

## Left ventricular function during isometric hand grip and cold stress in normal subjects

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**SUMMARY** Both isometric exercise and cold stress have been suggested as alternatives to dynamic exercise for the detection of obstructive coronary artery disease. A non-imaging nuclear probe was used to measure left ventricular ejection fraction and relative left ventricular volumes continuously during both of these stress tests in 24 normal subjects. There was a significant fall in left ventricular ejection fraction within 15 seconds of subjects starting a two minute isometric hand grip test at 50% maximal voluntary contraction, with a mean (SE) maximal fall of 10% (1.8) after 90 seconds. During two minutes immersion of the hand and wrist in iced water left ventricular ejection fraction fell significantly within 30 seconds with a mean maximal fall of 7% (1.7) after one minute. Nine subjects underwent repeat tests under identical conditions approximately two weeks later. The standard error of the change in ejection fraction on two occasions was 5.4% at rest, 7.0% at the peak of isometric exercise, and 4.8% at peak cold stress.

These results indicate that the reproducibility of both of these stress tests is acceptable when they are performed under carefully controlled conditions. The resulting changes in ejection fraction are transient, however, and moreover depend upon the choice of stress protocol. The discrepancies between published reports of such studies in coronary artery disease may be mainly due to methodological differences, and neither test is likely to be of sufficient discriminative ability to distinguish between individuals with obstructive coronary artery disease and normal subjects.

There are similarities between the cardiovascular responses to isometric exercise and cold stress, and both have been advocated for the detection of obstructive coronary artery disease.<sup>1 2</sup> Isometric exercise in normal subjects increases blood pressure by 30-35%, which together with an increase in heart rate produces a pronounced increase in the rate-pressure product. Cutaneous cold stimulation leads to a rise in blood pressure of 20-25% with little change in heart rate, although cold stress may also affect myocardial blood flow through an alteration in coronary artery tone.<sup>3 4</sup> Left ventricular function

during both these interventions can be assessed non-invasively by radionuclide angiography, but the reported results have been conflicting.<sup>5-7</sup> It is possible that some of the discrepancies have arisen as a result of differing patient selection, but there are also considerable methodological differences in the reported studies. In this study we set out to investigate the factors which may be important in determining the response of the left ventricle to these two stress tests. We used a non-imaging nuclear probe (Nuclear Stethoscope, Bios. Inc.) that allows continuous monitoring of precordial radioactivity from a <sup>99m</sup>Tc labelled blood pool, to measure left ventricular ejection fraction and relative left ventricular volumes and to establish the temporal relation between these and other haemodynamic variables. We have also examined the reproducibility of the responses and the effect of differing isometric and cold stress protocols.

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## Patients and methods

Twenty four male volunteers (mean age 32 years, range 25–43 years) took part in this study. All gave their informed consent and the study was approved by the hospital's ethical committee. Volunteers were screened by a full clinical examination and resting and symptom limited treadmill exercise testing; none had a history of cardiac disease.

### STRESS PROTOCOL

After 30 minutes of supine rest each subject performed isometric exercise with a hand grip dynamometer held at 50% of maximum voluntary contraction for two minutes. Five subjects also performed isometric exercise at 33% of maximum voluntary contraction for three minutes. Subjects were asked to count out aloud during isometric exertion and were observed closely for any tendency to perform a Valsalva manoeuvre. A cold stress test was performed by immersing a hand and wrist in iced water for two minutes. In five of these subjects the cold stress test was repeated with an immersion period of three minutes. Blood pressure was recorded every minute during stress and after three and five minutes of recovery by means of indirect auscultatory techniques, and heart rates were recorded from the cathode ray tube of the nuclear probe. After an average of two weeks (range 1–4) nine subjects underwent an identical programme of stress testing to establish the reproducibility of the responses.

### RADIONUCLIDE TECHNIQUE

The blood pool was labelled *in vivo* with stannous pyrophosphate (Pyrolite, New England Nuclear) followed 30 minutes later by 200 mg of sodium perchlorate and 740 MBq of  $^{99m}\text{Tc}$ . We used established routines to position the nuclear probe over the left ventricle.<sup>8–10</sup> Background activity was determined at the beginning of the investigation and before each intervention. The background and left ventricular regions of interest were marked and the probe was held in position during all interventions to limit errors due to movement. The background activity was also recalculated and corrected if necessary after one minute of each stress test in 14 subjects.

