Safety and Clinical Impact of Ergonovine Stress Echocardiography for Diagnosis of Coronary Vasospasm

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OBJECTIVES We sought to address the issues of safety, feasibility and clinical impact of noninvasive diagnosis of coronary vasospasm (CVS).

BACKGROUND The safety of ergonovine provocation for CVS performed outside the catheterization laboratory has been questioned.

METHODS We performed a retrospective analysis of the results of bedside ergonovine provocation testing by monitoring left ventricular regional wall motion abnormalities (RWMAs) using two-dimensional echocardiography (Erg Echo).

RESULTS After confirming that there was no significant epicardial coronary stenosis, Erg Echo was performed on 1,372 patients from July 1991 to December 1997. Ergonovine echocardiography was terminated prematurely in 13 patients (0.9%) because of limitations caused by side effects unrelated to myocardial ischemia. Among 1,359 completed tests, 31% (n = 421) showed positive results, with development of RWMAs in 412 tests (98%) or ST displacement in electrocardiograms of nine tests (2%). Arrhythmias developed in 1.9% (26/1,372), including transient ventricular tachycardia (n = 2) and atrioventricular block (n = 4), which were promptly reversed with nitroglycerin. There was no mortality or development of myocardial infarction. Based on the angiographic criteria of 218 patients, the sensitivity and specificity of Erg Echo for the diagnosis of CVS were 93% and 91%, respectively. Since 1994, Erg Echo has become a more popular diagnostic method than invasive spasm provocation testing in the catheterization laboratory and has comprised more than 95% of all spasm provocation tests during the last three years. In the outpatient clinic, 453 patients underwent Erg Echo safely.

CONCLUSIONS Although this is a retrospective study in a single center, we believe that Erg Echo is highly feasible, accurate and safe for the diagnosis of CVS and can replace invasive angiographic spasm provocation testing in the catheterization laboratory. (J Am Coll Cardiol 2000;35:1850–6) © 2000 by the American College of Cardiology

Coronary vasospasm (CVS) is a reversible constriction of epicardial coronary arteries, evoking acute myocardial ischemia (1). It has been considered as one of the major mechanisms causing dynamic stenosis of the coronary artery and has also been documented to be a contributor to the development of effort-induced angina, unstable angina, acute myocardial infarction and sudden cardiac death, as well as variant angina (2–4).

Classically, CVS has been diagnosed by an invasive provocative procedure during diagnostic coronary angiography (5). Considering that various noninvasive diagnostic tests for significant fixed atherosclerotic stenosis of epicardial coronary arteries (exercise electrocardiogram, stress echocardiography and nuclear tests) are being used routinely in daily practice, it would be very useful to have a reliable, noninvasive and safe diagnostic method to document CVS. However, some case reports of the development of fatal arrhythmias or acute myocardial infarctions during spasm provocation testing in the catheterization laboratory have discouraged physicians from attempting to establish a noninvasive diagnostic method (6–8).

The development of regional wall motion abnormalities (RWMAs) of the left ventricle is known to be an early phenomenon during myocardial ischemia (9), and many modalities of stress echocardiography for noninvasive diagnosis of significant fixed atherosclerotic stenosis of major epicardial coronary arteries have been established during the last two decades (10,11). Distante and colleagues (12,13)
reported that development of RWMAs due to CVS could be detected by echocardiography before any ECG change during spasm provocation testing in the catheterization laboratory. Several years ago, we proposed that a bedside ergonovine provocation test with two-dimensional echocardiographic monitoring of left ventricular wall motion (ergonovine echocardiography, Erg Echo) could be used as a reliable noninvasive diagnostic method for CVS in patients with near-normal angiographic findings (14,15). Our idea was to detect the development of RWMAs, which are sensitive and early markers of myocardial ischemia, and thereby contribute to the safety of the procedure by allowing us to terminate an ischemic cascade earlier during spasm provocation testing at bedside rather than in the catheterization room. However, the safety of ergonovine provocation for CVS performed outside the catheterization laboratory has been questioned (8), and the real clinical impact of this noninvasive testing in routine practice has not been analyzed. The purpose of this study was to address the issues of feasibility, safety and clinical impact of Erg Echo for noninvasive diagnosis of CVS.

METHODS

We reviewed the data for spasm provocation testing performed in the echocardiography or catheterization laboratories at our institution from 1990 to December 1997.

Erg Echo (14,15). An intravenous line was placed in the upper arm, and noninvasive blood pressure and lead II of the electrocardiogram (ECG) were monitored during the entire procedure. Figure 1 is a diagram showing the protocol of Erg Echo. Bolus injections of ergonovine maleate (50 μg) were administered intravenously at 5-min intervals until a positive response was obtained or a total dose of 0.35 mg was reached. The 12-lead ECG was recorded after each ergonovine injection, and left ventricular wall motion was monitored continuously. Regional wall motion was analyzed by two experienced echocardiography specialists (J.K.S., D.H.K.) using a side-by-side continuous cine-loop display method with a commercially available quad system. Regional wall motion abnormalities were generally used to describe any segment graded dyskinetic, akinetic or hypokinetic. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography with a 16-segment model (16), and the territory of CVS was diagnosed based on the segments showing wall motion abnormalities (Fig. 2, A and B).

Positive criteria for the 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 RWMAs 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 mm Hg 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 administration of these drugs was repeated as needed.

In a spasm provocation test, the possibility of significant fixed atherosclerotic stenosis of major coronary arteries was usually ruled out by treadmill testing or a dipyridamole-thallium-201 myocardial perfusion scan. For some patients, invasive coronary angiography was done to rule out the

**Abbreviations and Acronyms**

CVS = coronary vasospasm
ECG = electrocardiogram
Erg Echo = ergonovine echocardiography
RWMAs = regional wall motion abnormalities

**Figure 1.** Protocol of ergonovine echocardiography. ECG = electrocardiogram.
significant fixed lesion. All cardioactive drugs (beta-adrenergic blocking agents, calcium channel blocker and nitrates) were discontinued for at least five half-lives, but nitroglycerin was administered sublingually as necessary. Resting hypertension was usually controlled by using an angiotensin converting enzyme inhibitor; blood pressure $150/90$ mm Hg was an absolute contraindication for the test.

Diagnostic coronary angiography and invasive spasm provocations. Coronary angiography was performed according to the conventional Judkins or Sones technique. Patients with a significant fixed atherosclerotic stenosis ($\geq 50\%$ lumen diameter) were excluded from the spasm provocation test. A pharmacologic provocation test for CVS was done using intravenous (5), intracoronary ergonovine (17) or intracoronary acetylcholine (18), 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 typical chest pain, or both, was considered to be a manifestation of CVS (Fig. 2, C and D).

Statistical analysis. Results of analyses are expressed as mean $\pm$ standard deviation. The overall sensitivity and specificity of Erg Echo were calculated from $2 \times 2$ tables. Categorical variables were analyzed with chi-square, and a $p$ value $<0.05$ was considered as statistically significant.

RESULTS

Ergonovine echocardiography was performed on 1,372 patients from July 1991 to December 1997. There were 908 men and 464 women. The mean age was $53 \pm 10$ years (19–80). Before Erg Echo, significant atherosclerotic fixed disease was ruled out by negative results in exercise electrocardiographic tests in 46% of the patients, normal myocardial perfusion scan in 32% and normal coronary angiograms in 22%.

Ergonovine echocardiography was performed for differential diagnosis of chest pain syndromes in the majority of cases (91%). In 7%, the assessment of the efficacy of the prescribed medication for patients with documented CVS indicated the test, and in 2% the test was performed to monitor the activity of the spasm during clinical follow-up. Figure 3 shows the clinical impression of attending physicians before the testing. Variant angina was the most frequent referral diagnosis for the test (42%); however, Erg Echo was also requested for patients with a clinical diagnosis of non-ischemic chest pain, unstable angina, effort angina, myocardial infarction and aborted (successfully resuscitated) sudden cardiac death.

Feasibility, diagnostic validity and safety of Erg Echo. Ergonovine echocardiography was terminated prematurely in 13 patients (0.9%) because of limiting side effects during the procedure, without any evidence of myocardial ischemia. These side effects consisted of hypertension (systolic blood pressure $>200$ mm Hg) in five patients, hypotension (systolic blood pressure $<90$ mm Hg) in two patients, nausea with vomiting in three patients, headache in two patients and back pain in one patient. All the side effects in these patients with incomplete tests were reversed promptly with intravenous nitroglycerin.
Among 1,359 completed tests, 421 tests (31%) showed the positive response, while 938 tests were negative. Of 421 positive tests, 412 tests (98%) showed obvious RWMAs in two-dimensional echocardiography (echocardiographic criteria); in the remaining nine tests, ST segment displacement (elevation in six and depression in three) in the 12-lead ECG was the only criterion for positive response attributable to poor echocardiographic window (ECG criteria). The involved territories of the CVS, based on the echocardiographic criteria, were the left anterior descending artery in 49%, the left circumflex artery in 9% and the right coronary artery in 34%. Multiple RWMAs were documented in 6%: the left anterior descending and right coronary arteries in 3%, the left anterior descending and left circumflex arteries in 2%, and the left circumflex and right coronary arteries in 1%. In the remaining nine patients (2%), ECG changes without documentation of RWMAs (because of a poor echocardiographic window) made the correct diagnosis of the involved territory of CVS impossible.

In 218 patients, a pharmacological spasm provocation test during diagnostic coronary angiography in the catheterization laboratory was also performed several days before or after Erg Echo, and these data are summarized in Table 1. According to the coronary angiographic criteria, Erg Echo for the diagnosis of CVS had a sensitivity of 93% (142 of 152 patients), a specificity of 91% (60 of 66), a positive predictive value of 96% (142 of 146), and a negative predictive value of 86% (60 of 70). The overall accuracy was 93% (202 of 218 patients).

During Erg Echo, transient arrhythmias were observed in 1.9% of the patients (26/1,372). Sinus bradycardia was recorded in 10 patients, and ventricular premature beats in another 10, none of which precluded fully successful diagnostic testing. Their occurrence did not have any association with a positive test response. Short-run ventricular tachycardia was observed in two patients. In one patient, it occurred after the maximum cumulative dose of ergonovine (0.35 mg) was reached, without any evidence of RWMAs or ECG changes; in another patient, the tachycardia developed after intravenous injection of nitroglycerin to reverse RWMAs of the left anterior descending artery territory. Atroventricular block was recorded in four patients with positive tests showing CVS in the right coronary artery territory. All of these arrhythmias were transient and promptly reversed with the administration of nitroglycerin and nifedipine, as described earlier. There were no complications, including the development of myocardial infarction, fatal intractable arrhythmias or strokes. Because all patients became stable within 10 min after the test, no specific protocol for serial cardiac enzymes was used.

Among 421 patients with RWMAs on two-dimensional echocardiography, 34% showed characteristic ST segment elevation in the simultaneously recorded 12-lead ECG, 11% showed ST segment depression and another 9% had minor T wave changes without ST segment displacement. In 46%, two-dimensional echocardiography detected RWMAs without any ECG changes suggestive of myocardial ischemia.

Clinical impact. Table 2 summarizes the prevalence of positive test results for Erg Echo according to the clinical diagnosis. Ergonovine echocardiography was useful for diagnosing CVS in various clinical settings, including myocardial infarction and aborted sudden cardiac death. For patients with clinical diagnosis of unstable angina pectoris, Erg Echo was also useful in documenting the mechanism of myocardial ischemia if the diagnostic angiography revealed no evidence of significant fixed disease.

From 1990 to December 1997, a total of 2,033 spasm provocation tests were performed in either the catheterization or echocardiography laboratory. The invasive spasm provocation test in the catheterization laboratory was the main method of diagnosing CVS until 1992 and comprised about 25% of all diagnostic angiographic procedures (Fig. 4A). However, since 1994, noninvasive Erg Echo has become a more popular diagnostic method—almost replacing invasive coronary angiography and the spasm provocation test for the last three years (Fig. 4B). In recent days, the major indications for invasive angiography and spasm provocation tests for CVS have been poor echocardiographic window and uncontrolled hypertension.

Among 1,359 completed tests, 33% (453) were done on an outpatient basis after excluding the possibility of significant fixed atherosclerosis. The frequency of spasm provocation testing without hospital admission has increased dramatically (Fig. 5), and in 1997 more than half of the total number of Erg Echo procedures were requested in the outpatient clinic. The incidence of positive test response for Erg Echo did not differ whether it was performed with (37%, 331/906) or without (20%, 90/453) hospital admission. The incidence of side effects or arrhythmia during the procedure also did not differ.
DISCUSSION

In this study, we have demonstrated that Erg Echo is highly feasible, with excellent diagnostic sensitivity and specificity for CVS. Because this test is totally noninvasive and safe, it can virtually replace invasive coronary angiography with pharmacological spasm provocation. More frequent and repeated use of this noninvasive test may contribute to the possibility of achieving complete differential diagnosis of chest pain syndrome in routine daily practice.

Comparison with other stress tests. The incidence of limiting side effects and serious arrhythmias during Erg Echo was comparable to those studies of other widely accepted pharmacological stress tests for fixed atherosclerosis, such as dobutamine or dipyridamole (19,20). From the purely echocardiographic point of view, Erg Echo is the simplest among all kinds of stress tests, as there are no factors that might degrade the quality of the test, such as hyperventilation, tachycardia, excessive chest wall movement or significant changes in systemic hemodynamic (14). Unlike other stress tests for fixed atherosclerotic stenosis of coronary artery, this test shows a high sensitivity even in patients with single-vessel spasm; the transmural nature of supply ischemia resulting from CVS may explain this difference.

Safety consideration. Spasm provocation testing, undertaken either in the catheterization laboratory or at bedside, is a potentially risky and challenging procedure, demanding a high degree of skill on the part of the operator. Table 3 summarizes the issues regarding the safety of the test.

Although angiographic demonstration of reversible total occlusion of major epicardial coronary artery is, in itself, enough for a diagnosis of CVS, moderate vasoconstriction occurs more frequently in routine provocation testing. In these cases, other indexes of myocardial ischemia are necessary for a definite diagnosis of CVS. The development of chest pain or electrocardiographic changes, which are well known as relatively late events in ischemic cascade, are classic markers for myocardial ischemia used in the catheterization laboratory (21). The usual 3- to 4-min wait after each injection of the drug before serial angiography without sensitive monitoring of ischemic cascade may also contribute to the potential danger of the procedure. Moreover, because we cannot predict in which coronary artery territory the spasm develops, sometimes we spend another several minutes just switching the angiographic catheters for demonstration of reversible vasoconstriction. All these factors delay the termination of the vicious cycle of myocardial ischemia. Considering the fact that the development of serious arrhythmia or myocardial infarction depends on the duration of the preceding myocardial ischemia, spasm provocation testing in the catheterization laboratory is not a safe procedure at all. Other physicians also pointed out that injecting a contrast agent into the coronary circulation for demonstration of reversible vasoconstriction during a severe ischemic episode may increase the risk involved in the procedure (22); myocardial imaging rather than angiography has been proposed as a more sensitive, more specific and safer method of identifying CVS (22).

Conventional thinking has held intracoronary injection of nitroglycerin to be a prerequisite condition for spasm
provocation testing because it may resolve an otherwise refractory spasm (6,7). However, our data along with other published investigations (23–25) indicate that this test can be performed safely with sublingual and intravenous nitroglycerin if we can detect the myocardial ischemia resulting from CVS early.

The most important advantage of Erg Echo is its capacity to detect RWMAs, which are sensitive and specific markers of myocardial ischemia, even before the appearance of chest pain or ECG changes. Our finding, that 46% of patients diagnosed as having CVS based on development of RWMAs did not show any ECG changes, reinforces the importance and superiority of two-dimensional echocardiographic monitoring of ventricular wall motion for safety during the spasm provocation test. Our data also confirmed our initial hypothesis that early termination of the vicious cycle of myocardial ischemia resulting from CVS can be done safely by early detection of RWMAs. The only potential risk of Erg Echo is that temporary pacemaker backup is impossible during the spasm provocation test at bedside. The incidence of atrioventricular block in our study was very low, and it reversed promptly with intravenous and sublingual nitroglycerin. However, multicenter investigation is needed to determine whether early detection and termination of myocardial ischemia based on RWMAs can completely obviate the need for temporary pacemaker backup.

Study limitations. This is a retrospective analysis of data obtained in a single center. Clearly, independent confirmation and additional data on the test value would be required. The clinical usefulness of any noninvasive diagnostic test depends on the prevalence of the disease; therefore, multicenter study is necessary to clarify the clinical role of spasm provocation in routine clinical practice. Because we used only ergonovine for spasm provocation, it is impossible to compare our data with other noninvasive spasm provocation tests such as the hyperventilation test (26,27).

Ergonovine echocardiography can be safely performed without angiographic demonstration of insignificant fixed disease if noninvasive exercise ECG or myocardial perfusion scan shows negative or normal results. In this situation, because of false negative results of noninvasive stress tests, some patients with significant fixed disease may have no occasion for invasive diagnostic angiography until some adverse clinical event occurs. The safety of omitting invasive coronary angiography in the differential diagnostic work-up for patients with chest pain syndrome is, therefore, not confirmed.

Clinical implications. We have proved that noninvasive diagnostic test for CVS is feasible and can be done safely in daily clinical practice; complete work-ups for the differential diagnosis of chest pain syndromes are possible with Erg Echo. Even after invasive coronary angiography, a diagnosis of CVS is not complete, and a repeat angiography with spasm provocation test is necessary in most cases. Withdrawal of cardioactive drugs for certain periods, potential risk, and increased catheterization time for a repeat angiography and a spasm provocation test have discouraged physicians from a systematic approach to CVS. Absence of a reliable and safe noninvasive diagnostic method might contribute to a physician’s current underestimation of the clinical importance of CVS.

Another important finding of this study is that Erg Echo can be used in many different clinical situations to diagnose CVS. Although variant angina is the most common clinical diagnosis, patients with CVS also come to the hospital with clinical diagnoses of unstable angina, myocardial infarction or even aborted sudden cardiac death. A considerable number of patients with clinical presentation of unstable angina pectoris might reveal near-normal coronary angiograms, and Erg Echo has demonstrated CVS in some of those patients (28). Coronary vasospasm is also documented in some patients with a clinical history of aborted sudden cardiac death and documented malignant ventricular fibrillation (29).

All these findings confirm the value and clinical useful-

### Table 3. Comparison of Potential Advantages and Disadvantages of Ergonovine Echocardiography Versus Invasive Spasm Provocation Test During Angiography

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<tr>
<th>Advantage</th>
<th>Disadvantage</th>
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<td>Invasive provocation during angiography</td>
<td>Angiogram</td>
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<tr>
<td>Intracoronary nitroglycerin</td>
<td>Relatively late and insensitive ischemic markers (chest pain, electrocardiogram changes)</td>
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<td>Temporary pacemaker backup</td>
<td>Invasive, perturbing vasomotor tone</td>
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<tr>
<td>Regional wall motion abnormalities-sensitive &amp; specific; early detection and termination</td>
<td>Injection contrast agent into coronary circulation</td>
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<tr>
<td>Noninvasive, not perturbing vasomotor tone</td>
<td>Continuous monitoring of ischemic process impossible</td>
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<td>Repeat and follow-up studies</td>
<td>Ergonovine echocardiography can be safely performed without angiographic demonstration of insignificant fixed disease if noninvasive exercise ECG or myocardial perfusion scan shows negative or normal results. In this situation, because of false negative results of noninvasive stress tests, some patients with significant fixed disease may have no occasion for invasive diagnostic angiography until some adverse clinical event occurs. The safety of omitting invasive coronary angiography in the differential diagnostic work-up for patients with chest pain syndrome is, therefore, not confirmed.</td>
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