Limitations of radionuclide ventriculography in the non-invasive diagnosis of coronary artery disease

A correlation with right heart haemodynamic values during exercise

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SUMMARY A consecutive series of 56 patients with chest pain but no evidence of previous myocardial infarction was prospectively studied by radionuclide ventriculography to determine the value of global and regional radionuclide indices in detecting coronary artery disease. The results were correlated with the clinical judgment of chest pain, the results of the exercise electrocardiogram, and the right heart haemodynamic measurements during exercise. As a result of the criteria for entry, the study group was representative of the population seen in such a clinical setting. Only 25% of patients had coronary artery disease. The predictive power of radionuclide ventriculography was limited. The conventionally used criterion that normal subjects have an increase in left ventricular ejection fraction of at least 5% with exercise provided only 78% sensitivity and 57% specificity. Fourier analysis and visual interpretation of radionuclide studies wrongly diagnosed three out of 10 patients with extensive disease requiring surgery.

These results suggest that radionuclide ventriculography is of limited value in the non-invasive diagnosis of coronary artery disease.

The recent development of radionuclide ventriculography offers a non-invasive method of assessing global and regional left ventricular function. Early studies¹⁻³ suggested that this method might be an almost perfect screening procedure for coronary artery disease, while recent reports have raised serious doubts.⁴⁻⁷ Controversy continues to exist concerning the reliability of radionuclide ventriculography as a test for coronary artery disease before coronary angiography. Some previous studies are of limited value in this regard, because patients with a history of myocardial infarction were included, medications were not withdrawn before exercise stress testing, or

healthy asymptomatic volunteers were used as control groups.

Avoiding these potential shortcomings, this prospective investigation was performed (a) to determine the ability of radionuclide ventriculography to identify those subjects with significant coronary artery stenoses within a consecutive series of patients with chest pain and (b) to assess the extent to which additional diagnostic accuracy is gained with the use of global and regional radionuclide indices compared with the history, the exercise electrocardiogram, and the evaluation of right heart haemodynamics during exercise.

Patients and methods

STUDY POPULATION

The study population consisted of consecutive patients admitted for the evaluation of chest pain

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which their referring doctor considered might suggest coronary artery disease. Patient selection was prospective and based on the history, physical examination, resting electrocardiogram, pulmonary function test, and chest radiograph. With the exceptions noted below, the series included all patients referred between 1 September 1982 and 30 June 1983 who met the following criteria: age 30–65 years; no evidence of previous myocardial infarction defined as a hospital diagnosis of infarction or the presence of significant Q waves on the resting electrocardiogram; no evidence of congestive heart failure or valvar heart disease; no arterial hypertension; normal standard chest radiographs; regular sinus rhythm; stable angina allowing the withdrawal of all medications except for short acting nitrates one week before exercise stress testing; normal routine pulmonary function test; and no previous coronary angiography or bypass graft surgery. Exercise stress testing and coronary angiography were carried out within two months (35 (19) days) of each other without an episode or change in the resting electrocardiogram suggesting an intervening coronary event. Informed written consent was obtained.

CLINICAL CLASSIFICATION OF CHEST PAIN

Patients were classified on the basis of their presenting symptoms at the time of admission before exercise testing⁸ as having (a) typical angina if substernal chest discomfort precipitated by exercise and relieved by rest or glyceryl trinitrate within 10 minutes was present; (b) atypical angina if only two of the above features were present; or (c) non-anginal chest pain if only one or none of the above features was present.

RADIONUCLIDE AND HAEMODYNAMIC DATA ACQUISITION

Patients were instructed to stop taking all medications one week before the study. They were allowed to take only sublingual glyceryl trinitrate as necessary up until six hours before stress testing. They were familiar with supine bicycle exercise testing from a previous practice run.⁹ Two hours before the radionuclide study supine exercise was carried out with an electrically braked bicycle ergometer to determine the maximum workload. The initial workload was 25 W, which was increased by 25 W increments every minute until a symptom limited maximum (chest pain, shortness of breath, fatigue) was reached. A six lead electrocardiogram (I, III, aVF, V4–6), blood pressure, and symptoms were recorded at rest and at one minute intervals during exercise. The ST segment response was considered to be positive if at least 1 mm flat or downsloping ST depression persisted 0.08 s after the J point in three consecutive cardiac cycles immediately after stopping exercise. The electrocardiogram was considered to be non-diagnostic in

patients with bundle branch block.

