EXERCISE VS COLD-PRESSOR TEST/Manyari et al.

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Comparative Value of the Cold-pressor Test and Supine Bicycle Exercise to Detect Subjects with Coronary Artery Disease Using Radionuclide Ventriculography

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SUMMARY Left ventricular ejection fraction (EF) and wall motion studies were performed using blood pool cardiac scintigraphy before and during the cold-pressor test (CPT) and bicycle exercise. Twenty normal subjects responded to the CPT with no change or a significant increase (7% or more) of the EF and no new wall motion abnormalities. Mean EF increased significantly (p < 0.01). Two subjects responded abnormally to the CPT, one with a significant decrease (7% or more) in EF and another with the development of new wall motion abnormalities. During exercise, EF increased significantly in all but one subject (p < 0.001). No new wall motion abnormality was seen.

In 20 patients with coronary artery disease (CAD) and normal resting left ventricular function, mean EF decreased (p < 0.001) during the CPT, but only 11 patients could be identified individually by a drop in EF of 7% or more. During exercise, 18 of the 20 patients responded abnormally (failure to increase EF by 7% or more). Twelve patients showed new wall motion abnormalities during CPT and 15 during exercise. Three patients during the CPT and one during exercise had normal EF response while developing new wall motion abnormalities.

Thus, the sensitivity of radionuclide EF changes during the CPT to detect subjects with CAD was 55%. It increased to 70% when wall motion analysis and EF changes were considered. The specificity was then 90% and the predictive accuracy was 88%. The sensitivity of radionuclide studies during exercise, considering EF changes and wall motion analysis under otherwise similar conditions, was 95%. Specificity and predictive accuracy were also 95%. We conclude that the CPT is not as sensitive as exercise for detecting subjects with CAD by radionuclide cardiac angiography. The CPT may be a useful intervention in subjects in whom adequate exercise cannot be accomplished.

SINCE Hines and Brown described the cold-pressor test (CPT) in 1932,1 it has been used to identify subjects with hypertension2,3 and atherosclerosis.4,5 However, its acceptance in the clinical setting was limited, mainly because the initial hypothesis that the vascular reactivity in subjects with these conditions is different from that in normal subjects has not been verified.6-8 More recently, it has been reported that the CPT may induce local and global left ventricular dys-

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function in many patients with coronary artery disease (CAD).9-11 Furthermore, because assessment of left ventricular function during exercise may be cumbersome and time-consuming, the CPT may be a preferred method of stress to detect subjects with CAD.11,12 This alternative however, has not been adequately tested.

We undertook this study to determine the comparative values of isotonic leg exercise and the CPT for identifying subjects with CAD and normal left ventricular function, by noninvasively assessing left ventricular function changes during these forms of stress.

Methods

Patients

The control group included 20 normal subjects, ages 24–66 years (mean 39 years). Fifteen were males and
five were females. Twelve patients with atypical chest pain were normal at cardiac catheterization and coronary cineangiography. None of these patients showed clinical or electrocardiographic evidence of variant angina. The remaining eight were asymptomatic volunteers without evidence of cardiorespiratory disease or conditions known to affect cardiac function. All control subjects had normal physical examination, chest x-ray and resting and exercise ECG. Twenty patients with CAD as defined by the presence of at least 50% diameter reduction of one or more major coronary arteries, 28-68 years old (mean 45 years), were included in the second group. Seventeen were males and three were females. No subject with clinical, echocardiographic or angiographic evidence of mitral valve prolapse was included in the study.

Cardiac catheterization was carried out within 7 days of the study. In the interim there was no change in their clinical condition. All had normal left ventricular function at rest as determined by an angiographic ejection fraction (EF) of 65% or higher or a radionuclide EF of 55% or higher, and normal wall motion. Consecutive patients seen in our service, who met the above criteria, were selected for this investigation solely on the basis of willingness to participate, presence of sinus rhythm and absence of intermittent claudication, Raynaud's phenomenon or unstable angina.

