How useful are the cold pressor test and sustained isometric handgrip exercise with radionuclide ventriculography in the evaluation of patients with coronary artery disease?

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SUMMARY The feasibility of using the cold pressor test and the sustained isometric handgrip test as alternatives to dynamic exercise for stressing the heart was investigated. Serial changes in heart rate, blood pressure, and left ventricular performance induced by these tests were studied by radionuclide ventriculography in patients with coronary artery disease and in normal volunteers. Both tests significantly increased heart rate and blood pressure. The reproducibility of serial evaluation of ejection fraction response to cold pressor and isometric handgrip stresses was satisfactory but the sensitivity for detecting coronary artery disease was not.

Both stress tests are valuable interventions for the serial evaluation of left ventricular function by radionuclide ventriculography, but they should not be used to detect coronary artery disease.

Stressing the heart may uncover latent abnormalities of myocardial contractility. For example, patients with stable angina pectoris may have normal ventricular function at rest but may develop abnormalities during stress. Several interventions have been used to stress the heart during examination by radionuclide ventriculography. These include increasing left ventricular afterload by administering drugs such as angiotensin^{1 2} and phenylephrine³ and the provocation of ischaemia by atrial pacing.^{4 5}

Both the cold pressor test^{6 7} and sustained isometric handgrip^{8 9} are popular alternatives to dynamic exercise. Both tests eliminate movement artefact and can be applied to almost every patient. Dynamic exercise requires considerable cooperation from the patient and time to complete the tests; it is also more likely to precipitate symptoms in patients with ischaemic heart disease.

Several reports have examined the application of cold pressor test and sustained isometric handgrip exercise to the detection of coronary artery disease^{6 10-12} but not the reproducibility of the responses when left ventricular function studies are

used to determine serial changes in the same patient.

We have investigated the usefulness of both these interventions in the detection of coronary artery disease and their reproducibility in serial studies of left ventricular function.

Patients and methods

The protocol was approved by our local ethics committee and the Administration of Radioactive Substances Advisory Committee gave us permission to administer technetium-99m to three groups of subjects:

Group 1

Sixteen symptom free male volunteers were recruited from hospital staff and associates. All were in sinus rhythm; they were normotensive and lifelong non-smokers. They all had normal electrocardiograms at rest and during maximal graded exercise on a modified Bruce protocol.¹³ The chest x ray and the cardiothoracic ratio were normal, and no subject was taking any medication at the time of the study. None had evidence of valvar or congenital heart disease, respiratory disease, or peripheral vascular disease and all were presumed to have normal hearts (table 1).

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Table 1 Data on controls and subjects with coronary artery disease (CAD)

	Group 1 controls	Group 2 CAD subjects*
Age (yr)	45 (7.0) (36–60)	54 (8.1) (38–67)
Resting HR (beats/min)	63 (8.8)	67 (9.7)
Resting SBP (mm Hg)	119 (13.9)	135 (25.7)
Resting DBP (mm Hg)	69 (9.5)	80 (12.3)
Resting EF (%)	60.2 (11.4)	60.7 (8.3)

Results are expressed as mean (SD).

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; EF, ejection fraction.

*Normal or nearly normal resting ejection fraction (50–79%).

Group 2

We also studied 20 male patients (mean age (SD) 54 (8) years) in whom a diagnosis of coronary artery disease and stable angina pectoris (New York Heart Association grade II or III) had been confirmed by a positive exercise electrocardiogram and also by evidence of coronary artery disease at coronary arteriography ($n = 8$) or by a documented history of myocardial infarction ($n = 12$). A stenosis of a major artery of $>70\%$ of the luminal diameter was regarded as significant coronary artery disease and a myocardial infarction was diagnosed on the basis of a prolonged episode of central chest pain, with characteristic electrocardiogram and cardiac enzyme changes, occurring at least one year before the study. These subjects had normal or nearly normal resting ejection fractions (range of 50–79%) (table 1). None had a history of or evidence of respiratory disease, valvar or congenital heart disease, unstable angina, cardiac arrhythmias or conduction abnormality, or cardiac failure. In the two weeks before the study they had taken only glyceryl trinitrate.

