Role of Vasospasm in Acute Coronary Syndrome
—— Insights From Ergonovine Stress Echocardiography ——

Moo Hyun Kim, MD; En Hee Park, MD; Doo Kyung Yang, MD; Tae Ho Park, MD; Sang Gon Kim, MD; Jin Hyuk Yoon, MD; Kwang Soo Cha, MD; Dong Sung Kum, MD; Hye Jin Kim, RN; Jong Seong Kim, MD

Background
Previous studies have shown that ergonovine stress echocardiography (ESE) may be a valuable noninvasive tool for the diagnosis of vasospasm after the confirmation of no significant fixed stenosis.

Methods and Results
From May 1999 to January 2002, 52 patients who presented with acute coronary syndrome (ACS) and had normal or near-normal coronary angiograms were enrolled. A 50μg bolus of ergonovine was given intravenously at 5-min intervals, until a positive result was observed or a total dose of 350μg was given. After the ergonovine injection, positive results were found in 25 (48%) of 52 patients: 5 (26%) of 19 with unstable angina, 10 (53%) of 19 non-ST elevation myocardial infarction (MI) and 10 (71%) of 14 patients with ST elevation MI. Using univariate analysis, the elevation of troponin concentration, clinical diagnosis of MI, and ST segment elevation on initial electrocardiographic were significantly associated with positive stress test results.

Conclusions
Despite the limitation that coronary spasm was not confirmed angiographically with ergonovine provocation, ESE may be a useful technique for the noninvasive diagnosis of vasospasm.

Key Words:
Acute coronary syndrome; Ergonovine stress echocardiogram; Vasospasm

Although the most common pathophysiological mechanism of acute coronary syndrome (ACS) is rupture of vulnerable plaque, coronary spasm has also been implicated as an etiologic factor in unstable angina (UA), myocardial infarction (MI), and sudden cardiac death. In acute MI, coronary spasm may occur in patients with either a fixed stenosis or a normal coronary artery. During the early stages of ACS, demonstration of coronary spasm may be difficult to detect because of the use of vasodilators such as nitrates or calcium channel blockers. The results of previous studies have shown that ergonovine stress echocardiography (ESE) may be a valuable noninvasive tool for the diagnosis of vasospasm after the confirmation of no significant fixed stenosis in patients with UA or variant angina. The major advantage of this echocardiographic method is to circumvent the invasive ergonovine provocation test, which requires coronary angiography with repeated contrast injections.

In East Asia, including Korea and Japan, the incidence of vasospasm-induced acute MI has been reported to be higher than in Western countries, so the aim of the present study was to use ESE to evaluate the incidence of pure coronary spasm as the main cause of myocardial ischemia and infarction in patients who initially presented with ACS and were found to have normal coronary arteriograms.

Patient Selection
From May 1999 to January 2002, a total of 586 ACS patients were admitted and catheterized and of this group, 130 patients (22%) were recorded in the hospital database as having angiographically normal or near normal vessels. We enrolled the 52 (41 men; mean age, 52.9±11.4 years) patients who were assigned to Moo Hyun Kim or Jong Seong Kim and their clinical characteristics are summarized in Table 1.

Methods

Table 1  Clinical Characteristics of the Patients With Acute Coronary Syndrome (n=52)

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53±11</td>
</tr>
<tr>
<td>M/F</td>
<td>41/11</td>
</tr>
<tr>
<td>Pain duration (min)</td>
<td>39±23</td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>35 (67)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (27)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Clinical diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>19 (37)</td>
</tr>
<tr>
<td>Non-ST elevation MI</td>
<td>19 (37)</td>
</tr>
<tr>
<td>ST elevation MI</td>
<td>14 (26)</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; ST, ST segment.

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Section of Cardiology, Dong-A Medical College, Busan, South Korea
Mailing address: Moo Hyun Kim, MD, Department of Cardiology, Dong-A Medical College, 3-1 Dongdaeshin-Dong, Seo-Gu, Pusan, South Korea 602-715. E-mail: kmh60@damc.or.kr
or infarction. Acute MI was defined using the new European Society of Cardiology/American College of Cardiology (ESC/ACC) criteria. Two patients presented with syncope and one with dyspnea. All 3 patients had no chest pain, but had evidence of myocardial injury and ECG changes (according to criteria 2 and 3). Cardioversion or cardiac resuscitation was done in 3 patients.

The patients were treated with standard medical therapy for ACS, including administration of aspirin, intravenous nitroglycerine, calcium channel antagonists, β-blockers, and heparin (unfractionated or low molecular weight). Glycoprotein IIb/IIIa was used in 2 patients according to the attending physician’s choice. Unless contraindicated, patients with ST elevation MI who had continuing chest pain underwent thrombolytic therapy (3 patients) or emergency angiography for primary angioplasty (2 patients).

Serial 12-lead ECGs and cardiac enzymes (CK and troponin) were measured within the first few days of admission. Coronary angiography was done via the radial, brachial, or femoral artery within 4 weeks of episodes of chest pain. Coronary arteriograms results were considered to be normal or near normal if the luminal diameter was <30% and without evidence of plaque rupture.