Radionuclide Angiography

Electrocardiographically gated blood pool cardiac imaging was used to assess global and regional left ventricular function. After in vivo labeling of the red blood cells, each study consisted of 2-minute acquisition in the modified left anterior oblique projection. Care was taken to maintain the same view during each intervention. We used a conventional Anger-type scintillation camera with 37 photomultiplier tubes equipped with a high-sensitivity parallel-hole collimator, interfaced to a dedicated medical computer system (Technicare 460). Data were collected in a continuous ECG synchronized mode, 16 frames spanning the cardiac cycle, by previously described methods. The data were later analyzed using spatial smoothing, background subtraction and generation of the left ventricular time-activity curve, and EF. All EF determinations were performed by one blinded observer.

Regional wall motion was analyzed systematically by two blinded and independent observers in five segments (high septal, low septal, inferoapical, posterolateral and superolateral) by subjective assessment of the end-loop movie format and static mode and the aid of computer manipulation of images, which included the stroke volume image, EF image, and the superimposition of the end-diastolic and end-systolic perimeters. Each segment was classified as normal, hypokinetic, akinetic or dyskinetic (scored 0, 1, 2, and 3, respectively). Scores of all segments were then added and wall motion of each study expressed numerically (0-15) by each observer, which in turn were averaged to the nearest entire number and a single interpretation obtained.

In our laboratory, intra- and interobserver variability of wall motion interpretation, as described above, was calculated previously in 20 subjects with a variety of left ventricular function and the correlation coefficients obtained were 0.97 and 0.92, respectively. Radionuclide wall motion closely correlated with contrast studies, and radionuclide left ventricular EF had a coefficient of correlation of 0.87 with contrast EF.

Study Design

Participants were studied in a fasting state, in the supine position and without premedication. Patients who were treated with β blockers or long-acting nitrates did not receive these medications for at least 72 and 24 hours, respectively. None received sublingual nitroglycerin for at least 6 hours before the study.

Radionuclide angiography was carried out at five stages on each participant: (1) at rest, where two measurements (R-1 and R-2) were taken after at least a 30-minute period of lying quietly in the supine position; (2) during the cold-pressor test (CPT); (3) 60 seconds after the CPT was terminated (post-CPT); (4) at rest (R-3) 30 minutes after the CPT; and (5) at peak exercise. Care was taken to maintain the same camera and patient position throughout the study, and to avoid all possible physical or mental stimulation other than the CPT and exercise.

During the CPT, the left hand was immersed up to the level of the stiloid process into water at 0-2°C for 150 seconds, with acquisition made during the last 120 seconds and during minutes 2 and 3 of the post-CPT period. Symptoms, cuff-blood pressure taken in the right arm and a nine-lead ECG (standard, limb and precordial V \(_1\), and modified V \(_4\) and V \(_6\) leads) were recorded at 30-second intervals. The modified V \(_4\) and V \(_6\) ECG leads were placed in the sixth intercostal space so that they would not interfere with cardiac imaging. Maximal blood pressure and heart rate (HR) changes during the CPT were regarded as the CPT response.

After termination of the CPT, subjects remained at rest until study R-3 was terminated. Exercise was then started using a cycle ergometer. The initial work load was 25 W with successive increments of 25 W made at 3-minute intervals. Exercise was terminated because of marked fatigue or angina of severity customarily causing the patient to stop. Acquisition was made during the last 2 minutes at each work load, but only the study at peak exercise was stored on a separate magnetic tape for purposes of this investigation. Symptoms, cuff-blood pressure and a nine-lead ECG were monitored throughout exercise.