Group 3

To assess the variability of the resting ejection fraction and its response to the cold pressor test and sustained isometric handgrip exercise we studied 20 patients with chronic stable angina. Each underwent radionuclide ventriculography with a cold pressor test and sustained isometric handgrip exercise; ventriculography was repeated three times at intervals. After a baseline measurement, repeat studies were performed three and six months later. All were taking propranolol 80 mg three times a day and glyceryl trinitrate for chest pain. This treatment had been established for at least three months before these studies and remained unchanged.

STUDY PROTOCOL

Radionuclide ventriculography was performed at the same time of day in each subject. Red blood cells were labelled *in vivo* by giving an intravenous injection

of technetium-99m (740 MBq (20 mCi)) into the right antecubital vein 20–30 minutes after 15 mg of stannous pyrophosphate had been given by the same route.¹⁴ Radionuclide ventriculography was then performed in the left anterior oblique projection that gave the best separation of the right and left ventricles (usually 35–45°) and with a 10° caudal tilt. The same angle was used for each individual study interval. We used a Technicare Sigma 410 large field camera with a general all purpose low energy (140 KeV) parallel hole collimator. Before each set of investigations the camera uniformity correction memory was calibrated with a technetium-99m flood field. An electrocardiographic signal from the patient obtained on an Elcomatic EM810 monitor was used to trigger the computer to record images synchronised with the R wave. Images in histogram mode in 16 sequential frames in a 64×64 data matrix with the zoom set at $\times 3$ were stored in an ADAC (CGR) 7310 computer. Data collection stopped automatically after six minutes for resting studies and five minutes for stress studies. We used a framing rate of 16 frames per second for all studies. At the start of each study the computer calculated an average beat to beat interval from several cycles and then accepted image information from beats falling within a window ($\pm 20\%$) about the centre frequency. In the resting studies the centre frequency remained fixed throughout each study interval, thus excluding ectopic complexes. During stress studies the computer recalculated the mean beat to beat interval as the heart rate increased and thus retained the ability to reject ectopic complexes as it tracked steady changes in heart rate.

The composite 16 frame dynamic study was stored on disc for future analysis at the end of the study. Image analysis was performed by the Stanford Automatic left ventricular analysis program which constructs an activity-time curve from which indices of left ventricular performance can be calculated.^{15 16} Briefly, the edge detection algorithm is based on the application of a one dimensional Laplacian filter to the end diastolic image vertically, horizontally, and along both diagonals. A search is made for the first edge which completely encloses the left ventricle, and the left ventricle is located by calculation of the x and y coordinates of the centre of gravity of an amplitude image constructed by the system. The program transforms the data to a frequency domain and retains the zero, first, second and third harmonics as well as the diastolic image. A left ventricular region of interest is created and subsequently used for interpolative background subtraction. The region of interest is also used to create a 100 point volume curve from the frequency components. From this curve the system calculates

the ejection fraction, and from its first derivative ($\frac{dVs}{dt}$ and $\frac{dVd}{dt}$) it calculates the maximum rate of emptying and filling as end diastolic volumes per second in the control group.

To assess the reproducibility of the technique we performed two successive studies at rest. In all subjects the acquisition time was six minutes. An isometric handgrip test was followed by a cold pressor test. The right hand was used for both tests. There was an interval of at least 10 minutes between these studies, and blood pressure and heart rate had returned to basal values before the start of the cold pressor test. After the basal study at rest subjects performed a sustained isometric handgrip exercise with a hand dynamometer (Martin Vigorimeter). The patient's maximum voluntary contraction was determined and he was asked to maintain a handgrip at 30% of this value for five and half minutes; this allowed a lag period of 30 seconds before imaging started. Imaging was performed for five minutes in each subject.

The duration of the cold pressor test and time of the start of imaging have varied in previous studies. Some started 15–30 seconds after immersion of the hand in iced water with a 2–3 minute acquisition time.^{7 10 17} Wainwright *et al* delayed the start of imaging for one minute and acquired images for five minutes.⁶ We have found haemodynamic changes 15–30 seconds after immersion of the hand in ice, with maximal changes occurring between one and three minutes and being maintained for five minutes (unpublished observations). Because of these observations and because we were using a general purpose collimator we felt it appropriate to start imaging after 30 seconds and to acquire images for five minutes. In addition, this protocol allowed comparison with the almost identical protocol of Wainwright *et al*.⁶

For the cold pressor test the right hand was immersed to the level of the styloid process in a mixture of crushed ice and water. Throughout the test

the water and ice round the hand were mixed to maintain the cold stimulus. Heart rate and blood pressure were monitored each minute before, during, and after both interventions by a Hitachi HME-20 pulse and blood pressure monitor.¹⁸

STATISTICAL ANALYSIS

Discrete variables were analysed by Student's paired *t* test and a Wilcoxon signed rank test was used for paired observations. Unpaired observations were analysed by Student's unpaired *t* test and a Mann-Whitney test. (The most conservative estimates of significance are reported.)