In 19 subjects multiple electrocardiogram gated left ventricular time-activity curves were generated at rest and at peak stress. In the gated mode 10 000 counts per 10 ms were collected to obtain a gated left ventricular time-activity curve with a standard deviation of 1% caused by radioactive decay.

### CONTINUOUS MEASUREMENT OF LEFT VENTRICULAR TIME-ACTIVITY CURVES

A continuous analogue signal representing the time course of activity was also obtained from the nuclear probe. The pulse output of the photomultiplier preamplifier was taken directly to an external pulse amplifier (Ortec Model 485) and thence to a rate meter (Ortec 441) whose time constant was set at 50 ms. The analogue voltage output of this rate meter was passed, unfiltered, to a galvanometric pen recorder (0–75 Hz bandwidth; Watanabe Linearrecorder Series V). By this means, the nuclear probe's own rate-meter and filters were bypassed, so that the signal reaching the chart recorder was known to be free of important distortion. The background counts were also plotted on the chart recorder before and during each test.

The recordings from 16 subjects were later analysed by hand measurement of 15 beats after the initial 15 seconds and then every 30 seconds. Left ventricular ejection fraction was calculated for each cardiac cycle and averaged to produce a value which was expressed to an accuracy of one ejection fraction unit. Relative end systolic volume, end diastolic volume, and stroke volume were also calculated every 30 seconds, and serial changes were expressed as a percentage of the resting values.

### STATISTICAL METHODS

Ejection fractions at rest and peak of cold stress or isometric hand grip were compared by Student's *t* test (two tailed). Ejection fraction, heart rate, and blood pressure data obtained by continuous recordings were analysed by analysis of variance. Dunnett's *t* test was then used to compare resting values with each of the subsequent time points. Repeat measurements in the same subjects to assess reproducibility were analysed by three way analysis of variance.

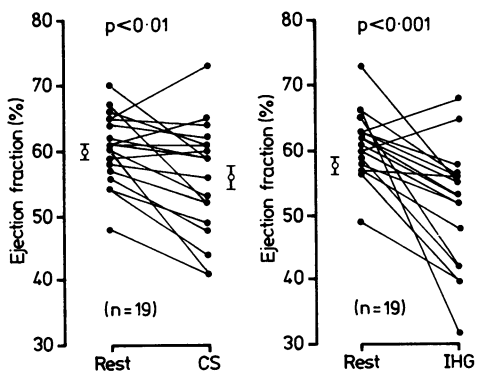


Fig. 1 Individual changes in left ventricular ejection fraction from rest to peak cold stress (CS) and peak isometric handgrip (IHG). Mean (SE) is indicated.

## Results

The mean (SD) count rate at rest was 4478 (599) counts/50 ms and the background counts were 57 (4)% of the mean count rate. Background counts increased by 5 (11)% during isometric exercise and by 3 (8)% during cold stress. Neither of these differences was statistically significant.

Fig. 1 shows the individual responses of left ventricular ejection fraction measured in the gated mode at rest and at the peak of both interventions. The mean (SE) resting left ventricular ejection fraction was 60 (1.2) before cold stress and fell to 56% (1.9) after two minutes, a mean fall of 4.5% ( $p < 0.01$ ). Before isometric hand grip, the resting left ventricular ejection fraction was 61% (1.1); this fell to 52% (2.0) after 2 minutes hand grip, a mean fall of 9.3% ( $p < 0.001$ ).