Statistical Analysis

Each hemodynamic measurement was analyzed by two-way analysis of variance to compare the mean response at the five stages, where the response for a given patient at stage 1 was defined as the average resting value (R-1 + R-2)/2. Post-hoc comparisons of stages 2, 3, 4 and 5 with stage 1 were performed using the Dunnett's multiple-comparison procedure. To
compare the data at a given stage between the two groups, the t test was used. Sensitivity, specificity and predictive accuracy were calculated as previously described, and expressed in percent units. The variability of sequential EF determinations was calculated using individual results of all participants at substages R-1 and R-2. The 95% confidence interval about a resting EF, used to define a subsequent significant change during the following stages in the individual subject, was determined by calculation of the pooled variance as described by Caldwell et al.

### Results

Coronary angiography showed minor luminal irregularities with less than 30% diameter reduction of a vessel in two of the control subjects. In the group with CAD, nine patients had three-vessel disease, four had two-vessel disease and seven had one-vessel disease. All patients had normal left ventricular wall motion and EF higher than 65% on contrast ventriculography. Both interventions were completed without complications, although during the CPT one patient with CAD complained of a severe headache and her blood pressure rose from 135/90 mm Hg to 185/110 mm Hg. Five subjects (three control and two patients with CAD) spontaneously complained of painful left hand. None experienced angina or had significant ST-segment depression on the ECG during the CPT. All control subjects terminated exercise because of fatigue; none of them developed abnormal ECG changes during exercise. Twelve patients with CAD stopped exercise because of angina and eight because of fatigue. In this group, 13 had 1 mm or more of horizontal ST-segment depression for at least 80 msec after the J point at peak exercise.

### Heart Rate and Blood Pressure

In each group, the mean values of HR, systolic and diastolic blood pressure (BP) and rate-pressure product (RPP) (tables 1 and 2) were not significantly different during any of the resting (R-1, R-2 and R-3) studies.

At rest, mean HR was similar in both groups (p > 0.05). Controls and patients with CAD increased the HR with the CPT and with exercise (tables 1 and 2), but in both groups it was significantly higher (p < 0.001) during exercise than during the CPT. Patients with CAD had a higher HR (p < 0.05) during the CPT and, since symptoms most often developed, HR achieved during exercise was lower (p < 0.01) than that of normal subjects at peak exercise. Individual responses are shown in figure 1. Two controls and two patients with CAD had a reduction of the HR during

### Table 1. Hemodynamic Data in Controls

<table>
<thead>
<tr>
<th>Stages</th>
<th>HR (beats/min)</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
<th>RPP (mm Hg/min × 10⁻²)</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rest (R-1)</td>
<td>71 ± 9</td>
<td>121 ± 13</td>
<td>80 ± 9</td>
<td>86 ± 14</td>
<td>66.6 ± 8.7</td>
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<tr>
<td>Rest (R-2)</td>
<td>69 ± 8</td>
<td>122 ± 15</td>
<td>77 ± 11</td>
<td>85 ± 16</td>
<td>65.9 ± 6.9</td>
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<td>2. CPT</td>
<td>79 ± 11*</td>
<td>147 ± 19*</td>
<td>95 ± 10*</td>
<td>116 ± 19*</td>
<td>69.3 ± 8.4†</td>
</tr>
<tr>
<td>3. Post-CPT</td>
<td>74 ± 11</td>
<td>127 ± 14*</td>
<td>83 ± 8†</td>
<td>93 ± 14†</td>
<td>67.2 ± 9.4</td>
</tr>
<tr>
<td>4. Rest (R-3)</td>
<td>70 ± 8</td>
<td>120 ± 14</td>
<td>76 ± 11</td>
<td>84 ± 13</td>
<td>64.9 ± 6.5</td>
</tr>
<tr>
<td>5. Exercise</td>
<td>143 ± 18*</td>
<td>183 ± 22*</td>
<td>92 ± 14*</td>
<td>261 ± 41*</td>
<td>76.4 ± 7.0*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*p < 0.001.

†p < 0.01.

‡p < 0.05.

