Clinical and laboratory characteristics in patients with acute myocardial infarction due to occlusive vasospasm

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KEYWORDS
Coronary vasospasm; Myocardial infarction; Pathophysiology; Coronary artery disease; Clinical laboratory information systems

Summary

Background: The purpose of this study was to determine the clinical and laboratory characteristics in patients with acute myocardial infarction (AMI) associated with coronary vasospasm.

Methods and results: Consecutive 231 patients with documented coronary vasospasm by ergonovine provocation test but with a normal-appearing coronary angiogram were divided into two groups, variant angina pectoris (VAP) patients (group I; \( n = 202 \), 49.5 ± 11.1 years) and AMI patients (group II; \( n = 29 \), 47.4 ± 11.2 years). Matched control patients were 84 AMI patients with significant stenosis (>50%) (group III; \( n = 84 \), 61.2 ± 11.8 years). Although, the incidence of hypertension, diabetes mellitus, and smoking were lower in group I than in group III, there was no difference between group II and III (diabetes, 7.9% vs. 13.8% vs. 29.8%; hypertension, 19.8% vs. 24.1% vs. 41.7%; smoking 48% vs. 48.3% vs. 61.9%; respectively, \( p < 0.01 \)). Measured high-sensitivity C-reactive protein (hsCRP) and fibrinogen level were higher (respectively, \( p < 0.001 \), \( p < 0.001 \)) in groups II and III (group II, 1.88 ± 2.9 mg/dl, 317.5 ± 51.2 mg/dl; group III, 2.92 ± 3.9 mg/dl, 326.8 ± 107.7 mg/dl) than those in group I (0.68 ± 1.5 mg/dl, 263.2 ± 70.3 mg/dl). A correlation was clearly seen between fibrinogen and hsCRP (\( r = 0.472 \), \( p < 0.001 \)).

Conclusion: The clinical characteristics of patients with AMI associated with spasm were similar to those with VAP, but laboratory findings were similar to those of AMI in patients with significant stenosis.

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Introduction

Variant angina pectoris (VAP) is a disease by which a transient abrupt marked reduction in the luminal diameter of an epicardial coronary artery leads to myocardial ischemia. This is characterized by spontaneous episodes of angina associated with ST segment elevation on electrocardiogram (ECG) and documented spasm of epicardial coronary artery by coronary angiography (CAG). It was initially described by Prinzmetal in 1959 [1—3]. Generally, patients with VAP responding to vasodilators such as nitrate have a good prognosis, but 7.4% of them progress to acute myocardial infarction with vasospasm (VAMI) [4].

The pathogenesis, predisposing factors, and risk factors for VAMI are not well known. Currently, several contributing factors have been identified. They include thrombin activation and fibrin formation induced by coronary spasm. Impaired fibrinolytic activity, reported in patients with variant angina, suggests that coronary spasm may trigger thrombus formation in coronary arteries and that the reduction in fibrinolytic activity may slow the removal of thrombus, ultimately leading to acute myocardial infarction (AMI) in some patients [5,6]. Fibrinogen, the precursor of fibrin, can promote the development of atherosclerosis and thrombosis. Fibrinogen can be a precursor of mural thrombi, which is important in the pathogenesis of acute coronary syndrome [7—13]. Lipoprotein(a) [Lp(a)] plays an important part in the genesis of thrombotic coronary occlusion subsequent to spasm because of a particular feature of its structure that is homology between apolipoprotein (Apo) (a) and plasminogen [13—15]. Apo B/A1 ratio is a good predictor of atherosclerotic cardiovascular disease, more so than low-density lipoprotein (LDL) or high-density lipoprotein (HDL) cholesterol [16,17]. The cause of development and risk factors for VAMI are unknown unlike those for AMI with coronary stenosis (SAMI).

The purpose of this study was to compare the clinical characteristics of SAMI, VAP, and VAMI, and to analyze the laboratory findings such as fibrinogen, Lp(a), Apo B/A1 ratio, and high-sensitivity C-reactive protein (hsCRP).

