Insensitivity of the Cold Pressor Stimulation Test for the Diagnosis of Coronary Artery Disease

ALAN G. WASSERMAN, M.D., LARRY REISS, M.D., RICHARD J. KATZ, M.D.,
ROY LEIBOFF, M.D., PATRICIA CLEARY, M.S., VIJAY M. VARMA, M.D.,
RICHARD C. REBA, M.D., AND ALLAN M. ROSS, M.D.

SUMMARY Cold pressor stimulation (CPS) was compared with supine bicycle exercise during radionuclide ventriculography as a procedure for diagnosing coronary artery disease (CAD). Thirty patients were studied. In the 18 patients with angiographically proved CAD, left ventricular ejection fraction (LVEF) decreased a mean of 5.0 ± 1.0 ejection fraction units (± sem) in response to CPS. Only two patients developed a new wall motion abnormality. In response to maximal supine exercise, the CAD group showed a mean decrease in LVEF from rest of 1.9 ± 1.1%. Nine patients developed an exercise-induced wall motion abnormality.

In the 12 patients with angiographically proved normal coronary arteries, LVEF decreased a mean of 5.8 ± 1.3 units in response to CPS and increased a mean of 9.2 ± 1.2% in response to exercise. Thus, the LVEF response to CPS was not significantly different in the CAD and normal groups (5.0 ± 1.0 vs 5.8 ± 1.3, NS). These same patients demonstrated the expected difference in LVEF response to exercise. We conclude that CPS produces similar changes in LVEF in patients with and without CAD, and therefore is not useful in diagnosing ischemic heart disease.

EXERCISE radionuclide ventriculography is widely used to diagnose coronary artery disease (CAD).1,2 Some patients, however, cannot adequately exercise to provoke underlying myocardial ischemia. Therefore, other forms of stress have been evaluated as alternatives to exercise, including isometric handgrip,3-7 atrial pacing8 and cold pressor stimulation (CPS).9

CPS is a potent α-adrenergic stimulus that causes an acute increase in heart rate and blood pressure.10 It requires only a few minutes of testing and can be easily administered to almost all patients. Wainwright et al.9 reported that CPS is a sensitive and specific method of provoking ischemic left ventricular dysfunction when used in conjunction with radionuclide angiography and has diagnostic accuracy similar to that of supine bicycle stress.

In this study we describe our experience with radionuclide imaging in patients who later underwent coronary arteriography and the limitations of the response to CPS compared with supine bicycle exercise for the diagnosis of CAD.

Methods

Study Population

The study group consisted of 30 consecutive subjects (23 men and seven women), mean age 55 years (range 38–69 years). All patients were referred to George Washington University Hospital for evaluation of chest pain. No patient had valvular heart disease, hypertension or unstable angina. All patients had a complete clinical history, physical examination and 12-lead rest ECG before cardiac catheterization. All medications, including nitrates, calcium blockers and β blockers, were stopped at least 12 hours before study. Seven patients with CAD and four normal subjects were taking β blockers and 10 CAD patients and five normal subjects were taking nitrates or calcium blockers at the time of study.

Coronary Arteriography

Coronary arteriography was performed within 24 hours of the radionuclide study. The percutaneous femoral technique was used in all patients. Studies were independently reviewed by two experienced angiographers without knowledge of the radionuclide results. Coronary stenoses were considered to be significant if luminal diameter was narrowed by 70% or more, except for the left main coronary artery, which was considered significantly narrowed if luminal diameter was reduced by 50% or more.

Eighteen patients (16 men and two women), mean age 55 years, had angiographically proved CAD as defined by significant stenoses of at least one major coronary artery. Ten had three-vessel disease, six had two-vessel disease and two had one-vessel disease, both with involvement of the left anterior descending coronary artery. Twelve patients (seven men and five women), mean age 56 years, had normal coronary arteries.

Cold Pressor Response

To establish optimal imaging techniques for patients undergoing CPS, we studied the hemodynamic responses of 10 consecutive patients during cardiac catheterization who were not included in the CPS protocol. A central arterial catheter was inserted and heart rate and blood pressure were monitored for 20 minutes to establish baseline readings. The patient’s hand was then immersed in ice water for 3 minutes and heart rate and pressure were monitored continuously. All patients showed an immediate response to the cold stimulation. Heart rate and mean blood pressure increased rapidly, peaked at 15–20 seconds and plateaued thereafter for the remainder of the immersion period. Heart
rate and blood pressure returned to baseline levels within 5 minutes in all patients. These results formed the basis of our cold pressor radionuclide scanning protocol.

