Diagnostic accuracy and prognostic implications of stress testing for coronary artery disease in the elderly

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Background. **The aim of this study was to define the diagnostic accuracy and the prognostic significance of stress electrocardiography (ECG) and of thallium-201 single-photon emission computed tomography (SPECT) in determining the incidence of coronary artery disease (CAD) in an elderly population.**

Methods. **A selected series of 132 patients (90 males, mean age 72.4 years; 42 females, mean age 68.2 years) hospitalized because of cardiac events associated with suspected CAD, underwent stress ECG and thallium-201 testing; as endpoints we considered the heart rate and the appearance of clinical symptoms or ST segment depression. Patients unable to develop an adequate exercise workload, were tested with dipyridamole. All patients also underwent coronary angiography following the stress test. One hundred and twenty-four patients had a mean follow-up of 2 years. Endpoints included subsequent coronary events or new serious disease. The sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values of both ECG and of thallium-201 SPECT were calculated.**

Results. **ECG findings were positive in 102 patients and coronary angiography confirmed the presence of CAD in 92 of them; ECG findings were negative in 30 patients, but only 14 were free from obstructive coronary lesions. Thallium-201 SPECT findings were positive in 112 patients (coronary angiograms confirmed CAD in 101) and negative in 20 patients (in 13 of whom angiography confirmed the absence of disease). The sensitivity of the stress tests was quite good: 85.1% for ECG and 93.5% for thallium-201 SPECT; conversely, the specificity of ECG was superior to that of SPECT (58.3 vs 54.1%). The sensitivity of both techniques was superior in males than in females and seemed to correlate with the extent of CAD.**

Conclusions. **The diagnostic accuracy of thallium-201 SPECT was 86.3% whereas that of ECG was 80.3%. Considering the overall cardiac events, the predictive value of SPECT was superior to that of ECG both in terms of the positive value (54 vs 51%, p = NS) and, more importantly, in terms of the negative value (84 vs 62%, p < 0.03). In fact, patients with normal thallium images were at low risk for future cardiac events.**

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Introduction

There is evidence that coronary artery disease (CAD) is a major cause of morbidity and mortality in the elderly population[1] and that clinical manifestations are more severe in patients older than 65 years of age[2].

Although autopsy studies have demonstrated a high incidence of CAD in the elderly, a significantly lower percentage of this population presents with clear clinical symptoms during life; epidemiological studies have demonstrated a decline in cardiovascular event-related mortality, but this decline is statistically more significant in younger than in older patients[3,4].

In addition, recent demographic data have suggested that life expectancy is increasing and thus it is reasonable to presume that the elderly population will grow significantly in the near future[5]. Thus, major attention is being paid to the prevalence of cardiovascular disease in this group of subjects, since many studies have shown that high technology procedures, both diagnostic and therapeutic, can be safely and successfully applied to old patients[6-9].

For the past two decades, exercise thallium scintigraphy has been routinely and

successfully used for the detection of CAD and has significantly increased the sensitivity of stress electrocardiography (ECG)[10,11]. In old patients unable to reach the level of exercise necessary in order to test the coronary reserve, pharmacological stress using intravenous dipyridamole has been used as well[12].

Thus the aim of this study was to define the sensitivity, specificity and finally the diagnostic accuracy of stress ECG and of thallium-201single-photon emission computed tomography (SPECT) in the determination of the incidence of CAD and to assess the prognostic significance of such testing in the elderly population.

Methods

Patient population. Between January 1990 through December 1998, 195 patients aged > 65 years were hospitalized because of cardiac events. All patients underwent stress ECG and thallium-201 SPECT testing as well as coronary angiography either for diagnostic or therapeutic purposes.

Patients with a history of myocardial infarction, those who had undergone a myocardial revascularization procedure, those with hemodynamically significant valvular disease and those affected by idiopathic dilated cardiomyopathy were excluded. We also excluded patients with left bundle branch block, with an equivocal ECG or SPECT examination and finally 5 patients who, at coronary angiography, presented with a borderline lesion (40-60% stenosis) of a single vessel.