Materials and methods

All the subjects were selected from patients who were hospitalized for CAG because of suspected VAP or of documented MI during 4 years. We classified these subjects into three groups. Consecutive 231 patients with documented coronary vasospasm with normal-appearing CAG by ergonovine provocation test were divided into two groups, VAP (group I; \(n = 202\), 49.5 ± 11.1 years) and VAMI (group II; \(n = 29\), 47.4 ± 11.2 years). And, matched control AMI patients with significant stenosis (diameter stenosis > 50%) [group III (SAMI)]; \(n = 84\), 61.2 ± 11.8 years] were selected randomly from patients during the same period. Clearly, the definition of VAP and VAMI were positive result in ergonovine test with normal-appearing coronary angiogram.

AMI was defined by typical chest pain over 20 min on admission, significant ST segment elevation on ECG, or elevation of cardiac enzymes. No patients with hematologic disease, hyperpyrexia (over 38 °C), viral, bacterial, or parasitic infection, sepsis, liver disease, renal failure, malignancy, prosthetic valves, or pacemaker were enrolled. Written informed consent was obtained from all the patients before entering the study.

CAG was performed by insertion of 5 Fr. or 6 Fr. arterial sheath through the right or left femoral or radial artery. Ergonovine provocation test was carried out after discontinuing nitrate, calcium channel blocker, and nicorandil for at least 3 days. Ergonovine, 5 μg, 10 μg, and 30 μg, was injected into the left and right coronary arteries separately in cases without spontaneous spasm at 3-min intervals until there was a positive result. CAG during ergonovine provocation test was performed immediately after each ergonovine injection and 3 min later after the injection. A coronary vasospasm was defined as a focal narrowing above 70% or a diffuse narrowing above 90%, reversible with isosorbide dinitrate, associated with chest pain and ST segment change such as elevation or depression on the ECG. On chest pain, we tried sublingual nitrate tablet or spray.

Venous blood samples for fibrinogen, hsCRP, Lp(a), Apo B/A1, and lipid profiles were withdrawn from the antecubital vein in the supine position without antianginal drugs at admission. Venous samples were obtained in the fasting state when the subjects were free of any acute illness. We used the samples that were obtained at discharge. Fibrinogen (reference value, 180—350 mg/dL) was determined with System CA-6000 Sysmex system (TOA Medical Electronics Co., Kobe, Japan) using thrombin reagent (Dade Behring Inc., Newark, DE, USA). hsCRP was determined with N High Sensitivity hsCRP (Dade Behring Inc.), Lp(a) was done with Behring Nephelometer II (Dade Behring Inc.) using N Latex Lp(a) reagent (Dade Behring Inc.). Reference value of hsCRP was below 0.5 mg/dL and that of Lp(a) was below 30 mg/dL.

Data are expressed as mean ± SD. The SPSS program for Windows package (version 11.0; SPSS Inc., Chicago, IL, USA) was used. Comparisons among the three groups were made using one-way analysis of variance (ANOVA). Turkey HSD was used for odds ratio and multinominal logistic regression analysis for relative risks. Statistical analysis such as multivariate logistic regression was used to evaluate the association between variables and we display as odds ratio with 95% confidence interval (CI). A probability level of \(p < 0.05\) was considered to be statistically significant.

Results

The subjects’ clinical characteristics including their risk factors for coronary artery disease are shown in Table 1. The patients with VAP and VAMI were younger than the patients with SAMI (mean age: 49.5 ± 11.5 years in VAP; 47.4 ± 11.2 years in VAMI; 61.2 ± 11.8 years in SAMI; \(p < 0.001\)). With regard to the proportion of males to females, the rate of females is significantly higher in VAP or VAMI than SAMI (male: 133 subjects in VAP (65.8%); 20 (69%) in VAMI; 69 (82.1%) in SAMI; \(p = 0.007\)). The incidence of diabetes was higher in SAMI than VAP or VAMI (8.7% in VAP and VAMI vs. 29.8% in SAMI, \(p < 0.001\)). Also, a higher rate of smoking in SAMI than VAP or VAMI was observed (48.1% in VAP and VAMI vs. 61.9% in SAMI, \(p = 0.031\)), and it was the same with hypertension (20.3% in VAP and VAMI vs. 41.7% in SAMI, \(p < 0.001\)) and hyperlipidemia (14.7% in VAP and VAMI vs. 40.5% in SAMI, \(p < 0.001\)). But, there was no statistically significant differ-
Table 1  Clinical characteristics of the patients.