In the nuclear imaging laboratory a flow guided open ended catheter (Flexo-Pulmocath (Grandjean), Intra Co, Saarbruecken, West Germany) was inserted into an antecubital vein and advanced into the pulmonary artery. Its position was verified by continuous pressure monitoring. Pressures were measured with a P23 Statham strain gauge from a reference level 5 cm below the sternal angle. They were averaged over 10 cardiac cycles at rest and during the fourth minute of the maximum workload. Electrocardiogram gated blood pool imaging of the heart was performed after in vivo labelling of red blood cells with 20 mCi (740 MBq) of technetium-99m. Patients were imaged in the left anterior oblique position which provided optimal ventricular separation on the storage oscilloscope. The scintillation camera was tilted to an angle of 15° caudally. This standard scintillation camera (LEM Scintillation Camera, Siemens Inc, Munich, West Germany) was equipped with a high sensitivity all purpose parallel hole collimator interfaced to a dedicated medical computer system (Digital Equipment Corporation, Maynard, Mass, USA). The image data were acquired in frame mode with 32 frames spanning the cardiac cycle. They were formatted into a 32×32 matrix. The pixel area was 6×6 mm². On completion of the resting study supine bicycle exercise was carried out as described above. Patient movement was minimised by the use of hand-grips, shoulder restraints, and foam wedges. When the previously determined maximum workload was reached the patient was asked to continue exercising. Imaging started two minutes after the maximum workload was begun to ensure a relative steady state and continued until approximately 100 000 counts per frame were obtained (2–3 minutes). The occurrence of exercise induced pain suggesting angina was noted.

LEFT HEART CATHETERISATION

Each patient underwent biplane radio-opaque ventriculography in the 30° right anterior oblique and the 60° left anterior oblique position. Selective coronary angiograms were obtained in multiple projections by Judkins's method. Coronary artery disease was diagnosed if at least one major coronary artery had a lesion occluding >75% of the lumen.¹⁰ The angiograms were interpreted by three observers. Disagreements were resolved by joint discussion.

RADIONUCLIDE DATA PROCESSING

The left ventricular ejection fraction was determined from the background corrected time-activity curve as previously described.¹¹ Briefly, the left ventricular regions of interest were manually outlined on the end systolic and end diastolic frames. Background activity was derived from a crescent shaped region adjacent to

Table 1 Clinical characteristics and angiographic data in 56 consecutive patients evaluated for chest pain. Figures are numbers of patients unless stated otherwise

	Normal coronary angiogram (n=42)	Coronary artery disease (n=14)
Mean (SD) age (yr)	49 (7)	49 (7)
Male	29	12
Female	13	2
History of:		
Typical angina	9	10
Atypical angina	16	2
Non-anginal chest pain	17	2
Coronary anatomy:		
Normal	42	0
One vessel disease	0	4
Two vessel disease	0	4
Three vessel disease	0	6
Subsequent operation	0	10

the inferolateral border of the end diastolic left ventricular outline. For the assessment of regional wall motion the left ventricular end diastolic cavity silhouette was divided into eight segments by axes passing through its geometric centre at 45° to each other. The phase and the amplitude of the first Fourier coefficient were determined for each segment using a normalising procedure which set the mean left ventricular amplitude of each study at unity.¹² The standard deviation of phases was calculated for each study. This value was regarded as an index of synchronicity of left ventricular wall motion. It provides a diagnostic accuracy equivalent to that obtained with the use of phase distribution histograms of the individual left ventricular pixels. Finally, each study was visually assessed in an endless loop cine format by two experienced observers who were unaware of any clinical or angiographic data and was classified as normal or abnormal. No borderline category was permitted. An image was considered to be abnormal if regional wall motion abnormalities appeared or increased in severity during exercise. In the case of disagreement the image was re-examined and a consensus obtained. Patients with bundle branch block

were excluded from the visual interpretation and the Fourier analysis.

STATISTICS

Values are expressed as mean (1 standard deviation). Only non-parametric procedures were used since some of the characteristics had non-Gaussian distributions. Individual changes in measurements from rest to exercise were compared by the Wilcoxon matched pairs signed rank test. The Mann-Whitney test was used for analysing intergroup differences. The beta function was used to illustrate the frequency distributions of the left ventricular ejection fractions.¹³

Results

PATIENT CHARACTERISTICS

Seventy three patients met the criteria for entering the study. Of these, 17 were excluded from the analysis: five patients refused coronary angiography; one had an acute myocardial infarction before angiography; in three the pulmonary artery pressures during exercise could not be determined; one had a psychoneurotic disorder; in four radio-opaque ventriculography showed a clinically unrecognised dilative cardiomyopathy; and in three the radionuclide study was technically inadequate. Table 1 summarises the clinical and angiographic data of the remaining 56 patients, only 25% of whom had angiographic evidence of coronary artery disease. Compared with the 42 patients with normal coronary angiograms those with coronary artery disease had a sex distribution consistent with a higher prevalence of coronary artery disease.