### Ergonovine Stress Echocardiography

We used HP Sonos 2500 in the first 12 patients without split screen mode and thereafter HP Sonos 5500 dynamic stress software with split screen cine loop, which displayed the images during rest, pharmacological testing, at peak stress and after the stress (nitroglycerine administration). The echocardiographic study was done 28±30 (range, 3–310) and 48±96 days (range, 3–361), respectively, after ACS presentation and coronary angiography. The study was approved by the hospital’s ethical committee and informed consent was obtained from each patient.

Antianginal medications were discontinued at least 3 days before the study (Fig 1). A 50μg bolus of ergonovine was given intravenously at 5 min intervals until a positive result was observed or a total dose of 350μg was given. Blood pressure was recorded at 5 min intervals. A 12-lead ECG was recorded before and after the examination as well as when necessary. Continuous limb-lead electrocardiographic and echocardiographic monitoring was done. Left ventricular wall motion was examined in the parasternal long- and short-axis views, as well as in the apical 4- and 2-chamber views. Regional wall motion was analyzed by 2 cardiologists experienced in echocardiography. The positive criterion was the development of a reversible wall motion abnormality. The criteria for terminating the test were a positive response, a total cumulative dose of 350μg ergonovine, or the development of significant arrhythmia or changes in vital signs (systolic blood pressure ≥200 or ≤90mmHg). As soon as a positive response was detected, an intravenous bolus injection of nitroglycerine (0.25 or 0.5mg with or without Isoket® Spray) was given. Sublingual nifedipine was also administered in all patients, to prevent the possible delayed effects of ergonovine.

### Statistical Analysis

All results are presented as mean±SD. The chi-square test was used to find the relationships between positive predictors of ESE and each explanatory categorical variable. In the chi-square test, p<0.05 was considered to be statistically significant. Multiple logistic regression analysis was also used to select important predictors to the positive predictors of ESE. For the variable selection in the multiple logistic regression analysis, p<0.20 was used.

### Results

#### Ergonovine Stress Echocardiography

The clinical diagnoses of the 52 patients included 19 cases of UA, 19 non-ST elevation MI, and 14 ST elevation MI. Baseline echocardiographic results showed normal wall motion in 39 patients (75%), and regional wall motion abnormalities were noted in 13 patients (25%) (Fig2). Baseline regional wall motion abnormalities were detected in 3 (23%) of the test subjects with UA, in 5 (46%) of those with non-ST segment elevation MI, and in 4 (41%) of those
with ST segment elevation MI. After the ergonovine injection, positive results were found in 25 (48%) of the 52 patients: 5 (26%) of the 19 patients with UA group, 10 (53%) of the 19 patients with non-ST elevation MI, and 10 (71%) of the 14 patients with ST elevation MI (Figs 3, 4). Regional wall motion abnormality was observed in the territory of the left anterior descending artery in 60% (15/25), in the right coronary artery in 5 (20%), in the left circumflex artery in 2 (8%), and in multiple vessels in 4 patients. The mean dose of ergonovine for a positive response was 167±77 μg (range, 50–350). One patient with the positive finding of multiple regional wall motion abnormalities developed cardiac arrest with severe bradycardia and was resuscitated successfully. Other adverse reactions were dizziness in 3, headache in 2, and hypertension and hypotension in 1 patient each.

Predictive Factors of Positive ESE

Among 15 variables, age, sex, and various other risk factors did not correlate with a positive examination result (p>0.05). Using univariate analysis, elevated troponin concentration, clinical diagnosis of MI, and ST segment elevation on initial ECG were significantly associated with a positive stress test (Table 2); however, multiple logistic regression analysis showed that an elevated troponin I concentration was the only predictor of a positive ESE result (odds ratio 7.90, p=0.0030).

ECG Changes and Chest Pain During ESE

There was an ECG change in 10 (40%) of 25 patients during the ESE (8 patients with ST elevation and 2 with ST depression). The region of wall motion abnormality corresponded to the ECG change in all 8 patients with ST segment elevation during ESE. Electrocardiographic change
was not documented in 15 patients (60%). Chest pain and chest discomfort developed in 14 and 5 patients (76%), respectively, of the ESE positive group, but in only 2 and 2 patients in the negative group (15%).

Clinical Follow-up

Patients were followed at the outpatient clinic or were contacted by telephone. Of the 27 patients who had a negative ESE result, 2 had a gastric ulcer, and 1 had hypertrophic cardiomyopathy. Another patient, who had a positive ESE result, 2 had a gastric ulcer, and 1 had no other causes of chest pain (2 had gastric ulcers and 1 had hypertrophic cardiomyopathy). The remaining 10 patients were considered to have either chest pain of unknown origin or chest pain attacks >5 times a week) was related to a positive test result. Therefore, an elevated troponin value represents prolonged duration of coronary spasm and could be used as a surrogate for high clinical activity in those patients who initially present with ACS. However, further study is necessary to elucidate this.