The variability of sequential ejection fraction measurements and the reproducibility in interventions were estimated by calculating the coefficient of variance. Values of $\leq 10\%$ were taken to indicate low variance and satisfactory reproducibility, values of 10–20% indicated moderate reproducibility, and values $> 20\%$ unacceptable reproducibility. The 95% confidence interval about a resting ejection fraction was used to define a subsequent significant change during cold pressor test or sustained isometric handgrip exercise in the individual subject. This interval was calculated from pooled variance as described elsewhere.^{19 20} Sensitivity (number of true positives divided by number of patients with coronary artery disease) and specificity (number of true negatives divided by number of patients without coronary artery disease) were calculated and expressed as percentages.

Results

Both the cold pressor test and sustained isometric handgrip exercise were tolerated well by all subjects. In each subject the tests were completed without the development of chest pain or electrocardiographic evidence of ischaemia. Several individuals complained of pain in the immersed hand during the cold pressor test which was most pronounced in the

Table 2 Comparative mean heart rate (beats/min) and blood pressure (mm Hg) responses to sustained isometric handgrip stress in subjects with coronary artery disease (group 2, *n* = 20) and a normal control group (group 1, *n* = 16)

	Time from start of isometric handgrip test (min)					
	Basal	1	2	3	4	5
CAD group:						
Heart rate	68 (9.0)	74 (9.3)	77 (10.1)	80 (12.9)	84 (15.7)	82 (15.6)
SBP	136 (25.3)	158 (32.0)	166 (32.3)	174 (32.3)	173 (29.3)	185 (34.5)
DBP	80 (12.1)	92 (15.4)	94 (16.7)	100 (10.6)	99 (12.7)	98 (15.7)
Normal control group:						
Heart rate	65 (8.1)	68 (6.9)	71 (9.9)	72 (9.3)	72 (8.3)	75 (11.8)
SBP	117 (16.5)	128 (15.3)	136 (17.5)	142 (22.8)	153 (29.9)	149 (22.8)
DBP	67 (15.4)	76 (15.1)	78 (15.0)	80 (14.9)	89 (15.7)	85 (20.4)

SBP, systolic blood pressure; DBP, diastolic blood pressure. Results are expressed as mean (SD).

Table 3 Comparative mean heart rate (beats/min) and blood pressure (mm Hg) responses to cold pressor test in subjects with coronary artery disease (group 2, $n = 20$) and a normal control group (group 1, $n = 16$)

	Time from immersion of hand in ice (min)					
	Basal	1	2	3	4	5
CAD group:						
Heart rate	68 (9.4)	74 (10.0)	75 (12.1)	73 (8.6)	74 (10.2)	73 (10.4)
SBP	138 (25.3)	171 (37.1)	174 (35.2)	160 (26.7)	164 (36.0)	172 (40.2)
DBP	80 (11.2)	99 (14.1)	96 (14.1)	94 (12.2)	94 (13.5)	92 (8.2)
Normal control group:						
Heart rate	63 (7.8)	66 (9.6)	69 (10.5)	69 (10.0)	65 (10.2)	65 (8.2)
SBP	119 (13.9)	148 (26.2)	156 (25.3)	156 (27.1)	153 (26.1)	154 (21.6)
DBP	69 (9.5)	89 (20.2)	88 (15.9)	84 (17.1)	87 (11.7)	79 (17.6)

SBP, systolic blood pressure; DBP, diastolic blood pressure. Results are expressed as mean (SD).

first 1–2 minutes after immersion and in the first few minutes after withdrawal. Groups 1 and 2 were similar in terms of age and resting heart rate, but both resting systolic and diastolic blood pressure were higher in those with coronary artery disease (table 1).

