

Prognostic Usefulness of Low Ischemic Risk SPECT in Non-ST Segment Elevation Acute Coronary Syndromes

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SUMMARY

Background

Myocardial perfusion imaging tests are used for the clinical assessment of patients hospitalized with non-ST segment elevation acute coronary syndromes (NSTACS) who have favorable in-hospital outcomes with medical therapy. However, the prognostic relevance of a “low ischemic risk” (LR) single photon emission computed tomography (SPECT) in patients with NSTACS managed with a conservative approach is uncertain, as most of the information derives from patients with chronic coronary artery disease.

Objectives

1) To analyze the outcomes of patients with NSTACS and LR SPECT at discharge, 2) to compare the results of a normal SPECT with transient perfusion defects (TPDs), permanent perfusion defects (PPDs) or combined defects (CPDs), and 3) to determine the additional value of SPECT to classic risk variables.

Material and Methods

Patients admitted to the CCU with a NSTACS were included. Follow-up was continued during 12 months. Definitions: Clinical risk based on TIMI risk score. LR SPECT (under exercise or pharmacological stress): TPDs $\leq$ 3/17 segments, PPDs $\leq$ 3/17 segments, CPDs: TPDs + PPDs and normal: absence of defects. Clinical events (CEs): death/infarction or rehospitalization due to angina.

Results

A total of 137 patients were included (median age 59 years, 60% were men). A low TIMI risk score was present in 54% of patients and 46% presented a moderate risk. CE: 5.8%. The incidence of clinical events related to perfusion defects was as follows: normal: 2.1%, TPD: 4.5%, PPD: 5.9% and CPD: 25% ($p < 0.02$). At multivariate analysis, which included age, previous myocardial infarction, TIMI risk score and TPD, only CPD was identified as an independent variable for CEs: OR 7.8 (95% CI 1.2-49); $p = 0.02$. Positive predictive value, negative predicted value, positive likelihood ratio and negative likelihood ratio were 25%, 96%, 5.3 and 0.7, respectively.

Conclusions

A LR SPECT is useful for the prognostic assessment of patients with low or moderate risk NSTACS, as it identifies a population with a low incidence of CEs during the first year. The presence of CPD individualizes patients with worse outcomes which is important at the moment of decision-making.

Key Words >

Myocardial Ischemia - Nuclear Medicine - Prognosis

Abbreviations >

LR	Low risk	NSTACS	Non-ST segment elevation acute coronary syndrome
CK	Creatine Kinase	SPECT	Single photon emission-computed tomography
CK-MB	Creatine Kinase MB fraction	CCU	Coronary care unit
CPD	Combined perfusion defect	PPD	Permanent perfusion defect
TPD	Transient perfusion defect	NPV	Negative predictive value
ECG	Electrocardiogram	PPV	Positive predictive value
AMI	Acute myocardial infarction		

BACKGROUND

Evidence from randomized trials including thousands of patients suggests a reduction in long-term adverse outcomes in patients with non-ST segment elevation acute coronary syndromes (NSTACS) assigned to an early invasive strategy; however, this approach is associated with greater in-hospital mortality, (1, 2). For this reason, it is important to determine the risk status of patients at presentation before decision-making. Despite the published evidence, several registries have noted that revascularization procedures are overused, generally based on the experience of the center or on particular interpretations of the results of randomized trials. These procedures are associated with a greater incidence of complications (AMI/mortality), especially in the subgroup of patients with low to moderate risk at presentation. (3-5) Myocardial perfusion imaging tests using echocardiography or radionuclides are used for the clinical assessment of patients hospitalized with NSTACS who have favorable in-hospital outcomes with medical therapy. However, there is not enough evidence regarding the real prognostic value of myocardial perfusion tests in this population, as most of the information derives from patients with chronic coronary artery disease. The goals of our study were: 1) to analyze the outcomes of patients with NSTACS and LR SPECT at discharge; 2) to compare the results of a normal SPECT with transient perfusion defects (TPDs), permanent perfusion defects (PPDs) or combined defects (CPDs); and 3) to determine the additional value of SPECT to classic risk variables.

