Lack of Correlation Between Noninvasive Stress Tests and Invasive Coronary Vasomotor Dysfunction in Patients With Nonobstructive Coronary Artery Disease

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Background—Despite a nonobstructive coronary angiogram, many patients may still have an abnormal coronary vasomotor response to provocation and to myocardial demand during stress. The ability of noninvasive stress tests to predict coronary vasomotor dysfunction in patients with nonobstructive coronary artery disease is unknown.

Methods and Results—All patients with nonobstructive coronary artery disease who had invasive coronary vasomotor assessment and a noninvasive stress test (exercise ECG, stress echocardiography, or stress nuclear imaging) within 6 months of the cardiac catheterization with provocation at our institution were identified (n=376). Coronary vasomotor dysfunction was defined as a percentage increase in coronary blood flow of ≥50% to intracoronary acetylcholine (endothelium-dependent dysfunction) and/or a coronary flow reserve ratio of ≥2.5 to intracoronary adenosine (endothelium-independent dysfunction). We determined the sensitivity and specificity of various noninvasive stress tests to predict coronary vasomotor dysfunction in these patients. On invasive testing, 233 patients (63%) had coronary vasomotor dysfunction, of which 187 patients (51%) had endothelium-dependent dysfunction, 109 patients (29%) had endothelium-independent dysfunction, and 63 patients (17%) had both. On noninvasive stress testing, 157 (42%) had a positive imaging study and 56 (15%) a positive ECG stress test. The noninvasive stress tests had limited diagnostic accuracy for predicting coronary vasomotor dysfunction (41% sensitivity [95% CI, 34 to 47] and 57% specificity [95% CI, 49 to 66]), endothelium-dependent dysfunction (41% sensitivity [95% CI, 34 to 49] and 58% specificity [95% CI, 50 to 65]), or endothelium-independent dysfunction (46% sensitivity [95% CI, 37 to 56] and 61% specificity [95% CI, 54 to 67]). The exercise ECG test was more specific but less sensitive than the imaging tests.

Conclusion—This study suggests that a negative noninvasive stress test does not rule out coronary vasomotor dysfunction in symptomatic patients with nonobstructive coronary artery disease. This underscores the need for invasive assessment or novel more sensitive noninvasive imaging for these patients. (Circ Cardiovasc Intervent. 2009;2:237-244.)

Key Words: vasomotor dysfunction ■ coronary artery disease ■ microcirculation ■ endothelium ■ stress test

Approximately 20% to 30% of patients undergoing invasive coronary angiography for chest pain have normal arteries or minimal atherosclerosis.1,2 Abnormal cardiac pain perception3,4 has been implicated as the etiology for the chest pain in these patients. However, a substantial number of patients with nonobstructive coronary anatomy may still have abnormalities in coronary vasomotor function in response to stress5-9 and possibly myocardial ischemia.10-13

Clinical Perspective on p 244

The diagnosis and treatment of patients with coronary vasomotor dysfunction remain a challenge in contemporary practice. The gold standard for the assessment of coronary vasomotor function is invasive cardiac catheterization with intracoronary infusion of endothelium-dependent and endothelium-independent vasodilators.14 However, such techniques have inherent risks and are limited to a few catheterization laboratories with expertise. Standard clinical noninvasive stress tests have been proposed to identify coronary vasomotor dysfunction,13,15 but to date their ability to detect endothelium-dependent dysfunction or endothelium-independent dysfunction in the setting of normal coronary arteries is unknown. This study evaluated the sensitivity and specificity of standard noninvasive stress tests for identifying coronary vasomotor dysfunction as identified by invasive studies in patients without obstructive epicardial coronary artery disease.
Non-invasive stress test

- 1,100 CVD catheterizations at Mayo (1992-2007)

Repeate CVD catheterization

- 389 CVD catheterizations with a non-invasive stress test within 6 months
- 385 patients had both a CVD catheterization and a non-invasive stress test

Research consented

- 376 consenting patients had both a CVD catheterization and a non-invasive stress test

Non-invasive stress tests

- 134 (36%) - Exercise SPECT
- 102 (27%) - Exercise Echo
- 66 (19%) - Vasodilator SPECT
- 33 (9%) - Vasodilator PET
- 22 (6%) - Dobutamine Echo
- 19 (5%) - Others

Methods

Study Design, Study Population, and Data Collection

After approval by the Mayo Clinic Institutional Review Board, all patients who had invasive coronary vasomotor assessment at the Mayo Clinic (Rochester, Minn) from December 1992 to August 2007 were identified (n=1100). These patients’ medical records were reviewed by 1 investigator for any type of noninvasive stress test (exercise ECG, stress echocardiography, or stress nuclear imaging) performed within 6 months of the invasive test. There were 389 invasive tests with a noninvasive stress test within this time period. Four patients had 2 invasive tests performed—only the earliest invasive test was included in the analysis. Thirty-two patients had >1 noninvasive stress test—only the noninvasive stress test in closest temporal relation to the invasive catheterization was included in the study. Nine patients refused use of their medical records for research and were excluded. After the exclusions, the final study population consisted of 376 patients (Figure 1).