RIGHT HEART HAEMODYNAMICS

Table 2 shows the haemodynamic data. The resting diastolic pulmonary artery pressures were consistently within normal limits in both groups. The exercise induced increase was greater in the group with coronary artery disease ($p < 0.01$).

A level of 25 mm Hg, which is similar to the upper

Table 2 Radionuclide and haemodynamic findings at rest and during maximum exercise stress testing in patients with and without coronary artery disease (CAD). Values are mean (SD)

	Without CAD (n=42)	With CAD (n=14)
At rest:		
Diastolic pulmonary artery pressure (mm Hg)	9 (3)	9 (3)
Left ventricular ejection fraction (%)	63 (6)	62 (6)
Standard deviation of phases (°)	5.9 (2.3)	6.4 (2.6)
During exercise:		
Diastolic pulmonary artery pressure (mm Hg)	24 (7)	30 (9)
Left ventricular ejection fraction (%)	68 (10)	53 (14)
Standard deviation of phases (°)	6.2 (2.8)	12.1 (8.1)
Heart rate (beats/min)	140 (16)	132 (16)
Rate-pressure product (beats/min $\times$ mm Hg $\times 10^{-3}$)	27 (5)	24 (5)
Exercise tolerance (W)	140 (40)	110 (30)

Table 3 Sensitivity, specificity, and predictive accuracy of clinical, electrocardiographic, haemodynamic and radionuclide findings. Values are percentages

Test	Sensitivity	Specificity	PA(+)	PA(-)
Clinical assessment of chest pain*	86	40	32	89
Exercise electrocardiography†‡	71	79	55	88
Right heart haemodynamics†	78	59	39	89
<5% increase in LVEF	78	57	38	89
Fourier analysis of regional wall motion‡	64	84	60	86
Visual interpretation of radionuclide studies‡	57	95	80	86

*Typical or atypical angina vs non-anginal chest pain.

†A diastolic pulmonary pressure of >25 mm Hg and an ST segment depression of at least 1 mm are required for test positivity.

‡Patients with bundle branch block are excluded.

LVEF, left ventricular ejection fraction; PA(+), predictive accuracy of a positive result; PA(-), predictive accuracy of a negative result.

limit of normal during exercise in healthy men aged 61–83 years,¹⁴ has been used in this laboratory to discriminate between positive and negative test responses. In this study this threshold value was diagnostically more accurate than a level of 20 mm Hg. Forty one per cent of the subjects with normal angiograms had pressures exceeding the normal range.

ELECTROCARDIOGRAPHY

The electrocardiogram was non-diagnostic in four patients, none of whom had coronary artery disease. Ten subjects failed to achieve at least 85% of their age related maximum heart rates without showing a significant ST depression and thus had unreliable though negative electrocardiograms. One of them was referred for coronary artery bypass surgery.

Figure Frequency distribution curves of the left ventricular ejection fractions as evaluated by the beta function in patients (a) with and (b) without coronary artery disease during rest and exercise.

CLINICAL ASSESSMENT OF CHEST PAIN

The predictive accuracy of the clinical assessment of chest pain compared favourably with that provided by non-invasive testing (Table 3). Typical angina, used as a separate criterion, yielded 71% sensitivity and 78% specificity. Although exertional chest pain was a feature of the history in most patients only 14% of those without but 78% of those with coronary artery disease had chest pain suggesting angina during exercise stress testing.

RADIONUCLIDE FINDINGS

As shown in the Figure the frequency distribution of the resting left ventricular ejection fraction was not significantly different in patients with and without coronary artery disease. The mean left ventricular ejection fraction increased from rest to exercise in the group with normal coronary angiograms. The group with coronary artery disease had a mean decrease in left ventricular ejection fraction during exercise. The individual variation was large.

The values for the standard deviation of phases, which are shown in Table 2, showed a tendency to increase with exercise in the group with normal angiograms ($p < 0.05$). The upper limits of normal were calculated from these values as the mean plus two standard deviations.¹¹ They were 10.5° at rest and 11.8° during exercise. If the latter was used as the diagnostic criterion only 43% of the group with coronary artery disease showed an abnormal phase distribution with exercise. All these patients were classified as having typical angina and experienced chest pain characteristic of angina during exercise stress testing. Phase analysis failed to detect coronary artery disease in any of the group with coronary artery disease who had atypical angina or non-anginal chest pain according to the clinical classification even if the threshold value for test positivity was lowered to the mean plus one standard deviation.

