Exercise digital subtraction ventriculography for the detection of ischaemic wall motion abnormalities in patients without myocardial infarction

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SUMMARY Digital subtraction angiography permits high resolution imaging of the left ventricle after an intravenous injection of contrast medium. The capacity of digital subtraction angiography to detect ischaemic wall motion abnormalities was tested in 150 consecutive patients without myocardial infarction who were referred for coronary angiography. Digital ventriculograms were considered to be abnormal if there was a severe wall motion abnormality at rest or if segmental wall motion deteriorated after exercise. The global ventricular response to exercise was considered to be abnormal if the ventricular ejection fraction computed by the Dodge area length formula was $< 50\%$ at rest or failed to increase after exercise. Seventy eight (52%) of these subjects had stenosis of $> 50\%$ of at least one major coronary artery. In 36 (24%) more than one major coronary vessel was affected. Sensitivities for the detection of stenoses $> 50\%$ coronary obstruction were 82% and 69% for an abnormal segmental wall motion response and an abnormal ejection fraction response respectively. The specificity of these test responses was 76% and 68% respectively. No complications resulted from the digital ventriculographic studies.

It is concluded that safe adequate digital ventricular imaging at rest and after exercise is possible and that an abnormal wall motion response is a sensitive indicator of important coronary obstructive disease.

Radionuclide ventriculography may be used to detect the exercise induced changes in left ventricular wall motion that indicate myocardial ischaemia. Early studies reported that it had a high sensitivity and specificity for the prediction of severe coronary obstructions.¹⁻³ Cross sectional echocardiography⁴⁻⁶ has shown promise as a technique for the study of left ventricular function after exercise, but it has low spatial resolution and it can be difficult to obtain adequate images in some patients. Digital subtraction ventriculography gives high resolution images of the left ventricle after intravenous injection of contrast. It may be able to detect exercise induced wall motion abnormalities caused by myo-

cardial ischaemia after exercise.⁷ We have tested this hypothesis.

Patients and methods

STUDY GROUP

Between November 1982 and April 1984 all consecutive patients referred to a group of participating cardiologists were screened for this investigation. Patients were excluded if they had a history of a myocardial infarction or diagnostic Q waves on their electrocardiogram. Diabetics on insulin (18) and those with evidence of valvar disease or cardiomyopathy (5) were also excluded as well as those with unstable angina (15) and those who refused to participate (16). In 157 patients resting and exercise digital subtraction ventriculography was successfully completed. In six patients the test was not completed—in three because we could not locate an adequate peripheral vein for catheter insertion and

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because diagnostic studies after exercise were inadequate in three. Seven subjects did not undergo coronary angiography (five with low probability of disease and two who refused). One hundred and two of the remaining 150 subjects were men and 48 were women (mean age 54 years). All of these subjects underwent selective coronary angiography within three days of their exercise ventriculograms. Seventy eight (52%) subjects were referred for coronary angiography because of chest pain that was typical of angina pectoris (pain in the upper part of the body precipitated by exertion and relieved within 20 minutes by rest). Sixty two (41%) subjects had atypical chest pain and ten subjects (7%) were symptom free. These latter subjects had been referred for angiography because of abnormal stress tests.

RESTING AND EXERCISE VENTRICULOGrams

The examinations were performed with a Philips Optimus M200 generator (continuous mode), a Philips 35/150 x ray tube, a caesium iodide image intensifier, a 525 line interlaced television camera, and a Philips DVI 1 videoprocessor. This system incorporates a dual-selectable aperture for the television camera that allows the operator to compensate manually for and reduce exposure to very large patients. Brass plate boluses placed over the x ray tube further reduce patient radiation dose, which is between 2000 and 4000 mR for an average study.

A 320 ms average mask was used for both resting and exercise studies. Mask acquisition was followed immediately by the injection of 40 ml of Renografin-76 through a 24 inch 16 gauge end hole catheter into the superior vena cava at a flow rate of 10–15 ml/s. X ray exposure settings were the same for the resting and exercise studies in each patient. A nine inch image intensifier was used for all but five studies in which a six inch camera was used because of small cardiac size. The x ray voltage was kept between 70 and 95 kV, and current between 50 and 100 mA. Continuous image acquisition at 30 frames/s ran for 15–25 s for resting studies and 10–16 s for exercise studies. A 512 × 512 pixel matrix was used. For both rest and exercise studies, image acquisition continued for a few seconds after the clearance of contrast from the left ventricle. These post-contrast frames were used for second order resubtraction. Three quarter inch videotape was used as the intermediate medium.