Invasive Testing

Study Population

The study population included patients with angiographic coronary artery lesions of <40% luminal diameter stenosis. Exclusion criteria for performing the invasive coronary vasomotor assessment at our institution include a history of ischemic heart disease (myocardial infarction, percutaneous coronary revascularization, coronary artery bypass grafting, and unstable angina), heart failure with an ejection fraction <40%, valvular heart disease, stroke or significant hepatic, renal, diabetic, or inflammatory disease within 6 months of the invasive study. Pregnant or lactating patients were excluded. Patients who required treatment with positive inotropic agents other than digoxin during the study were excluded. Long-acting nitrates or calcium channel blockers were withheld for 36 to 48 hours before the study to allow assessment of baseline coronary physiology.

Assessment of Coronary Vasomotor Function

Diagnostic coronary angiography and determination of endothelium-dependent and endothelium-independent function were performed as previously described.15-17 In brief, a Doppler guide wire (FloWire, Volcano Corp, Rancho Cordova, Calif) within a coronary infusion catheter was positioned in the midportion of the left anterior descending coronary artery. Average peak velocity was obtained from Doppler flow velocity spectra.18 Coronary artery diameter measurements were made in the segment 5 mm distal to the tip of the Doppler using an online quantitative coronary angiography program (Medis Corporation, Leiden, The Netherlands).19 Analysis of data from our laboratory demonstrates that the inter- and intraobserver variation is 8±3%.

Intracoronary bolus injections of incremental doses (18 to 42 µg) of adenosine were administered into the guiding catheter until maximal hyperemia was achieved. The endothelium-independent coronary flow reserve (CFR) ratio was calculated by dividing the average peak velocity after adenosine injection by the baseline average peak velocity.20 We performed intracoronary adenosine instead of intravenous adenosine to avoid confounding effects associated with intravenous use such as transient lowering of systemic blood pressure and changes in heart rate, both of which can decrease coronary perfusion pressure and alter coronary flow independent of the functional integrity of the coronary microcirculation. Assessment of the endothelium-dependent vasoreactivity was performed by selective infusion of increasing concentrations of acetylcholine (10^-6, 10^-5, and 10^-4 mol/L) at 1 mL/min for 3 minutes with Doppler measurements and coronary angiography after each infusion. Coronary blood flow (CBF) was determined from the equation: $\text{CBF} = \frac{\pi}{4}(\text{average peak velocity}/2)(\text{coronary artery diameter})^2$. 

Figure 1. Study cohort profile. Exercise SPECT indicates exercise sestamibi (n=114) + exercise thallium (n=20); vasodilator SPECT, adenosine sestamibi (n=55) + adenosine thallium (n=9) + dipyridamole thallium (n=2); vasodilator PET, adenosine PET (n=32) + dipyridamole PET (n=1); others are multiple-gated acquisition scan exercise protocol (n=10) + dobutamine PET (n=4) + dobutamine sestamibi (n=2) + exercise ECG only (n=2) + dobutamine thallium (n=1). CVD, coronary vaso-motor dysfunction; CBF, coronary blood flow; CFR, coronary flow reserve.
Definition of Coronary Vasomotor Dysfunction by Invasive Testing

Coronary endothelium-dependent dysfunction was defined as an increase in CBF of ≥50% in response to maximum dose acetylcholine compared with baseline. Coronary endothelium-independent dysfunction was defined as a CFR ratio of ≥2.5 during infusion of adenosine. Coronary vasomotor dysfunction was defined as endothelium-dependent dysfunction and/or endothelium-independent dysfunction. These parameters have been shown to have prognostic significance in patients without significant obstructive epicardial disease.16,21–23

Noninvasive Stress Testing

Patients underwent the following noninvasive stress studies using standard clinical institutional protocols. The choice of the noninvasive test was at the discretion of the attending clinician.

Stress Protocols

Exercise Stress Protocols

Two hundred thirty-five patients exercised on a treadmill according to the standard Bruce protocol.24 Four used the supine bike protocol,28 and 10 used the multiple-gated acquisition scan exercise protocol.26

Pharmacological Stress Protocols

Adenosine. Ninety-seven patients received a standard dose of 140 μg kg⁻¹ min⁻¹ for 6 minutes.27

Dipyridamole. Three patients received a dose of 0.56 mg/kg to a maximum dose of 60 mg over 4 minutes.27

Dobutamine. Twenty-nine patients received dobutamine starting at 5 to 10 μg kg⁻¹ min⁻¹ followed by stepwise increases to 20, 30, and 40 μg kg⁻¹ min⁻¹ for each consecutive 3-minute interval. If maximum heart rate was not achieved, 0.5 to 1.0 mg of atropine was administered.28

Stress Echocardiogram Protocol

Echocardiographic images using the 16-segment model were obtained at rest and compared with those obtained immediately (<1 minute) after treadmill exercise or during pharmacological stress.