HEART RATE AND BLOOD PRESSURE

Both the heart rate and systolic blood pressure rose significantly in response to the sustained isometric handgrip exercise (table 2) and cold pressor test (table 3) at each minute during these interventions. There was a mean increase of 21% in heart rate in group 2 in response to sustained isometric handgrip exercise at the five minute stage, but there was only a 15% increase in response in group 1 (normals). Similarly, there was a mean increase of 36% in systolic blood pressure in group 2, but only a 27% increase in group 1; however, diastolic blood pressure increased to a similar extent in both groups.

During the cold pressor test those with coronary artery disease (group 2) increased their heart rate by a mean maximum of 10% and the systolic blood pressure by 26%. In the controls (group 1) these variables increased by 10% and 31% respectively; diastolic blood pressure increased by a similar degree in both groups (table 3).

The maximum increase (mean (SD)) in heart rate during sustained isometric handgrip exercise was 14 (11) beats per minute ($p < 0.001$) in those with coronary artery disease (group 2) and 14 (13) beats per minute ($p < 0.01$) in the normal subjects (group 1); the difference between groups was not statistically significant. Systolic blood pressure increased by a mean (SD) of 51 (18) mm Hg in those with coronary artery disease ($p < 0.001$) and by 38 (21) mm Hg in controls ($p < 0.01$); the difference was not statistically significant.

During the cold pressor test, heart rate increased by a maximum of 10 (10) beats per minute in those with coronary artery disease (group 2) and by 8 (6) in controls (group 1); this difference between groups

was not statistically significant. Systolic blood pressure increased by a mean of 39 (18) mm Hg ($p < 0.001$) in those with coronary artery disease and by 44 (23) ($p < 0.001$) in controls; the difference in response between the groups was not significant.

During sustained isometric handgrip exercise heart rate and systolic blood pressure rose in all subjects. During the cold pressor test, heart rate fell in one subject with coronary artery disease and in two controls. Systolic blood pressure rose in all subjects.

Sustained isometric handgrip exercise caused greater heart rate and blood pressure responses than the cold pressor test, but these differences were not statistically significant. Maximal haemodynamic responses tended to occur 3–5 minutes into the sustained isometric handgrip exercise test and 1–2 minutes into the cold pressor test. The timing of these maximal responses was similar in groups 1 and 2.

In both tests the haemodynamic response was evident during the first minute and was maintained for the five minute period of imaging.

VARIABILITY OF EJECTION FRACTION DETERMINATIONS

We assessed the variability of ejection fraction measurements from two sequential resting studies in the 16 normal control subjects (group 1). The difference (1.25%) between the two means was not statistically significant (table 4). From the individual mean of the two resting values and knowledge of the pooled variance we calculated the 95% confidence limits for significant change of a subsequent ejection fraction measurement from the equation:

$$\bar{x} \pm 2.12\sqrt{S^2(1/n + 1)}$$

where x is the observed measurement, 2.12 is the value taken from the distribution of t when the number of observations is 16 at the 5% significance level, S^2 is the pooled variance, and n is the number of resting observations per patient. Thus for the 16 subjects, $S^2 = 19.6$ percentage units, $n = 2$, and the

Table 4 Results of sequential resting radionuclide ventriculograms in 16 control subjects

Variable	Rest ₁	Rest ₂	Difference
dVs/dt	-4.3 (0.46)	-4.3 (0.42)	NS
dVd/dt	4.0 (0.50)	3.94 (0.37)	NS
EF	61.5 (8.21)	60.2 (11.42)	NS

-dVs/dt = maximum rate of negative change of ventricular volume with time (ventricular emptying) measured as end diastolic volume/second.

+dVd/dt = maximum rate of positive change of ventricular volume with time (ventricular filling) measured as end diastolic volume/second.

Results are expressed as mean (SD).

95% confidence interval for a given patient is estimated to be -11.49 ejection fraction percentage units. This implies that the individual change of ejection fraction in response to any intervention must be 12% (absolute value) or more to be regarded as significant at the 5% level of significance. Variations of less than 12% could be the result of physiological and statistical fluctuations. This implies that a value would have to be 12% below the normal mean value to be regarded as an abnormal ejection fraction.

The coefficient of variance between two resting studies was 5.1%, indicating satisfactory reproducibility. Table 4 summarises the results of sequential resting radionuclide ventriculography studies in the normal subjects. No statistically significant differences for any variable were seen between the two resting studies. Linear regression analysis of ejection fraction response gave a correlation

coefficient of 0.85 between the two resting studies.

