ORIGINAL ARTICLE

Detection of myocardial ischaemia in the elderly vs the young by stress Thallium-201 scintigraphy and its relation to important coronary artery disease

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The prevalence and severity of coronary atherosclerosis increase dramatically with age, that more than so mush so half of all deaths in people aged over 65 are due to coronary arterial disease (CAD) and about three fourths of all deaths from CAD occur in the elderly. The aims of our study were, firstly, to detect myocardial ischaemia development in elderly versus younger people undergoing treatment for known CAD through the use of both conventional treadmill testing and Tl201 scintigraphy, and secondly, to determine the relationship between the above non-invasive tests and angiographically confirmed important coronary artery disease (iCAD).

A database from six hundred and six patients (Total=606, M=355, F=251) who had undergone coronary angiography, exercise ECG testing (ETT) using the treadmill Bruce protocol, and Tl^{201} scintigraphy was reviewed retrospectively.

All patients had displayed clinical expressions of CAD with or without the existence of an old myocardial infarction (MI). The patients were from both sexes (M=440, F=252) and divided into two groups, according to age.

Group A was composed of 265 patients aged over 65,(M=170, F=95, mean age=70.3 ± 5.3 years). Group B was composed of 341 patients aged under 65 (M=185, F=156, mean age 54.4 ± 9.1 years).

Patients with uncontrolled arterial hypertension, hypertrophic cardiomyopathy, severe valve diseases, severe chronic obstructive lung diseases, severe anemia, peripheral atherosclerosis, orthopedic problems, and Parkinson's disease were excluded from the study.

The term "important coronary artery disease" (iCAD) covers the following patterns of coronary anatomy: a) left main stem stenosis > 50% with or without disease elsewhere, b) proximal three vessel disease, c) three vessel disease including the proximal LAD, d) proximal two vessel disease including LAD and e) two vessel disease including the proximal LAD.

Biostatistical characteristics such as sensitivity, specificity, predictive values of ETT-Tl^{201} were estimated.

Analyzing our results we concluded that:

The biostatistical parameters in predicting important CAD in elderly and younger patients by means of exercise test and thallium scintigraphy need to be redefined through more closely scheduled and prospective studies.

In elderly coronary patients the appearance of positive results in both parameters of ETT-Tl^{201} indicates a significant possibility of iCAD existence.

In coronary patients younger than 65 years the appearance of negative results in both parameters of ETT-Tl^{201} almost excludes iCAD in contrast to elderly patients, who display a significant proportion of iCAD.

In elderly coronary patients the appearance of equivocal results in both tests indicates a significant possibility of the existence of iCAD in contrast to younger patients.
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Coronary artery disease in the elderly graphically illustrates many aspects of medicine of old age. Concurrent disease may precipitate or intensify symptoms. The historical aspect of CAD may be at best uncertain and occasionally misleading. Clinical features often differ from the classic manifestation of the disease in younger people, and may simulate other diseases or be dismissed as being part of the aging process[1-3].

The death rates from CAD rise almost exponentially with age, doubling with approximately every 9 years of age in men from middle age on, and every 7 in women. CAD is the largest single cause of death over the age of 65 in both sexes[4-6].

The diagnosis of CAD may be more difficult in older people, since the prevalence of diagnosed disease is only one-third to one-half the prevalence of autopsy-documented significant atherosclerosis; physical examination is of limited usefulness in the diagnosis of CAD[1-3,7].

Stress testing is useful in the diagnosis of an older patient's ischaemia with suspected or known coronary disease, but with certain caveats. The presence of resting-ST abnormalities or the use of digitalis, both of which are more common in the elderly, may invalidate the interpretation of the stress ECG (exercise tolerance test, ETT), and in this context stress testing using Thallium-201 (Tl^{201}) scintigraphy is helpful[8-10]. Thallium imaging is also helpful when the stress test is unexpectedly negative in an older person whose history suggests the presence of ischaemia, since the predictive accuracy of a negative test is low in a population with a high prevalence of the disease[11,12].