Stress Nuclear Protocols

Tc-99m Sestamibi (n = 172)

A 1-day rest-stress Tc-99m sestamibi protocol was performed with a 12-mCi resting Tc-99m sestamibi injection and single-photon emission computed tomography (SPECT) acquisition followed by a 48-mCi Tc-99m sestamibi injection at 90 seconds before peak exercise, 3 minutes into adenosine infusion, 4 minutes after dipyridamole infusion or at peak dobutamine infusion, followed by gated SPECT acquisition.

Thallium-201 (n = 32)

Three millicuries of thallium-201 was injected 60 seconds before peak exercise, 3 minutes into adenosine infusion, 4 minutes after dipyridamole infusion, or at peak dobutamine infusion followed by planar and SPECT acquisitions. At 4 hours, 1 mCi of thallium-201 was injected followed by image acquisition for redistribution.30

Positron-Emission Tomography (n = 37)

All scans were performed on an Advance scanner (General Electric, Waukesha, Wisc). After a 10-minute transmission scan for attenuation correction, N-13 ammonia (n = 21; 10 to 20 mCi) or rubidium-82 (n = 16; 45 to 60 mCi) was injected at rest, and static gated positron-emission tomography (PET) images were acquired for 10 minutes. After a 50-minute period of decay, the same tracer dose was injected during stress followed by a 10-minute static stress emission acquisition and a repeat transmission scan for attenuation correction of the stress images.31

Multiple Gated Acquisition Scan (n = 10)

Injection of in vitro labeled patient’s blood with 30 mCi of Tc-99m was performed before starting exercise. Regional wall motion was assessed at rest and after every stage during exercise.26

ECG and Imaging Interpretation

ECG

The interpretation of the exercise ECG was performed by an experienced cardiologist. The appearance of horizontal or downsloping ST depression of ≥1 mm at 0.08 seconds after the J-point was the criterion for a positive stress ECG.22 Patients with left bundle branch block, pacemaker, Wolff-Parkinson-White or ≥1 mm ST depression at rest or left bundle branch block on stress were considered nondiagnostic.

Echocardiogram

The echocardiographic images were interpreted by an experienced staff cardiologist using the 16-segment model.29 The stress test was considered positive if wall motion abnormalities developed with exercise or pharmacological stress in previously normal territories or worsened in an already abnormal segment. Fixed wall motion abnormalities were considered negative.

Nuclear Scans

All nuclear images were interpreted by a consensus of a nuclear cardiologist and a nuclear medicine specialist, using a 5-point semiquantitative scale and a 16-segment model.27 Images were considered positive if a new perfusion defect of at least 1 grade developed after stress or a worsening in perfusion of 1 or more grades was observed after stress compared with the rest images. Fixed defects were considered negative.

Statistical Analysis

The statistical analysis was performed by a statistician (R.J.L.). Sensitivity, specificity, positive predictive value, and negative predictive value of the noninvasive stress tests for predicting invasive coronary vasomotor function was performed. Continuous variables are summarized as mean±SD (unless otherwise noted); discrete variables are presented as frequency (percentage). Exact binomial methods were used to calculate 95% CIs. Logistic regression was used to test whether the association between noninvasive tests and the invasive coronary vasomotor function were different according to the type of noninvasive test done. The model consisted of indicator variables for the different test types with the end point being agreement between the noninvasive test and invasive coronary vasomotor function. If the overall likelihood ratio test for the model was nonsignificant, then all tests were declared to be equivalent. Otherwise, Wald tests were used to determine which pairs of tests were significantly different.

Results

The characteristics of the 376 patients under study are shown in Table 1. Sixty-six percent of patients were female, and the average age was 51.3 years (range, 17 to 84). There were no statistical differences between the 2 groups with regard to medication use (aspirin, β-blockers, lipid-lowering drugs, calcium channel blockers, angiotensin-converting enzyme inhibitors, and nitrates). Of the 376 patients, 310 stress tests (82%) were performed within 1 month of the invasive test, and the median time between tests was 0.7 weeks. Data on CBF on 9 patients (2%) and CFR on 2 patients (0.5%) were not available, and these were excluded from the data analyses (Figure 1). On invasive testing, 233 of 367 patients (63%) had coronary vasomotor dysfunction, of which 187 of 367 patients (51%) had endothelium-dependent dysfunction, 109 of 374 patients (29%) had endothelium-independent dysfunction, and 63 of 365 patients (17%) had both. On noninvasive...
Patients (77%) had symptoms of chest pain (n = 203 [54%]) or shortness of breath (n = 157 [49%]) during the noninvasive stress testing, 185 (49%) during the noninvasive imaging test, and of these, 249 (66%) were before the imaging test, and of these, 249 (66%) were.