Measurement of the mean ejection fraction after 15 seconds and then every 30 seconds showed that cold stress produced a significant fall in ejection fraction after 30 seconds with a mean maximal fall of

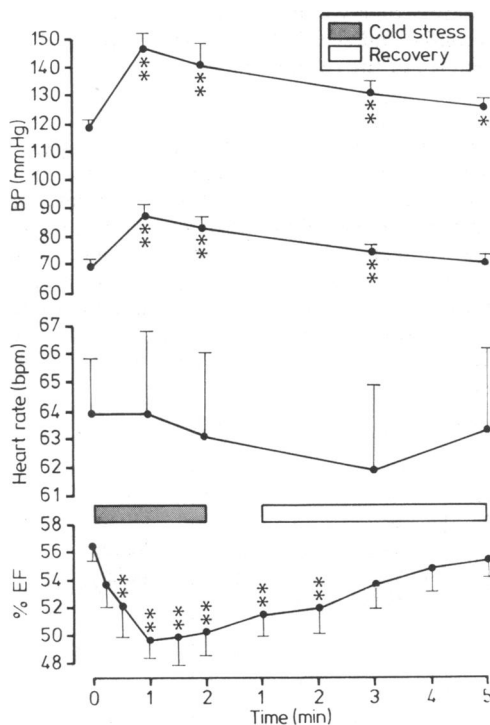


Fig. 2 Mean (SE) response of systolic and diastolic blood pressure (BP), heart rate, and ejection fraction (EF) to two minutes' cold stress ( $n = 15$ ). \* $p < 0.05$ ; \*\* $p < 0.01$  when compared with value at rest.

7% occurring after one minute (Fig. 2). The ejection fraction subsequently increased but was still 6% below the resting value after two minutes. The recovery from cold stress was protracted; and left ventricular ejection fraction had still not returned to baseline levels after five minutes.

In contrast, isometric exercise (Fig. 3) produced a significant fall in ejection fraction after 15 seconds, reaching a nadir after 90 seconds. The recovery phase after stopping the hand grip was more rapid than with cold stress and the mean values were not significantly different from baseline at three minutes with an overshoot at five minutes. The fall in ejection fraction induced by isometric hand grip was significantly different from that induced by cold stress only after 90 seconds of stress ( $p < 0.05$ ).

Cold stress did not produce a significant change in mean heart rate. The maximum rise in blood pres-

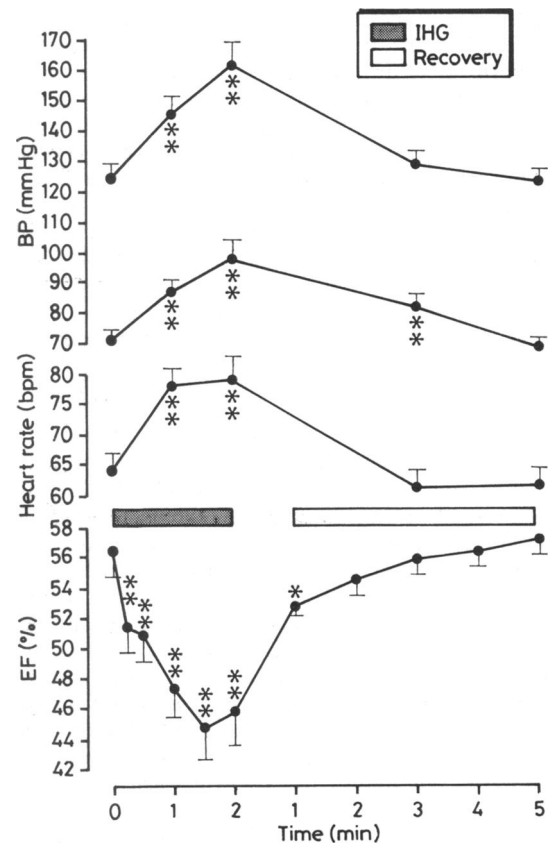


Fig. 3 Mean (SE) response of systolic and diastolic blood pressure (BP), heart rate, and ejection fraction (EF) to two minutes' isometric hand grip at 50% maximum voluntary capacity ( $n = 15$ ). \* $p < 0.05$ ; \*\* $p < 0.01$  when compared with value at rest.