A combination of clinical and ex-Tl^{201} variables provides greater diagnostic and prognostic information than a combination of clinical and angiographic data[13].

The aims of our study are, firstly, to detect myocardial ischaemia development in elderly versus younger people undergoing treatment for known CAD through the use of both conventional treadmill testing and Tl^{201} scintigraphy, and secondly, to determine the relationship between the above non-invasive tests and angiographically confirmed important coronary artery disease (iCAD).

MATERIAL AND METHODS

A database from six hundred and six patients (Total=606, M=355, F=251) who had undergone coronary angiography, exercise ECG testing (ETT) using the treadmill Bruce protocol, and Tl^{201} scintigraphy was reviewed retrospectively. Data was obtained from the medical files of patients who had been admitted into the Cardiology Unit of the 2nd Department of Internal Medicine, Hippokration Hospital, Aristotelian University of Thessaloniki or had been examined in our outpatients clinic or were exercised in the «Bioiatriki Medical Center» during the period September 1995 to December 2000.

All patients had displayed clinical expressions of CAD with or without the existence of an old myocardial infarction (MI). The patients were from both sexes (M=440, F=252) and divided into two groups, according to age.

Suspected clinical manifestations of CAD, according to the medical files, were considered to be only the appearance of known forms of stable angina and/or exertional dyspnea.

A diagnosis of Q-wave or non-Q-wave myocardial infarction, no earlier than three months prior to recruitment, was based on (1) enzyme elevation three times higher than normal laboratory values (CK-MB, GOT, LDH) in serial determination and (2) typical evolutionary ECG changes in myocardial infarction during the hospitalization. The clinical picture was not taken into account because of its wide variety in the elderly.

Patients with uncontrolled arterial hypertension, hypertrophic cardiomyopathy, severe valve diseases, severe chronic obstructive lung diseases, severe anemia, peripheral atherosclerosis, orthopedic problems, and Parkinson's disease were excluded from the study.

The time interval between the clinical diagnosis of MI and the exercise Tl^{201} scintigraphy was 4 to 6 months (completion of MI process); between the stress Tl^{201} and the coronary angiography there was an interval of one week to two months.

The ETT was terminated when ECG criteria for ischaemia were met, or the patient experienced extensive fatigue, angina and/or dyspnea. The qualifying ECG criteria for myocardial ischaemia were (1) ST segment depression > 0.15 mV at 80 msec after J point, (2) 0.1 mV flat or down-sloping ST segment depression and (3) ST segment upward slope >1 mV/sec.

The Tl^{201} radionuclide was injected one minute before the termination of exercise, whilst the first

imaging of the myocardium by gamma-camera was carried out after 10 minutes and the second after four hours. The Tl^{201} scintigraphy study was evaluated for the site of the perfusion defect (local site defects) as well as for evidence of reperfusion with the resting scan.

The term "important coronary artery disease" (iCAD) covers the following patterns of coronary anatomy: a) left main stem stenosis > 50% with or without disease elsewhere, b) proximal three vessel disease, c) three vessel disease including the proximal LAD, d) proximal two vessel disease including LAD and e) two vessel disease including the proximal LAD.

All patients were receiving anti-anginal therapy, low doses of aspirin and 81% were receiving lipid - lowering therapy.

Group A was composed of 265 patients aged over 65 (> 65 years, M=170, F=95, mean age 70.3±5.3 years) (Table 1).

Group B was composed of 341 patients aged under 65 (< 65 years, M=185, F=156, mean age 54.4±9.1 years) (Table 1).

Biostatistical analysis was applied using SPSS (Statistical Package for Social Sciences) for Windows, Rel. 10.0. Non-parametric tests (variations of chi-square test) were performed to compare the proportions of qualitative variables. Less than a 0.05 level of p value ($p<0.05$) was considered significant.

The assessment of the biostatistical characteristics such as sensitivity, specificity and the predictive values of this non-invasive method of predicting iCAD was made with the coronary arteriographic findings as the «gold standard» (Table 2).