Our study shows that in a selected population with chest pain and angiographically normal or nonsignificant obstructive coronary artery disease, noninvasive stress tests used in contemporary practice have limited diagnostic accuracy for predicting coronary vasomotor dysfunction or endothelium-independent dysfunction. For endothelium-dependent dysfunction, dobutamine echocardiogram was inferior to all other imaging tests except for vasodilator PET. The exercise ECG test was more specific than the imaging tests (80% [95% CI, 71 to 88] for coronary vasomotor dysfunction; 78% [95% CI, 69 to 85] for endothelium-dependent dysfunction; and 75% [95% CI, 68 to 81] for endothelium-independent dysfunction), but it was also the least sensitive test (18% [95% CI, 12 to 25] for coronary vasomotor dysfunction; 18% [95% CI, 12 to 27] for endothelium-dependent dysfunction; and 16% [95% CI, 8 to 27] for endothelium-independent dysfunction).

By logistic regression, none of the individual noninvasive imaging stress tests was superior for predicting coronary vasomotor dysfunction or endothelium-independent dysfunction. Of the noninvasive tests for predicting invasive coronary vasomotor dysfunction, endothelium-dependent dysfunction, or endothelium-independent dysfunction between men and women. One hundred thirty-seven (63%) of the 219 patients who had a negative noninvasive imaging stress test had 1 or more abnormalities on invasive catheterization testing. There was no significant difference between the mean percentage change in CBF or mean CFR ratio on invasive testing of all the patients who had positive imaging tests compared with all patients who had negative imaging tests (Figure 2).

### Discussion

Our study shows that in a selected population with chest pain and angiographically normal or nonsignificant obstructive coronary artery disease, noninvasive stress tests used in contemporary practice have limited diagnostic accuracy for predicting coronary vasomotor dysfunction or endothelium-independent dysfunction. For endothelium-dependent dysfunction, dobutamine echocardiogram was inferior to all other imaging tests except for vasodilator PET. The exercise ECG test was more specific than the imaging tests (80% [95% CI, 71 to 88] for coronary vasomotor dysfunction; 78% [95% CI, 69 to 85] for endothelium-dependent dysfunction; and 75% [95% CI, 68 to 81] for endothelium-independent dysfunction), but it was also the least sensitive test (18% [95% CI, 12 to 25] for coronary vasomotor dysfunction; 18% [95% CI, 12 to 27] for endothelium-dependent dysfunction; and 16% [95% CI, 8 to 27] for endothelium-independent dysfunction). Combining the results of the stress ECG test with the imaging findings improved specificity but substantially reduced sensitivity (see Tables 2 through 4). On subgroup analysis, there was no significant difference in the sensitivity, specificity, negative predictive value, or positive predictive value of the noninvasive tests for predicting invasive coronary vasomotor dysfunction, endothelium-dependent dysfunction, or endothelium-independent dysfunction between men and women. One hundred thirty-seven (63%) of the 219 patients who had a negative noninvasive imaging stress test had 1 or more abnormalities on invasive catheterization testing. There was no significant difference between the mean percentage change in CBF or mean CFR ratio on invasive testing of all the patients who had positive imaging tests compared with all patients who had negative imaging tests (Figure 2).