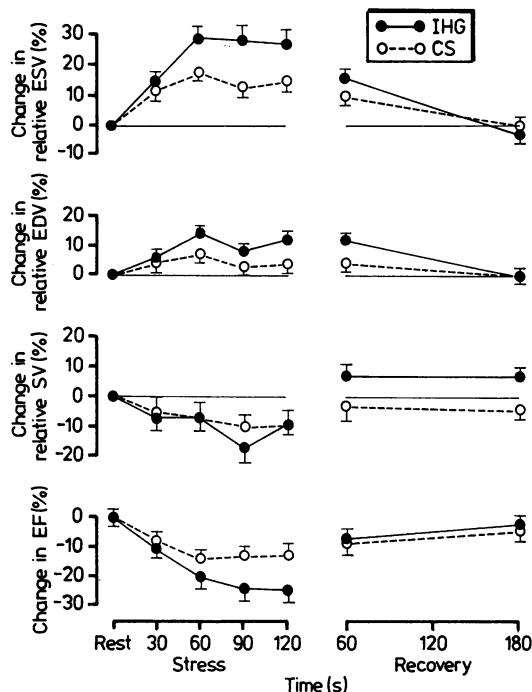


Fig. 4 Mean (SE) percentage change in relative end systolic volume (ESV), end diastolic volume (EDV), stroke volume (SV), and ejection fraction (EF) during two minutes' isometric hand grip (IHG) and cold stress (CS).

sure occurred after one minute and therefore occurred at the same time as the maximum fall in ejection fraction. Isometric exercise produced a significant increase in heart rate and a pronounced increase in the blood pressure with a maximum measured rise after two minutes.

In order to obtain an estimate of changes in relative left ventricular volumes, changes in total counts were assumed to be proportional to changes in volume. Figure 4 shows the percentage change from rest in relative end systolic volume, end diastolic volume, stroke volume, and ejection fraction. Isometric exercise produced a maximum increase of 29% in end systolic volume and 14% in end diastolic volume ( $p < 0.001$ ) with a maximum decrease in stroke volume of 17% and ejection fraction of 24% ( $p < 0.001$ ). Cold stress induced a maximum increase of 18% in end systolic volume ( $p < 0.001$ ) and 7% in end diastolic volume ( $p < 0.01$ ) and a maximum fall of 10% in stroke volume and 14% in ejection fraction ( $p < 0.01$ ).

The response of the left ventricular ejection fraction to two and three minutes of cold stress is shown in Fig. 5. The mean fall in ejection fraction was

identical during both stress periods after two minutes (8% below baseline). When cold immersion was prolonged for three minutes the ejection fraction remained significantly depressed until the end of the stress period. Figure 6 shows the ejection fraction response to two minutes and three minutes of isometric hand grip. Two minutes' exertion at 50% maximum voluntary contraction induced a maximum fall in ejection fraction of 12% after 90 seconds with recovery at two minutes. Three minutes of isometric hand grip at 33% maximum voluntary contraction induced a fall of 7% at 90 seconds which then remained depressed until the end of exercise.

There were no statistically significant differences between the falls in ejection fraction during two minutes and three minutes of cold stress or two minutes and three minutes of isometric exercise; however, the number of subjects may have been too small to establish such a difference.

Nine subjects underwent repeat testing two weeks later (range 1-4 weeks). The standard error of the change in ejection fraction on the two separate occasions was 5.4% at rest, 4.8% for cold stress, and 7.0% for isometric exercise.

### Discussion

Early studies of isometric exercise suggested that measurement of the haemodynamic response to this form of exertion may provide a useful index of myo-

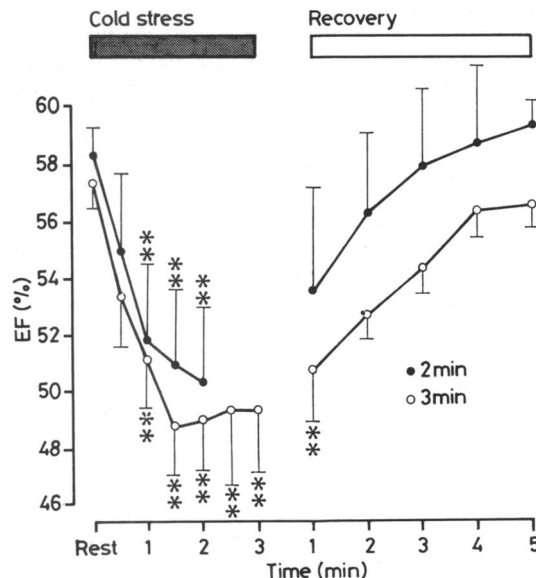


Fig. 5 Mean (SE) left ventricular ejection fraction during two minutes' and three minutes' cold stress ( $n = 5$ ). \*\* $p < 0.01$  when compared with values at rest.