MATERIAL AND METHODS

From January 2004 to April 2006, we prospectively included 137 patients consecutively admitted to our coronary care unit (CCU) with a NSTACS and low or moderate risk at presentation who underwent early conservative strategy. During hospitalization these patients did not present complications and were eligible to undergo SPECT (under exercise or pharmacological stress) before discharge. Patients were excluded if they presented AMI (n = 1), recurrent angina (n = 13) or died (n = 1) during hospitalization; other exclusion criteria were history of hospitalizations due to congestive heart failure (n = 8), atrial fibrillation (n = 2), frequent ventricular premature beats (n = 4), left bundle branch block (n = 2), coronary artery revascularization (either by surgery or percutaneous coronary intervention) within the previous year (n = 10), and angina associated with ST-segment changes and extensive perfusion defects (> 3 segments) in the SPECT before discharge (n = 5). Stratification of NSTACS was defined according to TIMI score: a score of 1-2 was considered low risk and a score between 3 and 5 was defined as moderate risk. (6) In 4/137 patients a non Q-wave AMI was diagnosed according to the classic definition of infarction. Acute myocardial infarction was defined as angina lasting more than 20 minutes with one the de following criteria: 1) CK/CK-MB elevation two times above the upper normal limit, and, 2) development of new Q waves 24 hours from symptoms onset in two contiguous leads. Rehospitalization was defined as angina associated with electrocardiographic changes (ST-segment shifts or negative T waves). Exercise

stress test was performed using a symptom-limited Bruce protocol. Pharmacological stress was carried out using the conventional protocols with dipyridamole (0.56 mg/kg in 4 minutes) or dobutamine (intravenous infusion up to a maximum of 40 γ /kg). The test was considered positive if ischemic symptoms and ST-segment depression > 1mm or greater developed.

Gated-SPECT images were obtained from an ADAC GENESIS gamma camera using a processor Pegasys/Veccsa, along a 180° orbit using step and shoot method with 32 projections per detector and 40 seconds per projection. Dose of 99mTc sestamibi ranged from 15 to 30 mCi according to patient's weight.

Images were evaluated based on a semiquantitative visual analysis using a validated model of 17 segments: 16 segments in the short-axis view and 1 segment in the vertical long-axis (apical) view; 4 apical, 6 mid-ventricular and 6 basal segments were considered in the short-axis view. Low ISCHEMIC risk SPECT was defined by the presence of: 1) transient perfusion defects (TPDs) in ≤ 3 segments, 2) permanent perfusion defects (PPDs) limited to ≤ 3 segments, 3) combined defects (CPDs) (TPDs + PPDs) ≤ 6 segments; and, 4) normal perfusion (absence of perfusion defects). No complications related to exercise or pharmacological stress were reported during the study. Follow-up was performed by telephone contact 3, 6 and 12 months after discharge. Mortality, myocardial infarction or rehospitalizations due to angina were recorded. Only 3 (2.1%) patients out of 137 were lost from follow-up at 1 year.

Statistical Analysis

Quantitative and qualitative variables were evaluated with ANOVA and chi-square test, respectively. Significant variables underwent multivariate logistic regression analysis. All calculations were performed using Epi-Info 3.4.1 and Statistix 7 software packages.

RESULTS

The demographic characteristics of the study population are described in Table 1. A low TIMI risk score was present in 54% of patients and 46% presented a moderate risk. The percentage of patients with electrocardiographic changes at admission or during hospitalization was 70%, and 4.7% had positive troponin. Medical treatment included aspirin (100%), clopidogrel (30%), heparin (44%), beta blockers (77%), calcium channel blockers (10%), statins (43%) and angiotensin-converting enzyme inhibitors (30%).

The SPECT scan was performed within a median of 2 days (1-3). Exercise stress test was used in 83% of studies, while dipyridamole and dobutamine were used in 16% and 1% of patients, respectively. Exercise stress test was positive in 9% of patients, negative in 59% and 32% of studies were inadequate to rule out ischemic heart disease. The peak exercise workload achieved by 75% of patients ranged between 450 and 750 kgm. Table 2 describes the perfusion defects and their correlation with the presence of events. It should be mentioned that 66% of patients presented some kind of perfusion defect, while perfusion was normal in the remaining patients. The incidence of total events at one year was 5.8% (8/137 patients): mortality (n = 1),

Table 1. Basal characteristics of the population (n = 137)

Median age (years)	59
Male gender	60%
Hypertension	60%
Diabetes	26%
Dyslipemia	49.5%
Current smoking	31%
FH	7%
Previous AMI	9%
Previous angina	17%
Previous angioplasty	6%
Previous CABGS	4%
Previous aspirin	43%
Previous BB	28%

FH: Family history. CABGS: Coronary artery bypass graft surgery
BB: Beta blockers

Table 2. Perfusion defects and events after one year

SPECT	Normal (%)	DT (%)	DP (%)	DC (%)	p
n	47 (34)	44 (32)	34 (25)	12 (9)	
Events (%)	2	4.5	6	25	0.02
S (%)		25	25	37.5	
SP (%)		67.5	75	93	