The patients recruited into group 3 underwent three separate studies, with the first and second and the second and third 3 and 6 months apart respectively. Table 5 shows the responses to sustained isometric handgrip exercise and a cold pressor test. The coefficient of variance was 10% for sustained isometric handgrip exercise and 9% for cold pressor test, indicating satisfactory reproducibility.

RADIONUCLIDE VENTRICULOGRAPHY

Table 6 summarises the results of radionuclide ventriculography in groups 1 and 2 in response to sustained isometric handgrip exercise and a cold pressor test. In both groups the mean left ventricular ejection fraction fell in response to sustained isometric handgrip exercise and a cold pressor test. In normal subjects this fall was significant for only cold pressor testing. Both the cold pressor test and sustained isometric handgrip exercise tended to reduce dVs/dt.

Figures 1 and 2 show the group and individual changes in left ventricular ejection fraction in both groups 1 and 2 in response to both interventions. Sustained isometric handgrip exercise caused a mean (SD) reduction of 5 (8.3)% in those with coronary artery disease and a reduction of 4 (6.5)% in controls. This difference was not statistically significant. The cold pressor test caused a mean reduction of 10 (8)% in those with coronary artery disease and a reduction of 7 (5.6)% in controls; this

Table 5 Coefficient of variance for ejection fraction response to sustained isometric handgrip (SIHG) and cold pressor test (CPT)

	S ₁	S ₂	S ₃	Mean SD
SIHG:				
Column mean (SD)	49 (12.2)	51 (11.8)	51 (13.1)	5.04
Overall mean		50.3		
Mean SD ÷ overall mean (%)		Coefficient of variance = 10.02%		
CPT:				
Column mean (SD)	47 (9.7)	48 (9.8)	48 (12.8)	4.29
Overall mean		47.67		
Mean SD ÷ overall mean (%)		Coefficient of variance = 8.99%		

S₁₋₃ = studies 1-3.

Table 6 Results of radionuclide ventriculography during sustained isometric handgrip (SIHG) and cold pressor test (CPT) in 16 controls and 20 patients with coronary artery disease (CAD)

	Rest	SIHG	CPT
Group 1 (controls):			
dVs/dt (ED vol/s)	-4.3 (0.42)	-3.9 (0.37)**	-3.9 (0.51)
dVd/dt (ED vol/s)	3.94 (0.37)	3.7 (0.35)*	3.9 (0.53)
EF	60.2 (11.42)	57.9 (10.18)	54.4 (10.64)***
Group 2 (patients with CAD and normal EF):			
dVs/dt (ED vol/s)	-4.6 (0.37)	-3.8 (0.61)***	-4.1 (0.48)***
dVd/dt (ED vol/s)	3.6 (0.48)	3.4 (0.74)	3.4 (0.57)
EF	60.7 (8.28)	55.7 (11.42)*	51.1 (9.96)

See table 4 for abbreviations.

*p < 0.05; ** p < 0.01; *** p < 0.001.

Results are expressed as mean (SD).

Fig 1 Individual and group responses of the ejection fraction to sustained isometric handgrip in subjects with coronary artery disease (CAD) and a normal or near normal ejection fraction (group 2) and controls (group 1).

Fig 2 Individual and group responses of ejection fraction to cold pressor test in subjects with coronary artery disease (CAD) and normal or near normal ejection fractions (group 2) and controls (group 1).

difference between the groups was not statistically significant.

DETECTION OF CORONARY ARTERY DISEASE

Cold pressor testing caused a significant fall ($\geq 12\%$) in ejection fraction in three controls and six patients with coronary artery disease. Thus the sensitivity for the detection of coronary artery disease was 30% and the specificity was 85%. In two controls and one subject with coronary artery disease the ejection fraction increased but not significantly.

Sustained isometric handgrip exercise caused a significant fall in ejection fraction in three patients

with coronary artery disease, but there was no significant reduction in any of the controls. The ejection fraction increased in three controls and in two patients with coronary artery disease; the increase was significant in one patient from each group. Thus the sensitivity of the handgrip test for the detection of coronary artery disease was 15% and the specificity was 100%.

When both tests were combined the sensitivity increased to 35% and the specificity remained at 85%.