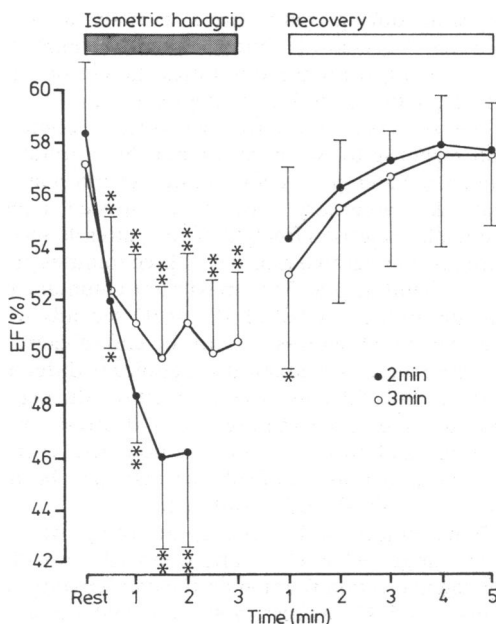


Fig. 6 Mean (SE) left ventricular ejection fraction during two minutes' isometric hand grip at 50% maximum voluntary capacity and three minutes' isometric hand grip at 33% maximum voluntary capacity ( $n=5$ ) \* $p < 0.05$ ; \*\* $p < 0.01$  when compared with values at rest.

cardial dysfunction.<sup>2</sup> Helfant *et al*, however, found isometric exercise to be of no value for the detection of coronary artery disease and suggested that the increase in diastolic blood pressure that occurs during the test may prevent the development of myocardial ischaemia.<sup>11</sup> Using radionuclide techniques, Bodenheimer *et al* suggested that the assessment of regional ejection fraction during isometric hand grip may also be of value,<sup>12</sup> but more recently the same group of workers found a specificity of only 50% for the detection of coronary artery disease when considering global ejection fraction.<sup>5</sup> During cold stress, Wainwright *et al* reported a clear separation in the response of left ventricular ejection fraction between normal subjects and patients with coronary artery disease or cardiomyopathy,<sup>13</sup> whereas Jordan *et al* and Wasserman *et al* were unable to detect a clinically important difference between normal and diseased subjects.<sup>6,7</sup> In one of these studies, the fall in left ventricular ejection fraction in response to cold was slightly more pronounced in normal subjects than in patients with coronary artery disease.<sup>6</sup> Using techniques similar to our own, Giles *et al* found a mean fall of 11% in both patients and controls in response to cold stress and isometric hand grip.<sup>14</sup> These studies were limited to the in-

vestigation of ejection fraction, however, and little attention has been paid to changes in relative volumes.

Several factors may be responsible for this wide variation in reported results. These include differing selection criteria for both patients and normal controls. In previously reported studies normal controls were patients who had undergone coronary arteriography for investigation of chest pain, with negative results.<sup>7,13</sup> This group of patients has been shown to have a highly variable response when the ejection fraction during dynamic exercise is studied.<sup>15</sup> It is debatable therefore whether they should be considered as truly normal, particularly when their response to cold stress is measured.