S: Sensitivity SP: Specificity. TPD: Transient perfusion defects. PPD: Permanent perfusion defects. CPD: Combined defects.

myocardial infarction (n = 3) and rehospitalization due to angina in 4. Patients with normal perfusion had an incidence of events of 2%, while it was higher, though no significant, in patients with transient and permanent defects (4.5% and 6%, respectively). The incidence of events at one year was greater in the group of patients with combined defects (n = 12, 3/12, 25% versus 5/125, 2.4% in patients without combined defects; OR 95% CI 8 (1.2-49); $p < 0.05$). This difference was also significant when they were compared to the population with normal perfusion (2% versus 25%; $p < 0.02$). Patients with combined defects had more frequently a past medical history of coronary artery disease (revascularization surgery/percutaneous coronary interventions and myocardial infarction 58% versus 12.8%; $p < 0.001$) without other differences in demographics, risk factors or clinical presentations, included electrocardiographic changes (at admission and during hospitalization) or elevation of biomarkers (CK or troponins) compared to patients without combined defects. Figure 1 illustrates multivariate analysis which included age, TIMI risk score, previous AMI, TPDs

and CPDs; only the presence of CPDs was identified as a dependent variable to predict risk of events (OR 7.8 95% CI, 1.2-49; $p = 0.02$). Positive predictive value (PPV), negative predicted value (NPV), positive likelihood ratio and negative likelihood ratio were 25%, 96%, 5.3 and 0.7, respectively. Figure 2 shows that 99% of patients without CPDs were free from events at one year compared to 76% of patients with CPDs (log-rank test = 0.006).

DISCUSSION

The incidence of in-hospital cardiovascular events of NSTACS is low particularly due to progress in antithrombotic therapy. Several scores have emerged with the goal of stratifying the clinical risk at admission and determining the best therapeutic strategy. According to the bibliography, the TIMI risk score is the most frequently used. When the TIMI risk score was developed in a selected population of patients with NSTACS, its application evidenced that only 10% were high risk patients (mortality/AMI: 19.4%) while 90% were at low to moderate risk of events, and the incidence of the composite end point of mortality/AMI was 3% and 11%, respectively. It should be mentioned that this is a selected population of patients included in intervention studies and thus does not represent the entire population of patients presenting in daily practice. In fact, the global incidence of AMI and in-hospital mortality in NSTACS patients reported in the last registry performed in our country was 3.8% and 1.7%, respectively. (7) It is difficult to find a decisive prognostic predictive variable in a population with low risk of events; even more, the positive predictive value of the different scores of clinical risk to predict AMI and mortality has proved to be modest (60-70%). (8) Under these limitations, the paradigm of applying interventional strategies to this entire population was associated with greater risk of early mortality. We believe that our decision-making will depend on observing the patient's clinical evolution. The presence of recurrent angina during hospitalization has demonstrated to be a powerful predictor of events and it correlates with a high rate of mortality and AMI. (9, 10) Functional test are important prognostic tools in asymptomatic patients during hospitalization. (11-17) Yet, functional tests before discharge are seldom indicated in our environment (27%); myocardial perfusion scintigraphy is performed in half of the cases and exercise stress test and echo-stress test are indicated in the remaining 50%. (7) According to data from the SAC registry, coronary angiography was indicated in most cases (49%), soon after admission (median: 3 days) despite the population was at low risk of severe events (as we have previously mentioned) and with an incidence of recurrent ischemia of 23%. Even if we consider the hypothetical situation that early coronary angiography was indicated due to high risk at admission (5% to

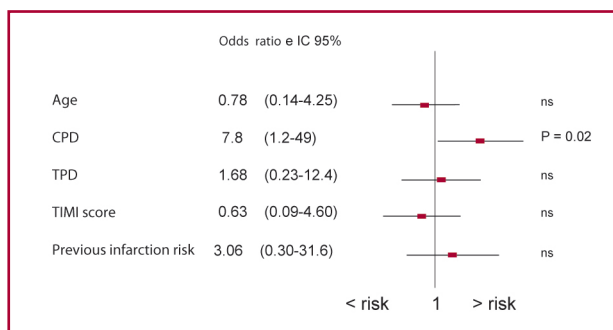


Fig. 1. Multivariate analysis for composite events. TPD: Transient perfusion defects. CPD: Combined defects.