Resting studies were performed with the patient in the supine position and the right anterior oblique projection at held inspiration. The exercise bicycle was then moved into place and the patient's feet raised into the stirrups. The patient was then carefully instructed on the breath holding exercises that were needed for adequate images to be obtained

after bicycling had stopped. Exercise started at 25 W and was increased by 25 W every 2 min. The electrocardiogram was monitored on leads II, aVF, and V5 throughout exercise. Pulse and blood pressure were monitored every 2 min. Exercise was stopped because of exhaustion, dyspnoea, progressive angina, or leg pain and fatigue.

Immediately after the end of exercise the subject was asked to hold his breath at deep inspiration (2–4 s). Under fluoroscopic guidance the x ray image intensifier was repositioned. The subject was then allowed to exhale and again inhale deeply and hold his breath. A mask image was then taken, the subject was told to breathe normally, and contrast was injected. Subtracted image acquisition and fluoroscopy began immediately before the contrast injection so that the progress of the contrast bolus and the movements of the diaphragm could be monitored. As soon as the bolus had cleared the right ventricle, the subject was instructed to inspire deeply and hold his breath a third time. A few seconds after the contrast had cleared from the left ventricle, image acquisition was stopped and the patient was able to breathe normally.

The resting and exercise ventriculograms were immediately reviewed to determine their diagnostic adequacy. Electronic contrast enhancement and mask resubtraction were applied to enhance the visualisation of the endocardial edges. This remasking used mask images that followed the clearance of iodinated contrast from the left ventricle. All resting studies were considered to be adequate after a single contrast injection. In six cases exercise studies had to be repeated to obtain adequate images.

CORONARY ANGIOGRAPHY

Between one and three days after the exercise digital subtraction ventriculographic study, selective coronary angiography was performed by the Sones's or Judkins's techniques.

TEST ANALYSES

Rest and exercise digital subtraction ventriculograms were interpreted by the consensus of two observers who were unaware of the clinical and angiographic data. The videotaped runs of ventriculographic images were post-processed as described above and analysed for the presence and severity of segmental wall motion abnormalities. Though misregistration artefacts are more common after exercise than during resting studies, the non-shifted mask resubtractions improve image quality sufficiently to allow diagnostic interpretation in 90% of cases. The left ventricle was divided according to the American Heart Association Qualitative Report-

ing System into five segments: anterobasal, anterolateral, apical, diaphragmatic, and inferobasal.⁸ Each segment was given a grade from 1 to 6 as follows: 1 normal contractility, 2 mild hypokinesis, 3 moderate hypokinesis, 4 severe hypokinesis, 5 akinesis, 6 dyskinesis. Resting and exercise digital subtraction ventriculograms were considered to be abnormal if any of the five segments were grade 4 or higher at rest or if the grade of any segment was higher at exercise than rest. To estimate inter-observer agreement, these visual assessments were repeated blindly by a third observer who was an experienced cardiac angiographer without extensive experience of interpreting digital angiographic studies.

The resting and exercise ventriculographic studies were transferred from videotape to an analytical image processor (Data General Nova/4) in 128 × 128 pixel format and global ejection fraction was calculated by means of MDS A2 software. The investigator who calculated the ejection fraction was also blinded to the clinical, angiographic, and wall motion results. End diastolic and end systolic image frames were taken to be those with the largest and smallest endocardial contours. The observer used a light pen to draw the endocardial perimeters. The computer then calculated the ejection fraction by means of the Dodge area length formula. Ejection fractions which were <50% at rest or failed to increase with exercise were considered to represent abnormal responses.⁷

Selective coronary cineangiograms were interpreted by experienced angiographers not directly involved in the study protocol. These cardiologists were not told the results of the exercise studies although they were aware of the clinical data.

Results

ADEQUACY OF EXERCISE

The mean duration of supine bicycle exercise was 6.8 min (range 3.5 to 13.5). Forty eight (32%) subjects complained of exercise induced chest pain during the test. Seventy six (51%) subjects had exercise induced ST depression of >1 mm during the test. The mean heart rate achieved was 133 beats/min, the mean peak systolic blood pressure was 180 mm Hg, and the mean rate pressure product at peak exercise was 23 884 beats × mm Hg per minute.