### Discussion

Our results demonstrate the clinical value of ESE for the diagnosis of possible coronary spasm in patients with ACS who present with a normal or near-normal coronary arteriogram. Of the 52 patients studied, 25 (48%) developed left ventricular wall motion abnormalities after the intravenous bolus administration of ergonovine. The results of previous studies have shown that ESE may be used as a noninvasive tool for the diagnosis of vasospasm after the confirmation of no significant coronary disease in patients with unstable or variant angina.9,8

### Comparison With Previous Study Results

Studies that have used ESE for the diagnosis of coronary spasm have been limited. Song et al7,8 used this noninvasive echocardiographic tool for the diagnosis of vasospastic angina before coronary angiography and the diagnosis of coronary spasm in patients with a clinical presentation of UA. They reported a sensitivity and specificity of 91% and 88%, respectively. In the present study, we extended the study subjects to include not only those with UA but also those with non-ST or ST elevation MI and our findings support the contention of Song et al that noninvasive ESE is a useful method for assessing the possible role of coronary spasm in coronary ischemic syndrome. In our study, most of the patients had pain that lasted less than 1 h, so emergency angiography was not necessary in most cases. In addition, although primary angioplasty was indicated in 2 patients with the typical ECG findings of acute MI and chest pain, we did not perform angioplasty because the coronary arteriogram was normal or near normal.

### Predictors of Positive ESE

Our study demonstrated that elevated troponin I concentration was the most important predictor of a positive ESE test. In a previous report, a high index of clinical activity (chest pain attacks >5 times a week) was related to a positive test result. Therefore, an elevated troponin value represents prolonged duration of coronary spasm and could be used as a surrogate for high clinical activity in those patients who initially present with ACS. However, further study is necessary to elucidate this.

### Etiology of Chest Pain in Negative ESE

Of the 19 patients categorized with UA, 13 had negative ESE test results, and 3 of these patients were later found to have other causes of chest pain (2 had gastric ulcers and 1 had hypertrophic cardiomyopathy). The remaining 10 patients were considered to have either chest pain of unknown etiology or variant angina with low clinical activity. Of the patients who had acute MI but a negative ESE result, one who had non-ST elevation MI was later diagnosed with pheochromocytoma. Two patients had positive results after repeated tests. These findings suggest that specific provocative situations, such as high sympathetic activity, heavy alcohol drinking, or local inflammation could cause acute chest pain in patients with no previous history of variant angina or with a history of variant angina with low clinical activity. Another explanation could be the residual effect of vasodilatory drugs administered during the acute stages of MI. The discontinuation of drugs for at least 3 days may not be enough to eliminate drug effects. Also, the time gap between pain onset and ESE might affect test results. Although we excluded patients with evidence of plaque rupture on the coronary arteriogram, it is impossible to rule out the role of microfissuring of the plaque in the pathogenesis of ACS.

### Possible Different Pathogenic Mechanisms in Acute MI Between East Asian and Western Countries: Insights From ESE

Previous pooled data of Japanese studies showed a lower rate of total occlusion during the first 6 h after infarct onset than Caucasians (65% vs 82%). Furthermore, in patients with insignificant coronary artery disease, between 0% and 31% of Caucasians demonstrated inducible spasm with ergonovine provocation, which is lower than for Japanese patients with angiographically normal/near-normal coronary arteries (75%). Another interesting study of the racial differences in the coronary constrictor response in recent MI showed that Japanese patients exhibited a 3-fold greater incidence of spasm and greater vasocostriction in the nonspasitic segments after the administration of acetylcholine than Caucasians. Our data, which show 61%
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(20/33) positivity by ESE in patients with acute MI who had angiographically normal coronary arteries, is comparable to Fukai et al’s data5 and therefore we assume that the pathogenic mechanism of acute MI in East Asia, including Korea and Japan, differs from that in Western countries. It has been found that in a higher percentage of Asian patients, spasm rather than plaque rupture is involved in the pathogenesis of acute MI, which results in more cases of spontaneous reperfusion during the acute phase of MI3 and our data support this finding.

Safety Issues

Although the safety of ESE has been addressed16 one of the present patients had a cardiac arrest, but completely recovered after cardiac resuscitation. The cardiac arrest was partly caused by delayed administration of nitroglycerine and by multivessel spasm. Although intravenous nitrate can relieve both symptoms and the wall motion abnormality in patients with a positive response, it usually takes 2–5 min to take effect. There have been no further major adverse events in 250 cases in our study so far. This result tells us that, during the initial stages of ESE, cardiac arrest is a possibility.

Study Limitations

First, we did not perform routine intravascular ultrasound to rule out the possible role of plaque rupture. Second, we did not perform an invasive ergonovine challenge test in the catheterization room for these patients. Therefore, we cannot tell the exact sensitivity and specificity of the diagnosis of coronary spasm in our study cohort.

Conclusion

In spite of the study’s limitation that coronary spasm were not confirmed angiographically with ergonovine provocation, ESE may be a useful technique for the noninvasive diagnosis of vasospasm.

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References