Ergonovine Echocardiography as a Screening Test for Diagnosis of Vasospastic Angina Before Coronary Angiography

JAE-KWAN SONG, MD, PhD,* SIMON JONG-KOO LEE, MD, FACC, DUK-HYUN KANG, MD, SANG SIG CHEONG, MD, MYEONG KI HONG, MD, JAE-JOONG KIM, MD, PhD, SEONG-WOOK PARK, MD, PhD, SEUNG-JUNG PARK, MD, PhD, FACC

Seoul, South Korea

Objectives. In patients with chest pain suggestive of variant angina, we performed this prospective study to test the specificity and diagnostic validity of ergonovine echocardiography (detection of regional wall motion abnormality during bedside ergonovine challenge) as a screening procedure before coronary angiography.

Background. Spasm provocation test outside the catheterization room has generally not been accepted as a safe diagnostic method.

Methods. Ergonovine echocardiography was performed in 80 consecutive patients with chest pain syndrome after confirmation of negative treadmill or normal stress myocardial perfusion scan results using thallium-201. A bolus of ergonovine maleate was injected at 5-min intervals up to a total cumulative dosage of 0.35 mg with echocardiographic monitoring of left ventricular wall motion. A 12-lead electrocardiogram (ECG) was also recorded every 3 min after each ergonovine injection. Positive test results were development of regional wall motion abnormalities or transient ST segment elevation or depression >0.1 mV in any single lead of the 12-lead ECG. Coronary angiography was undertaken within 2 ± 4 days (mean ± SD) after ergonovine echocardiography, and the spasm provocation test with acetylcholine or ergonovine was performed in patients with normal angiographic findings or lumen diameter narrowing <70%.

The usual diagnostic method for coronary artery spasm includes an invasive provocation of spasm after coronary angiographic confirmation of the absence of a high degree of fixed atherosclerotic stenosis (1–3). Because of the potential fatal risk of the spasm provocation test and the advantage of intracoronary injection of nitroglycerin in the catheterization laboratory, spasm provocation testing outside the catheterization laboratory is not accepted as a safe diagnostic method by most clinicians.

Results. On the basis of angiographic criteria, 56 patients had coronary vasospasm; this finding was later ruled out in 19 patients with near-normal angiographic results by a negative response on the spasm provocation test. In the remaining five patients, coronary spasm provocation was not performed because they revealed a high degree of fixed stenosis (lumen diameter narrowing 97 ± 4%). Ergonovine echocardiography could diagnose coronary vasospasm before angiography, with a sensitivity of 91% (51 of 56 patients, 95% confidence interval [CI] 84% to 98%) and specificity of 88% (21 of 24 patients, 95% CI 75% to 100%). Of 53 patients showing regional wall motion abnormalities during ergonovine echocardiography, characteristic ST segment elevation in the simultaneously recorded ECG was observed in only 20 (38%). There were no complications, including myocardial infarction or fatal arrhythmia, during the test.

Conclusions. Ergonovine echocardiography before coronary angiography is safe and can be used as a reliable diagnostic screening test for coronary vasospasm in patients with negative treadmill or normal stress myocardial perfusion scan results. These findings suggest that invasive coronary angiography can be avoided in selected patients for the diagnosis of vasospastic angina.

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Recently, we reported (4) that a bedside ergonovine provocation test with two-dimensional echocardiographic monitoring of left ventricular regional wall motion (ergonovine echocardiography) can be used as a safe and reliable noninvasive diagnostic method in patients with near-normal angiographic findings. However, in that study, coronary angiography was performed before ergonovine echocardiography to exclude patients with severe atherosclerotic stenosis; thus, the safety of ergonovine echocardiography before coronary angiography was not tested. The aim of the present study, therefore, was to establish the safety and diagnostic validity of ergonovine echocardiography as a screening test for vasospastic angina before invasive angiography in patients with chest pain syndromes.

Methods

Patients. Patients with chest pain syndromes suggesting variant angina and negative exercise electrocardiographic test...
or normal dipyridamole-thallium-201 myocardial perfusion scan results were included in the study. Exclusion criteria included a history of myocardial infarction; clinical presentation of unstable angina; and bundle branch block or rhythm disturbances, including atrial fibrillation.

From March 1993 to June 1994, 80 consecutive patients were enrolled in the study (mean ± SD age 53 ± 10 years, range 33 to 75; 56 men, 24 women). After discontinuation of cardiovascular drugs for at least 5 half-lives, except for application of sublingual nitroglycerin as needed, all patients underwent the same diagnostic workup according to the following protocol. After written informed consent had been given, an exercise electrocardiographic (ECG) test or dipyridamole-thallium scan was done to exclude significant fixed stenotic disease. Treadmill test results were negative in 55 patients, and 15 patients had equivocal exercise ECG but normal dipyridamole-thallium myocardial perfusion scan results. Dipyridamole-thallium scanning only was performed in 10 patients with poor exercise capacity and revealed normal myocardial perfusion. During the brief hospital period (usually 3 or 4 days) before coronary angiography, spontaneous coronary spasm with symptoms and ST segment elevation were documented in only six patients (8%).

**Ergonovine echocardiography.** Ergonovine echocardiography with two-dimensional echocardiographic monitoring of left ventricular regional wall motion was done as described previously (4). An intravenous line was placed in the upper arm, and noninvasive blood pressure and lead II of the ECG were monitored during the entire procedure.

At 5-min intervals a bolus injection of ergonovine (0.025 or 0.05 mg) was administered intravenously until the appearance of a positive response or a total dose of 0.35 mg was reached. The 12-lead ECG was recorded 3 min after each ergonovine injection, and left ventricular wall motion was monitored continuously at standard parasternal long- and short-axis views and apical four- and two-chamber views with a 2.5-MHz probe (Sonos 1000, 21200C, Hewlett-Packard). Regional wall motion was analyzed by a side by side continuous cine-loop display method with a commercially available quad system (CineView Plus, Freeland Systems) by two experienced echocardiographers (J.K.S., D.H.K.). *Regional wall motion abnormality* was generally used to describe any segment graded dyskinetic, akinetic or hypokinetic. Positive criteria for the bedside ergonovine test included the appearance of transient ST segment elevation or depression >0.1 mV at 0.08 s after the J point (ECG criteria) or reversible wall motion abnormality by two-dimensional echocardiography (echocardiographic criteria). The criteria for terminating the test were as follows: positive response defined as ECG or echocardiographic criteria, total cumulative dose of 0.35 mg ergonovine or development of significant arrhythmia or changes in vital signs (systolic blood pressure ≥200 or ≤90 mm Hg). An intravenous bolus injection of nitroglycerin (0.25 mg) and sublingual nitroglycerin (0.6 mg) was given as soon as a positive response (ECG or echocardiographic criteria) was detected or at the end of a test with a negative response. Sublingual nifedipine (10 mg) was also administered for possible delayed effects of ergonovine.

The territory of coronary vasospasm was tentatively diagnosed according to segments that developed regional wall motion abnormalities during ergonovine echocardiography (Fig. 1) and comparison with coronary angiographic results. Figure 2 shows one representative example of ergonovine echocardiography according to our study protocol.

**Coronary angiography and spasm provocation test.** After ergonovine echocardiography, all patients underwent diagnostic coronary angiography with the conventional Judkins technique. Patients with a high degree of atherosclerotic stenosis (≥70% lumen diameter) were diagnosed as having fixed disease and were excluded from the spasm provocation test. In patients with normal angiographic results or lumen diameter narrowing <70% without spontaneous spasm, a provocative pharmacologic test for coronary artery spasm was done using intravenous (1), intracoronary ergonovine (5) or intracoronary acetylcholine (6), according to the methods described elsewhere. The appearance of total or subtotal occlusion of a major coronary artery associated with ST segment elevation or depression on the ECG or chest pain, or both, was considered to be a manifestation of spasm.

In patients with vasospastic angina, the disease activity was assessed clinically according to the frequency of chest pain attacks before hospital admission (4); patients with chest pain...
motion abnormality with two-dimensional echocardiography was impossible. In these patients, ST segment changes on the 12-lead ECG during ergonovine provocation was the only diagnostic criterion of coronary artery spasm (7). Two patients had negative test results, and one patient revealed characteristic ST segment elevation at the total cumulative dosage of 0.15 mg. Another patient complained of chest pain with the ergonovine dosage of 0.05 mg without definite ECG changes, but further administration of ergonovine was not done because of worsening of chest pain; in this patient, ergonovine echocardiography was incomplete but the response was considered negative because of the failure to demonstrate definite objective evidence of myocardial ischemia.

In the remaining 76 patients, two-dimensional echocardiographic monitoring of left ventricular wall motion was possible during ergonovine echocardiography. Fifty-three of 76 patients revealed wall motion abnormality with ergonovine provocation (mean ergonovine dose 160 ± 117 μg). Regional wall motion abnormalities were detected in the left anterior descending coronary artery territory in 27 patients (50%), the right coronary artery in 20 (37%), the left circumflex coronary artery in 3 (7%), the left anterior descending and right coronary arteries in 2 and the left anterior descending and left circumflex coronary arteries in 1.

Among 53 patients with regional wall motion abnormalities on two-dimensional echocardiography, 20 (38%) showed characteristic ST segment elevation in the simultaneously recorded 12-lead ECG. 4 (8%) showed ST segment depression, and 7 (13%) had minor T wave changes without ST segment displacement. In 22 patients (42%), two-dimensional echocardiography detected wall motion abnormalities without any ECG changes suggestive of myocardial ischemia. During ergonovine echocardiography in 80 consecutive patients, no serious procedure-related arrhythmia or myocardial infarction occurred.

Coronary angiography with spasm provocation. Diagnostic coronary angiography was performed 2 ± 4 days after ergonovine echocardiography in all 80 patients. Five patients (6%) without a spasm provocation test were diagnosed as having fixed disease because of lumen diameter narrowing of major epicardial coronary arteries >70% (mean 97 ± 4%). Spontaneous spasm was documented in 12 patients (15%). The remaining 63 patients underwent a pharmacologic provocative test for coronary artery spasm. Intracoronary ergonovine was administered in 26 patients, intracoronary acetylcholine in 18, intravenous ergonovine in 14 and consecutive intracoronary acetylcholine and ergonovine in 5.

Diagnostic coronary angiography and the spasm provocation test revealed coronary artery spasm in 56 patients, significant fixed disease in 5 and near-normal findings without evidence of spasm in 19 (Table 1). Among the 56 patients with documented coronary artery spasm, 46 had pure spasm, 10 had mixed disease with a mean lumen diameter narrowing of 60 ± 7%, and 10 (18%) had multivessel spasm. During the spasm provocation test in the catheterization laboratory, marked sinus bradycardia developed in one patient and transient
nonsustained ventricular tachycardia in another, but no serious complications, including death or myocardial infarction, occurred. Results of ergonovine echocardiography, diagnostic coronary angiography and spasm provocation tests are summarized in Table 1.

According to the coronary angiographic criteria, ergonovine echocardiography for diagnosis of coronary artery spasm before invasive angiography had a sensitivity of 91% (51 of 56 patients, 95% confidence interval [CI] 84% to 98%), a specificity of 88% (21 of 24, 95% CI 75% to 100%), a positive predictive value of 94% (51 of 54) and a negative predictive value of 81% (21 of 26). Of three patients with false positive results on ergonovine echocardiography, two had severe fixed atherosclerotic stenosis requiring revascularization. In the two patients with fixed coronary artery disease, treadmill or thallium perfusion scan did not demonstrate myocardial ischemia, but ergonovine echocardiography revealed either ECG changes or regional wall motion abnormalities in the territories of significant fixed coronary disease. Of five patients with false negative results on ergonovine echocardiography, one had a poor echocardiographic window, and ergonovine echocardiography was terminated because of worsening chest pain; the remaining four patients had coronary artery spasm with low disease activity (Table 2).

Documented sites of coronary vasospasm during ergonovine echocardiography and diagnostic coronary angiography are summarized in Table 3. Among 27 patients with wall motion abnormality in the left anterior descending coronary artery territory during ergonovine echocardiography, 24 showed angiographic evidence of spasm in the corresponding artery. One patient showed a high degree of fixed stenosis on the basal angiogram, and coronary vasospasm in the proximal left circumflex coronary artery was observed in another. In one other patient, spontaneous spasm developed in the proximal right coronary artery requiring infusion of nitroglycerin, and pharmacologic provocation testing was not done. Wall motion abnormalities in the right coronary artery territory were present in 20 patients during ergonovine echocardiography, and angiographic spasm in the same territory was present in 17 at catheterization. Of the remaining three patients, one had false positive results on ergonovine echocardiography, one developed spontaneous vasospasm in the distal left circumflex coronary artery, and one developed simultaneous coronary artery spasm in the left anterior descending and left circumflex coronary arteries with intracoronary injection of acetylcholine, which made a spasm provocation test of the right coronary artery redundant because of nitroglycerin administration.

In five patients with fixed atherosclerotic disease, exercise ECG and thallium perfusion scan results were negative, and they underwent ergonovine echocardiography. Two of these patients had positive ergonovine provocation results according to the ECG or echocardiographic criteria. The other three patients did not develop ECG changes or regional wall motion abnormality with ergonovine up to a total cumulative dose of 0.35 mg. None of these five patients with significant coronary artery stenosis (mean lumen diameter narrowing 97 ± 4%, range 90% to 100%) experienced serious complications during ergonovine echocardiography.