Thus, the 132 patients were included in the present series. Among these, 90 were male (mean age 72.4 years, range 65-76 years) and 42 female (mean age 68.2 years, range 65-73 years).

Patients in whom orthopedic, neurological or peripheral vascular disease precluded an adequate exercise workload, were tested with dipyridamole administered at 0.56 mg/kg/min for 4 min.

Beta-blockers, calcium channel antagonists and nitrates were suspended at least 24 hours before the stress test. Any substance containing methylxanthines was also suspended in those patients who underwent dipyridamole testing.

Stress test. Having obtained the patient's informed consent, baseline 12-lead ECGs were recorded. Then, patients underwent a symptom-limited bicycle ergometry test with an increment of 25 W every 2 min according to a modified Balke protocol.

ECGs and blood pressure were recorded every minute during exercise and recovery.

The ECG was considered conclusive when the subject achieved a heart rate equivalent to 80% of the age-predicted maximal heart rate. Criteria for stopping exercise were physical exhaustion, severe chest pain or dyspnea, serious ventricular arrhythmias and a drop in systolic pressure > 10 mmHg compared to baseline. Exercise was also terminated in the presence of an ST segment depression > 2 mm.

At peak exercise, a bolus of approximately 100 MBq of thallium-201 was injected intravenously and patients were encouraged to continue exercise for another 30-60 s unless contraindicated. For those under dipyridamole infusion, 3 min after the administration of the radiotracer, aminophylline was slowly injected in all cases.

Imaging started within 8 min of the injection of thallium-201 using a rotating large field gamma camera (Starcam 2000, G.E., Milwaukee, WI, USA) equipped with a low-energy all-purpose parallel-hole collimator. A 20% energy window centered on the 68 to 80 KeV peak and a 10% window centered on the 167 KeV peak were used. Thirty-two views were collected for 35 s each by rotation of the camera through a 180° arc and recorded on a 64 × 64 word matrix. Approximately 4 hours later, redistribution imaging was performed in the same way.

Each study was reconstructed by filtering back projection using a Butterworth filter, a cut-off frequency of 0.3 cycles/pixel and a power factor of 5.

Test interpretation. Regardless of the type of stress, either physical or pharmacological, exercise ECG was considered diagnostic of ischemia if there was at least > 1 mm horizontal or downsloping depression of the ST segment 0.08 s after the J point.

The scintigraphic examination was considered positive for ischemia if an area of decreased activity was seen during the peak stress test and resolved, either partially or totally, during redistribution, since severely ischemic myocardium may be detected as fixed defects at 4 hours[13].

Selective coronary arteriography was performed in all patients within 2 weeks of the exercise test with the standard multiple projection Judkins technique. Angiograms were reviewed on a Vanguard projector equipped with a television camera. A lesion was considered significant when at least 60% of the lumen diameter was obstructed. If the same lesion appeared in two different views, the degree of narrowing considered was that present in the projection showing the greatest degree of stenosis[14]. A coronary artery was considered to be normal when it contained no lesion or when less than 40% of the luminal diameter was obstructed. Patients with left main stenosis were considered as having two-vessel disease.

The degree of the lesion was estimated visually; in cases of borderline lesions, quantitative angiographic analysis was performed: selected cine frames were acquired and digitized by an array processor-based computer for medical image processing, using a previously described and validated method[15].

All results (ECG, thallium-201 and angiography) were reviewed by two experienced observers who were unaware of the patient's history; in case of disagreement, results were adjudicated by subsequent joint review. All analogue and computer analyzed scintigraphic images were interpreted by observers who were blinded with regard to the patient's electrocardiographic or angiographic data.

Follow-up. A minimum follow-up lasting 2 years (mean 27.8 months, range 24-48 months) was available for 124 patients. Follow-up data were obtained either by telephone interview or by clinical chart review for those who underwent an ambulatory check-up or who were rehospitalized for whatever reason. The information regarding either major events such as death (whether or not related to heart problems) and non-fatal acute myocardial infarction, or minor events such as rehospitalization for the reemergence of primary symptoms, revascularization procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting), was accurately documented. Subsequent coronary events or new serious disease (that might have changed the clinical course) were considered as the endpoint of the follow-up. Cardiac death or myocardial infarction was considered as the primary endpoint.