Discussion

The cold pressor test and sustained isometric handgrip exercise have been used in previous studies to unmask latent abnormalities of left ventricular function and to aid in the diagnosis of coronary artery disease.^{6 7 10 17 21-25} The reproducibility of the responses to these interventions has not been adequately assessed. We have found these interventions to be useful for comparative studies because of their ease of application and ability to stress the myocardium without inducing angina pectoris or ST segment changes indicative of ischaemia. In comparison, dynamic exercise tends to cause these phenomena in a high proportion of subjects undergoing radionuclide ventriculography.⁶ Both tests were simple and accessible and they were less cumbersome and time consuming than dynamic exercise.

COLD PRESSOR TEST

Heart rate and blood pressure

In patients with coronary artery disease and in normal controls heart rate increased by a mean of 10% in both groups and systolic pressure increased by 26% and 31% respectively. All these increases were statistically significant; but there were no significant differences between the two groups. Previous studies (table 7) have shown increases in heart rate ranging from +4 beats per minute²² to +12 beats per minute^{7 10} in normal subjects and +1²⁵ to +10¹⁰ in patients with coronary artery disease. Systolic blood pressure rises in the present study were higher in both normal controls and subjects with coronary artery disease than in previous studies. There is no obvious explanation for this. Only one of our subjects (aged 54 years) with coronary artery disease was considered to have hypertension (184/103 mm Hg at rest). Most studies have reported that changes in blood pressure and heart rate in controls and patients with coronary artery disease are similar (table 7); and we too found no significant difference in response between these groups. Rootwelt *et al*²² and Raizner *et al*²⁶ did not find a significant change in heart rate in normal subjects in response to the cold pressor test.

Table 7 Comparison of studies that used cold pressor test in conjunction with radionuclide ventriculography

	Normal group				CAD group				Sensitivity (%)	Specificity (%)
	No	HR (beats/min)	SBP (mm Hg)	EF (%)	No	HR (beats/min)	SBP (mm Hg)	EF (%)		
Wainwright <i>et al</i> ⁶	22	NA	NA	+2	24	NA	NA	-13	79	100
Manyari <i>et al</i> ¹⁷	20	+8	+26	+3	20	+9	+30	-5	55	95
Wasserman <i>et al</i> ¹⁰	12	+11	+27	-6	18	+10	+22	-5	NA	NA
Vojacek <i>et al</i> ²⁵	10	+5	+13	-3	12	+1	+29	-5	NA	NA
Verani <i>et al</i> ⁷	18	+11	+28	0	34	NA	NA	-6	NA	NA
Dymond <i>et al</i> ²⁷	12	+12	+16	-5	12	+9	+29	-8	NA	NA
Rootwelt <i>et al</i> ²²	11	+4	NA	+2	22	+6	NA	-3	50	100
Present study	16	+8	+44	-7	20	+14	+39	-10	50	37.5

HR, heart rate; SBP, systolic blood pressure; EF, ejection fraction; NA, not available. Results expressed are mean value for each variable.

This variability of heart rate and systolic blood pressure response in these studies may be because the cold pressor test was differently applied in different studies. In the present study, the hand was immersed in iced water (0–2°C) up to the level of the styloid process and the ice and water mixture was stirred continuously to maintain a constant adequate cold stimulus; also a fresh ice and water mixture was prepared for each patient. If this is not done the cold stimulus may be inadequate; this may explain the early decay in haemodynamic response reported by Dymond *et al*²⁷ but not by others.^{6,10} The haemodynamic response to the cold pressor test reaches a maximum 60–90 seconds after immersion and basal values are quickly restored after the hand is withdrawn.^{6,28–30} In our patients the haemodynamic responses were evident throughout the five minutes of imaging although some decay was noted after three minutes.

The haemodynamic changes are mediated by a predominantly α adrenergic stimulus³¹ and an increase in systemic and pulmonary vascular resistance.^{28,32} These haemodynamic changes increase myocardial oxygen consumption. Such changes may be enough to precipitate ischaemia in those with pre-existing coronary artery disease.

Radionuclide ventriculography

The cold pressor test induced significant falls in left ventricular ejection fraction in both normal subjects and patients with coronary artery disease; the difference between the two groups was not statistically significant. Two previous studies have reported falls in the ejection fraction in response to the cold pressor test,^{10,25} whereas others have noted no change or a small increase.^{6,7,17,22} In contrast, all studies consistently report falls in ejection fraction in patients with coronary artery disease. These range from a mean of -3 to -13% (table 7).

