintigraphy, 40% of a stress echocardiogram and 5% of a coronary angiography.

Based on our results, the Duke score presented a good performance in separating patients with altered scintigraphy results and events at the follow-up from the remaining patients. The area below the ROC curve for this score was 0.85 (95% CI: 0.81-0.90).

As previously mentioned, the main application of Duke would not be for the whole group of patients, but for those

whose risk of obstructive coronary disease had not been significantly decreased by the clinical-epidemiological analysis. For the patients with a clinical-epidemiological score > 4, if the investigation were carried on only in those patients with Duke score < 7.5, approximately 35% of these patients would not undergo further exams, with no significant risk for diagnostic loss (Tab. 5). If the patients with Duke score > 3 were excluded from the investigation, 60% of these patients would not undergo further exams, with a high sensitivity (around 90%) for the detection of those with altered scintigraphy results who presented events (Tab. 5).

Therefore, if both scores were utilized to define the appropriateness of performing the scintigraphy, approximately 55% of the patients from the studied population would not be submitted to this exam, with a minimal risk for diagnostic loss. This would reduce the costs of positive scintigraphy detection that presented event from R$50,000 reais to around R$20,000 reais, which obviously would bring a great economy of costs for the healthcare system. A possible criticism for this study is the fact that positive scintigraphies that presented event were classified as true positive ones, whereas the 47 scintigraphies without events were classified as false positives. Given that the minimal follow-up period was 9 months, one cannot be sure that some of these scintigraphies are really false positive ones, as not all these patients were submitted to cardiac catheterism. However, when looking at the dispersion diagram, one can notice that most positive scintigraphies (approximately 75%) that did not present events showed Duke and clinical-epidemiological scores within the region established as pertinent for the carrying out of the scintigraphy (CE > 4 and Duke < 7.5), which would have had very little influence on this work results had they been false-positive ones. Only 12 patients (approximately 25%) presented a clinical-epidemiological score < 5 or Duke score > 7 in this group. Of these, three

Duke score	Sensitivity	Specificity
-19.75	0.00	1.00
-18.5	0.03	1.00
-15.5	0.05	1.00
-14	0.08	0.99
-12.75	0.11	0.99
-10.75	0.14	0.98
-10.25	0.16	0.98
-9.75	0.16	0.97
-8.25	0.19	0.97
-7.25	0.22	0.95
-6.25	0.24	0.95
-5.25	0.38	0.93
-3.25	0.51	0.91
-2.25	0.59	0.85
-1.5	0.65	0.85
-0.25	0.70	0.81
0.25	0.78	0.77
1.25	0.78	0.76
2.25	0.86	0.69
2.75	0.89	0.66
3.5	0.92	0.65
5.25	0.95	0.53
5.75	0.95	0.53
6.25	0.97	0.53
6.75	0.97	0.52
7.25	1.00	0.39
7.75	1.00	0.39

Table 4 - Sensitivity and specificity levels of the different Duke score values for the indication of true positive scintigraphies

Duke score	Sensitivity	Specificity
-19.75	0.00	1.00
-18.5	0.03	1.00
-15.5	0.05	1.00
-14	0.08	0.99
-12.75	0.11	0.99
-10.75	0.14	0.98
-10.25	0.16	0.98
-9.75	0.16	0.97
-8.25	0.19	0.97
-7.25	0.22	0.94
-6.25	0.24	0.94
-5.25	0.38	0.92
-3.25	0.51	0.89
-2.25	0.59	0.84
-1.5	0.65	0.83
-0.25	0.70	0.79
0.25	0.78	0.75
1.25	0.78	0.74
2.25	0.86	0.67
2.75	0.89	0.64
3.5	0.92	0.63
5.25	0.95	0.50
5.75	0.95	0.50
6.25	0.97	0.50
6.75	0.97	0.49
7.25	1.00	0.36
7.75	1.00	0.36

Table 5 - Sensitivity and specificity levels of the different Duke Score values for the indication of true positive scintigraphies. in the group of patients with a clinical-epidemiological score > 4

underwent coronary arteriography, with no significant coronary disease; three did not present events during a period of over 30 months; one presented asymmetric septal hypertrophy, thus the ischemia was due to an increased myocardial demand and not to coronary disease. Two presented negative scintigraphy a few months later, with the former scintigraphy being considered false positive. The three remaining patients did not present events after 14 months of follow-up. Hence, the positive scintigraphies in patients with high Duke scores and low clinical-epidemiological scores must correspond, most of the times, to false-positive exams, corroborating the considerations depicted in the Introduction, i.e., that exams with specificity < 100% carried out in a population with low pre-test probability of the disease have a great likelihood to present false-positive results. Additionally, even if some of these results are true positive ones, they must represent coronary alterations with a better prognosis, as none of them presented coronary events at the follow-up. Thus, when the scintigraphy is not carried out in these patients, they are not being exposed to a considerable event risk. Another point to be discussed is the lack of follow-up of patients with normal scintigraphy results. Although this segment is important for the knowledge of the prognostic value of a normal scintigraphy result (these data have been extensively demonstrated in previous studies[15-19]) this follow-up is irrelevant for the objectives of this work, as the main purpose here is to determine, before the scintigraphy is carried out, which patients have a higher probability to present a true positive result, and consequently, whether the negative scintigraphy result is false or true, it will not affect the findings of this work.

Conclusion

The use of well-defined criteria based on Duke score and the clinical epidemiological score can be of great help for the clinician upon requesting a myocardial perfusion scintigraphy, thus preventing a large number of unnecessary exams, with no significant risk for diagnostic loss.

Potencial Conflict of Interest

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

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