Protocols for isometric hand grip have ranged from two minutes exertion at 50% maximum voluntary contraction to three or four minutes at 30% maximum voluntary contraction,<sup>12,16</sup> and for cold stress from two to five minutes of hand immersion.<sup>6,7</sup> In all these studies different radionuclide techniques have also been used including gated radionuclide angiography with a data acquisition time of two to five minutes<sup>6</sup> and first pass radionuclide angiography with both <sup>99m</sup>Tc<sup>16</sup> and <sup>195m</sup>Au.<sup>17</sup>

The nuclear stethoscope has been fully validated for the measurement of resting left ventricular ejection fraction.<sup>8,9</sup> In a recent study of 54 patients we compared the resting left ventricular ejection fraction measurements from the nuclear probe with those from a gamma camera.<sup>18,19</sup> The mean (SE) difference between the two methods was 1.4 (0.8)%, confirming the validity of the nuclear probe. It is reasonable to expect this accuracy to apply during isometric hand grip and cold stress, which involve no additional patient movement. One important source of error during these interventions might be expected from significant changes in background activity. We are able, however, to reassess background counts during each stress test and make any necessary corrections. Using a positron camera, Nichols *et al* have shown that cardiopulmonary blood volume increases in patients with coronary artery disease during exercise testing.<sup>20</sup> The background counts in our normal population may not, however, be appropriate when applied to patients.

The overall fall in ejection fraction of 4.5% obtained by gated measurement at the peak of cold stress is in the middle of the range of other reported studies in "normal" subjects (+3% to -11%).<sup>4,11,21</sup> Only three of our subjects increased their ejection fraction during cold stress and in seven a fall of >4.8% developed. The maximum fall occurred after one minute, in keeping with the results obtained by Dymond *et al*.<sup>17</sup> When the cold stress

test was prolonged for three minutes, the ejection fraction remained depressed for the period of the intervention and the recovery was again slow. These results are in contrast with those obtained by Manyari *et al* who demonstrated an abnormal ejection fraction response in only two out of 20 "normal" subjects.<sup>21</sup>

The mean fall in left ventricular ejection fraction of 9.3% in response to 50% maximum voluntary contraction during isometric hand grip contrasts with one earlier study reporting a rise of 3%, but compares well with more recent studies reporting a 7–12% fall.<sup>5,11</sup> Fifteen of our subjects decreased their ejection fraction by more than 7% and only two subjects demonstrated an increase in ejection fraction at peak intervention. The maximal fall during 50% maximum voluntary contraction occurred after 90 seconds with a slight recovery at two minutes. This is probably related to the fact that subjects found it difficult to maintain this degree of contraction, and some relaxation of grip occurred. During three minutes of hand grip at 33% maximum voluntary contraction left ventricular ejection fraction was less severely affected, but remained depressed for the duration of the stress. It was apparent that the subjects were better able to maintain this degree of grip.

Our measurements of resting left ventricular ejection fraction made with the nuclear probe on two occasions showed a standard error that resembles those reported in other studies in which the non-imaging nuclear probe<sup>9,10</sup> and gamma cameras<sup>22–24</sup> were used. The standard error of the ejection fraction at the peak of cold stress was similar but the response to isometric hand grip was less reproducible.

The findings in this study are not surprising in the light of the sequence of physiological events. Both these stress tests lead to an increase in aortic diastolic pressure. The normal left ventricle must first overcome this pressure during the isovolumetric phase of contraction before blood is ejected. As the aortic pressure begins to rise, the volume of blood ejected from the left ventricle will be reduced for the first few beats. If the aortic diastolic pressure were then maintained at a constant level the ventricle would restore the initial ejection fraction by the Frank-Starling mechanism. As the systemic diastolic pressure continues to rise, a progressive fall in ejection fraction occurs until the point at which blood pressure decreases. This sequence of events is important in determining the left ventricular response, irrespective of the presence or absence of coronary artery disease.

There was considerable inter-subject variability in response to both of these stress tests. There was

only moderate agreement between repeat measurements under stress conditions in any individual although for the group as a whole the reproducibility was good. This intra-subject variability may in part have reflected the methods we used, although neither of these interventions provoked any additional patient movement, particularly of the chest wall. Our results suggest that the maximum fall in left ventricular ejection fraction does not necessarily occur at the peak of the stress and therefore techniques requiring data acquisition times of two to five minutes may, as a result of the inherent averaging which occurs, underestimate the induced changes.

In conclusion therefore, it appears that a combination of inter-subject variability and considerable methodological differences have contributed to the reported discrepancies between published reports. These factors, as well as the physiological responses to these stress tests, are likely to limit severely the usefulness of these tests for the detection of coronary artery disease, particularly in an unselected population.

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