Abbreviations: HR = heart rate; BP = blood pressure; RPP = rate-pressure product; EF = left ventricular ejection fraction; CPT = cold-pressor test.

### Table 2. Summary of Hemodynamic Data in Patients with Coronary Artery Disease

<table>
<thead>
<tr>
<th>Stages</th>
<th>HR (beats/min)</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
<th>RPP (mm Hg/min × 10⁻²)</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rest (R-1)</td>
<td>75 ± 13</td>
<td>124 ± 15</td>
<td>76 ± 7</td>
<td>93 ± 22</td>
<td>64.1 ± 5.8</td>
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<tr>
<td>Rest (R-2)</td>
<td>76 ± 13</td>
<td>126 ± 14</td>
<td>78 ± 8</td>
<td>96 ± 21</td>
<td>65.0 ± 5.8</td>
</tr>
<tr>
<td>2. CPT</td>
<td>84 ± 13*</td>
<td>155 ± 23*</td>
<td>97 ± 10*</td>
<td>131 ± 33*</td>
<td>59.1 ± 8.7*</td>
</tr>
<tr>
<td>3. Post-CPT</td>
<td>79 ± 12†</td>
<td>129 ± 15†</td>
<td>80 ± 9</td>
<td>102 ± 22†</td>
<td>61.2 ± 7.9†</td>
</tr>
<tr>
<td>4. Rest (R-3)</td>
<td>74 ± 10</td>
<td>123 ± 14</td>
<td>75 ± 9</td>
<td>92 ± 16</td>
<td>64.0 ± 6.1</td>
</tr>
<tr>
<td>5. Exercise</td>
<td>135 ± 16*</td>
<td>179 ± 19*</td>
<td>93 ± 10*</td>
<td>237 ± 40*</td>
<td>57.9 ± 9.9*</td>
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</tbody>
</table>

Values are mean ± SD.

*p < 0.001.

†p < 0.01.

‡p < 0.05.

Abbreviations: See table 1.
the CPT by 5 beats/min or more, while all participants increased HR with exercise by at least 45 beats/min.

Systolic and diastolic BP at rest were similar ($p > 0.05$) in both groups. They consistently increased during both interventions (tables 1 and 2). During the CPT, systolic BP increased by $25 \pm 12$ mm Hg (mean $\pm$ SD) in controls and by $30 \pm 14$ mm Hg in subjects with CAD; with exercise it rose by $63 \pm 18$ mm Hg in control subjects and by $56 \pm 15$ mm Hg in patients with CAD. In both groups, systolic BP changes produced by exercise were significantly higher ($p < 0.001$) than changes produced by the CPT (fig. 2). Finally, systolic BP during the CPT was higher ($p < 0.01$) in patients with CAD than in controls, while both groups achieved similar systolic BP with exercise. Diastolic BP increased to a similar extent in both groups and with both interventions (tables 1 and 2). With the CPT, it rose by $16 \pm 8$ mm Hg in control subjects and by $20 \pm 8$ mm Hg in patients with CAD; with exercise, it increased by $17 \pm 13$ mm Hg in the control group and by $17 \pm 14$ mm Hg in the CAD group (fig. 3).

The RPP at rest was similar ($p > 0.05$) in both groups. It was significantly higher ($p < 0.001$) during exercise than during the CPT. In controls, the RPP increased by $37 \pm 18\%$ with the CPT and by $216 \pm 55\%$ during exercise. In patients with CAD, it increased by $39 \pm 18\%$ with the CPT and by $158 \pm 42\%$ with exercise from the respective resting values (fig. 4).

Maximal BP response to the CPT occurred at 30 seconds in 15 subjects, at 60 seconds in 22, and at 90 seconds in three subjects. There was no difference in the timing of the maximal BP response between the two groups.