Statistical analysis. The sensitivity, specificity and diagnostic accuracy of both ECG and thallium-201 SPECT were calculated according to standard definition. In particular, the diagnostic accuracy was estimated by the following equation: [(true positive + true negative)/total number] × 100, where the true positives were those patients in whom an abnormal stress test was confirmed by the finding of an obstructive lesion at coronary angiography and the true negatives were those patients in whom a negative stress test was confirmed by a normal coronary angiography.

The term "predictive value" defines the ability of each stress test to predict patient's outcome during the follow-up period. The positive predictive value may be estimated by the following equation: [true positive/(true positive + false positive)] × 100. The negative predictive value is given by the following equation: [true negative/(true negative + false negative)] × 100. The individual result was considered as a "true positive" when an abnormal stress test was followed by the occurrence of a cardiac event in the follow-up period and as a "false positive" when it was not. On the other hand, a "true negative" test was one in which a normal stress test was followed by a healthy condition during follow up and a "false negative" test was one in which a normal stress test was followed by a cardiac event during follow-up.

Data were analyzed using the χ^2 and Fisher's exact tests: a p value < 0.05 was considered to be statistically significant.

Results

Among the 132 patients enrolled in the study, 36 presented with stable angina, 19 with unstable angina, 8 with recent acute angina, 25 with dyspnea or symptoms/signs of congestive heart failure, 24 with cardiac rhythm disturbances, clinically referred as palpitations and/or syncope, and 20 with chest pain referred as being "atypical" for location, irradiation and duration (Table I). One hundred and ten patients underwent bicycle ergometry while 22 patients who were unable to perform exercise were submitted to the dipyridamole stress test.

Exercise ECG testing was positive in 102 patients (Table II): in 92 coronary angiography confirmed the presence of obstructive CAD and, in particular one-vessel disease in 22, two-vessel disease in 33 and three-vessel disease in 37 patients. In the other 10 subjects, the angiograms were normal (false positives). A negative result was found in 30 patients; among these, coronary angiography confirmed the absence of obstructive disease in 14, but detected CAD in 16 patients (false negative): one-vessel disease in 7, two-vessel disease in another 7 and three-vessel disease in 2 patients.

Stress thallium testing was positive in 112 patients (Table II); in this group, coronary angiography showed

Table I. Clinical characteristics of the study population.

	Male	Female	Total
Mean age (years)	72.4	68.2	70.8
Reason for admission			
Stable angina	26	10	36
Unstable angina	14	5	19
Acute angina	6	2	8
Dyspnea, CHF	18	7	25
Arrhythmias	15	9	24
Atypical chest pain	11	9	20
Total	90	42	132

CHF = congestive heart failure.

Table II. Results of stress testing and coronary angiography.

	Male	Female	Total
Exercise ECG			
Positive	76	26	102
Negative	14	16	30
Thallium-201			
Positive	79	33	112
Negative	11	9	20
Coronary angiography			
Normal	10	14	24
One-vessel disease	17	12	29
Two-vessel disease	30	9	39
Three-vessel disease	33	7	40
Total	90	42	132

one-vessel disease in 28, two-vessel disease in 35, and three-vessel disease in 38; thus, 101 tests were true positives, while in the remaining 11 patients, the angiograms were not suggestive of the presence of obstructive lesions (false positives). Stress thallium testing was negative in 20 patients; among these, angiography confirmed the absence of disease in 13, but was diagnostic of one-vessel disease in 4 and of two-vessel disease in 3 patients (false negatives).