Table 1. Demographic data concerning the distribution of CAD risk factors in Groups A (> 65 years) and B (< 65 years).

	Group A n=265 (m=170, f=95)	Group B n=341 (m=185, f=156)
Hyperlipidaemia	181*	220
Diabetes mellitus	121*	152
Smoking	130*	180
Family history	185*	222
Blood Pressure	203*	251
Obesity (BMI)	102*	119

*NS compared to Group B.

Table 2. Biostatistical characteristics of ETT and Tl^{201} in predicting iCAD.

		Group A	Group B	Total
Sensitivity %	ETT	86.9	97.8	92.9
	Tl	86.7	96.2	92.2
Specificity %	ETT	53.7	37.2	43.9
	Tl	61.6	30.8	43.1
Positive predictive accuracy %	ETT	75.7	68.5	71.4
	Tl	78.2	66.7	70.8
Negative predictive accuracy %	ETT	71.3	92.4	80.5
	Tl	74.5	84.9	78.7

Sensitivity: Percentage of all patients with coronary artery disease who have an abnormal diagnostic test - (TP/TPxFN)x100

Specificity: Percentage of negative diagnostic tests in normal patients without coronary artery disease - (TN/TNxFP)x100

Predictive accuracy: Positive or negative accuracy is defined as the percentage of positive or negative diagnostic tests that are true positives or negatives respectively - (TP/TPxFP)x100 or (TN/TNxFN)x100.

TN=Total negatives, TP=Total positives, FN=Total false negatives, FP=Total false positives.

RESULTS

In Group A, an old myocardial infarction was present in 126 patients (M=89, F=37) [non Q = 19 (15%), extended antero-lateral = 25 (20%), antero-septal = 44 (35%), inferior = 38 (30%)] (Table 3).

Clinically suspected expressions of CAD without the existence of an old MI, appearing after the age of 65, were present in 139 (M=81, F=58) patients under treatment (Table 3).

Old myocardial infarctions which had happened before the age of 65 (Group B), were present in 183 patients (M=102, F=81) [non Q = 35 (19%), extended antero-lateral = 38 (21%), antero-septal = 53 (29%) and inferior = 57 (31%)] (Table 4).

Clinically suspected expressions of CAD without the existence of an old MI were present in 158 patients (M=83, F=75) under treatment (Table 4).

There were no significant differences in the distribution of MI location between Groups A and B.

There were no significant differences between the two groups in terms of their medication or

Table 3. Important CAD in Group A (> 65 years) and its correlation to ETT - Tl^{201} non-invasive test.

Group A ≥ 65 years n=265, m.a.=70.3±5.3 years				
Subgroup with old MI (n=126)			Subgroup with clinical CAD (n=139)	
Angiography (n=126)	iCAD (n=81)*	#ETT-Tl^{201}	Angiography (n=139)	iCAD (n=77)
95 (75.4%)	67 (70.5%)*	(+)	69 (49.6%)	51 (73.9%)
5 (4%)	5 (100%)***	(-)	48 (34.67%)	10 (28.8%)
26 (20.6%)	11 (42.3%)**	(±)	22 (15.8%)	16 (72.7%)

*NS, **p<0.05,***p<0.001 compared to iCAD of subgroup with clinical expressions of CAD.

Table 4. Important CAD in Group B (> 65 years) and its correlation to ETT - Tl^{201} non-invasive test.

Group B < 65 years n=341, m.a.=54.4±8.6 years				
Subgroup with old MI (n=183)			Subgroup with clinical CAD (n=158)	
Angiography (n=183)	iCAD (n=89)*	#ETT-Tl^{201}	Angiography (n=158)	iCAD (n=64)
149 (81.44%)	81 (54.4%)*	(+)	87 (55%)	56 (64.4%)
4 (2.2%)	0 (0%)*	(-)	26 (16.5%)	1 (3.8%)
30 (16.4%)	8 (26.7%)*	(±)	45 (28.5%)	7 (15.5%)

* NS compared to iCAD of subgroup with clinical expressions of CAD.