### Table 1. Patient Characteristics: Vasomotor Function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal (n=134)</th>
<th>Dysfunctional (n=233)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.8±11.2</td>
<td>52.9±12.0</td>
<td>0.001</td>
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<tr>
<td>Men, n (%)</td>
<td>48 (36)</td>
<td>74 (32)</td>
<td>0.43</td>
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<tr>
<td>Body mass index</td>
<td>28.9±6.4</td>
<td>29.2±5.7</td>
<td>0.63</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>59 (44)</td>
<td>98 (42)</td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>8 (6)</td>
<td>28 (12)</td>
<td>0.06</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>69 (51)</td>
<td>127 (55)</td>
<td>0.34</td>
</tr>
<tr>
<td>Former smoker</td>
<td>47 (35)</td>
<td>84 (36)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>18 (13)</td>
<td>20 (9)</td>
<td></td>
</tr>
<tr>
<td>Positive family history, n (%)</td>
<td>79 (60)</td>
<td>148 (65)</td>
<td>0.38</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>71 (53)</td>
<td>137 (59)</td>
<td>0.29</td>
</tr>
<tr>
<td>hsCRP, mg/L, median (Q1, Q3)</td>
<td>0.4 (0.2, 1.5)</td>
<td>0.5 (0.3, 1.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Vascular disease,* n (%)</td>
<td>6 (5)</td>
<td>23 (10)</td>
<td>0.07</td>
</tr>
<tr>
<td>Other vasospasm,† n (%)</td>
<td>34 (26)</td>
<td>48 (21)</td>
<td>0.29</td>
</tr>
<tr>
<td>% Chg CBF (Ach)</td>
<td>140.2±79.8</td>
<td>11.9±62.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Max CFR</td>
<td>3.3±0.6</td>
<td>2.7±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate at baseline</td>
<td>70.2±12.3</td>
<td>74.1±15.4</td>
<td>0.015</td>
</tr>
<tr>
<td>Heart rate at hyperemia</td>
<td>68.9±12.5</td>
<td>72.5±14.6</td>
<td>0.018</td>
</tr>
<tr>
<td>Change in HR (baseline to hyperemia)</td>
<td>-1.4±6.8</td>
<td>-1.4±8.1</td>
<td>0.95</td>
</tr>
<tr>
<td>Base MAP</td>
<td>100.0±14.0</td>
<td>100.8±15.1</td>
<td>0.62</td>
</tr>
<tr>
<td>MAP at hyperemia</td>
<td>98.2±13.5</td>
<td>100.8±14.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Change in MAP (baseline to hyperemia)</td>
<td>-2.2±8.8</td>
<td>-0.0±8.9</td>
<td>0.031</td>
</tr>
</tbody>
</table>

hsCRP indicates high-sensitivity C-reactive protein; HR, heart rate; MAP, mean arterial pressure.

*Peripheral artery disease, abdominal aortic aneurysm, transient ischemic attack.

†Migraine, Raynaud phenomenon.

### Table 2. Predicting Coronary Vasomotor Dysfunction

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>% (+)</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise echocardiogram</td>
<td>99</td>
<td>40.4</td>
<td>38 (26 to 51)</td>
<td>55 (38 to 71)</td>
<td>36 (24 to 49)</td>
<td>58 (41 to 73)</td>
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<tr>
<td>Dobutamine echocardiogram</td>
<td>21</td>
<td>33.3</td>
<td>29 (8 to 58)</td>
<td>57 (18 to 90)</td>
<td>29 (8 to 58)</td>
<td>57 (18 to 90)</td>
</tr>
<tr>
<td>Exercise SPECT</td>
<td>131</td>
<td>38.2</td>
<td>40 (29 to 51)</td>
<td>65 (49 to 78)</td>
<td>38 (28 to 50)</td>
<td>66 (51 to 79)</td>
</tr>
<tr>
<td>Vaso dilator SPECT</td>
<td>64</td>
<td>50.0</td>
<td>51 (35 to 68)</td>
<td>52 (31 to 72)</td>
<td>41 (24 to 59)</td>
<td>63 (44 to 79)</td>
</tr>
<tr>
<td>Vaso dilator PET</td>
<td>33</td>
<td>36.4</td>
<td>35 (16 to 57)</td>
<td>60 (26 to 88)</td>
<td>29 (11 to 52)</td>
<td>67 (35 to 90)</td>
</tr>
<tr>
<td>All imaging</td>
<td>365</td>
<td>41.4</td>
<td>41 (34 to 47)</td>
<td>57 (49 to 66)</td>
<td>36 (30 to 43)</td>
<td>62 (54 to 70)</td>
</tr>
<tr>
<td>Exercise ECG</td>
<td>242</td>
<td>16.1</td>
<td>18 (12 to 25)</td>
<td>80 (71 to 88)</td>
<td>41 (33 to 48)</td>
<td>69 (52 to 83)</td>
</tr>
<tr>
<td>All imaging+ ECG</td>
<td>365</td>
<td>6.3</td>
<td>6 (3 to 10)</td>
<td>90 (83 to 94)</td>
<td>37 (32 to 43)</td>
<td>61 (39 to 80)</td>
</tr>
</tbody>
</table>

NPV indicates negative predictive value; PPV, positive predictive value.
detecting coronary vasomotor dysfunction. These results highlight the continuing challenges in the diagnosis of patients with chest pain in the absence of obstructive epicardial coronary arteries.