ANGIOGRAPHIC RESULTS (DISEASE SEVERITY)

Seventy eight (52%) patients had important coronary disease defined as at least one stenosis producing >50% obstruction of a major coronary vessel. Thirty six subjects (24%) had a >50% obstruction of more than one vessel (multivessel disease). Twenty two had double vessel and 12 had triple vessel disease. Two subjects had a stenosis of ≥50% in the left main coronary artery.

OBSERVER AGREEMENT

In 80% (120/150) of cases the third independent observer agreed with the consensus assessments of the first two observers on the presence or absence of a resting or exercise wall motion abnormality. Agreement was slightly higher (81%) in studies of subjects without coronary artery disease than it was in those with coronary artery disease (78%).

SENSITIVITY AND SPECIFICITY OF EXERCISE VENTRICULOGRAPHIC RESULTS

Tables 1 and 2 show the comparative sensitivities and specificities of the various exercise ventricu-

Table 1 Important disease: any obstruction >50%

	Electrocardiogram > 1 mm ST depression (%)	(A) Resting wall motion abnormality (%)	(B) Exercise induced worsening of wall motion (%)	A or B (%)	Rest ejection fraction < 50% or exercise ejection fraction ≤ rest ejection fraction (%)
Sensitivity	56 (44/78)	24 (19/78)	76 (59/78)	82 (64/78)	69 (54/78)
Specificity	56 (40/72)	96 (69/72)	79 (57/72)	76 (55/72)	68 (49/72)

Table 2 Multivessel disease: obstruction of >50% in more than 1 vessel

	Electrocardiogram > 1 mm ST depression (%)	(A) Resting wall motion abnormality (%)	(B) Exercise induced worsening of wall motion (%)	A or B (%)	Rest ejection fraction < 50% or exercise ejection fraction ≤ rest ejection fraction (%)
Sensitivity	64 (23/36)	39 (14/36)	81 (29/36)	89 (32/36)	75 (27/36)
Specificity	54 (61/114)	93 (106/114)	61 (69/114)	57 (65/114)	56 (64/114)

Fig. 1 Resting digital subtraction ventriculogram in a 60 year old man without a history or electrocardiographic evidence of myocardial infarction. Note akinesis of the inferior wall.

lographic and electrocardiographic variables used to detect important disease and multivessel disease respectively.

There were resting wall motion abnormalities (at least grade 4) (Fig. 1) in 24% of subjects with important disease and in 39% with multivessel disease. Such resting abnormalities occurred in only 4% of subjects without important coronary obstructions. Exercise induced a worsening of segmental wall motion (Fig. 2) in 76% of subjects with important disease and in 81% of subjects with multivessel disease. Either a severe resting wall motion abnormality (at least grade 4) or an exercise induced worsening of wall motion occurred in 82% of subjects with important disease and in 89% of subjects with multivessel disease. Neither resting nor exercise induced wall motion abnormalities (Fig. 3) were present in 76% of subjects without important coronary obstructions.

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EJECTION FRACTION RESPONSE

The mean ejection fractions at rest and at peak exercise in patients with important coronary obstructions were 73.3 and 67.5 respectively ($p < 0.01$). For those subjects who did not have important coronary obstructions, the resting and exercise ejection fractions were 78.7 and 80.1 ($p = 0.14$). Sixty nine per cent of the subjects with important coronary obstructions had a resting ejection fraction $< 50\%$ or they failed to increase their ejection fraction with exercise, while 75% with multivessel disease had abnormal ejection fractions. Of those subjects without any important coronary obstructions, 68% had normal rest and exercise ejection fractions. Thus both the sensitivity and specificity of abnormal ejection fractions were less than the sensitivity and specificity of segmental wall motion abnormalities.

Because many cardiologists refer their patients with typical angina pectoris directly for cardiac catheterisation without preliminary testing, we divided our study group into subgroups with and without a history of typical angina pectoris. Of those with typical angina pectoris, 76% (59/78) had important coronary artery disease. Of those without angina only 26% (19/72) had important coronary obstructions. The sensitivity of exercise digital subtraction ventriculographic wall motion abnormalities for the detection of important coronary artery disease was 0.83 (49/59) for patients with angina and 0.79 (15/19) for those without angina. The respective specificities were 0.84 (16/19) and 0.74 (39/53).