As shown in table II, overall, coronary angiography was normal in 24 patients, but diagnostic of one-vessel disease in 29, of two-vessel disease in 39, and of three-vessel disease in 40 patients. Table III summarizes the stress testing data according to the results obtained at coronary angiography. With regard to the clinical symptoms, all patients who were admitted to hospital because of stable angina (36 patients) or acute recent-onset angina (8 patients) presented with at least one-vessel disease. Coronary angiography was also positive in 17 out of 19 patients who were hospitalized because of unstable angina, in 23 out of 25 patients who were hospitalized because of dyspnea or other symptoms related to congestive heart failure, in 14 out of 24 patients who were hospitalized because of cardiac arrhythmias (clinically manifested as palpitations or syncope) and in 7 out of 20 patients who were hospitalized because of "atypical angina". It is noteworthy that 58% of patients with normal angiograms were female and that 50% of these subjects complained of atypical chest pain.

Considering the whole group of patients, the sensitivity of stress testing (Table IV) was quite high for both techniques; conversely, the specificity of both techniques was lower than expected. Thus the diagnostic accuracy of SPECT was superior to that of ECG. With regard to gender, ECG appeared to be more sensitive in males than in females ($p = 0.006$); on the other hand, no difference was found in specificity. SPECT did not show any significant gender-related difference in sensitivity ($p = NS$); the specificity was superior in males, although this difference did not reach statistical significance. Finally, the diagnostic accuracy of both techniques was found to be significantly superior in males than in females (Table IV). With regard to the extent of CAD, the sensitivity of ECG was 75.8% in patients with one-vessel disease and reached 94.8% in those with three-vessel disease. Thallium-201 SPECT was even more sensitive and increased from 87.5% in case of one-vessel disease to 100% in case of three-vessel disease (Table V).

Follow-up data were available for 124 of 132 patients (94%). These patients were divided into two groups: those with a negative test and those with a positive examination, regardless of the results of coronary angiography; we separately evaluated the ECG and scintigraphic results to compare the predictive values (both positive and negative) of each technique.

Table III. Results of stress testing in relation to the coronary angiography data.

	Male	Female	Total
ECG			
True positive			
One-vessel disease	13	9	22
Two-vessel disease	29	4	33
Three-vessel disease	30	7	37
False positive	4	6	10
True negative	6	8	14
False negative	8	8	16
Total	90	42	132
Thallium-201			
True positive			
One-vessel disease	16	12	28
Two-vessel disease	28	7	35
Three-vessel disease	31	7	38
False positive	4	7	11
True negative	6	7	13
False negative	5	2	7
Total	90	42	132

Table IV. Sensitivity, specificity and diagnostic accuracy of stress testing in relation to sex.

	Total	Male	Female	p
ECG				
Sensitivity (%)	85.1	90	71.4	0.006
Specificity (%)	58.3	60	57.1	NS
Diagnostic accuracy (%)	80.3	86.6	66.6	0.007
Thallium				
Sensitivity (%)	93.5	93.7	92.8	NS
Specificity (%)	54.1	60	50	NS
Diagnostic accuracy (%)	86.3	90	78	0.04

Table V. Sensitivity, specificity and diagnostic accuracy of stress testing in relation to the extent of the disease*.

	ECG	Thallium
One-vessel disease	75.8%	87.5%
Two-vessel disease	82.5%	92.1%
Three-vessel disease	94.8%	100%

* only the sensitivity can be detected.

As may be seen in table VI, 29 patients had a negative ECG examination. In this group, 15 were found to be in good conditions, while 10 had to be rehospitalized because of the recurrence of primary symptoms: 3 of these had developed a non-fatal myocardial infarction and underwent coronary artery bypass grafting. Two patients died: one patient of an acute myocardial infarction and one of malignancy. Another patient had a cerebrovascular attack and the last one developed hepatic cirrhosis. Out of 95 patients with a positive ECG test, 39 who were under medical treatment were found to be in

Table VI. Results concerning the predictive value of stress testing.

	Thallium-201	ECG
True positive	57	49
True negative	16	16
False positive	48	46
False negative	3	13
Total	124	124

acceptable conditions. Rehospitalization was necessary in 44 patients: in 3 because of a non-fatal myocardial infarction and in 41 because of the recurrence of primary symptoms. In 28 patients, a revascularization procedure (either coronary angioplasty or bypass surgery) was necessary. Seven patients died and in 5 of these the cause was clearly related to cardiac events. An additional 5 patients complained of other serious non-cardiac-related problems.