**Variability of EF Determinations**

The variability of EF measurements was determined using the results of the 40 participants of this study. The difference of less than 1% (absolute value) between the means at substages R-1 and R-2, was not statistically significant. From the individual mean of the two resting values at stage 1, and knowledge of the pooled variance, the 95% confidence limits for significant change of a subsequent EF measurement was given by

\[ \bar{X} \pm 2.02 \sqrt{S^2 \left( \frac{1}{n} + 1 \right)} \]

where $S^2$ de-

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**Figure 1.** Group and individual heart rate responses to both interventions. CAD = coronary artery disease; R-1,2 = average of two resting studies (stage 1); CPT = cold-pressor test (stage 2); R-3 = rest (stage 4); Ex = peak exercise (stage 5).

**Figure 2.** Group and individual systolic blood pressure responses to the cold-pressor test and peak exercise. Abbreviations are as in figure 1.

**Figure 3.** Group and individual diastolic blood pressure responses. Abbreviations are as in figure 1.

**Figure 4.** Group and individual rate-pressure product changes during the cold-pressor test and peak exercise. Abbreviations are as in figure 1.
notes the pooled variance and n is the number of rest-
ing observations per patient. For the 40 participants
of the study, $S^2 = 7.74$ percent units, n = 2, and the
95% confidence interval for a given patient may be
calculated as $X \pm 6.88$ EF percent units. This implies
that the individual change of EF to any intervention
must be 7% (absolute value) or more to be considered
significant at the 5% level. Variations of less than 7%
can be attributed to physiologic and statistical noise.

**EF Changes**

Mean resting EF was similar in both groups. In
controls, mean EF increased slightly, but significantly
($p < 0.01$), with the CPT (table 3) by 3.05% (absolute
value). When examining individual values, 13 sub-
jects did not increase the EF significantly (as defined
above) with the CPT, and in fact in six of these sub-
jects there was a decrease in EF. However, in only one
of them was this drop significant (subject 8). With
exercise, all controls but one showed a significantly
increased EF (average increase 11.55%). Mean EF dur-
ing exercise was significantly higher ($p > 0.001$) than
mean EF during the CPT. The subject whose EF
decreased significantly during the CPT was a woman
with atypical chest pain who had no angina, abnor-
mal ECG, or abnormal wall motion during either
stress, and her EF response to exercise was normal.

The control who failed to increase EF during exercise
(subject 11) was an asymptomatic young woman with
normal exercise ECG and wall motion.

Based on these results, the following criteria were
defined for a given patient: The normal response to the
CPT is either no significant change or a significant in-
crease of the left ventricular EF. This implies, then,
that an abnormal response to the CPT is a decline in
EF by 7% (absolute value) or more. During peak ex-
ercise, the normal response is a significant increase of
EF; thus, an abnormal response to peak exercise is
failure of the EF to increase by 7% (absolute value) or
more.

In patients with CAD, the mean EF decreased signifi-
cantly with the CPT (tables 2 and 4). On examin-
ing individual responses, in 11 patients the EF
decreased by 7% or more; in seven, EF remained
within 6.5% of resting values; and in two, EF increased
significantly (patients 3 and 7). With exercise, 18 pa-
tients failed to increase EF significantly (table 4).
Mean EF during exercise decreased significantly, to
an extent comparable to that caused by the CPT. Pa-
tients with CAD had a significantly lower mean EF
during both forms of stress than normal subjects ($p <
0.001$). Patients 6 and 11, whose EF increased sig-
nificantly with exercise, had one-vessel CAD. The
RPP was $328 \times 10^5$ mm Hg/min for patient 6 and 230