**Imaging Procedure**

Red blood cells were labeled in vivo by injecting 25–30 mCi of technetium-99m pertechnetate 20 minutes after the i.v. administration of 7.5 mg of stannous pyrophosphate. Gated radionuclide ventriculography was performed with an Ohio Nuclear Series 420 portable scintillation camera interfaced to a Medical Data Systems computer. An all-purpose, parallel-hole collimator was used. The camera was positioned to record the left anterior oblique view that maximized separation of the ventricular images. Gated images were acquired over 2-minute intervals, at 20 frames/cardiac cycle, at rest, during CPS and during the last 2 minutes of each 3-minute stage of exercise. Only the study acquired at peak exercise was used for analysis.

The left ventricular time-activity curve was generated by using a conventional software program (MDS) with a semiautomatic edge-detection system and computer-determined background. Left ventricular ejection fraction (LVEF) was calculated after background subtraction from the time-activity curve. This method correlates with results obtained in our cardiac catheterization laboratory when compared with single-plane contrast ventriculography in 50 consecutive patients ($r = 0.89$) (unpublished data).

Wall motion was evaluated by two independent, experienced observers without knowledge of cardiac catheterization data. The rest and stress (CPS or exercise) studies were viewed side by side to detect the development of a stress-induced wall motion abnormality. Wall motion in each of three anatomic sites (septal, inferoapical and posterolateral) was graded as follows: $3 =$ normal, $2 =$ mild hypokinesis, $1 =$ moderate–severe hypokinesis, $0 =$ akinesis, and $- 1 =$ dyskinesis. A change in score of at least two grades was considered to represent a stress-induced abnormality. Differences between observers were resolved by joint review and arbitration of the studies by a third observer.

A normal response to exercise has been defined as an absolute increase of at least 5% in ejection fraction units without development of a regional wall motion abnormality.

**Cold Pressor Images**

After resting supine imaging, the patient's hand was immersed in ice water (0–2°C) for 2 minutes and 15 seconds. Heart rate and blood pressure were monitored after 15 seconds and then at 1-minute intervals. After 15 seconds of immersion, radionuclide imaging was initiated and continued for 2 minutes.

**Exercise Protocol**

After return of blood pressure and heart rate to baseline values, another left anterior oblique image was obtained at rest at least 20 minutes after CPS and before supine exercise. Maximal graded supine bicycle exercise was then performed, starting at a work load of 200 kg-m/min and increasing by 200 kg-m/min every 3 minutes. Exercise was continued until the development of angina pectoris, dyspnea or fatigue. Electrocardiographic lead 2 was monitored continuously during exercise and for 5 minutes after exercise.

**Analysis of Data**

All statistical analyses were performed with the Statistical Analysis System (SAS) and the BMDP statistical software. Data are presented as mean ± SEM. A two-way analysis of variance for repeated measures was used to test the significance of the differences between the two types of patients, the significance of the differences between the four kinds of stimulation conditions (rest, CPS, preexercise and exercise), and the interaction between the type of patient and the stimulation condition. The $t$ test was used to compare the data at a given stage between the two groups.

**Results**

**Heart Rate and Blood Pressure Data**

Figure 1 shows the mean hemodynamic response to CPS in all 30 patients. The mean heart rate rose 10% (from 69 ± 2 to 76 ± 3 beats/min) and the mean blood pressure increased 23% (from 100 ± 4 to 123 ± 5 mm Hg). These results are similar to those from our catheterization laboratory.

Resting or preexercise heart rate, systolic blood pressure and double product were not significantly different in the two groups (table 1). In both groups, heart rate increased significantly with CPS ($p < 0.001$), but there was no significant difference between the groups. In response to exercise, heart rate increased significantly in both groups ($p < 0.001$), but the normal patients had a greater increase (NS).