LOCALISING CORONARY ARTERY OBSTRUCTIONS

In order to determine whether obstructions of the left anterior descending coronary artery caused anterior segmental wall motion abnormalities and obstructions of the right coronary artery caused inferior abnormalities, we calculated the sensitivities and specificities of anterior and inferior segmental abnormalities for the prediction of significant coronary obstructions in the respective coronary arteries. Of 53 subjects with important disease in the left anterior descending coronary artery, 39 (74%) had an anterior wall motion abnormality. Of 97 subjects without disease in the anterior descending, 67 (69%) did not have an anterior abnormality. Of 37 subjects with important obstructions in the right coronary artery, 26 (70%) had a motion abnormality in one of the inferior segments. Of 114 subjects without right coronary artery disease, 106 (93%) did not have an inferior abnormality. Obstructions of the circumflex coronary artery might be expected to cause wall motion abnormalities not visible in the right anterior oblique projection. For this reason, we calculated the sensitivity of segmental wall motion abnormal-

Fig. 2 Resting and exercise digital subtraction ventriculograms of a 48 year old man with disease in the anterior descending and circumflex coronary artery. Note normal end diastolic (left) and end systolic (right) outlines at rest. After exercise, systolic outline shows hypokinesis of the anterior wall and apex.

ities for the prediction of important disease in the circumflex artery. Thirty six subjects had important obstruction of the circumflex coronary artery. Thirty two (89%) had segmental wall motion abnormalities in the right anterior oblique projection.

Discussion

The results of this investigation suggest that exercise digital subtraction ventriculography is a sensitive method for detecting ischaemic wall motion abnormalities produced by coronary obstructions in patients without previous myocardial infarction. Its specificity and its accuracy in localising coronary obstructions are not as impressive as its high sensitivity.

In this investigation subjective analysis of wall motion at rest and after exhausting exercise was more accurate in predicting important coronary obstruction than was an abnormal resting ejection fraction or an exercise induced change in ejection fraction. This result is contrary to that of other

investigators who used resting and exercise radionuclide ventriculography to predict important coronary artery disease.⁹ Though one explanation of this discrepancy may derive from the choice of patients without infarction, we can suggest three possible explanations. First, the high spatial resolution of radiographic images compared with the relatively low resolution of radionuclide images might explain the high sensitivity of digital ventriculography in the detection of segmental wall motion abnormalities. A possible explanation for the relatively poor performance of the ejection fraction response to exercise might be the use of the Dodge single plane area length formula. This method of determining ejection fraction was standardised on resting ventriculograms in subjects with relatively normal hearts.¹⁰⁻¹² Segmental wall motion abnormalities caused by coronary artery disease reduce the accuracy of the Dodge method.

Gibbons *et al* have reported a high false positive rate of the ejection fraction response in patients with normal coronary arteries, especially in women and in

Fig. 3 Normal resting and exercise ventriculograms in a 43 year old woman with atypical chest pain and normal coronary arteries.

subjects with low resting ejection fractions.¹³ Inclusion of these patients might account for the low specificity of the ejection fraction in our investigation.

The low sensitivity of the ejection fraction response may also find an explanation in the delay between the completion of exercise and left ventricular imaging. This did not exceed 30 s in any case and was usually <15 s. Dymond *et al*, however, have reported that the sensitivity of the ejection fraction response is reduced when radionuclide ventriculography follows the completion of exercise by less than 15 s.¹⁴

Most of the patients studied were able to hold their breath long enough for adequate post-exercise studies to be performed. Post-exercise contrast injection was well tolerated and not often associated with complaints of flushing or nausea, as was the case with resting injections.

Despite the encouraging results of this investigation we do not believe that digital subtraction ventriculography should replace con-

ventional techniques of screening patients for coronary obstructions. Digital ventriculography has disadvantages that are not shared by other methods of exercise testing. Venous access was impossible in three subjects of this investigation. Three exercise studies could not be interpreted. The interobserver discordance was high (20%). Exercise digital subtraction ventriculography may be contraindicated in subjects with renal impairment and in those with severe cardiac failure. The radiation dose is considerably higher during digital subtraction ventriculography than during radionuclide examinations. High resolution continuous digital subtraction radiographic imaging is cumbersome and requires the use of an expensive angiographic laboratory. In the course of the present investigation no serious complications were encountered. There is, however, the possibility of serious angiographic contrast reaction. Further study and investigation are needed to determine the appropriate clinical and research applications of exercise digital subtraction ventriculography.

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