**Discussion**

**Diagnostic validity of ergonovine echocardiography.** Establishment of a noninvasive and reliable method of diagnosing coronary artery spasm would be useful in the management of patients with variant angina because such a method can be used for screening patients with chest pain syndromes, and the therapeutic efficacy of prescribed drugs can be evaluated. In the present study, the sensitivity and specificity of ergonovine echocardiography for diagnosis of coronary artery spasm were 91% and 88%, respectively, including those patients with a poor echocardiographic window. The specificity of the test was

### Table 1. Final Results of Ergonovine Echocardiography and Coronary Angiography With Spasm Provocation Test

<table>
<thead>
<tr>
<th>Erg Echo</th>
<th>Vasospasm +</th>
<th>Vasospasm -</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ (n = 54)</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td>- (n = 26)</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Erg Echo = ergonovine echocardiography; Fixed Disease = lumen diameter narrowing ≥70%; Mixed = moderate lumen diameter narrowing (>50%, <70%) with superimposed coronary vasospasm; Normal = no fixed disease, negative spasm provocation test results; Pure Spasm = coronary vasospasm in normal or near-normal (lumen diameter narrowing <50%) coronary artery; + = positive results; - = negative results.

### Table 2. Clinical Data for Five Men With False Negative Results on Ergonovine Echocardiography

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age (yr)</th>
<th>Activity</th>
<th>Chest Pain</th>
<th>ECG</th>
<th>RWMA</th>
<th>CAG</th>
<th>Spasm Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>Low</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Normal</td>
<td>mLAD, dRCA</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>Low</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Normal</td>
<td>pRCA</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>Low</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Normal</td>
<td>mLAD, dRCA</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>Low</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Normal</td>
<td>dRCA</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>High</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>pLAD 60%</td>
<td>pLAD</td>
</tr>
</tbody>
</table>

*Poor echocardiographic window made definite demonstration of regional wall motion abnormalities (RWMA) impossible. CAG = diameter narrowing (%) by coronary angiography; d = distal; ECG = electrocardiogram; LAD = left anterior descending coronary artery; Low = chest pain attack less than five times a week; – = no change, negative test results; m = mid; p = proximal; Pt = patient; RCA = right coronary artery.
somewhat low compared with that in our previous study (4). This low specificity is due to the fact that in the present study we used a noninvasive method to rule out significant fixed coronary artery disease, whereas in the previous study coronary angiography had been performed before the ergonovine echocardiography. Two patients with severe fixed coronary artery stenosis >90% were inadvertently enrolled in the study because of negative stress test results, but these were considered false positive results because spasm induction was not attempted during coronary angiography. Had we performed the spasm provocation, they could have shown positive results. Thus, if we exclude the patients with significant fixed disease, the specificity of ergonovine echocardiography would increase to 94% (17 of 18).

Of three patients with false positive results on ergonovine echocardiography, two had a high degree of fixed stenosis on the basal angiogram and showed positive ergonovine echocardiographic results with ST segment displacement on the ECG or wall motion abnormalities. These results may be explained by some clinical reports demonstrating a high association between fixed atherosclerotic lesions and coronary artery spasm (8-11). But because the ergonovine provocation test results were negative with ergonovine injection up to 0.35 mg in the other three patients with a high degree of fixed stenosis, coronary artery spasm and fixed stenosis must be considered two independent mechanisms evoking myocardial ischemia (2,3).

The term “mixed disease” needs some clarification. The aforementioned two patients with a high degree of fixed lumen narrowing of epicardial coronary arteries and definite ECG changes or regional wall motion abnormalities during ergonovine echocardiography can be considered to have mixed disease. However, in the present study we somewhat arbitrarily defined mixed disease as superimposed spasm in the presence of a moderate degree of fixed stenosis (lumen diameter narrowing between 50% and 70%). With different definitions of mixed disease, the sensitivity and specificity of a noninvasive diagnostic method may change. It would be of interest to perform ergonovine provocation in the patients with significant organic stenosis (lumen diameter narrowing >70%) for evaluation of possible association between fixed stenosis and coronary vasospasm.