In the group of patients with a negative test (19 patients), 14 were in good conditions, free from cardiac problems and, in particular, were not assuming any drug during follow-up. Three patients were rehospitalized owing to the recurrence of cardiac problems: 1 patient necessitated a revascularization procedure. Another patient died of malignancy and one had a transient ischemic attack. Among the group of 105 patients with a positive test, 40 who were under medical treatment were considered to be in acceptable conditions. Fifty-one patients were rehospitalized owing to the recurrence of primary symptoms: in 6 a non-fatal myocardial infarction was diagnosed and 30 patients underwent a revascularization procedure. Eight patients died, and in 6 of them the death was clearly related to major events (fatal myocardial infarction, intractable congestive heart failure). An additional 6 patients complained of non-cardiac problems: 2 had a cerebrovascular attack.

Thus, compared to ECG, thallium-201 SPECT proved to be a better technique for the prediction of the outcome of these patients: in terms of the endpoints considered globally, the difference was irrelevant for positive values (54 vs 51%, $p = NS$) but significant for negative values (84 vs 62%, $p < 0.03$).

If we consider only the primary endpoint (such as cardiac death or myocardial infarction), SPECT is still slightly superior to ECG; obviously the positive value drops to 11% (vs 8% for ECG), and the negative value rises to 100% (compared to 86% for ECG). Neither difference reaches statistical significance.

Discussion

Even though coronary atherosclerosis begins in early life and evolves episodically[16], this disease has recently been found to be progressive even in patients aged 75 years. The unexpected presence of active atherosclerosis even in the late elderly has been documented[17]. Therefore, even during the late decades of life, the early diagnosis of CAD is essential in order to prevent or limit the effects of the disease.

The lifestyle of the great majority of elderly persons is definitely sedentary and this is almost the rule for those with associated peripheral vascular disease or problems related to the musculo-skeletal apparatus which limit their physical activity. Therefore the typical effort angina is less likely to manifest in this age group[18]. Thus exercise testing, either physical or pharmacological, is a suitable procedure for the identification of those elderly patients who are at risk for the early development of cardiac events and who consequently need further evaluation.

Our experience shows that exercise-thallium imaging provides further information in addition to that provided by stress ECG even in the elderly population, but in a more limited way with respect to the younger population, mostly because the sensitivity of stress ECG is, in our series, higher than expected[19].

This observation may be explained on the basis of the selection of the study population: since cardiovascular disease is more frequent in the elderly, this population constitutes a preselected group with a higher probability of developing CAD; according to the Bayes' theorem, the likelihood of a test is correlated with the prevalence of the disease in the age group being studied and thus it is not surprising to find an elevated sensitivity of stress ECG in this age group. In accordance with this hypothesis, we reported that 2 patients had a true positive stress ECG and a false negative thallium scintigraphy test.

In this group, clinical symptoms appear to be good predictors of the presence of CAD; in fact, typical stable angina or recent-onset angina was invariably associated with the presence of CAD, while atypical (in terms of onset, irradiation and duration) chest pain and rhythm disturbances were associated with a lower prevalence of CAD. This finding becomes more evident for female subjects since the vast majority of normal coronary angiograms belonged to female patients, mostly complaining of atypical chest pain.

As expected, the sensitivity of both ECG and thallium-201 SPECT seems to correlate with the extent of the disease: in fact, there is a linear relationship between the number of vessels involved and the increase in the sensitivity of stress testing. Conversely, the specificity of ECG was similar to that of the thallium test in males but superior in females: this reflects the high prevalence of false positives in females, probably linked to breast attenuation[20].

In patients who were unable to exercise, pharmacological stress testing was employed. Intravenous dipyri-

damole has been used for the past 20 years as a coronary vasodilator and increases blood flow approximately 2 to 4 times baseline values. The injection of dipyridamole is safe with side effects, at standard doses, which are very similar to those observed in the younger population, even if old patients seem to be more sensitive to heart-active drugs. However, whenever necessary, aminophylline efficaciously antagonized the pharmacological side effects of dipyridamole.