<table>
<thead>
<tr>
<th></th>
<th>VAP (n = 202)</th>
<th>VAMI (n = 29)</th>
<th>SAMI (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.5 ± 11.5</td>
<td>47.4 ± 11.2</td>
<td>61.2 ± 11.8‡</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>133(65.8)</td>
<td>20(69.0)</td>
<td>69(82.1)†</td>
</tr>
<tr>
<td>Female</td>
<td>69(34.2)</td>
<td>9(31.0)</td>
<td>15(17.9)†</td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>16(7.9)</td>
<td>4(13.8)</td>
<td>25(29.8)†</td>
</tr>
<tr>
<td>Smoking</td>
<td>97(48.0)</td>
<td>14(48.3)</td>
<td>52(61.9)†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40(19.8)</td>
<td>7(24.1)</td>
<td>35(41.7)†</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>30(14.9)</td>
<td>4(13.8)</td>
<td>18(22.8)</td>
</tr>
</tbody>
</table>

VAP, vasospastic angina; VAMI, acute myocardial infarction with vasospasm; SAMI: acute myocardial infarction with significant stenosis.

†p < 0.05 vs. VAP.
‡p < 0.05 vs. VAP and VAMI.

The mean age of patients with VAP was lower than that in VAMI and SAMI. Age and sex differences between VAP and VAMI were not significant. Age and sex were significant risk factors for VAMI and SAMI. Smoking and hypertension were the most common risk factors for VAMI and SAMI.

Discussion

It is well known that vasospasm plays a major role not only in angina pectoris but also in other acute coronary syndromes. Angina pectoris or AMI due to vasospasm is more prevalent in the East, such as in Korea or in Japan than in the Western countries. Smoking is considered as one of the major risk factors for vasospasm. According to some reports, magnesium deficiency [18], hyperinsulinemia [19], vitamin E deficiency [20], high level of Lp(a) [21,22], and hypereosinophilia [23] were responsible for vasospasm. Therefore, risk factors for vasospasm are somewhat different from that for typical coronary artery disease. Despite smoking being a major predictive factor for vasospasm, smoking incidence in VAP or VAMI was lower than in SAMI in the present study. It may be due to a higher proportion of females, whose smoking rate was usually lower than that of men in Korea, in VAP or VAMI and than in SAMI. Also, age and sex differences between groups may be responsible for higher incidence of diabetes and hypertension in SAMI.

Our study showed that Lp(a) in SAMI was significantly higher than that in VAP, but there was no significant difference between VAP and VAMI. These results are in discord with the reports from Tsuchida et al. [21] and Miwa et al. [24]. But, the current study showed that Lp(a) in VAMI tends to be higher than that in VAP. So, if more subjects are enrolled or if VAMI due to vasospasm coexistent with stenosis is included like in the study from Tsuchida et al., the current study may have obtained the same results. We showed that fibrinogen, an index for formation of atheromatous plaque and key to blood flow and platelet aggregation, was higher in VAMI or SAMI than in VAP. This result indicates...
Table 2  Fibrinogen, high-sensitivity C-reactive protein, lipoprotein(a), and lipid levels.

<table>
<thead>
<tr>
<th></th>
<th>VAP</th>
<th>VAMI</th>
<th>SAMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>263.2 ± 70.3</td>
<td>317.5 ± 51.2†</td>
<td>326.8 ± 107.7‡</td>
</tr>
<tr>
<td>hsCRP (mg/dL)</td>
<td>0.6 ± 1.5</td>
<td>1.8 ± 2.9†</td>
<td>2.9 ± 3.9†</td>
</tr>
<tr>
<td>T-cholesterol (mg/dL)</td>
<td>184 ± 37.8</td>
<td>174.1 ± 45.7</td>
<td>191.5 ± 42.9</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>124.6 ± 33.8</td>
<td>106.8 ± 44.4</td>
<td>135.3 ± 40.7†</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>50.4 ± 14.7</td>
<td>49.8 ± 11.4</td>
<td>40.3 ± 12.7†</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>100.6 ± 59.9</td>
<td>108.9 ± 50.2</td>
<td>120.6 ± 63.0</td>
</tr>
<tr>
<td>Lp(a)(mg/dL)</td>
<td>20.6 ± 16.1</td>
<td>29.6 ± 24.8</td>
<td>33.0 ± 29.2†</td>
</tr>
<tr>
<td>Lp(a) &gt; 25 mg/dL</td>
<td>49(26.3%)</td>
<td>9(32.1%)</td>
<td>40(48.2%)†</td>
</tr>
<tr>
<td>Apo B/A1</td>
<td>0.8 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.9 ± 0.4†</td>
</tr>
</tbody>
</table>

hsCRP, high-sensitivity C-reactive protein; T-cholesterol, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; VAP, vasospastic angina; VAMI, acute myocardial infarction with vasospasm; SAMI, acute myocardial infarction with stenosis; Lp(a), lipoprotein(a); Apo, apolipoprotein.

