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Value of thallium-201 imaging in detecting adverse cardiac events after myocardial infarction and thrombolysis: a follow up of 100 consecutive patients

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Abstract

Objective—To determine the prognostic role of thallium-201 imaging compared with that of exercise electrocardiography in patients with acute myocardial infarction treated by thrombolysis.

Design—Patients who remained free of adverse cardiac events six weeks after myocardial infarction had stress and rest ²⁰¹Tl imaging and exercise electrocardiography and were followed up for 8-32 months. Adverse cardiac events (death, reinfarction, unstable angina, and congestive heart failure) were documented.

Setting—Large district general hospital, Middlesex.

Subjects—100 consecutive male and female patients who were stable six weeks after thrombolysis for myocardial infarction.

Main outcome measures—Prediction of occurrence of adverse cardiac events after myocardial infarction by exercise cardiography and ²⁰¹Tl myocardial perfusion imaging.

Results—Reversible ischaemia on ²⁰¹Tl imaging predicted adverse cardiac events in 33 out of 37 patients with such events during follow up (hazard ratio 8.1 (95% confidence interval 2.7 to 23.8), $P < 0.001$). Exercise electrocardiography showed reversible ischaemia in 33 patients, of whom 13 had subsequent events, and failed to predict events in 24 patients (hazard ratio 1.1 (0.56 to 2.2), $P = 0.8$).

Conclusion—²⁰¹Tl imaging is a sensitive predictor of subsequent adverse cardiac events in patients who have received thrombolysis after acute myocardial infarction, whereas exercise electrocardiography fails to predict outcome.

Introduction

Thrombolysis after acute myocardial infarction has clearly reduced mortality,^{1 2} but the reperfusion due to thrombolysis produces myocardial salvage where a partial thickness infarct supplied by a stenotic artery remains and may present a greater risk of future ischaemic events.²⁻⁴ In Britain the current practice after acute myocardial infarction is to perform a treadmill exercise test for risk stratification, as invasive or interventional procedures are not available in most district general hospitals. Recent studies have shown, however, that exercise testing in this group of patients is a poor

predictor of future cardiac risk.⁵ Despite the wide availability of radionuclide imaging in district general hospitals, there is lack of understanding about the use of myocardial perfusion imaging and its relation to thrombolysis.

The value of thallium-201 imaging after acute myocardial infarction in stratifying groups at high and low risk of having further cardiac events has been shown to be greater than either exercise electrocardiography or coronary arteriography.⁶⁻⁸ Most of the imaging studies, however, were performed before the widespread use of thrombolysis.

We aimed to assess the value of ²⁰¹Tl imaging in risk stratification of stable patients with acute myocardial infarction after thrombolysis and to compare the results with standard exercise electrocardiography.

Patients and methods

PATIENT SELECTION

Patients admitted to our coronary care unit with typical signs and symptoms of acute myocardial infarction who had received thrombolysis and remained stable were investigated five to seven weeks after infarction. (Acute myocardial infarction was diagnosed in the presence of chest pain for over 30 minutes' duration, typical ST segment elevation or appearance of pathological Q waves in the 12 lead electrocardiogram, and a creatine kinase concentration over twice the normal with 6% or more membrane bound fraction.) All patients gave informed consent, and the study was approved by the hospital's ethics committee.

We excluded patients with left bundle branch block or other electrocardiographic abnormalities interfering with diagnosis, those with Killip class IV failure, those with other severe or life threatening illnesses, those who would not be able to perform maximal symptom limited exercise, and those who did not remain stable or had an adverse cardiac event before investigation.

STUDY DESIGN

All patients underwent symptom limited treadmill exercise testing and stress and separate day rest ²⁰¹Tl imaging five to seven weeks after infarction. We followed up all patients until the last patient had reached six months after infarction. The following cardiac events were documented: death, reinfarction, unstable angina, and new congestive heart failure.