### Table 3. Group and Individual Left Ventricular Function Assessment During the Entire Study in 20 Controls

<table>
<thead>
<tr>
<th>Pt</th>
<th>R-1 EF (%)</th>
<th>R-2 EF (%)</th>
<th>WMS</th>
<th>CPT EF (%)</th>
<th>WMS</th>
<th>Post-CPT EF (%)</th>
<th>R-3 EF (%)</th>
<th>WMS</th>
<th>Ex EF (%)</th>
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<td>±0.22</td>
<td>±9.4</td>
<td>±6.5</td>
<td>±0.00</td>
<td>±7.0</td>
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<td>p</td>
<td>&lt;0.01</td>
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<td>&lt;0.001</td>
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</tbody>
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** Abbreviations: EF = left ventricular ejection fraction; WMS = wall motion score; R = rest; CPT = cold-pressor test; Ex = peak exercise. **
TABLE 4. Group and Individual Values of Left Ventricular Ejection Fraction and Wall Motion Scores During the Study in 20 Patients with Coronary Artery Disease

<table>
<thead>
<tr>
<th>Pt</th>
<th>R-1 EF (%)</th>
<th>R-2 EF (%)</th>
<th>CPT EF (%)</th>
<th>Post-CPT EF (%)</th>
<th>R-3 EF (%)</th>
<th>Ex EF (%)</th>
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Mean: 64.1 ± 5.8; 65.0 ± 5.8; 0.00; 59.1 ± 1.40; 61.2 ± 8.7; 64.0 ± 1.54; 74.0 ± 7.9; 66.0 ± 6.1; 0.00 ± 9.9; 2.48

*p* < 0.001 < 0.001 < 0.01 < 0.001 < 0.001 < 0.001

Abbreviations: See table 3.

× 10² mm Hg/min for patient 11 and neither of them developed angina or significant ST-segment changes at peak exercise.

Segmental Wall Motion Studies

Individual and group wall motion scores are listed in tables 3 and 4. At rest, all subjects, by virtue of patient selection, had normal segmental wall motion. Normal subjects did not change significantly the mean score with either stress. Patients with CAD increased significantly the mean score with both interventions.

On examination of individual response, only one normal subject had an increased wall motion score during the CPT. During exercise, all control subjects had normal wall motion. Twelve patients with CAD during the CPT and 15 during exercise had increased wall motion scores. In these patients, the EF response to the CPT was normal in three, and EF response to exercise was normal in one.

Sensitivity and Specificity

Considering global left ventricular function changes, indicated by EF, radionuclide cardiac scintigraphy during the CPT, detected 11 of 20 patients with CAD (sensitivity 55%), had a specificity of 95% and a predictive accuracy of 92%. When wall motion analysis was considered in addition to EF changes, the sensitivity was 70% (detected 14 of 20 patients with CAD), the specificity was 90% and the predictive accuracy was 88%. The CPT detected seven of nine patients (78%) with three-vessel CAD, three of four (75%) with two-vessel CAD and four of seven (57%) with one-vessel CAD.

In similar conditions, radionuclide EF changes during exercise detected 18 of 20 patients with CAD (sensitivity 90%), had a specificity of 95% and a predictive accuracy of 95%. When wall motion analysis and EF changes were considered together, the sensitivity increased to 95% and the specificity and the predictive accuracy remained at 95%. The one patient not detected by exercise studies had one-vessel CAD.

The significance of the differences in sensitivity and specificity of both interventions in the identification of patients with CAD was assessed by McNemar's test. When only the EF changes are considered, the difference is significant (*p* < 0.05); but when both EF changes and development of wall motion abnormalities are considered, the difference is not significant (*p* = 0.10).

Discussion

We evaluated the relative merits of the CPT and of supine bicycle exercise in the detection of subjects with CAD, using multigated blood pool cardiac scintigraphy. Our results indicate that both interventions may induce segmental and global left ventricular dys-
function; however, the sensitivity and the predictive accuracy are higher for studies during exercise than during the CPT.