**Figure 1.** Mean heart rate and blood pressure response to cold pressor stimulation for the entire group. The peak response was at 15–20 seconds and then plateaued for the remainder of hand immersion.
TABLE 1. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Double product (mm Hg-min × 10^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>66 ± 3</td>
<td>145 ± 6</td>
<td>97 ± 7</td>
</tr>
<tr>
<td>CPS</td>
<td>77 ± 3*</td>
<td>172 ± 7*</td>
<td>132 ± 8*</td>
</tr>
<tr>
<td>Preexercise</td>
<td>67 ± 3</td>
<td>143 ± 6</td>
<td>96 ± 7</td>
</tr>
<tr>
<td>Exercise</td>
<td>118 ± 7*</td>
<td>199 ± 8*</td>
<td>236 ± 20*</td>
</tr>
<tr>
<td>CAD patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>65 ± 2</td>
<td>135 ± 5</td>
<td>88 ± 3</td>
</tr>
<tr>
<td>CPS</td>
<td>75 ± 2*</td>
<td>158 ± 6*</td>
<td>119 ± 6*</td>
</tr>
<tr>
<td>Preexercise</td>
<td>68 ± 3</td>
<td>136 ± 5</td>
<td>92 ± 4</td>
</tr>
<tr>
<td>Exercise</td>
<td>105 ± 4*</td>
<td>174 ± 6*</td>
<td>184 ± 12*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
*p < 0.001.
Abbreviation: CPS = cold pressor stimulation.

In both groups, both systolic blood pressure and double product increased significantly in response to CPS (p < 0.001). The CPS blood pressure and double product were both higher in the normal group (NS). The exercise systolic pressure and double product also increased significantly from the preexercise values in both groups (p < 0.001). The normal patients had a greater increase in both exercise systolic blood pressure (p < 0.05) and double product (p < 0.05) than the CAD patients. The exercise double product was significantly higher than the CPS double product in both groups (p < 0.01).

Ejection Fraction Changes

The mean LVEFs are listed in table 2. Analysis of variance revealed that the difference between the mean LVEFs for exercise was the only significant difference between the normal and CAD patients (p = 0.0001).

In response to CPS, LVEF decreased in 14 of 18 patients with CAD, did not change in two and decreased in two. The mean fall in LVEF was 5.0 ± 1.0 units. The response of the LVEF to CPS in the normal subjects was similar. In 11 of 12 patients with normal coronary arteries, LVEF decreased by a mean of 5.8 ± 1.3 units (fig. 2).

In 13 of 18 patients with CAD, LVEF either did not change or showed an absolute reduction during exercise, and in five patients it increased slightly; but in only one patient was the increase greater than 4 units. The mean change of the entire group was a reduction of 1.9 ± 1.1 units. In all normal subjects, however,

LVEF increased during exercise by at least 5 units (mean increase of 9.2 ± 1.2 units) (fig. 3).

Thus, in patients with and without CAD, LVEF decreased in response to CPS by 5.0 ± 1.0 units and 5.8 ± 1.3 units, respectively. In contrast, in response to supine bicycle exercise, mean LVEF in the group with CAD decreased by 1.9 ± 1.1 units, whereas it increased by 9.2 ± 1.2 units in the normal groups.

Wall motion was normal at rest in all patients. Only two patients developed a new wall motion abnormality in response to CPS; both had CAD. Nine patients showed an exercise-induced wall motion abnormality, all of whom had CAD.

Discussion

Cold cutaneous stimulation was developed during the 1930s to measure the response of the blood pressure in hypertensive subjects and as a harbinger of the development of hypertension in normal patients.11-13 The circulatory effects of CPS were further delineated by Greene et al.14 They found no difference between patients with hypertension and normal subjects with respect to their blood pressure response to CPS. It was postulated that CPS elevated blood pressure by increasing peripheral vascular resistance as opposed to isotonic exercise, which also elevates blood pressure but with no change or a decrease in peripheral vascular resistance. Thus, CPS usually increases afterload, whereas isotonic exercise has the opposite effect.

Wainwright et al.,15 using radionuclide imaging, reported that CPS was a highly sensitive method for provoking myocardial ischemia and differentiating pa-
patients with and without CAD. In their study, all 28 patients with CAD or cardiomyopathy had no change or decreased their LVEF significantly. In their control group of 22 patients without CAD, LVEF increased significantly over rest values in response to CPS.

