Although acute myocardial infarction (AMI) is mostly associated with obstructive coronary artery disease, myocardial infarction with normal epicardial coronary arteries has been documented. The overall prevalence of myocardial infarction (MI) with a normal coronary angiogram is low, approximately 3%, but the incidence of this condition appears to vary with age, with higher rates in younger patients. In some patients with a diagnosis of vasospastic angina (VA), dangerous complications such as AMI, or a high-degree of atrioventricular block, ventricular tachycardia, fibrillation or electromechanical dissociation, are observed during an ischemic attack, and all of these maladies can lead to sudden death. Coronary artery spasm has been proposed as a classic etiologic factor for AMI with normal coronary arteries, but the actual prevalence of this event has remained ill-defined because of a lack of data from spasm provocation tests in a large series of patients.

In the present study we evaluated the clinical and angiographic characteristics of VA with AMI in patients without organic coronary heart disease.

**Methods**

**Patients**

Between January 2003 and June 2005, 672 coronary spasm provocation tests were performed at Kangnam St Mary’s hospital and 292 patients were diagnosed with VA. Among these 292 patients, 21 had an AMI. In this study, the diagnosis of VA was made when patients met all of the following criteria: (1) burning or squeezing retrosternal chest pain, (2) positive spasm provocation test, and (3) no significant organic lesion (<50% narrowing of the coronary luminal diameter according to quantitative coronary angiography (QCA)). AMI with VA was defined by elevation of the cardiac markers (troponin-I > upper normal limit and creatine kinase-MB > 3-fold the upper normal limit) with no organic coronary heart disease being identified on angiography. We excluded patients with takotsubo cardiomyopathy.

After the procedure was explained, written informed consent for the spasm provocation test was given by all the patients.

**Spasm Provocation Test**

All the patients’ medications, except for nitroglycerin, were discontinued for >48 h before the start of the study, and nitroglycerin was discontinued at least >4 h before the start of the study. Cardiac catheterization was performed through the right femoral artery while the patient was in a fasting state. Control angiograms of the left coronary artery (LCA) were obtained in the right anterior oblique view with caudal projection, before imaging of the right coronary artery (RCA) in the left anterior oblique view with straight projection after the injection of 4–6 ml of contrast medium.
A temporary pacemaker was inserted through the femoral vein into the apex of the right ventricle for each patient and the pacing rate was set at 50 beats/min.

Acetylcholine chloride (Neocholin-A, 30 mg/2 ml; Zeria Shinyaku, Tokyo, Japan) was injected first into the RCA in incremental doses of 20 and 50 μg in 5 ml of 0.9% saline solution, and followed by similar injection into the LCA in incremental doses of 20, 50 and 100 μg over 20 s. The time interval between each injection was at least 3 min. The patients were asked to report any chest pain. A standard 12-lead ECG was recorded every 30 s. Coronary arteriography was performed when ST segment changes, chest pain or both occurred, and at 1 min after the completion of each injection.7,8

The degree of ST-segment elevation was measured 80 ms after the J point. We considered a positive ST-segment elevation to be present when it was more than 0.2 mV or 1.9 mm in 5 ml of 0.9% saline over 20 s. The time

### Results

#### Clinical Findings

Between January 2003 and June 2005, 672 patients underwent coronary angiography and spasm provocation test at Kangnam St Mary’s hospital as investigations of typical chest pain associated with VA. There were 345 patients with normal coronary angiograms and negative spasm provocation tests, and 35 patients were diagnosed as having organic coronary disease with narrowing of >50% according to the QCA; 292 patients were diagnosed as having pure VA and 21 them developed an AMI.

Among the 21 VA patients with AMI, 1 patient, diagnosed as having VA by a previous spasm provocation test, suffered an AMI after not taking his medication. There were 20 VA patients with AMI who initially visited the emergency room (ER) for AMI without a diagnosis of VA. Of these, 16 patients had ST-segment elevation on the initial ECG; 9 patients had inferior and 7 patients had anterior wall ST-segment elevation MI (STEMI).