Table 5. Important CAD and its correlation to ETT - Tl^{201} in Groups A and B.

Group A (n=265)			Group B (n=341)	
Angiography (n=265)	iCAD (n=158)* - (9.6%)	#ETT-Tl^{201}	Angiography (n=341)	iCAD (n=153) – (44.5%)
164 (61.9%)	116 (70.7%)*	(+)	236 (69.2%)	137 (58%)
53 (20%)	15 (28.3%)*	(-)	30 (8.8%)	1 (3.3%)
48 (18.1%)	27 (56.2%)**	(±)	75 (22%)	15 (20%)

*p<0.01, **p<0.001 compared to iCAD of Group B.

ETT-Tl^{201} (+) = both parameters positive (treadmill exercise testing and Tl^{201} scintigraphy).
ETT-Tl^{201} (-) = both parameters negative (treadmill exercise testing and Tl^{201} scintigraphy).
ETT-Tl^{201} (±) = results in disagreement (e.g. ETT = negative and Tl^{201} = positive).

their risk factors, such as hyperlipidaemia, diabetes mellitus, smoking, family history, blood pressure and obesity (Table 1).

In Group A, there was no significant difference in terms of the percentage with iCAD between those who had both positive ECG and thallium tests and those with clinically suspected CAD (Table 3). All five patients in the old MI group with both tests negative had iCAD, whereas in the clinically suspected CAD group only 20.8% had iCAD (p<0.001) (Table 3). In the 26 patients in the old MI group with equivocal tests (one test negative and the other one positive) 42.3% had iCAD, whereas in the 22 patients in the clinically suspected CAD group, 72.7% had iCAD (p<0.05) (Table 3).

In Group B, in both the subgroup with old MI and the one with clinically suspected CAD, the percentage with iCAD was similar in those subgroups with both positive ECG and thallium tests, both tests negative and equivocal (p>0.05) (Table 4).

There was a significant difference (p<0.01) in the total percentage with iCAD between Group

A and Group B (Table 5). In Group A, there was a significant difference ($p<0.01$) in terms of the percentage with iCAD between those who had both positive ECG and thallium tests and those in Group B (Table 5). The 28.3% of the patients in Group A with both tests negative had iCAD, whereas in Group B only 3.3% had iCAD ($p<0.01$)). In the 48 patients in Group A with equivocal tests, 56.2% had iCAD, whereas in the 75 patients in Group B, 20% had iCAD ($p<0.0001$) (Table 5).

The distribution of ETT- Tl^{201} results (positive, negative and adverse) between Groups A and B was without statistical significance ($p>0.05$).

The sensitivity and negative predictive accuracy of both exercise and scintigraphy in predicting iCAD were higher in Group B, whilst the specificity and positive predictive accuracy were higher in Group A (Table 2).

DISCUSSION

The symptoms of heart disease are often modified in the elderly. Cardiac pain, both that of angina pectoris and that of cardiac infarction, may be either greatly reduced in intensity, or overshadowed by the simultaneous development of mental confusion, presumably because of reduction in cardiac output and cerebral blood flow[1-3,14,15].

The lack of classic symptomatology may also be related to an age-associated decline in physical activity to the point where ischaemic symptoms are not present. The disease remains silent in the elderly; in addition, dyspnea, rather than pain, may be the most prominent feature of the clinical picture in angina as well as infarction, possibly because of the age-related changes in myocardial and pericardial compliance, diastolic relaxation, different responses to catecholamines and neuropathy. However, the transient features associated with acute ischaemia are often present in older people, even in the absence of ischaemia[1-3,14-21].

Hypertension or severe anemia may precipitate or exacerbate cardiovascular symptoms in the presence of coronary heart disease of moderate severity. Anemia can induce sub-endocardial ischaemia and infarction even in the absence of significant coronary arterial disease[1-3,14,22].

Angina pectoris is the clinical symptom, which may be the only manifestation of ischaemic heart disease in the case history. It is a complex symptom that progressively diminishes in frequency after the age of 80[1-3,11,22,23].