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EXERCISE ELECTROCARDIOGRAPHY

Exercise testing was performed on a motorised treadmill with continuous computer averaged electrocardiographic signal analysis (CASE 12, Marquette Electronics, Milwaukee, Wisconsin) with a 13 lead system (12 leads plus CM5 lead), and the standard Bruce protocol was used. The tests were symptom limited, and the standard criteria for terminating the test were used.⁹ Myocardial ischaemia was considered to be present when horizontal or downsloping ST segment depression greater than 1 mm at the J point plus 1.5 mm (or 60 ms) occurred.⁹

THALLIUM-201 SCINTIGRAPHY

All patients underwent radionuclide imaging about six weeks after infarction. At peak exercise, 74 MBq ²⁰¹Tl was injected intravenously, and patients were encouraged to continue exercising for a further minute whenever possible. Images were acquired by a mobile gamma camera (Elscint, 205M) attached with a low energy all purpose collimator. The energy window setting was around 68-83 KeV. Planar images were obtained within 5-10 minutes of the injection of ²⁰¹Tl, in the anterior, 45° left anterior oblique and left lateral views and 10 minutes per view. Separate day rest ²⁰¹Tl imaging was performed within five days of the exercise imaging. To avoid the difficulties of inadequate redistribution, ²⁰¹Tl was injected 10 minutes after sublingual nitroglycerine (0.5 mg), and imaging was performed 60 minutes later.¹⁰ Correct angulation was obtained for each image, and the position of the patient was strictly controlled.

IMAGE ANALYSIS

²⁰¹Tl images were analysed semiquantitatively (by visual interpretation of a colour coded computer image) by two independent observers blinded to the patient's identity and clinical diagnosis. Differences in interpretation were resolved by consensus. Five myocardial regions were defined from each of the three planar views, and these were interpolated into a polar map with four segments in each of the following regions: anterior, lateral, inferior, and septal, with two segments forming the apex, as has been described elsewhere.¹¹⁻¹³

Planar images were assessed semiquantitatively by using both unenhanced images on a computer grey scale as well as processed images with smoothing and colour coding. Matching views from the initial scan and the separate day rest scan were displayed side by side for comparison. The ²⁰¹Tl activity in each segment was graded as normal, mildly reduced, moderately reduced, severely reduced, or absent on the basis of a score

(1 = normal uptake, 5 = absent). The initial scan was considered normal if all 18 segments were reported as normal. Reversible defect in a segment was thought to be present when there was a shift towards normal of at least two grades or complete normalisation of a resting image compared with the initial exercise image (fig 1). Patients were categorised on the basis of presence or absence of at least two partially or fully reversible segments from the initial stress image to the subsequent rest image. For the purpose of this study, either fully or partially reversible scans were thought to indicate ischaemia induced by exercise.

STATISTICAL ANALYSIS

Statistical analysis was performed using Cox's proportional hazards survival analysis to predict time to an event. The variables considered were positive or negative exercise test, presence or absence of reversible ischaemia on ²⁰¹Tl imaging, plus other clinical variables (age, sex, race, site of myocardial infarction, history of coronary artery disease, treatment with β blockers, and peak serum creatine kinase concentration). Cox's regression was performed for each variable separately (univariate) and also for all variables together (multivariate) with both forward and backward variable selection. A cut off point of $P = 0.01$ was used to select significant variables. Kaplan-Meier survival curves were also plotted for the two categories of patients with and without evidence of ischaemia on ²⁰¹Tl imaging (the most significant variable), together with the survival curves for positive and negative exercise test for comparison. Sensitivity, specificity, and predictive values were also calculated for both tests. McNemar's test was used to compare the sensitivities and specificities of the two investigations.

Results

DEMOGRAPHY

In all, 230 consecutive patients admitted to the coronary care unit for suspected myocardial infarction were screened. Despite fulfilling the electrocardiographic entry criteria of the study, 83 patients were excluded because they were elderly, infirm, or had arthritis, precluding treadmill exercise (22 patients); had severe heart failure (18); had severe asthma or chronic pulmonary disease, limiting exercise capacity (15); were unable to participate in the study owing to personal reasons (17); or were from outside our region and unable to attend follow up clinics (11).

Thus, 147 patients were initially identified for the study. Subsequently, 28 were excluded for the following events, which occurred before investigation at six weeks after myocardial infarction: four deaths; reinfarction (8 patients), unstable angina or revascularisation (11), and new or worsening heart failure (5). A further six patients were unable to exercise, five had incomplete ²⁰¹Tl imaging, five were judged not to have sustained an acute myocardial infarction on the basis of serial testing for cardiac enzymes, and three were lost to follow up. Hence 100 patients remained in the study.

The average age was 61 (range 34-81) years; 88 were men. Fifty five patients were current or former smokers, 15 had a history of coronary artery disease, 15 were hypertensive, and 13 diabetic. Fifty patients had anterior (including septal and lateral) infarction, and 50 had inferior (including posterior) infarction. The mean peak creatine kinase concentration was 1767 IU. All patients had thrombolysis. Ninety seven had streptokinase, while three had tissue plasminogen activator (tPA) by the conventional regimen.¹⁴ All patients were treated with aspirin and subcutaneous heparin, 55 patients were taking β blockers, and sublingual nitrates were prescribed when necessary. Treatment was not

Fig 1—Planar ²⁰¹Tl scans in anterior projection with exercise (left) and rest images (right) in patient with inferior myocardial infarction. The exercise image shows lack of ²⁰¹Tl uptake in the inferior wall (arrow). The rest image shows almost complete normalisation, indicative of reversible ischaemia. This patient had a negative exercise test and no angina but had a subsequent adverse cardiac event

Table 1—Distribution of adverse cardiac events during follow up and their prediction by ^{201}Tl imaging and exercise electrocardiography. Values are numbers of patients

Adverse cardiac event	Total No of events	Predicted by:	
		^{201}Tl Imaging	Exercise electrocardiography
Death	3	2	0
Reinfarction	5	4	1
Unstable angina	17	16	8
Congestive heart failure	12	11	4
Total	37	33	13

Table 2—Sensitivity, specificity, and positive and negative predictive values for exercise electrocardiography and ^{201}Tl imaging. Values are percentages (confidence interval; proportion) of patients

Test	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Ischaemia on exercise electrocardiography	35 (20 to 53); 13/37	68 (55 to 79); 43/63*	39 (13/33)	64 (43/67)
Reversible ischaemia on ^{201}Tl	89 (75 to 97); 33/37**	44 (32 to 58); 28/63	49 (33/68)	88 (28/32)

*P = 0.004.

**P < 0.001.

withdrawn before investigations, except for sublingual nitrates, which were stopped within four hours of the exercise test.

All patients were followed up for a period of 8-32 (mean 21) months after infarction. Of the 100 patients, 37 had adverse cardiac events during the follow up period (table 1).

EXERCISE ELECTROCARDIOGRAPHY

Thirty three patients had a positive exercise test based on the ST segment criteria with or without anginal symptoms; 13 (39%) of these had adverse cardiac events during follow up, compared with 24 (36%) of the 67 patients with no evidence of ischaemia on exercise (hazard ratio 1.1 (95% confidence interval 0.56 to 2.2), P = 0.8).

THALLIUM-201 IMAGING

Exercise and separate day rest ^{201}Tl imaging showed that 68 patients had significant reversible ischaemia, of whom 33 (49%) subsequently had cardiac events. ^{201}Tl imaging detected reversible ischaemia in 33 (89%) of the 37 patients who had an adverse cardiac event. Of the 32 patients who did not have evidence of reversible ischaemia, only four (13%) had adverse cardiac events. This was a highly significant result (hazard ratio 8.1, 95% confidence interval, 2.7 to 23.8, P < 0.001).

Sensitivity, specificity, and positive and negative predictive values were calculated for exercise electrocardiography and ^{201}Tl imaging (table 2). ^{201}Tl imaging had a significantly higher sensitivity than exercise electrocardiography (P < 0.001), while the specificity of the latter was higher (P = 0.004). The positive and negative predictive values depended on the prevalence of events and were calculated accordingly. Both the positive and negative predictive values were greater for ^{201}Tl imaging than for exercise electrocardiography (table 2).

With multivariate analysis only two variables were found to predict risk independently: the presence of reversible ischaemia by ^{201}Tl imaging (P < 0.001) and history of coronary artery disease (P < 0.01). History of coronary artery disease, however, was present in only 15 of the 100 patients.

Kaplan-Meier survival curves were plotted from the ^{201}Tl imaging data and the exercise test for comparison. The groups with and without ischaemia on ^{201}Tl

imaging showed a clear and significant separation beginning at about two to three weeks after imaging. The two curves continued to diverge throughout the follow up period. In contrast, the survival curves for positive and negative exercise tests do not separate at all at any time (figs 2 and 3).

Discussion

RISK STRATIFICATION BEFORE THROMBOLYSIS

There have been many attempts to stratify high and low risk patients after acute myocardial infarction. Norris *et al* and Peel *et al* used clinical variables in risk stratification.^{15 16} Other investigators used infarction exercise testing after infarction and identified ST segment depression of ≥ 1 mm as a marker of increased mortality at one year.¹⁷⁻¹⁹ Others described total exercise time and frequency of arrhythmia as a superior predictor of adverse events to ST segment depression.²⁰ Left ventricular ejection fraction has also been described as a sensitive marker of prognosis in this setting.²¹

Before the use of thrombolysis Gibson *et al* showed that presence of defects on ^{201}Tl imaging in more than one vascular zone, redistribution of ^{201}Tl , and increased lung ^{201}Tl uptake were better predictors of future cardiac events than either exercise electrocardiography or coronary angiography.⁶ Leppo *et al* and Brown *et al* have shown by dipyridamole ^{201}Tl imaging both late and early after infarction that ^{201}Tl redistribution predicted future cardiac events.^{22 23} In contrast, Hung *et al*, in a study of 117 male patients studied by exercise electrocardiography, ^{201}Tl imaging, and radionuclide ventriculography three weeks after infarction, found that a reduced treadmill workload and a fall in ejection fraction on exercise were the only significant predictors of hard cardiac events—that is, death and reinfarction.²⁴

Fig 2—Kaplan-Meier survival curves for patients with and without ischaemia on exercise electrocardiography (hazard ratio 1.1 (95% confidence interval 0.56 to 2.2), P = 0.8)

Fig 3—Kaplan-Meier survival curves for patients with and without reversible ischaemia on ^{201}Tl imaging (hazard ratio 8.1 (95% confidence interval 2.1 to 23.8), P < 0.001)

Key messages

- Thrombolysis has reduced mortality but increased ischaemic events after infarction
- Exercise electrocardiography is a poor predictor of such events
- Presence of reversible ischaemia on ^{201}Tl imaging identifies 89% of patients who subsequently have such events

RISK REDUCTION BY THROMBOLYSIS

The use of thrombolysis has greatly reduced mortality after myocardial infarction.^{1,2} The salvaged myocardium in the infarct related arterial territory, however, is likely to place the patient at higher risk of future cardiac events, especially in the presence of residual critical stenosis of the infarct related artery. An area of such viable but ischaemic myocardium may be the cause of angina, myocardial infarction, arrhythmia, and sudden death.²⁻⁴

We studied a group of clinically stable patients—who had received thrombolytic treatment—six weeks after infarction. This strategy tended to eliminate those patients who were most unstable after myocardial infarction as they would already have had an adverse cardiac event or undergone invasive studies and intervention and thus would have been excluded from this study. Even in this apparently “stable” group of patients, however, the event rate was 37% during a follow up of 8 to 32 months. The population studied is typical of a district general hospital, and the events were clearly predefined by standard criteria—thus highlighting the need for an investigation which can accurately stratify these patients.

STRATIFICATION SINCE THROMBOLYSIS

Stevenson *et al* showed that among 256 patients given thrombolysis for myocardial infarction, of whom 41 had events, ST segment depression at low workload and low exercise capacity identified only 50% and 70% respectively of those having cardiac events, and the positive predictive accuracy of exercise electrocardiography was poor.⁵ In this study the use of stress and rest ^{201}Tl imaging to show reversible ischaemia was superior to conventional exercise electrocardiography for detecting adverse cardiac events. During a 21 month (mean) follow up period, ^{201}Tl imaging identified 33 out of the 37 (89%) of the patients with subsequent adverse cardiac events. Although the positive predictive value of neither test was particularly high, the negative predictive value of ^{201}Tl imaging was excellent (88%)—only 4 of the 32 patients without reversible ischaemia on ^{201}Tl imaging had cardiac events.

Technical difficulty with ^{201}Tl protocols may reduce the sensitivity of the test if only exercise and redistribution imaging are used.²⁵ Using such a protocol, Tilkemeier *et al* failed to show the discriminating value of ^{201}Tl imaging.²⁶ Jain *et al* improved the detection of jeopardised myocardium (74%) in patients who had undergone thrombolysis after infarction, using 24 hour delayed ^{201}Tl imaging after vasodilator stress testing using dipyridamole, but did not address the prognostic significance of this finding.²⁷

In this study we used a cut off of two segments of reversibility as significant. This was based on previous data.²⁸ However, different segmental cut offs may be used, and this will alter the sensitivity and specificity obtained. The positive predictive value of the test was 49%. More patients with reversible defects, however, may have events on longer follow up (some patients on this study were followed up for less than one year). We consider that the relevant finding is that large numbers

of patients have reversible defects after thrombolysis. Early invasive investigations in this group would identify those who need further intervention. This may lead to invasive procedures in some who remain completely stable but is likely to lead to improved management for those at high risk. In this context, the financial and human costs involved in ^{201}Tl imaging and angiographic studies are likely to be substantially smaller than those involved in actually admitting these patients for reinfarction, unstable angina, or heart failure.²⁹

CONCLUSION

The most widely used investigation, exercise electrocardiography, failed to identify correctly patients with a high risk of developing future cardiac events in an otherwise clinically stable group of patients with myocardial infarction who had received thrombolysis. However, reversible ischaemia by stress and rest ^{201}Tl imaging identified 89% of patients who had adverse cardiac events. Moreover, the lack of reversible ischaemia by ^{201}Tl had a high negative predictive accuracy for assessing risk.

These data also suggest that, though thrombolysis has significantly reduced mortality, a large proportion of patients are left with viable but potentially ischaemic myocardium, and thus routine evaluation with myocardial perfusion imaging may help to stratify those at high risk. Resources can then be appropriately allocated by selecting these patients for early intervention and management.

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Differences in mortality and morbidity in African Caribbean and European people with non-insulin dependent diabetes mellitus: results of 20 year follow up of a London cohort of a multinational study

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Abstract

Objective—To examine differences in morbidity and mortality due to non-insulin dependent diabetes in African Caribbeans and Europeans.

Design—Cohort study of patients with non-insulin dependent diabetes drawn from diabetes clinics in London. Baseline investigations were performed in 1975-7; follow up continued until 1995.

Patients—150 Europeans and 77 African Caribbeans with non-insulin dependent diabetes.

Main outcome measures—All cause and cardiovascular mortality; prevalence of microvascular and macrovascular complications.

Results—Duration of diabetes was shorter in African Caribbeans, particularly women. African Caribbeans were more likely than the Europeans to have been given a diagnosis after the onset of symptoms and less likely to be taking insulin. Mean cholesterol concentration was lower in African Caribbeans, but blood pressure and body mass index were not different in the two ethnic groups. Prevalence of microvascular and macrovascular complications was insignificantly lower in African Caribbeans than in Europeans. 59 Europeans and 16 African Caribbeans had died by the end of follow up. The risk ratio for all cause mortality was 0.41 (95% confidence interval 0.23 to 0.73) ($P = 0.002$) for African Caribbeans v Europeans. This was attenuated to 0.59 (0.32 to 1.10) ($P = 0.1$) after adjustment for sex, smoking, proteinuria, and body mass index. Further adjustment for systolic blood pressure, cholesterol concentration, age, duration of diabetes, and treatment made little difference to the risk ratio. Unadjusted risk ratios for cardiovascular and ischaemic heart disease were 0.33 (0.15 to 0.70) ($P = 0.004$) and 0.37 (0.16 to 0.85) ($P = 0.02$) respectively.

Conclusions—African Caribbeans with non-insulin dependent diabetes maintain a low risk of heart disease. Management priorities for diabetes

developed in one ethnic group may not necessarily be applicable to other groups.

Introduction

People with non-insulin dependent diabetes mellitus continue to be at a greater risk than the general population of dying young, particularly of ischaemic heart disease.¹⁻⁴ Morbidity, generally related to the microvascular complications of diabetes, is also high. The avoidance of these complications and the reduction in the risk of excess mortality are prime therapeutic aims of caring for people with diabetes. Management guidelines to achieve these aims are informed by studies that examine relations between risk factors and disease to show where scarce resources should be targeted. But most of these studies have been performed in European populations, with the assumption that the risk factors and their relations are consistent across all ethnic groups. These assumptions may not, however, be true.⁵⁻⁷ This has important implications for funding health care where people from minority ethnic groups constitute a substantial proportion of the diabetic population.

Studies examining mortality and complication rates in minority ethnic groups are limited and have generally been performed in the United States, where access to health care is highly inequitable,^{8,9} potentially confounding comparisons of complication rates and mortality by ethnic group. To our knowledge, no study determining ethnic differences in mortality has been completed in the United Kingdom, where access to appropriate health care is less likely to be a key factor in determining the burden of disease and subsequent risk of death. We examined the morbidity and mortality associated with diabetes in a 20 year follow up study of African Caribbeans and Europeans with non-insulin dependent diabetes in the United Kingdom.

Subjects and methods

Data from the London cohort of the World Health Organisation's multinational study of vascular disease in diabetes were used for these analyses. Detailed methods

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