The lower limit of a normal amplitude during exercise was calculated for each segment from the patients with normal coronary angiograms as the mean relative

amplitude minus two standard deviations. An abnormal left ventricular amplitude distribution was considered to be present if at least one myocardial segment showed an amplitude below this threshold level. The presence of an abnormal amplitude pattern during exercise proved to be more sensitive (57% *vs* 43%) but less specific (89% *vs* 95%) for coronary artery disease than an abnormal phase distribution. If an abnormal phase distribution or at least one abnormal segmental Fourier amplitude is regarded as indicating coronary artery disease the specificity is reduced to 84% and the sensitivity increased to 64% (Table 3). No significant additional diagnostic accuracy was obtained with the Fourier analysis compared with the visual interpretation by two experienced observers. The last approach yielded a fairly high specificity (95%) but proved to be insensitive (57%) in detecting coronary artery disease. The diagnostic accuracy of the conventionally used criterion that normal subjects have a $\geq 5\%$ increase in left ventricular ejection fraction during exercise was almost identical to that of the evaluation of right heart haemodynamics during exercise.

SEX DIFFERENCES

Only two women had coronary artery disease. In the remaining 13 women the haemodynamic and radionuclide responses to exercise were not significantly different from those of the men with normal coronary angiograms.

Discussion

The results of this study reflect wide variations in the left ventricular ejection fraction during exercise in patients with coronary artery disease. This fact, which confirms the findings of Gibbons *et al.*,⁵ should not be surprising since a multitude of factors will interrelate to determine this complex variable. The resulting poor predictive power of the ejection fraction response to exercise indicates that the assessment of global left ventricular function cannot be relied on to predict the presence of coronary artery disease with acceptable accuracy. The Fourier analysis, as introduced by Geffers *et al.*,¹⁵ offers a means of objectively evaluating the regions of dyskinesia, which are considered to be a distinguishing feature of coronary artery disease.^{16,17} The left ventricular phase distribution with exercise was recently suggested to be a highly sensitive and specific marker of regional myocardial ischaemia that was slightly superior to the visual interpretation of regional wall motion.¹¹ In this study, however, Fourier analysis as well as visual interpretation failed to detect coronary artery disease in three out of 10 patients who were referred for coronary artery bypass surgery on the basis of their angiographic findings. Two of these subjects were

classified as having typical angina and had positive exercise electrocardiograms. One patient had two vessel disease with a 90% stenosis of the left circumflex artery and an occlusion of the right coronary artery with poor retrograde filling from the left circumflex artery. This patient had no significant increase in left ventricular ejection fraction and normal pulmonary artery pressures during exercise. The second patient also had two vessel disease with an 80% stenosis of the left anterior descending artery and an occlusion of the right coronary artery with poor retrograde filling from the left anterior descending artery. This patient had a normal ejection fraction response but raised pulmonary artery pressures during exercise. The third patient had an occlusion of the left anterior descending artery with fair retrograde filling from the right coronary artery. This patient had an entirely normal ejection fraction and pulmonary artery pressure response to exercise but failed to achieve 85% of the maximum predicted heart rate owing to severe angina without showing significant ST segment depression. Thus radionuclide ventriculography falls short of the demands for sensitivity that a screening test for coronary artery disease should satisfy. This finding requires careful scrutiny since it is at variance with a large number of previous reports.¹⁻³

In our study exercise was performed supine. It is well known that there are important physiological differences in the results of supine and upright exercise tests. Upright and supine radionuclide studies are, however, equally effective in detecting coronary artery disease.^{18,19} Patients were encouraged to exercise to a maximum. Patient movement and gating artefacts at maximum workload may produce less accurate radionuclide measurements. For optimum sensitivity, however, exercise stress testing must be carried out to maximum effort. A submaximal test may miss up to 50% of the ischaemic responses that could be elicited by performing the test to maximum effort.²⁰ The radionuclide studies were technically adequate in all patients included in the final analysis. Previous reports indicate that a standardised exercise protocol for radionuclide ventriculography does not exist. To prevent non-cardiac symptoms such as muscle weakness or internal heat burden from terminating exercise we used an exercise protocol with stages of only one minute in duration. A similar protocol was used by Christopher *et al.*²¹ We conclude that a relative circulatory steady state did exist during radionuclide data acquisition at maximum workload since no significant change occurred in heart rate, blood pressure, or pulmonary artery pressure from the start of image collection until its end.