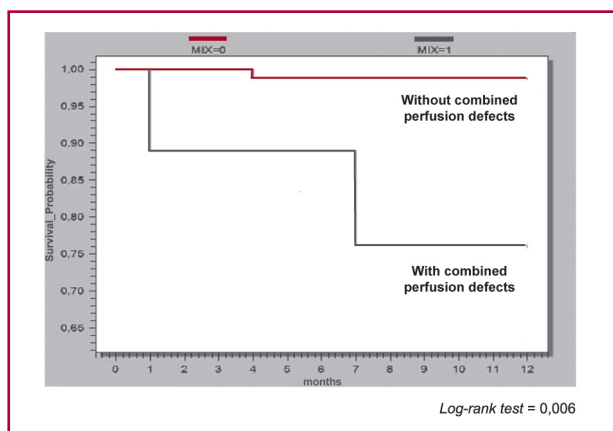


Fig. 2. One-year survival free from events according to the presence or absence of combined perfusion defects.

10% of NSTACS according to the series), there is still a 20% to 30% of patients without a clear indication. The population included in our study had low risk at admission (mortality 1.4%; AMI 2.1%) and after 1 year of follow-up (0.7% and 2%, respectively), and in this type of patients it is difficult to find clinical signs or prognostic functional parameters. However, the presence of combined defects (permanent and transient) allowed us to detect a subgroup of patients at high risk of events (1 to 4) after uncomplicated hospital stay. We consider that this finding is very important as it gave additional information to the prognostic clinical parameters usually used. The ability of combined perfusion defects to predict cardiovascular events may have several explanations. Firstly, CPDs may identify a population with a better delineated coronary artery disease; in this sense, the presence of CPDs proved to have a high discriminatory power to individualize 1 out of 3 patients with events during follow-up, even among those who were more likely to develop adverse outcomes (history of previous coronary artery disease, electrocardiographic changes and positive troponin at admission). Secondly, the sensitivity of rest SPECT to detect infarct areas at admission is greater than that of the classic electrocardiographic or enzymatic variables, and thus this test identifies a subgroup of

patients with greater incidence of events. Finally, SPECT using ^{99m}Tc sestamibi might underestimate the real burden of transient ischemia, a determinant of clinical events during follow-up. In fact, Kong et al. (18) recently reported that in patients with large fixed MIBI defects the addition of a thallium (Tl)-201 study demonstrated significant Tl-201 redistribution (70%), and these patients had significantly higher rate of cardiac events (mortality, infarction and rehospitalization due to angina) after 3 months of follow-up. This finding might be explained by the different physical properties of both radiotracers. Unlike thallium 201, Tc-99m sestamibi uptake is not dependent on active transport and has minimal myocardial redistribution. Hence, it might underestimate ischemic but viable myocardium in patients with reduced regional perfusion. The prognostic value of perfusion scintigraphy has been studied mostly in patients with chronic coronary artery disease. A meta-analysis (19) reported that in 8000 patients with normal exercise SPECT scan (absence of transient or permanent perfusion defects) the risk of the composite event mortality/infarction was 1.2% (NPV: 99%); in addition, the incidence of unstable angina or need for revascularization was 3.4 (NPV: 97%) after 36 months of follow-up. There is scarce information regarding the usefulness of SPECT in NSTACS in the long-term follow-up, and the little data available are not updated despite the level of recommendation (I-C) of practice guidelines. (20-22) Our study suggests that: 1) patients with low to moderate risk NSTACS and a low ischemic risk SPECT have favorable outcomes (NPV: 96%), and 2) SPECT imaging of combined defects (a finding not very prevalent) determines a 5-fold increase in the probability of developing an ischemic event after one year. This finding is useful to individualize high-risk patients in a low-risk population.

Study Limitations

The definition of angina not associated with other variables (ECG or biomarkers) may overestimate the diagnosis of NSTACS. In our population, only 1 out of 3 patients had electrocardiographic changes at admission, and only 5% had positive troponin. We can neither rule out the presence of confounders which might bias the results in such a small population. Yet, this is the population we have to deal with in daily practice: patients with symptoms suggestive of angina and a functional study with a small area of myocardial ischemia. Our experience demonstrates that: 1) this population has a low risk of events with appropriate therapy, as it is well-known, and 2) the presence of combined defects in the SPECT may identify a subgroup of patients with high clinical risk. Most of the evidence regarding the usefulness of SPECT derives from the evaluation of chronic patients, while there is little prognostic evidence of SPECT in populations with low risk NSTACS under full therapy.

Clinical implications

The findings our study provide updated information about the importance of radionuclide studies in the prognostic assessment of low to moderate clinical risk NSTACS patients by determining that the presence of combined defects individualizes patients with worse outcomes and gives additional value to the classic risk cores. This information, frequently underestimated, provides a valuable tool at the moment of decision-making.

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