Thus the response to cold pressor test in normal subjects is inconsistent. This may be explained by differences in study protocol—in some studies

images were collected for two minutes¹⁷ and in others for five minutes,⁶ in the latter study imaging was delayed for one minute. Dymond *et al* used sequential first pass radionuclide ventriculography during cold pressor test. They found that the ejection fraction fell significantly in both controls and those with coronary artery disease after one minute; but this fall was maintained at 2.5 and 4 minutes only in those with coronary artery disease.²⁷ In both groups the maximum reduction in ejection fraction occurred after one minute, despite the rise in blood pressure reaching a maximum after 2.5 minutes. They postulated that changes in afterload induced by cold pressor test are not the only reason for changes in left ventricular function. They concluded that left ventricular function changes rapidly during a period of cold stimulation, and that if the prime purpose is to detect coronary artery disease it would be prudent to delay the onset of imaging for one minute because normal subjects will be less likely to show a fall in ejection fraction after this. We started imaging after 30 seconds because this had been the practice of others who have assessed the cold pressor test under similar circumstances.^{7,10,17,25}

SUSTAINED ISOMETRIC HANDGRIP EXERCISE Heart rate and blood pressure

Heart rate rose more during this test than during the cold pressor test. It increased by a mean of 14 beats per minute both in patients with coronary artery disease and in normal controls. The increase in systolic blood pressure was also greater (by 51 and 38 mm Hg respectively). These changes are consistent with previous reports of increases ranging from 15% to 40%.^{33,34} Bodenheimer *et al*, using a protocol similar to ours, observed blood pressure increases of 32 mm Hg in normal subjects and 33–44 mm Hg in patients with coronary artery disease.⁸ In the present study the pronounced rise in heart rate and blood pressure was maintained for the five minute imaging period and the pattern of the response tended to be a sequential rise with little

decay in the response, unlike the response to the cold pressor test. This was also the experience of Lind *et al* who found that blood pressure increased as fatigue developed.³⁵ In those with normal hearts an increase in blood pressure is primarily the result of an increase in cardiac output.³⁶ When the left ventricle is impaired the rise in blood pressure can be enhanced by an increase in systemic vascular resistance caused by stimulation of the adrenergic receptors by a fall in cardiac output.³⁶

Radionuclide ventriculography

Although sustained isometric handgrip exercise caused a fall in ejection fraction in normal subjects this did not reach statistical significance, unlike the response to cold pressor test. The falls in ejection fraction experienced in those with coronary artery disease were significant, however. Bodenheimer *et al* found that in normal subjects the ejection fraction increased by a mean of 3% and in those with coronary artery disease it fell by 4% ($p < 0.005$),²¹ yielding 86% sensitivity and 87% specificity for the detection of coronary artery disease. The present study demonstrated a sensitivity of 15% and a specificity of 100%. Others have reported that mean ejection fraction does not change in normal subjects³⁷; however, individual normal subjects may have falls of 5% or more.^{37 38}

It is possible that individuals with coronary artery disease will respond by a significant reduction in ejection fraction either to the cold pressor test or to the sustained isometric handgrip exercise but not to both. When the results of both tests were combined, however, the sensitivity improved to only 35%.

Variability of ejection fraction responses

Because we used a fully automatic method of analysing radionuclide ventriculograms we eliminated intra- and interobserver variation.

Two sequential resting studies in the normal controls gave a coefficient of variance of 5% and a correlation coefficient of 85%. No significant differences were found between studies for any indices of left ventricular function. In addition, the results were used to calculate the absolute change from normal that would be regarded as significant in our laboratory. The spontaneous variability in ejection fraction of 12% or more that we used to exclude non-random physiological change is more than that found in some laboratories^{6 12 37} but comparable to others.³⁹

In patients with normal left ventricular performance there is greater ventricular reserve and hence a greater probability of responding to stimuli with augmentation of cardiac pump function.³⁹ In those with subnormal basal ventricular per-

formance, the ventricle may already be working at close to maximal effort and will therefore be less likely to manifest comparable spontaneous fluctuations in ejection fraction. Thus the variability in our repeat studies in normal subjects is probably higher than the variability that would be shown by a group of patients with coronary artery disease. In the present study large (up to 13%) individual inter-study differences were noted although the mean difference between the first and second study was -1.2 (6.16). Large individual changes (up to 21%) with a mean change of $+4.6$ (4.70) were reported by Wackers *et al* in a similar study population.³⁹

The responses to both the cold pressor test and sustained isometric handgrip exercise had an acceptable reproducibility, with coefficients of variance of 9% and 10% respectively and no significant differences in the mean response on three separate occasions. This indicates that these interventions are suitable for studies of changes in left ventricular performance over time. In this respect both interventions are suitable alternatives to dynamic exercise.