Manyari et al.,15 who used a CPS protocol similar to ours, concluded that CPS was not as sensitive as exercise for detecting CAD, but may be useful in subjects who cannot exercise. They considered a positive EF response to be a decrease in LVEF with CPS of 7% or greater. Their control group of 23 patients had a slight but significant increase in LVEF with CPS (3.05%); however, in six of these patients, LVEF decreased. In only one patient was the decrease greater than 7%. Their 20 patients with CAD had a mean decrease in LVEF similar to ours — approximately 5% — in response to CPS. Eleven patients had a decrease greater than 7%. Twelve patients with CAD and one control subject developed wall motion abnormalities in response to CPS.

Recently, the validity and utility of CPS with radionuclide imaging in evaluating patients with myocardial ischemia have been questioned.16,17 Jordan et al.16 showed that while 88% of their patients with CAD had a reduction in LVEF in response to CPS, five of 10 normal subjects also had a fall in LVEF of at least 5 units. Giles et al.,17 using the nuclear probe, found that 23 of 25 patients with CAD and nine of 11 normal patients decreased their LVEF by 5% with CPS. They concluded that CPS could not distinguish CAD patients from normal subjects.

Our study supports the work of Jordan et al.16 and Giles et al.17 Both our CAD patients and normal subjects decreased their LVEF in response to CPS by similar amounts, 5.0 and 5.8 units, respectively. This same population demonstrated the expected different EF response to supine bicycle exercise: Patients with CAD showed a mean reduction in LVEF of 1.9 units and the normal subjects increased their LVEF by 9.3 units.

LVEF, a standard hemodynamic measure of left ventricular contractility, is dependent on changes in both afterload and contractility. CPS induces opposing hemodynamic changes that probably account for the variable net effect on EF, as seen in a normal population. The endogenous catecholamine outpouring caused by CPS augments contractility and increases the EF. However, as previously described, in contrast to bicycle exercise, peripheral vascular resistance rises in response to CPS and afterload increases, resulting in a decrease in EF. The net effect of these two opposing forces can determine the direction (increase, decrease or no change) of the EF response in an individual patient irrespective of the presence or absence of CAD. This can explain the low predictive value that CPS has in the diagnosis of CAD. Furthermore, similar to data previously reported,15 the magnitude of the double product increase with exercise far exceeded that during CPS. The lower double product might contribute to a reduced sensitivity of this form of stress; however, it is unlikely to relate to the poor specificity observed. Regional wall motion abnormalities, another criterion for CAD, may be more specific, but, as in this study, may be very insensitive. Only two of our CAD patients (11%) developed a new wall motion abnormality in response to CPS. We postulate that provocative tests for ischemia may lead to incorrect conclusions when patients are receiving medical therapy. In our study, patients in both groups were taking β blockers and calcium blockers, but these were stopped at least 12 hours before the study.

It is difficult to fully explain the discrepancies among various reports on CPS. There are significant differences in technique employed between our study and that of Wainwright et al.9 We used a 2-minute scanning time during CPS after having verified that hemodynamic changes were maintained for such a period of time. The patients studied by Wainwright et al. were imaged for 5 minutes. Four of their patients were considered to have early congestive cardiomyopathy with normal coronary arteries.

The protocol of Manyari et al.15 was similar to ours. The reasons for the differing results may be the variable response to CPS among patients. Table 3 is a summary of the previous studies. Although this table does not take into account wall motion abnormalities or differences in technique, it does reveal the marked differences in results. It is likely that some patients will manifest dominant peripheral vascular constriction and others will show marked increases in contractility. This variability may account for the differences in results of similarly designed studies.

We conclude that as usually applied clinically, CPS
TABLE 3.  Comparison of Cold Pressor Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Normal group</th>
<th>CAD group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>EF with CPS</td>
</tr>
<tr>
<td>Wainwright et al. 9</td>
<td>22</td>
<td>+2%</td>
</tr>
<tr>
<td>Manyari et al. 15</td>
<td>20</td>
<td>+3%</td>
</tr>
<tr>
<td>Jordan et al. 16</td>
<td>10</td>
<td>+1%</td>
</tr>
<tr>
<td>Giles et al. 17</td>
<td>11</td>
<td>-11%</td>
</tr>
<tr>
<td>Present report</td>
<td>12</td>
<td>-5.8%</td>
</tr>
</tbody>
</table>

Abbreviation: EF with CPS = mean change in ejection fraction with cold pressor stimulation.

produces similar changes in LVEF in patients with and without CAD. Thus, CPS cannot be considered a useful diagnostic intervention.

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INSENSITIVITY OF COLD PRESSOR TEST IN CAD/Wasserman et al.
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