† p < 0.05 vs. VAP.
‡ p < 0.05 vs. VAP and VAMI.

that increased thrombus may be important in the occurrence of not only SAMI but also VAMI. However, the precise mechanisms by which coronary spasm leads to coronary thrombosis and angina or AMI remain unknown. And, in our results, the myocardial infarction size tended to be smaller in the VAMI than SAMI group. The impact of infarction between VAMI and SAMI group may differ. It may influence the laboratory data.

Possible causes of VAP are endothelial dysfunction, spasm of vascular smooth muscle, or autonomic nervous dysfunction [25–27]. And, a possible mechanism of VAMI is that coronary spasm itself induces formation of thrombus and impairment of fibrinolysis and consequently MI occurred. Ogawa et al. [28] reported that the plasma levels of fibrinopeptide A, a sensitive marker of thrombin generation, and plasminogen activator inhibitor (PAI) activity, an indicator of the impairment of fibrinolysis, increased in patients with coronary spastic angina. In general, the turnover of thrombus depends not only on formation, but also on lysis. The key components of the fibrinolytic system are tissue-type plasminogen activator (t-PA) and PAI. Fibrinolytic activity reflects the balance between t-PA and PAI, and PAI is a major factor in determining overall fibrinolytic activity. Zouaoui Boudjeltia et al. [29] reported the relationships between euglobulin clot lysis time (ECLT), a test representing the balance between t-PA and PAI-1 activities, and cardiovascular risk factors. They advocated that ECLT had a significant relationship with fibrinogen, monocyte, and LDL-cholesterol by multivariate analysis. Funayama et al. [30] observed that monocytes modulate the production of t-PA of endothelial cells in vitro, and that C-reactive protein and fibrinogen circulating in the blood can modulate or potentiate the production of interleukin-1β and tumor necrosis factor-α by monocytes. The current study showed significant elevation of CRP and fibrinogen levels in VAMI than in VAP, despite not doing analysis for monocytes. This result may support the previous theory that impairment of fibrinoly-

Figure 2  Serum high-sensitivity C-reactive protein (hs-CRP) concentrations of the study groups. The hsCRP was higher in patients with acute myocardial infarction with vasospasm (VAMI; Group II) or in those with AMI with coronary stenosis (SAMI; Group III) than in those with variant angina pectoris (VAP; Group I) (0.6 ± 1.5 mg/dL in VAP, 1.8 ± 2.9 mg/dL in VAMI, 2.9 ± 3.9 mg/dL in SAMI). *p < 0.05, Group I vs. Group II, Group I vs. Group III.

Figure 3  Relationship between the levels of fibrinogen and high-sensitivity C-reactive protein (hs-CRP) showed good correlation (r = 0.472, p < 0.001).
sis has a major role for the development of MI in coronary spasm. But, although mentioned elevated fibrinogen was found to be associated with AMI with coronary spasm, we do not explain the association between coronary spasm, fibrinogen, and myocardial infarction in more detail. Because, SAMI patients have the elevation of fibrinogen level, therefore elevated fibrinogen level is not thought to be a specific phenomenon in VAMI.

Sniderman and Rosenbloom [16] emphasized the role of Apo B in the development of coronary artery disease. They suggested that the level of Apo B, and the increased number and density of LDL-cholesterol, might be an important coronary risk factor in patients with high level of triglyceride. In the AMORIS study, they observed that Apo B and Apo A1 had little influence by age and sex, compared with the fact that LDL-cholesterol had significant meaning in men below 70 years [17]. The authors tried to analyze Apo B/A1 ratio between different groups. The Apo B/A1 ratio in VAMI was not significantly different compared with that in VAP, but significantly low compared with that in SAMI. These results explain that risk factors of coronary vasospasm might be different compared with typical coronary risk factors. Our study is a single center study with a small sample size.

Conclusions

The clinical characteristics of VAMI patients were similar to patients with VAP, but the laboratory characteristics were similar to those patients with SAMI.

Acknowledgments

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