In old age coronary atherosclerosis is widespread, and areas of myocardial fibrosis are often irregularly disposed throughout the myocardium, particularly in the sub-endocardial region[22,23]. Hibernating myocardium and collateral circulation are also features that frequently appear in old age[23-25].

The present study addresses an important question regarding the diagnosis of CAD in elderly versus younger patients. Coronary artery disease is typically more prevalent, extensive, and severe in older than in younger patients, although non-cardiac factors such as chronic obstructive lung disease, peripheral atherosclerosis, arthritis, orthopedic problems, Parkinson's disease, etc. might interfere with exercise in very frail elderly patients[11,14,26,27], and therefore, exercise ECG and thallium201 perfusion imaging appear to have normal or enhanced sensitivity, with only a modest reduction in specificity in older versus younger patients[7,28].

Our results, however, indicate that both ETT and Tl^{201} have lower sensitivity and negative predictive accuracy in predicting important CAD in elderly than in younger patients, with an increase in specificity and positive predictive accuracy in older versus younger patients (Table 2). Although, it is well known that in elderly patients the clinical manifestations of CAD are very atypical[1-3,11,14,26], only angina and/or dyspnea have been regarded as CAD symptoms in this study and that may be one of the reasons for these results; the moderately elevated mean age (Table 1) and the possibly reduced "biological" mean age, accompanied by "good" fitness in the elderly patients, may also be another one of the causes for these results; but a likelies reason seems to be the increasing incidence of CAD in younger people.

Of the total of angiographically evaluated patients in Group A (> 65 years), a high percentage (59.6%) appears iCAD whilst the corresponding percentage in Group B (<65 years) is 44.5% ($0.001<p<0.01$) (Table 5). This significant difference is attributable to typically more prevalent, extensive, and severe CAD in older patients compared with younger ones[1,3,11,14,22,26], and a more detailed clinical evaluation and

classification of elderly patients before they reach the angiographic laboratory.

Although the sensitivity, specificity, and predictive values of ETT and Tl^{201} have been widely studied, it has also been realized that the results of a test must be interpreted with reference to Bayes' theorem[29-31]. Our results reveal a greater positive predictive value of this test combination for important CAD in the older group but a greater negative predictive value in the young (Table 5). Also, single positive tests are more predictive of significant CAD ($p<0.01$) in older than in younger patients (Tables 3,4,5). These valid findings are more or less predictable by Bayes' theorem[7,29-33].

The younger patients with negative results in both tests have a greater possibility of not displaying iCAD with statistical significance ($p<0.01$) compared to older patients[33] (Table 5).

The older patients with equivocal results in both tests (one positive and the other negative) have an impressively greater possibility of iCAD existence with high statistical significance ($p<0.001$) compared to younger patients (Table 5). This group of patients may need more attention from physicians.

Among the older patients with old MI and clinical CAD expressions who had negative results in both tests (Table 3), there is a highly significant difference in presence of iCAD ($p<0.001$) attributable to the existence of the old MI, and probably to the small size of the old MI sample (5 patients). However, these patients with equivocal results in both tests display a significantly higher rate of iCAD ($p<0.05$) in the subgroup with clinical CAD expressions compared to the subgroup with clinically documented CAD (old MI) (Table 3).

Although, at baseline the existence of an old MI and/or clinical manifestations of CAD was necessary for a patient to be accepted in the study, the interpretation of negative results in both tests and its strong relation to iCAD, especially in older patients, could be attributed to non-typical CAD expressions, collateral circulation, hibernated myocardium, the existence of silent ischaemia in a significant proportion of the elderly, and perhaps also the existence of preconditioned myocardium, although it has been claimed that there is an age-related reduction of ischaemic preconditioning in the aging heart[24,25,34-36].

The fact that there was a non-selective recruitment of patients across the two groups is supported by the random distribution of positive, negative, and equivocal results in both tests ($p>0.05$).