According to classic concepts of the pathophysiology of ischemic heart disease, myocardial ischemia is produced by an increase in the myocardial metabolic demands without a parallel augmentation of its blood supply. Thus, any intervention that increases the myocardial metabolic demands could produce transient myocardial ischemia in subjects with fixed stenosis of the coronary arteries. Because in some patients with chronic stable angina pectoris, the supply-demand equilibrium is maintained at rest, various interventions have been designed. Among these, isotonic exercise (on the treadmill or bicycle) is widely used, partly because of its relative simplicity and availability. Recently, the CPT was shown to be a useful intervention in the detection of patients with CAD. Since the CPT is more accessible and less time-consuming than exercise, it may become an alternative to this intervention, the extent of which would be directly related to its relative effectiveness.

We chose not to alternate or randomize the order of the interventions. Instead, the CPT was performed first in all subjects because its hemodynamic effects are usually short, while the hemodynamic changes produced by bicycle exercise may last for longer than 30 minutes. Maximal BP changes are achieved within 60–90 seconds after initiation of the CPT, and rapidly return to resting values upon withdrawal of the CPT. Thus, we considered it appropriate to start imaging 30 seconds after hand immersion in ice water and to maintain the cold stimulus for the 2 minutes required for the radionuclide study.

The hemodynamic changes produced by supine bicycle exercise in the present study are similar to those reported in normal persons and in patients with CAD. Patients with CAD failed to increase the left ventricular EF, and new wall motion abnormalities were detected at peak exercise as a result of transient myocardial ischemia. Although exercise may induce coronary arterial spasm in selected patients, exercise precipitates myocardial ischemia in patients with typical angina by increasing myocardial metabolic demands in face of a limited supply.

Likewise, the sensitivity and specificity of exercise cardiac scintigraphy in this study to detect CAD in symptomatic patients are similar to those reported by Borger et al. and others. The improved sensitivity when wall motion analysis is performed in addition to global EF is now well recognized.

Our results are different from those of Brennand-Roper et al., who reported that radionuclide studies during exercise have a sensitivity of 40% in detecting patients with CAD. Their patients, however, appeared not to have exercised to adequate levels; they achieved a mean RPP of only 166 × 10³ mm Hg/min, compared with 261 × 10³ mm Hg/min in controls and 237 × 10³ mm Hg/min in those with CAD in our study. This fact is relevant because many reports indicate that the sensitivity of exercise EF studies may, in part, depend on the intensity of exercise. Some patients with CAD may increase the EF at low levels of exercise before it shows a decline at higher exercise work loads. This may also explain why their normal subjects had no change or slight increase of EF during exercise. Brady et al. suggested that adequate exercise be defined as that limited by typical angina, significant ST-segment depression on the ECG, or a RPP equal or higher than 250 × 10³ mm Hg/min. The marked difference in exercise intensity between their study and ours may explain the different results.

One subject in our control group, an asymptomatic 21-year-old woman, failed to increase the EF on exercise. She was normal as judged by current standard clinical criteria except cardiac catheterization, for which she had no indication. Other authors have reported similar false-positive results, especially in women. These responses may be explained by subclinical cardiomyopathy, exercise-induced coronary arterial spasm without symptoms or ECG changes, or a normal variant. We have no information to assess these possibilities. One of the two patients with CAD whose EF increased at peak exercise did not exercise adequately by the criteria of Brady et al., and may explain one of the two false-negative results.

Hemodynamic changes produced by local cold stimulation common to normal persons and to subjects with CAD include a rapid increase in systolic and diastolic arterial pressure mediated by a predominant α-adrenergic stimulation, a modest but significant increase in HR, and myocardial oxygen consumption. In normal subjects, the coronary blood flow increases slightly, while the coronary vascular resistance does not change. In patients with CAD, coronary vascular resistance increases, and the coronary blood flow may increase or decrease. Recently, Raizner et al. showed that the CPT may induce coronary artery spasm in some subjects. Thus, there is experimental evidence that myocardial ischemia may be precipitated by the CPT in subjects with CAD by either increasing cardiac metabolic demands or limiting coronary blood supply or both.