Within the coronary circulation, vasomotor dysfunction results in lack of appropriate coronary vasodilatation in response to stress caused by mental10 or physical14 exercise or by pharmacological stimuli (such as acetylcholine7 or adenosine9). This may occur at the level of the epicardial vessels or the microcirculation, leading to impairment of CBF during stress and a subsequent imbalance between oxygen demand and supply (myocardial ischemia5–11). The underlying mechanism for coronary vasomotor dysfunction may be endothelium-dependent or endothelium-independent. Endothelium-dependent dysfunction occurs with loss of balance between endothelium-derived relaxing factors (eg, nitric oxide) and endothelium-derived constrictors (eg, endothelin). In a functional endothelium, acetylcholine causes vasodilatation at both the epicardium and microcirculation by stimulating the synthesis of nitric oxide via muscarinic receptors. In a dysfunctional endothelium, acetylcholine causes paradoxical vasoconstriction.7 Endothelium-independent function depends on myocyte tone and adenosine causes microvascular dilatation by increasing intracellular cAMP.7 Coronary vasomotor dysfunction has been implicated in the pathogenesis and clinical course of atherosclerosis35,36 and is associated with a 10-fold increased risk of cardiovascular events.5,16,21–23

To our knowledge, this is the first study to address the sensitivity and specificity of the various clinically available noninvasive stress tests in identifying invasively determined coronary vasomotor dysfunction, specifically endothelium-dependent dysfunction, and endothelium-independent dysfunction. Prior studies examining the ability of noninvasive stress tests to identify patients with coronary vasomotor dysfunction often did not perform direct coronary physiological assessment invasively as in our study and have reported conflicting results. Palinkas et al37 correlated stress ECG and echocardiography to assess for endothelial dysfunction measured by flow-mediated dilatation of the brachial artery during reactive hyperemia by ultrasound. They found stress-induced ST-segment depression but not stress echocardiography to be a predictor of endothelial dysfunction. Youn et al38 demonstrated a sensitivity of 58% and specificity of 95% for stress-induced ST-segment depression on ECG to predict a CFR <2.1 detected by Doppler echocardiography. Similar findings were reported in another study.39 This study extends these previous observations and demonstrates that the stress ECG is the most specific (20–25%) noninvasive test for detecting coronary vasomotor dysfunction. Similar to the prior study, sensitivity of the exercise ECG in this study was also low (<20%). These findings are in contrast to the study by Camici et al40 who demonstrated high sensitivity (86%) of the exercise ECG in identifying patients with blunted CFR but a rather low specificity (45%). This latter study, however, used quantitative myocardial blood flow by PET rather than invasive physiological measurements as the gold standard. The ECG stress test is speculatively the most specific test for coronary vasomotor dysfunction because the latter may cause heterogeneous nontransmural ischemia resulting in small changes in depolarization that in turn produce ST-segment depression. Its lack of sensitivity may be explained by the hypothesis that the minor changes in depolarization may not

Table 3. Predicting Endothelium-Dependent Dysfunction

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>% (+)</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise echocardiogram</td>
<td>100</td>
<td>40.0</td>
<td>42 (28 to 57)</td>
<td>62 (47 to 75)</td>
<td>52 (38 to 65)</td>
<td>53 (36 to 68)</td>
</tr>
<tr>
<td>Dobutamine echocardiogram</td>
<td>21</td>
<td>38.1</td>
<td>18 (2 to 52)</td>
<td>40 (12 to 74)</td>
<td>31 (9 to 61)</td>
<td>25 (3 to 65)</td>
</tr>
<tr>
<td>Exercise SPECT</td>
<td>131</td>
<td>38.2</td>
<td>37 (26 to 50)</td>
<td>61 (48 to 73)</td>
<td>48 (37 to 60)</td>
<td>50 (36 to 64)</td>
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<tr>
<td>Vasodilator SPECT</td>
<td>63</td>
<td>50.8</td>
<td>61 (42 to 78)</td>
<td>59 (41 to 76)</td>
<td>61 (42 to 78)</td>
<td>59 (41 to 76)</td>
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<tr>
<td>Vasodilator PET</td>
<td>33</td>
<td>36.4</td>
<td>20 (4 to 48)</td>
<td>50 (26 to 74)</td>
<td>43 (22 to 66)</td>
<td>25 (5 to 57)</td>
</tr>
<tr>
<td>All imaging</td>
<td>365</td>
<td>46.7</td>
<td>41 (34 to 49)</td>
<td>58 (50 to 65)</td>
<td>49 (42 to 56)</td>
<td>50 (42 to 58)</td>
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<tr>
<td>Exercise ECG</td>
<td>233</td>
<td>15.5</td>
<td>18 (12 to 27)</td>
<td>78 (69 to 85)</td>
<td>51 (43 to 59)</td>
<td>61 (43 to 77)</td>
</tr>
<tr>
<td>All imaging + ECG</td>
<td>365</td>
<td>6.3</td>
<td>8 (4 to 12)</td>
<td>90 (85 to 94)</td>
<td>50 (45 to 56)</td>
<td>61 (39 to 80)</td>
</tr>
</tbody>
</table>

NPV indicates negative predictive value; PPV, positive predictive value.

