Clinical Characteristics and Outcomes in Patients with Variant Angina

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Objectives: We retrospectively analyzed the clinical and angiographical characteristics between variant angina and non-variant angina. Methods: We diagnosed 902 patients with coronary spastic angina from Jan 1991 to Mar 2019. Variant angina was observed in 105 patients, while the remaining 797 patients had non-variant angina. Acetylcholine was injected in incremental doses of 20/50/100/200 μg into the left coronary artery (LCA) and 20/50/80 μg into the right coronary artery (RCA), whereas 64 μg ergonovine was administered into the LCA and 40 μg into the RCA. Positive spasm was defined as > 90% stenosis and usual chest pain or ischemic ECG changes. Clinical outcomes under medications were investigated during 1462±960 days of follow-up.

Results: There were no differences regarding the clinical characteristics between the two groups. Significant organic stenosis was frequently observed in patients with variant angina compared with non-variant angina. Although the administration of two types of calcium channel blocker (CCBs), nitrates, and aspirin was markedly higher in patients with variant angina than in those with non-variant angina, the number of clinical outcomes including sudden cardiac death, acute coronary syndrome, ventricular fibrillation, and percutaneous coronary intervention was significantly higher in patients with variant angina than in those with non-variant angina. Clinical outcomes in patients with variant angina and organic stenosis was markedly worse than other 3 groups: variant angina with nonorganic stenosis, non-variant angina with organic stenosis, and non-variant angina and nonorganic stenosis.

Conclusions: Clinical outcomes in patients with variant angina was unfavorable compared with those with non-variant angina. Variant angina requires more percutaneous coronary intervention therapy compared with non-variant angina.

KEY WORDS: intervention, non-variant angina, prognosis, spasm provocation test, variant angina

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I. Introduction

Variant angina was first reported by Prinzmetal in 1959. