Use of radionuclide angiography and an electrocardiographic stress test to diagnose multivessel disease after a first episode of uncomplicated myocardial infarction

ALBERTO FUBINI,* ENRICO CECCHI,* MARIA T SPINNLER,*
MARGHERITA DI LEO,* SERENA BERGERONE,* FULVIO ORZAN,*
PATRIZIA PRESBITERO,* PIERO MORELLO,† GIANCARLO CASTELLANO,†
GIANLUIGI TURCO,† ANTONINO BRUSCA*

*From the *Istituto di Medicina e Chirurgia Cardiovascolare, and †Cattedra di Medicina Nucleare, Istituto di Medicina Interna, Università di Torino, Turin, Italy*

SUMMARY Sixty consecutive patients who were symptom free 2–12 months after an uncomplicated acute myocardial infarction underwent maximal treadmill exercise testing, radionuclide angiography before and during submaximal bicycle stress test, and coronary angiography. The results of the non-invasive procedures were compared with those of coronary angiography. The sensitivity and specificity of electrocardiogram stress test for detection of multivessel disease were 40% and 77% respectively. Failure of left ventricular ejection fraction to increase at least 5% with exercise identified 20 of the 25 patients with multivessel disease (sensitivity 80%) and 23 of the 35 patients with no additional coronary artery stenosis (specificity 66%). In patients with anterior Q waves the sensitivity was 78% and the specificity 50%, whereas in the presence of inferior Q waves these values were 81% and 87% respectively. Loss of left ventricle synchronicity during effort, as indicated by failure of the standard deviation of the phases to decrease during exercise, demonstrated a radionuclide angiography sensitivity of 80% (77% for anterior myocardial infarction and 81% for inferior myocardial infarction) and a specificity of 50% (33% for anterior myocardial infarction and 64% for inferior myocardial infarction). When the test was considered to be positive if either the ejection fraction or the standard deviation of the phases criteria were positive, the sensitivity was 100% and specificity 46% (30% for anterior myocardial infarction and 65% for inferior myocardial infarction).

It is concluded that in patients who are free from angina 2–12 months after an episode of uncomplicated myocardial infarction, a simple exercise electrocardiogram cannot be relied upon to detect residual ischaemia. An abnormal ejection fraction response or an increased standard deviation of the phases during exercise nuclear angiography or both identified all the patients with multivessel disease. None of the patients in whom radionuclide angiographic criteria were negative had multivessel disease.

Several post-myocardial infarction risk stratification studies have identified three major variables related to subsequent coronary events: the extent of myocardial damage, residual coronary artery disease,

and the degree of electrical instability.^{1–3} In the first year after hospital discharge roughly 5%–10% of patients will die, 6% will experience a new episode of non-fatal myocardial infarction, and 16% will develop angina.^{4–6} Contrast ventriculography and coronary angiography have been widely used to evaluate the left ventricular function and the extent of coronary disease in post-myocardial infarction patients, and both have proved to be highly predic-

Requests for reprints to Professor A Brusca, Divisione Universitaria di Cardiologia, Corso Polonia 14, 10123 Turin, Italy.

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tive of subsequent cardiac death, reinfarction, and angina.⁷⁻⁹

It is not practicable, or necessarily desirable, to recommend coronary arteriography to every patient recovering from myocardial infarction, especially when the clinical course is uncomplicated and the patient is symptom free.

Coronary angiography, however, is usually advised in younger patients and those with evidence of residual reversible myocardial ischaemia suggestive of additional coronary artery disease. We have assessed the value of exercise test and of exercise radionuclide angiography in detecting residual coronary arterial stenoses in such a group of patients.

Patients and methods

We studied sixty consecutive patients under the age of 60 years who were referred to our outpatient department 2-12 months after the diagnosis of uncomplicated myocardial infarction.

The diagnosis of myocardial infarction was based on the history of typical chest pain, the appearance of abnormal Q waves or evolutionary ST-T changes, and an increase in cardiac enzymes. We excluded patients with residual resting and effort angina, congestive heart failure (S3, cardiomegaly, need for digitalis and diuretics), and valvar heart disease. Patients with a history of previous myocardial infarction were excluded because they were likely to have had coronary angiography.^{2,10}

Cardioactive drugs were discontinued at least two days before the various tests. Each test was assessed by two investigators who were unaware of the results of the other two studies. The non-invasive tests were performed on two successive days; coronary angiography followed two days to two weeks later.

ELECTROCARDIOGRAM

The development of Q wave or loss of R wave voltage >50% in leads I, aVL, or V1-V6 was taken as evidence of anterior myocardial infarction (27 patients), and that in leads II, III, and aVF was taken to indicate an inferior myocardial infarction (33 patients).

EXERCISE TESTING

A maximal treadmill exercise test was performed according to the Bruce protocol.¹¹ Twelve lead electrocardiograms were recorded before exercise with the patient supine and standing and during the Val-salva manoeuvre; and again after each minute of exercise, and 1, 3, 5, and 10 minutes after exercise, and at the onset of angina and a peak exercise. Exercise was stopped when any of the following

occurred: incapacitating fatigue, dyspnoea or progressive angina, major arrhythmias (ventricular extrasystoles that increased during exercise, polymorphic ventricular extrasystoles, couplets, sustained or non-sustained ventricular tachycardia) or a systolic blood pressure drop of more than 15 mm Hg.

The test was deemed to be positive if angina occurred and/or horizontal or downsloping ST segment depression >1 mm at 0.08 s after the J point in a non-Q wave lead was recorded. In patients with resting ST-T segment abnormalities an additional shift of 1 mm or more was considered to be important.¹²

CARDIAC CATHETERISATION

Coronary angiography was performed in multiple projections. Left ventriculography was done in both left anterior oblique and right anterior oblique projections. Each patient had three, two, or single vessel disease.¹³ Coronary artery lesions with a luminal narrowing $\geq 70\%$ in diameter were regarded as important. Where there were multiple stenoses of the same vessel only the most severe one was noted. Considerable narrowing in a large diagonal or obtuse marginal branch was recorded as left anterior descending and left circumflex disease respectively.

RADIONUCLIDE ANGIOGRAPHY

Radionuclide counts were acquired by the blood pool gating technique, with the patients at rest in upright position on the bicycle, at a stable heart rate. In our experience a count of 400 000-600 000 per frame is adequate; this can be done in five to eight minutes at rest. During the exercise test the workload was increased by 30 W every three minutes until 90% of the predicted maximal heart rate was attained. At this level the heart rate is steady and normal and abnormal ejection fraction responses to exercise can be easily identified.¹⁴ The count acquisition at submaximal exercise level was begun when a steady state was achieved and could not be prolonged for more than 4 minutes; this allowed us to acquire 150 000-300 000 counts per frame.

Red blood cells were labelled in vivo with 15-20 mCi of technetium-99m, after administration of a stannous agent.¹⁵ We used a standard Anger camera equipped with a slant-hole collimator connected online to a dedicated minicomputer.

We used the left anterior oblique projection with craniocaudal tilt of 15-30°, which offers the best separation between atria and ventricles and between left and right ventricle.

Data were acquired in frame mode, 64 × 64

matrix, dividing the heart cycle in 16 equal intervals. Extrasystoles were rejected.

ANALYSIS OF RADIONUCLIDE ANGIOGRAPHY VENTRICULOGRAMS

The rough data were spatially smoothed by means of a conventional nine point convolutive filter (weights 4, 2, 1), then a pixel by pixel discrete Walsh-Hadamard transformation¹⁶ was applied to obtain phase and amplitude parametric images.

We used an interpolative method derived by Goris *et al*¹⁷ based on the technique of the subtract background activity from the smoothed sequences. The left ventricular ejection fraction was calculated by a standard technique from the background-corrected time-activity curve that was constructed over the diastolic region of interest of the left ventricle. Finally, we applied the left ventricular region of interest curve to the phase maps and calculated the mean value and the standard deviation of the phases by the Ratib *et al* procedure.¹⁸

CRITERIA FOR POSITIVE RADIONUCLIDE ANGIOGRAPHIC TESTS

The criteria for a positive radionuclide angiographic test were failure of left ventricular ejection fraction to increase by $\geq 5\%$ on exercise and/or failure of the standard deviation of the phases to decrease during effort. We also investigated whether a positive result for either of the tests would have increased the detection of residual coronary arterial stenoses when the information that they provided was combined with the results of other tests.

STATISTICAL ANALYSIS

Data were stored on disc and analysed with the SAS package on a IBM 370 compatible computer system. The diagnostic success of the variables was calculated as sensitivity (true positive $\div$ (true positives + false negative)) and specificity (true negatives $\div$ (true negatives + false positives)). We used χ^2 and Fisher's exact tests to assess the relation between the diagnostic tests and the results of coronary angiography. One way analysis of variance was applied for continuous variables in order to evaluate the differences between patient subgroups. A value of $p < 0.05$ was taken to be statistically significant.

Table 1 Results of coronary angiography

Myocardial infarction	0 vessel	1 vessel	2 vessel	3 vessel
Anterior	3 (11%)	15 (56%)	6 (22%)	3 (11%)
Inferior	2 (6%)	15 (46%)	12 (36%)	4 (12%)
Total	5 (8%)	30 (50%)	18 (30%)	7 (12%)

Results

ANGIOGRAPHIC FINDINGS

Clinically unimportant lesions were found in four patients, and another patient had entirely normal coronary arteries (Table 1). Thirty patients (50%) had important lesions or complete occlusion only of the infarct related coronary artery. We found multivessel disease in 25 patients (42%); 18 had two vessel (30%), six (10%) had three vessel, and one had left main stem disease. We included the patient with left main stem disease, who also had a 50% lesion on the right coronary artery, in the three vessel group for statistical analysis.

Twenty nine patients had important lesions of the left anterior descending coronary artery, 15 had single vessel disease and 14 had multivessel disease.

Multivessel disease was more frequent in patients with inferior Q waves (45%) than in patients with anterior Q waves (33.5%), but the difference was not significant ($p < 0.1$) (Table 1).

EXERCISE TEST

Eighteen patients had a positive exercise test by electrocardiographic criteria; 10 of the 18 had multivessel disease. Forty two patients had a negative exercise test. Fifteen of them had multiple coronary stenoses, and they were regarded as false negatives. Thus this test had a sensitivity of 40% and specificity of 77% (Table 2). Only two of the seven patients with three vessel or left main coronary artery disease had a positive exercise test.

Of 27 patients with anterior Q wave myocardial infarction, only four had a positive test; ST depression was present in the lateral leads of three and in the inferior leads of one. Additional coronary artery disease was present in only one (left anterior descending and right coronary artery). Thus in this group sensitivity was 11% and specificity was 83% (Table 2).

In patients with inferior Q wave myocardial infarction sensitivity was 56% and specificity 70% (Table 2).

RADIONUCLIDE ANGIOGRAPHY FINDINGS

The radionuclide angiographic test was positive by the ejection fraction criterion alone in 20 of the 25 patients with multivessel disease (sensitivity 80%) and negative in 23 of the 35 patients with no addi-

Table 2 Results of exercise test

Exercise test	ACD	No ACD	Total	p value
		Complete group*		
Positive	10	8	18	NS
Negative	15	27	42	NS
Total	25	35	60	
		Anterior myocardial infarction†		
Positive	1	3	4	NS
Negative	8	15	23	NS
Total	9	18	27	
		Inferior myocardial infarction‡		
Positive	9	5	14	NS
Negative	7	12	19	NS
Total	16	17	33	

ACD, additional coronary disease.

*Sensitivity, 40%; specificity, 77%.

†Sensitivity, 11%; specificity, 83%.

‡Sensitivity, 56%; specificity, 70%.

Table 3 Results of radionuclide angiography and ventriculography as related to coronary angiography

	No ACD*	ACD†	Sensitivity	Specificity	p
Ejection fraction:	23/35	20/25	83%	66%	<0.001
Anterior MI	9/18	7/9	78%	50%	NS
Inferior MI	14/17	13/16	81%	87%	<0.001
SD of phases:	17/35	20/25	80%	48%	<0.01
Anterior MI	6/18	7/9	78%	33%	NS
Inferior MI	11/17	13/16	81%	64%	=0.002
Ejection fraction or					
SD of phases:	16/35	25/25	100%	46%	<0.001
Anterior MI	5/18	9/9	100%	30%	NS
Inferior MI	11/17	16/16	100%	65%	<0.001

*Ratio of patients with negative radionuclide angiographic test to patients without additional coronary disease.

†Ratio of patients with positive radionuclide angiographic test to patients with additional coronary disease.

ACD, additional coronary disease; MI, myocardial infarction.

Table 4 Relation of results of radionuclide angiography to coronary angiography in patients with left anterior descending artery disease

	No ACD	ACD	Sensitivity	Specificity
Ejection fraction or SD phase:	3/15	14/14	100%	20%
Inferior MI	1/2	7/7	100%	50%
Anterior MI	2/13	7/7	100%	15%

Table 5 Clinical, angiographic, and haemodynamic correlates (mean (SD)) in cases with false positive and with true negative and true positive results at radionuclide angiographic testing

	False positive	True negative	True positive
Age (years)	47 (6.8)	50 (6.8)	48 (9)
Systolic arterial pressure (mm Hg)	125 (16)	125 (19)	130 (18)
Diastolic arterial pressure (mm Hg)	80 (11)	82 (14)	85 (15)
LAD disease	63%†	19%†	57%
*ST elevation	80%‡§	15%†	20% (2/11)§
Resting ejection fraction (%)	45 (16)	49 (12)	52 (3)
Resting SD phase (°)	18 (2)	17 (6)	16 (1.6)
LVEDP (mm Hg)	14 (7)	13 (5)	15 (9)

*On the resting electrocardiogram.

LVEDP, left ventricular end diastolic pressure; LAD, left anterior descending.

Group comparisons: †p < 0.001; ‡p < 0.001; §p < 0.002.

tional coronary artery stenosis (specificity 66%) (Table 3). In patients with anterior Q waves the sensitivity was 78% and the specificity was 50%, whereas in the presence of inferior Q waves these values were 81% and 87% respectively.

Loss of left ventricular synchronicity as indicated by an increase of the standard deviation of the phases during exercise had a sensitivity of 80% (77% for anterior myocardial infarction and 81% for inferior myocardial infarction) and a specificity of 48% (33% for anterior myocardial infarction and 64% for inferior myocardial infarction).

If the test was considered to be positive when either the ejection fraction or the standard deviation of the phases criterion was positive, sensitivity increased to 100% and specificity decreased to 46% (30% for anterior myocardial infarction and 65% for inferior myocardial infarction).

Tables 4 and 5 show that of several different variables, only the presence of left anterior descending artery disease and of ST segment elevation on the resting electrocardiogram were significantly associated with false positive results by radionuclide angiography. All patients with three vessel or left main stem disease were positive at radionuclide angiography and in all of them the ejection fraction decreased on exercise.

Discussion

The management of symptom free patients several months after an uncomplicated myocardial infarction is a common and yet controversial clinical problem. This study attempts to delineate the prevalence of multivessel disease in this particular subset of patients and to relate the results of the exercise test and of exercise radionuclide angiography to the degree and extent of coronary arterial obstructions.

Many other studies have correlated the results of non-invasive functional tests after myocardial infarction with the coronary angiographic findings,^{12 19-26} but most of the authors had conducted their investigations within the first few weeks after the acute episode, when mortality is highest,²⁷ and they have examined a mixed population that included both patients with symptoms and those without. Most deaths and cardiac events occur in the first 8-12 weeks after an acute myocardial infarction, and this is the rationale for performing a pre-discharge exercise test. Such policy, however, is not universal, and patients who are symptom free after an acute myocardial infarction and have not yet been evaluated are often seen in the outpatient clinic several months after the acute episode.

CORONARY ANATOMY

Several groups have studied the extent and distribution of coronary arterial disease in patients after an acute myocardial infarction. Williams *et al* found multiple vessel disease in 67% of patients with angina after myocardial infarction.²⁸ In a similar population Hamby *et al* found multivessel disease in 86% of patients with previous inferior myocardial infarction and in 82% of patients with previous anterior myocardial infarction.²⁹ Turner *et al* found that 73% of 61 patients studied within 30 days after an uncomplicated myocardial infarction had multivessel disease.³⁰ Miller *et al* examined 84 patients with previous uncomplicated inferior myocardial infarction who were in functional class NYHA II or III, and found multivessel disease in 80%.³¹ In a similar group of 108 patients with inferior myocardial infarction in NYHA class II or III Chaitman *et al* found 79% of multivessel disease.³² In a group of symptomatic and asymptomatic patients studied within 6-8 weeks after the acute episode the prevalence of multivessel disease was 63% in inferior and 42% in anterior myocardial infarction.²¹ Similarly Gibson *et al* found multivessel disease in 56% of 140 patients in Killip class 1-3 who were studied about 11 days after myocardial infarction.²² Betriu *et al* found that 59% of 259 survivors who were studied one month after myocardial infarction had multivessel disease.³³

Unlike the groups above we selected only patients who were symptom free two or more months after acute myocardial infarction.

The prevalence of multivessel disease is lower (42%) in our population than in previous studies. The longer interval in our study between the acute episode and the time of evaluation may have favoured the occurrence of angina and/or a new acute myocardial infarction in patients with more advanced disease, and such patients would therefore have been excluded. In fact in most of the previous reports asymptomatic and symptomatic patients as well as patients with more than one acute myocardial infarction were studied, and the likelihood of multivessel disease is higher in such a mixed population.

EXERCISE TEST

In the present study only 10 (40%) of the 25 patients with multivessel disease had 1 mm or greater depression of the ST segment or angina or both during a maximal treadmill stress test. These results accord with some of the previous studies which showed low sensitivity of stress induced electrocardiographic changes after an acute myocardial infarction.^{19-23 25 32 34-38} The low sensitivity of electrocardiographic exercise test may also be due to the large number of patients with anterior Q wave

myocardial infarction.³⁹ The sensitivity of the test improves when analysis is restricted to patients with inferior Q waves. By an exercise test alone, however, 60% of our patients with multivessel disease would have been missed. Our results are somewhat at variance with those obtained by others.^{12 40} This may be explained by different criteria in the selection of patients and by the time at which electrocardiographic exercise stress test and coronary angiography were performed.

The reduced frequency of positive electrocardiographic exercise stress test after myocardial infarction may be related to the loss of large amounts of viable myocardium, cancellation of electrical forces as a result of diffuse ischaemia, and the presence of ST changes on the resting electrocardiogram, especially in patients with anterior myocardial infarctions.

RADIONUCLIDE ANGIOGRAPHY

For the evaluation of radionuclide angiographic results we considered two variables—the ejection fraction and the standard deviation of the phases. In normal individuals the ejection fraction is known to increase during exercise.^{41 42} The variation of the standard deviation of the phases with exercise is a more controversial concept.

We agree with Ratib *et al* that the variability of the standard deviation of the phases is due to opposite mechanisms¹⁸—(a) an increase is related to the different relative duration of systolic and diastolic phases at rest compared with during exercise and (b) a decrease is due to improved synchronicity of systolic wall motion with exercise. The influence of total acquired counts and of noise on the images is relatively unimportant because first harmonic phase analysis is in itself a heavy low-band filter. In 20 subjects with no evidence of cardiovascular disease we found that the standard deviation of the phases at rest (16.3 (3.6)) fell significantly on exercise (10.7 (2.6)) (unpublished data).

In our population the failure of ejection fraction to increase or an increase in the standard deviation of the phases during exercise were both more sensitive than conventional exercise electrocardiographic changes in detecting residual myocardial ischaemia. Furthermore, all the patients with three vessel disease or with previous inferior myocardial infarction and left anterior descending stenosis were correctly identified. The addition of either of these two criteria substantially increased the sensitivity of radionuclide angiography and all cases with multivessel disease were detected by either of these combinations. Ratib *et al* reported that the standard deviation of phase can increase even when the ejection fraction response to exercise is normal.¹⁸ When both

criteria were negative multivessel disease could be ruled out in all of our patients.

The specificity of radionuclide angiography studies was lower than that of exercise electrocardiogram criteria especially in patients with previous anterior myocardial infarction.⁴³ The presence of left anterior descending disease was significantly associated with false positive responses (Tables 4 and 5). This finding suggests that the integrity of the myocardial territory supplied by the left anterior descending is the major determinant of the increased ejection fraction during exercise. Furthermore in the modified left anterior oblique projection, the territory of the left anterior descending artery is the area of the left ventricle that is nearest the gamma camera crystal, and small variations in end diastolic/end systolic count excursion are better detected in this area than in the rest of the left ventricle.⁴⁴ Therefore exercise induced ischaemia of viable myocardium may also be important in producing false positive responses in this group of patients.

Coronary artery spasm of uninvolved arteries during exercise and underestimation of the extent of coronary artery disease by coronary angiography in the presence of a diffuse atherosclerotic process are other possible explanations for the false positive results of nuclear stress tests.

Finally, the presence of ST elevation in the leads with abnormal Q waves was significantly related to false positive responses (Tables 5 and 6) suggesting that aneurysm formation and increased wall tension in the border zone may be an important cause of false positive results.²³

CLINICAL IMPLICATIONS

Exercise electrocardiography often failed to identify residual ischaemia in patients who were free from angina 2–12 months after an uncomplicated acute myocardial infarction. In every patient with multivessel disease radionuclide angiography during exercise showed an abnormally low ejection fraction and an increase in the standard deviation of the phases. The percentage of false positives was high, especially in patients with previous anterior myocardial infarction.

None of the patients in whom both radionuclide angiographic criteria were negative had multivessel disease.

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