Table 4. Predicting Endothelium-Independent Dysfunction

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>% (+)</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise echocardiogram</td>
<td>101</td>
<td>40.6</td>
<td>42 (25 to 61)</td>
<td>60 (48 to 72)</td>
<td>70 (57 to 81)</td>
<td>32 (18 to 48)</td>
</tr>
<tr>
<td>Dobutamine echocardiogram</td>
<td>21</td>
<td>33.3</td>
<td>33 (4 to 78)</td>
<td>67 (38 to 88)</td>
<td>71 (42 to 92)</td>
<td>29 (4 to 71)</td>
</tr>
<tr>
<td>Exercise SPECT</td>
<td>134</td>
<td>38.8</td>
<td>51 (34 to 68)</td>
<td>66 (56 to 75)</td>
<td>78 (68 to 86)</td>
<td>37 (24 to 51)</td>
</tr>
<tr>
<td>Vasodilator SPECT</td>
<td>66</td>
<td>48.5</td>
<td>41 (18 to 67)</td>
<td>49 (34 to 64)</td>
<td>71 (53 to 85)</td>
<td>22 (9 to 40)</td>
</tr>
<tr>
<td>Vasodilator PET</td>
<td>33</td>
<td>36.4</td>
<td>50 (23 to 77)</td>
<td>74 (49 to 91)</td>
<td>67 (43 to 85)</td>
<td>58 (28 to 85)</td>
</tr>
<tr>
<td>All imaging</td>
<td>372</td>
<td>41.4</td>
<td>46 (37 to 56)</td>
<td>61 (54 to 67)</td>
<td>73 (67 to 79)</td>
<td>32 (25 to 40)</td>
</tr>
<tr>
<td>Exercise ECG</td>
<td>237</td>
<td>15.2</td>
<td>16 (8 to 27)</td>
<td>75 (68 to 81)</td>
<td>71 (64 to 77)</td>
<td>31 (16 to 48)</td>
</tr>
<tr>
<td>All imaging + ECG</td>
<td>372</td>
<td>6.2</td>
<td>6 (3 to 13)</td>
<td>89 (85 to 93)</td>
<td>71 (66 to 76)</td>
<td>30 (13 to 53)</td>
</tr>
</tbody>
</table>

NPV indicates negative predictive value; PPV, positive predictive value.
produce a sufficient ST-segment depression to reach criteria for positivity (≥1 mm at 0.08 seconds from the J-point).

Conversely, vasomotor dysfunction is not associated with stress-induced myocardial contractile dysfunction on echocardiography.\(^{37,41}\) The latter requires not only flow reduction of >50%, but also reduced flow in at least 20% of transmural wall thickness and in 5% of the total cardiac mass.\(^{42}\) In patients with abnormal coronary vasomotion, absence of wall motion abnormalities by stress echocardiography may be caused by impaired myocardial perfusion limited to only the subendocardium, with preserved transmural perfusion, as demonstrated on myocardial perfusion MRI.\(^{43}\)

Studies with myocardial perfusion have shown inconsistent correlation with coronary vasomotor dysfunction. Some studies have reported an association between coronary vasomotor dysfunction and perfusion defects on SPECT perfusion imaging.\(^{13,15,44}\) However, myocardial blood flow is abnormally heterogeneous in patients with cardiac syndrome X, compatible with the presence of dynamic alterations of the microcirculation.\(^{45}\) These alterations are sparse and may not be detected when myocardial perfusion is assessed using conventional methods that do not detect small myocardial regions. Alternatively, decreased myocardial perfusion throughout the entire myocardium may not be detected on SPECT perfusion scans, similar to patients with 3-vessel disease, because of the relative nature of the technique.

In this study, all noninvasive stress tests performed less favorably for the diagnosis of invasive coronary vasomotor dysfunction than for the diagnosis of angiographic epicardial obstructive coronary artery disease. Our experience with noninvasive stress tests for identifying significant epicardial obstructive coronary artery disease has been previously published (Table 5).\(^{28–32}\) Despite their limitations and only moderately high diagnostic accuracy for some techniques, these noninvasive tests remain useful tools for the diagnosis, management, and risk stratification of patients with known or suspected epicardial coronary artery disease.\(^{46}\) On the other hand, the significantly lower diagnostic accuracy of these noninvasive tests for the detection of coronary vasomotor dysfunction suggests more limited usefulness of these noninvasive tests in the subset of patients referred for possible coronary vasomotor dysfunction. This underscores the importance of using invasive assessment or novel more sensitive noninvasive imaging modalities for symptomatic patients with nonobstructive coronary artery disease.