Interviews revealed that 14 of the 21 patients with AMI had experienced severe emotional stress before their AMI. As shown in Table 1, there was no difference in the baseline characteristics between the 2 groups except for the C-reactive protein (CRP) level and the ejection fraction. The level of CRP was higher in the VA patients with AMI than in those without AMI (3.2±4.2 vs 0.02±1.9, respectively, p<0.001). On echocardiography, there were no differences between the VA patients with AMI and those without AMI, except for the ejection fraction (42±19.1% and 67±12.5%, respectively, p<0.001). After taking medication for VA, the patients with AMI did not experience severe chest pain or recurrent AMI, nor did any of them visit the ER.

#### Angiographic Findings

On the spasm provocation test, the VA patients with AMI had multivessel spasm and diffuse spasm more often than the VA patients without AMI (76% vs 57%; 86% vs 59%, respectively, p<0.001) (Table 2). In the VA patients with or without AMI, the LAD was the most commonly involved artery according to the results of the spasm provocation test (Table 3). Both groups showed the most frequent induction of vasospasm with 50 μg of acetylcholine (Table 4). All the patients with STEMI showed coronary artery spasm and this was consistent with the ST elevation observed on the ECG during the spasm provocation study.

#### Medical Treatment

Patients received antiplatelet agents (aspirin and clopidogrel), heparin and nitrate when visiting the hospital for STEMI patients.
chest pain. After being diagnosed with VA, the patients received a nitrate, a calcium-channel blocker and nicorandil.

Discussion

STEMI patients are usually treated with fibrinolytic therapy or primary PCI, but sometimes their coronary angiograms are normal. The most common cause of AMI with an absolutely normal coronary angiogram for patients in Western countries is reported to be VA.13

Coronary spasm is defined as abnormal contraction of an epicardial coronary artery, resulting in myocardial ischemia. The commonly associated manifestations of myocardial ischemia are chest symptoms and ST elevation. ST elevation on ECG denotes transmural myocardial ischemia. The precise mechanism of coronary spasm remains obscure, but endothelial dysfunction and smooth muscle hypercontraction have been reported as important factors.12 Kaneda et al recently reported that polymorphisms of the endothelial nitric oxide synthase gene are associated with coronary artery spasm13 and Mashiba et al reported that VA is influenced by polymorphism of the paraoxonase 1 gene A632G.14

Racial differences in the angiographic patterns and prevalence of coronary spasm appear to exist between Asian and Caucasians, and the prevalence of VA appears to be higher in Asians than in Caucasians.15–17 Furthermore, the only controlled study concerning racial differences in vasomotor reactivity between Asian and Caucasian patients with recent MI showed that Asian patients exhibited a greater vasoconstriction of the non-spastic segments after a challenge with ergonovine than Caucasians.18 Kim et al insist that spasm is involved in the pathogenesis of AMI in a greater percentage of Asian patients than Caucasians.19 Kim et al insist that spasm is involved in the pathogenesis of AMI in a greater percentage of Asian patients than Caucasians in a study that used ergonovine stress echocardiography.18

Our study showed that 7.2% of the VA patients suffered an AMI without organic coronary disease. There were 20 AMI patients who were not diagnosed with VA before the AMI, and their first presenting symptom of VA was MI. Among them, 14 patients had emergency coronary angiography performed at the onset of AMI, and there were no significant lesions identified on the angiogram. They underwent a spasm provocation test within 1 week after the onset of AMI, which lead to the first diagnosis of VA. Two patients were treated with fibrinolytic therapy, but angiography performed 5 days after the onset showed normal coronary arteries with a positive spasm provocation test. Four patients initially showed chest pain and typical STEMI, but while we were preparing to perform emergency CAG or fibrinolytic therapy, their chest pain disappeared and the ST-segment elevation became normal on ECG. CAG and spasm provocation tests were performed after 3 days and showed normal CAG and a positive result for the spasm provocation test.

There were no differences in the baseline patient characteristics of the VA patients with AMI and those without AMI. However, the CRP level was significantly higher in the VA patients with AMI compared with those without AMI. The inflammation associated with AMI would have increased the CRP level in the VA patients with AMI.