In stress echocardiography for fixed organic stenosis, it is well known that regional wall motion abnormalities on two-dimensional echocardiography can accurately predict the sites of organic stenosis on coronary angiography (12-14). In the present ergonovine echocardiographic studies, wall motion abnormalities on two-dimensional echocardiography correlated well with the vascular territory of the coronary artery that had spasm. The rare cases of discordant results may be explained by the difficulty of performing a pharmacologic provocative test after spontaneous spasm or development of multivessel spasm.

Safety of ergonovine echocardiography. We believe that the present study confirms the safety of ergonovine echocardiography as a screening diagnostic test for coronary spasm that can be done before coronary angiography because there were no serious complications among 80 consecutive patients with negative stress test results. Because ergonovine echocardiography can detect regional wall motion abnormalities, a sensitive marker of myocardial ischemia, even before the appearance of chest pain or ECG changes (15,16), it is theoretically safer than spasm provocation during catheterization, with the usual 3- or 4-min wait after each administration of drug before performance of repeat angiography. In fact, two patients developed marked sinus bradycardia and ventricular tachycardia during the spasm provocation test at catheterization but had no complications during ergonovine echocardiography. This finding reinforces the importance and superiority of continuous monitoring of ventricular wall motion for safety during the spasm provocation test.

Our results also proved that intracoronary administration of nitroglycerin is not an absolute prerequisite for the spasm provocation test. Intravenous bolus injection and sublingual application of nitroglycerin were effective in safely reversing coronary artery spasm in all 54 patients with positive tests on ergonovine echocardiography. As pointed out previously, earlier detection of myocardial ischemia with wall motion monitoring is important for patient safety because ischemic cascade can be terminated earlier and the risks associated with prolonged ischemia reduced. Of 53 patients with definite wall motion abnormalities, 22 (42%) revealed no ECG changes suggestive of myocardial ischemia, which strengthens our contention. Safe performance of ergonovine echocardiography in the five patients with a high degree of fixed stenosis is another demonstration of the importance of wall motion abnormality detection and of the safety of this test.

Table 3. Comparison of Documented Sites of Spasm During Ergonovine Echocardiography and Diagnostic Coronary Angiography

<table>
<thead>
<tr>
<th>Erg Echo</th>
<th>LAD territory (n = 27)</th>
<th>RCA territory (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pLAD</td>
<td>mLAD</td>
<td>pLAD</td>
</tr>
<tr>
<td>Main</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pLAD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diag</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>pLAD</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>mLAD</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>pRCA</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>pLAD</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>dLAD</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>pRCA</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>mLAD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>RCA</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diag = diagonal branch; LCX = left circumflex coronary artery; other abbreviations as in Tables 1 and 2.
Limitations of the study. Poor echocardiographic window is one of the inherent limitations of echocardiographic techniques. In 5 patients, echocardiographic monitoring of left ventricular wall motion was impossible, and in an additional 12 (15%), left ventricular wall motion could be monitored in only two standard views. As has been confirmed in stress echocardiography for fixed organic stenosis (17), observation through more than two standard views is usually sufficient for diagnosis of wall motion abnormality and prediction of involved territories of coronary arteries. Thus, this limitation should not significantly alter our conclusions with regard to the diagnostic validity of ergonovine echocardiography.

In our study, both ergonovine and acetylcholine were used for provocation of coronary spasm during coronary angiography. Although ergonovine is a more widely used drug for spasm provocation, intracoronary acetylcholine is also a valid method, as was demonstrated by Yashue et al. (6).

Ergonovine echocardiography may be insensitive in the detection of multivessel spasm. Fujii et al. (18) reported that they could diagnose simultaneous multivessel spasm in 30% of patients with variant angina using hyperventilation as a spasm provocation method. According to the present angiographic results, multivessel spasm was diagnosed in 10 (18%) of 56 patients, but only three were diagnosed as having multivessel spasm during ergonovine echocardiography. Definite diagnosis of multivessel spasm is a complex problem. The limitation of ergonovine echocardiography in the diagnosis of multivessel spasm is real, but the same limitation applies to spasm provocation during cardiac catheterization unless provocation is performed in each artery separately or simultaneous coronary angiography is obtained in two coronary arteries.

Conclusions. Despite the difficulty of monitoring wall motion because of a poor echocardiographic window and the unproved diagnostic validity of multivessel spasm, ergonovine echocardiography is a safe and reliable screening test for diagnosis of coronary artery spasm in selected patients with chest pain syndromes. Thus, invasive coronary angiography and a spasm provocation test during catheterization may be unnecessary for diagnosis of vasospastic angina in most patients with negative treadmill or normal thallium perfusion scan results.

References