Limitations to our study include its retrospective nature, but this should not alter the results of the invasive or noninvasive tests. A major limitation is referral bias—the study population was referred by physicians due to more “worrying” chest pain than in the general population because they all underwent invasive coronary angiography, many (58%) despite their negative noninvasive stress test. The period of time between the invasive and noninvasive tests of up to 6 months may have resulted in changes in the coronary circulation. However, 82% of our patients had less than a 1-month period of time between the 2 tests. CFR interrogates both the microcirculation as well as the epicardial vessels, and thus not measuring epicardial resistance or fractional flow reserve may have misclassified some patients with silent epicardial atherosclerosis as having vasomotor dysfunction. Several additional noninvasive tests have been used for the measurement of coronary vasomotor function including Doppler echocardiography,\(^{47}\) phase contrast MRI,\(^{48}\) and electron beam computed tomography.\(^{49}\) These have been shown to correlate with invasive coronary vasomotor measurements but have not gained widespread application for stress imaging in the evaluation of chest pain. Although results of static PET acquisition and semiquantitative visual analysis were reported in this study, PET dynamic acquisition and quantification of CFR has been shown to have good correlation with invasive coronary physiology measurements\(^{50}\) but is more time consuming, lacks standardization, and is not clinically available at most centers. The absence of follow-up does not allow us to compare the prognostic validity of the invasive or noninvasive stress tests as predictors of future cardiovascular events in this study population.

Conclusions

This study suggests that the majority of widely used noninvasive stress tests have limited diagnostic accuracy for identifying coronary vasomotor dysfunction in patients with nonobstructive coronary artery disease, with the exercise ECG test being more specific but less sensitive than imaging tests. The presence of a negative noninvasive stress test does not rule out coronary vasomotor dysfunction in symptomatic patients with nonobstructive coronary artery disease. This

### Table 5. Predicting Obstructive Coronary Artery Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise echocardiogram</td>
<td>88</td>
<td>72</td>
</tr>
<tr>
<td>Dobutamine echocardiogram</td>
<td>97</td>
<td>65</td>
</tr>
<tr>
<td>Exercise/Vasodilator SPECT</td>
<td>98*</td>
<td>13†</td>
</tr>
<tr>
<td>Vasodilator PET</td>
<td>96‡</td>
<td>34§</td>
</tr>
<tr>
<td>Exercise ECG</td>
<td>53 to 69</td>
<td>69 to 74</td>
</tr>
</tbody>
</table>

After correction for referral bias: *67%, †75%, ‡82%, §73%.
underscores the need for invasive assessment or novel more sensitive noninvasive imaging for these patients.

Acknowledgments
We thank Jonella M. Tilford and Teresa L. Jarland for their valuable help in collecting the data.

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Disclosures
None.

References
Coronary vasomotor dysfunction may lead to potential impairment of coronary blood flow during stress and a subsequent imbalance between oxygen demand and supply (myocardial ischemia). Coronary vasomotor dysfunction has been implicated in the pathogenesis and clinical course of atherosclerosis and is associated with a 10-fold increased risk of cardiovascular events. This study suggests that the majority of widely used noninvasive stress tests have limited diagnostic accuracy for identifying coronary vasomotor dysfunction in patients with nonobstructive coronary artery disease, with the exercise ECG test being more specific but less sensitive than imaging tests. This may potentially impact the clinical practice associated with exercise-induced myocardial ischemia. *Circulation*. 1995;91:2345–2352.


**CLINICAL PERSPECTIVE**

Coronary vasomotor dysfunction may lead to potential impairment of coronary blood flow during stress and a subsequent imbalance between oxygen demand and supply (myocardial ischemia). Coronary vasomotor dysfunction has been implicated in the pathogenesis and clinical course of atherosclerosis and is associated with a 10-fold increased risk of cardiovascular events. This study suggests that the majority of widely used noninvasive stress tests have limited diagnostic accuracy for identifying coronary vasomotor dysfunction in patients with nonobstructive coronary artery disease, with the exercise ECG test being more specific but less sensitive than imaging tests. This may potentially impact the clinical practice of physicians because the presence of a negative noninvasive stress test does not rule out coronary vasomotor dysfunction in symptomatic patients with nonobstructive coronary artery disease. This underscores the need for further assessment using invasive cardiac catheterization with vasoactive provocation or novel more sensitive noninvasive imaging for diagnosing coronary vasomotor dysfunction in these patients.
Lack of Correlation Between Noninvasive Stress Tests and Invasive Coronary Vasomotor Dysfunction in Patients With Nonobstructive Coronary Artery Disease
Andrew Cassar, Panithaya Chareonthaitawee, Charanjit S. Rihal, Abhiram Prasad, Ryan J. Lennon, Lilach O. Lerman and Amir Lerman

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