Changes in HR and BP produced by the CPT in our investigation were similar to those reported previously. A significant increase in the RPP, implying increased myocardial metabolic demands, was consistently present. In normal subjects, although mean EF increased significantly with the CPT, individual subjects had either no change or an increase of the EF. This is in agreement with previous reports. Kurtz et al. reported basically similar response in their control subjects, but changes were considered significant if a difference of 3% or more was present (as opposed to 7% or more in our study). We cannot discuss further their results because limited information is given in their abstract; however, in most laboratories the spontaneous variability of radionuclide EF determinations are 5–10%.

In one of our control subjects, EF fell significantly and another subject developed a new wall motion abnormality during the CPT. Both were patients with
atypical chest pain who underwent full cardiovascular investigation. The CPT may have induced coronary arterial spasm.\textsuperscript{7, 8} We have no information to assess this possibility, although the absence of angina or ST-segment changes on the ECG during the CPT were relevant negative findings.

Despite the uniform stimulation during the CPT, the individual EF response in the control group were inconsistent. In some subjects, EF did not change significantly, while in others, it increased as much as 15%. This is similar to the variable hemodynamic response reported previously.\textsuperscript{8, 9, 12} Several investigators have shown that the HR, systemic vascular resistance, cardiac output and stroke volume might change in opposite directions.\textsuperscript{8, 9, 12}

In subjects with CAD, although the mean EF decreased significantly with the CPT, the sensitivity to detect CAD in an individual patient was only 55%. This finding contradicts previous reports.\textsuperscript{15-18} On studying 33 patients with CAD and normal resting left ventricular function, Kurtz et al.\textsuperscript{12} reported a sensitivity of 94%. However, their criteria for abnormal EF response to the CPT was different from ours. Wainwright et al.\textsuperscript{10} reported a sensitivity of 92% in one report and 79% in another,\textsuperscript{11} and Brennand-Roper et al.\textsuperscript{12} also reported a sensitivity of 79%. The specificity according to one of their figures\textsuperscript{11} appears to have been 100%. They used a CPT that lasted for 5 minutes while collecting the radionuclide data.\textsuperscript{11} In some patients with CAD, more than 2½ minutes of cold stimulus may be required to provoke global or regional abnormalities on the radionuclide angigram. The rapid return toward baseline values of all hemodynamic changes produced by the CPT after the first 2-3 minutes of continuous cold stimulation\textsuperscript{8, 30, 31} does not support this assumption. Nevertheless, future studies are needed to assess this possibility. There were several methodologic differences between their study\textsuperscript{11} and ours, but those were not likely the cause of the divergent results since they reported an intra- and interobserver variability similar to that in our laboratory. In fact, their cutoff point for a change in EF to be significant in the individual subject was 9%, while that in the present study was 7%.

In a previous report from our institution,\textsuperscript{16} the CPT showed an even lower sensitivity (38%) when patients with previous myocardial infarction were included. Patients with left ventricular asynergy could have had a blunted pressor response,\textsuperscript{4} imposing less metabolic demands than in those with normal pressure response. As with exercise studies, wall motion analysis improved the sensitivity of the CPT in the present investigation to levels similar to those of other studies.\textsuperscript{11, 18} However, with or without wall motion analysis, the sensitivity, specificity and predictive accuracy of radionuclide cardiac angiography were in our laboratory, higher during supine bicycle exercise than during the CPT in detecting subjects with CAD. Nonetheless, the CPT may be used in subjects who cannot exercise adequately. Patients with more extensive CAD, i.e., three-vessel CAD, may be more susceptible to developing abnormal left ventricular function with exercise (100% of the subjects in our small sample) or with the CPT (78%) than those with one-vessel CAD (86% and 57%, respectively). Finally, examination of the wall motion improves the sensitivity of both interventions, although it is relatively more important during the CPT.

**Acknowledgment**

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D E Manyari, A J Nolewajka, P Purves, A Donner and W J Kostuk

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