In a previous study, Lam et al.[21] compared the diagnostic accuracy of dipyridamole-thallium imaging in patients aged 70 years or more with that observed in another group of younger patients. They concluded that the sensitivity and specificity of this pharmacological stress test in the elderly were similar to those in younger subjects and were comparable with the results reported for standard exercise thallium imaging.

In the elderly, a normal stress ECG appears to be inadequate for the risk stratification of future cardiac events: in fact, in the group of patients with a negative examination, only 52% were found to be in good conditions during follow-up, whereas 36% were rehospitalized because of the recurrence of primary symptoms and 1 patient even died of a myocardial infarction. In addition, 3 out of 6 patients who experienced a myocardial infarction during follow-up, had a normal stress test. This datum confirms the results of a study by Iskandrian et al.[22] who found that "with aging, neither the presence of angina nor that of ST segment depression during exercise were useful in identifying patients at risk". In the same study, they used exercise thallium-201 imaging to stratify the elderly population into different groups on the basis of the presence and extent of exercise-induced thallium-201 abnormalities.

In our series, the positive predictive value of thallium scanning, even if superior to that of ECG (54 vs 51%), was lower than expected. The possible explanation of this apparent discrepancy may be related to the selection of determinants: in the evaluation of the predictive value as "false positive", we identified those patients with a positive stress test who, during follow-up do not develop any cardiac events. In fact, patients with CAD under treatment with standard therapy such as nitroderivatives and/or calcium antagonists, can sustain an acceptable sedentary lifestyle. These patients may therefore live for long periods in acceptable conditions without relevant complaints. In our series, such patients were quite numerous and we considered them all the same as being "false positives" because they did not present with any of the above-mentioned events. Thus, the "positive predictive value" must be interpreted with caution since therapy with coronary vasodilators, as well as other factors, may interfere with the natural history of the disease.

On the other hand, in the group of patients with a negative test, no specific therapy was being administered and therefore the disease followed its natural evolution. For this reason, the "negative predictive value" appears to be a more reliable parameter. Under these circumstances, SPECT was far superior to ECG in selecting low risk patients: in fact, in the group of patients with a negative scan examination, the great majority was found to be in good conditions, only 11% had to be hospitalized, and no fatal cardiac event occurred. These data confirm a previous study by Shaw et al.[23] who investigated the prognostic utility of dipyridamole thallium-201 myocardial imaging in elderly patients and documented a highly predictive value of this technique for cardiac events: in particular, a subgroup of patients with a normal scan had a favorable survival rate.

In conclusion, the present study was undertaken to assess the diagnostic accuracy and predictive value of stress testing in the elderly population.

In our series, the diagnostic accuracy of stress ECG was good and appeared to be superior to that reported in younger populations, being slightly increased by thallium testing.

We found a high sensitivity for both techniques and the correlation with the extent of CAD was excellent; conversely the specificity of the thallium test was found to be lower than expected, even inferior to ECG testing, probably because, due to "breast attenuation", false positives are frequent in women.

With regard to gender, the sensitivity of ECG and the diagnostic accuracy of both techniques were significantly superior in males than in females.

Thallium-201 scanning was superior to ECG in predicting the probability of future cardiac events; in fact, patients with normal thallium images were at low risk of future cardiac events, whereas those with abnormal scans were at a relatively high risk.

However, when we considered only the primary endpoint such as myocardial infarction, the difference in the prognostic values of thallium-201 and ECG testing became less relevant even for the negative value: this is due to the fact that "myocardial infarction is a very rare, occasional event even in patients with extensive coronary atherosclerosis"[24].

Study limitations. In the evaluation of the patient population we tried to select a homogeneous population by identifying patients who possibly were being admitted for heart problems for the first time or who at least presented with only a recent history of coronary artery disease. Unfortunately, the wide spectrum of clinical manifestations of CAD prevented us from achieving such a result and the heterogeneity of the patient population constitutes a possible limitation of the study: this is a real but not unusual problem when we are dealing with the broad angina pectoris clinical syndrome which may result from different pathogenetic mechanisms[25].

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