The combination of these two tests appears to have great sensitivity and sufficient predictive values in predicting iCAD in the general population (Table 2).

CONCLUSIONS

The biostatistical parameters such as sensitivity, specificity and predictive values in predicting important CAD in elderly and younger patients by means of exercise test and thallium scintigraphy need to be redefined through more closely scheduled and prospective studies.

In elderly coronary patients the appearance of positive results in both parameters of ETT-Tl^{201} indicates a significant possibility of the existence of iCAD.

In coronary patients younger than 65 years the appearance of negative results in both parameters of ETT-Tl201 almost excludes iCAD, in contrast to elderly patients, who display a significant proportion of iCAD.

In elderly coronary patients the appearance of equivocal results in both tests indicates a significant possibility of the existence of iCAD in contrast to younger patients.

ΠΕΡΙΛΗΨΗ

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Στους ηλικιωμένους η συχνότητα και η σοβαρότητα της στεφανιαίας νόσου αυξάνουν σημαντικά Οι στόχοι της μελέτης ήταν, πρώτον, να ανιχνεύσει την ύπαρξη μυοκαρδιακής ισχαιμίας στους ηλικιωμένους συγκριτικά με νεώτερους μέσω δυναμικού και στατικού σπινθηρογραφήματος με Tl^{201} και, δεύτερον, να καθορίσει τη σχέση ανάμεσα στο συνδυασμό δοκιμασίας κόπωσης και σπινθηρογραφήματος με την αγγειογραφικά επιβεβαιωμένη σημαντική στεφανιαία νόσο (iCAD).

Οι ιατρικοί φάκελοι 606 ασθενών (Α=355, Γ=251) που είχαν υποστεί καρδιακό καθετηριασμό και συνδυασμένη δοκιμασία κόπωσης με σπινθηρογράφημα μελετήθηκαν αναδρομικά.

Την ομάδα Α αποτέλεσαν 265 ασθενείς με ηλικία πάνω από 65 έτη (Α=170, Γ=95, μέση ηλικία=70.3±5.3 έτη). Την ομάδα Β αποτέλεσαν 341 ασθενείς με ηλικία ίση ή κάτω των 65 ετών (Α=185, Γ=156, μέση ηλικία 54.4±9.1 έτη).

Μετρήθηκαν τα βιοστατικά χαρακτηριστικά ευαισθησία, ειδικότητα και προγνωστικοί δείκτες της δοκιμασίας κόπωσης και του σπινθηρογραφήματος.

Η ανάλυση των αποτελεσμάτων της μελέτης υποδεικνύει ότι:

Οι προγνωστικοί βιοστατικοί παράμετροι της σημαντικής στεφανιαίας νόσου μέσω της δοκιμασίας κόπωσης και του σπινθηρογραφήματος με Tl^{201} φαίνεται ότι έχουν ανάγκη επανεκτίμησης μέσω καλύτερα σχεδιασμένων και προοπτικών μελετών.

Στους ηλικιωμένους στεφανιαίους ασθενείς η εμφάνιση θετικών αποτελεσμάτων στη δοκιμασία κόπωσης και στο σπινθηρογράφημα υποδεικνύει σημαντική πιθανότητα ύπαρξης σημαντικής στεφανιαίας νόσου.

Στους νεώτερους στεφανιαίους ασθενείς η ύπαρξη αρνητικών αποτελεσμάτων στη δοκιμασία κόπωσης και στο σπινθηρογράφημα σχεδόν αποκλείει την ύπαρξη σημαντικής στεφανιαίας νόσου σε αντίθεση με τους μεγαλύτερους σε ηλικία ασθενείς.

Στους ηλικιωμένους στεφανιαίους ασθενείς η ύπαρξη αντίθετων αποτελεσμάτων στη δοκιμασία κόπωσης και στο σπινθηρογράφημα υποδεικνύει σημαντική πιθανότητα ύπαρξης σημαντικής στεφανιαίας νόσου σε αντίθεση με τους νεώτερους ασθενείς.

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