Stress testing does not detect anatomical lesions but reflects exercise induced abnormalities that are usu-

ally linked to an imbalance of oxygen supply and demand. A decrease in ejection fraction or an increase in the filling pressures may indicate functional impairment, but they are not specific for angiographically visible coronary artery disease. A normal angiogram does not necessarily imply normal function and vice versa. Thaulow *et al* found an abnormal ejection fraction response to exercise in a significant number of patients with normal coronary angiograms and anginal chest pain or positive exercise electrocardiograms.²² They presumed that the abnormal radionuclide findings reflected heart muscle disease at an early stage. We suppose that many of our patients with patent vessels probably also had unidentifiable cardiac disease associated with abnormal function. This population was therefore considerably different from groups of healthy asymptomatic volunteers who are frequently studied to establish the range of the normal response to exercise.^{1 23 24} The application of diagnostic criteria derived under such biased conditions to the routine patient with chest pain will inevitably be misleading. These criteria have to be defined and validated in a study group that is representative of the population encountered in such a clinical setting. Though five subjects who refused coronary angiography had to be excluded, we are convinced that the remaining patients were representative in terms of prevalence, symptoms, age, and sex distribution of those seen in a major diagnostic centre. A pretest or post-test referral bias⁷ was avoided. We proceeded to angiography in each patient regardless of whether or not the non-invasive tests were positive. We presume that the fulfilment of this prerequisite for an accurate evaluation of test sensitivity and specificity²⁵ was a major reason why radionuclide ventriculography was found to be less reliable than previously reported. Numerous reports have included patients with a history of myocardial infarction,^{11 23 26} which improves the sensitivity values. The rationale for excluding these subjects was that we considered it invalid to apply a test for determining whether or not coronary artery disease is present to a patient with documented coronary artery disease.

Except for short acting nitrates all medications were withdrawn one week before stress testing to ensure complete recovery from the effects of any cardioactive agent. Previous work has suggested that beta blockade improves exercise induced global and regional left ventricular dysfunction in subjects with coronary artery disease.²⁷ Battler *et al* reported a mean increase in exercise left ventricular ejection fraction of 22% with propranolol above that during the same exercise test without beta blockade.²⁸ Jones *et al* found that excluding patients receiving propranolol from the study group produced a considerable increase in sen-

sitivity.²⁹ These data show that the results of studies that include patients receiving beta adrenergic blockade^{6 11 30} are of questionable value. The relatively high sensitivity and specificity of the clinical assessment of chest pain in our study agree with those reported by others.^{31 32} The limited predictive power of the ST segment response to exercise is also consistent with previous findings.^{33 34}

The increase in the left ventricular diastolic pressure with exercise has been well documented in patients with coronary artery disease.³⁵⁻³⁷ In the absence of clinical, laboratory, and radiological evidence of pulmonary or mitral valve disease the pulmonary artery diastolic pressure was used to reflect the left ventricular filling pressure.^{14 38 39} Our findings indicate that the diagnosis of coronary artery disease cannot be excluded even if the threshold value for the positivity of the diastolic pulmonary artery pressure measurement is lowered to only 20 mm Hg. Two patients who were referred for bypass surgery would not have been diagnosed as having coronary artery disease if the assessment of right heart haemodynamics had been the criterion for proceeding to angiography. The disturbingly low specificity of this procedure is a serious limitation to its use as a screening method for coronary artery disease. Why many of our patients with normal coronary angiograms had a pronounced increase in diastolic pulmonary artery pressure to clearly abnormal values is still unclear. A diminished left ventricular compliance secondary to arterial hypertension cannot account for this finding, since subjects with this problem were excluded from the study. This study was not designed to establish the reason for abnormal radionuclide and haemodynamic responses to exercise in patients with normal angiograms. The responses do indicate, however, that the group of patients with normal coronary angiograms probably included a considerable number of patients with non-coronary heart disease. Such a group should therefore not be referred to as normal.

Our findings show that a direct move from clinical judgment to angiography is mandatory in patients classified as having typical angina, since non-invasive testing would only marginally alter the high pretest probability of coronary artery disease in these subjects. Bayes's theorem implies that screening procedures make their major diagnostic contribution when applied to the difficult group of patients with an intermediate level of disease prevalence.^{40 41} In this study, however, the predictive power of all the screening procedures used was substantially limited. To compensate for this finding a combination of screening tests might be advocated. As a reflection of the relatively high false positive and false negative rates serial testing frequently provides contradictory results and thus does not appreciably modify the clinical

estimate of disease prevalence.

Radionuclide ventriculography is valuable in assessing surgical and medical treatment. Because of our findings, however, we do not recommend its use in the non-invasive testing of patients with chest pain that might be of ischaemic origin. In the primary diagnosis of coronary artery disease this technique supplies little more information than that provided by the clinical judgment of chest pain.

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