In the spasm provocation test, the VA patients with AMI had a higher rate of multivessel involvement and diffuse spasm than the VA patients without AMI. Multivessel coronary spasm can cause sudden cardiac death, most likely because of a lethal arrhythmia.19 However, the factors related to the severity of coronary spasm remain unknown; important factors include endothelial dysfunction and impaired autonomic nervous activity. Endothelial dysfunction may be associated with a greater severity of coronary spasm in response to acetylcholine as the provoking agent.20 A study demonstrated that relatively enhanced sympathetic nervous activity may be involved in the mechanism of multivessel coronary spasm.21 Sueda et al have reported that patients with diffuse spasm had poor responses to medical therapy, thought to be because diffuse spasm produces more extensive areas of endothelial dysfunction than focal spasms.22 Therefore, the VA patients with diffuse spasm are susceptible to AMI.

The LAD was the most frequently involved vessel in our study. Spasm of both coronary arteries was most frequently observed when we used 50μg of acetylcholine. The culprit vessels for an AMI contracted as a result of the spasm provocation test, so localization of AMI to the distribution of the coronary arteries supports the idea that coronary artery spasm was the cause of MI.

The 16 patients with STEMI took a nitrate compound for relief of their chest pain; 5 patients immediately improved to a normal ST segment after administration of nitrate po or iv, but the others did not show a good response to nitrate for the following reason. Coronary vasospasm causes an AMI by reducing the coronary blood flow. The thrombosis that may accompany vasospasm could be the result of a grossly reduced blood flow, which is secondary to a critical site of vascular constriction; the interaction of platelets with the damaged vascular wall may further aggravate the coronary spasm.22

Among the 21 VA patients with AMI, 14 had experienced emotional stress before they visited the ER for severe chest pain. It has been reported that ischemic changes can be induced by mental stress and this has been demonstrated by electrocardiography and echocardiography.23,24 A recent report showed that psychological stress induced an attack of chest pain and ST-T change in VA patients;25 thus, mental stress may be an important cause of VA. The mechanism

<table>
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<tr>
<th>Table 3</th>
<th>Involved Artery in the Spasm Provocation Test</th>
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<tr>
<td>VA patients with AMI (n=21)</td>
<td>VA patients without AMI (n=271)</td>
</tr>
<tr>
<td>Left main artery</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>LAD</td>
<td>15 (76%)</td>
</tr>
<tr>
<td>LCX</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>RCA</td>
<td>15 (71%)</td>
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</tbody>
</table>

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery. Other abbreviations see in Table 1.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Acetylcholine Dose for Spasm Induction</th>
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<tr>
<td>VA patients with AMI (n=21)</td>
<td>VA patients without AMI (n=271)</td>
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<tr>
<td>Dose (μg)</td>
<td>LCA</td>
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<tr>
<td>----------</td>
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</tr>
<tr>
<td>20</td>
<td>4 (19%)</td>
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<tr>
<td>50</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>100</td>
<td>4 (19%)</td>
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</table>

Abbreviations see in Tables 1,3.
of mental stress-induced myocardial ischemia is likely to be associated with the coronary vasoconstriction resulting from sympathetic and/or hormonal reflexes. Previous studies have suggested that the vagal tone is depressed during mental stress. Sympathetic activity may be increased, as a result, and it is known that sympathetic activity associated with the β-adrenergic system. Many vasoactive substances, (ie, serotonin, histamine, thromboxane A2, endothelin, angiotensin II etc) may induce coronary vasoconstriction during periods of mental stress. Yoshida et al showed that the serum level of catecholamine was higher in patients with an ST-T change induced by mental stress. Two-thirds of the VA patients with AMI had experienced emotional stress, but further study is necessary to investigate the relationship between VA patients with AMI and emotional stress.

Study Limitations
The angiographic demonstration of “normal” and “not significantly narrow” coronary arteries cannot exclude the presence of significant pathological disease. Therefore, we could not exclude other causes of AMI for the patients with normal coronary arteries, such as embolism or a coagulation disorder.

Conclusion
Our findings support the role of coronary spasm as a cause of MI. Clinically, a known VA patient had his first attack of AMI after discontinuing his medication; this could be an important cause of AMI among known VA patients. Two-thirds of the VA patients with AMI had experienced emotional stress before their AMI attacks. The spasm provocation tests in the VA patients with AMI showed more multivessel and diffuse spasm than in VA patients without AMI.

References