DETECTION OF CORONARY ARTERY DISEASE

Wainwright *et al* claimed a sensitivity of 79% and specificity of 100% for the cold pressor test in detecting coronary artery disease (table 7).⁶ In that study a change of 8% in ejection fraction was regarded as abnormal, although from their data there does not seem to be any clear reason for this limit. All normal subjects increased their ejection fraction by a mean of 2% in response to cold pressor test. These findings are unexpected because ventricular performance, even in normal subjects, is not enhanced by an increase in left ventricular afterload or systemic vascular resistance.^{3 40}

In the present study, no normal subject had an increase in ejection fraction during the cold pressor test and three had significant ($> 12\%$) falls in ejection fraction. Although the mean fall in ejection fraction was greater in patients with coronary artery disease, the sensitivity (30%) and specificity (38%) in this group showed that in our laboratory and with this protocol the cold pressor test is not a useful intervention for the detection of coronary artery disease. It is possible that the responses obtained in these controls may reflect the presence of subclinical cardiomyopathy, intervention induced coronary artery spasm in the absence of symptoms or electrocardiogram changes, asymptomatic coronary artery disease, or a normal variation. But this was a group of symptom free lifelong non-smokers with no other major coronary artery disease risk factors. Each had a normal chest x ray and resting and treadmill exercise electrocardiogram, and all were presumed to

have normal hearts. The study is open to criticism because coronary arteriography was not performed to exclude coronary artery disease, but in our unit the main indication for coronary arteriography is for the preoperative assessment of patients with angina pectoris; invasive investigation of our control group was not ethically justifiable.

Several studies have assessed the value of cold pressor test in detecting coronary artery disease. In studies comparing it with dynamic exercise Manyari *et al*¹⁷ and others^{7 22 25} have found it to be an inferior discriminator although possibly useful in subjects who are unable to perform dynamic exercise.

Though the sustained isometric handgrip exercise test produced greater increases in heart rate and blood pressure than the cold pressor test, it was only successful in detecting three subjects with coronary artery disease and gave a sensitivity of only 15%. The specificity was more acceptable, however. Several studies that compared sustained isometric handgrip exercise with dynamic exercise showed that it was of limited value in the detection of coronary artery disease.⁴¹⁻⁴³ In contrast, Bodenheimer *et al*, using radionuclide ventriculography, found a sensitivity of 86% and specificity of 87%.^{8 21} These findings are of limited value, however, because most of their subjects had abnormalities at rest.

Some authorities have suggested that a patient may respond to only one or the other of these tests and that both should be performed. Our results do not support this because when both tests were combined the sensitivity for the detection of coronary artery disease was only 35%.

Conclusions

This study has demonstrated satisfactory reproducibility of resting radionuclide ventriculography in a control group and of cold pressor test and sustained isometric handgrip exercise in a group with coronary artery disease. Significant heart rate and blood pressure responses were seen in both normal subjects and those with coronary artery disease; increases were higher with sustained isometric handgrip exercise.

Both cold pressor test and sustained isometric handgrip exercise are useful for serial comparisons of myocardial performance—for example the assessment of the effect of drugs on the myocardium. Coronary artery disease is not reliably detected if the left ventricular ejection fraction alone is used; however, when dynamic exercise is not possible these tests may be used as alternatives. In our laboratory the sensitivity was inadequate in patients with coronary artery disease who had normal or near normal resting electrocardiograms. Patients with coronary artery disease may not be able to complete an ade-

quate dynamic exercise test without precipitating angina. Neither the cold pressor test nor sustained isometric handgrip exercise caused angina in our patients with coronary artery disease. One major advantage of cold pressor test and sustained isometric handgrip exercise is their ease of application without the risk of patient movement or excessive use of camera time. These factors are of obvious importance when serial evaluations are necessary.

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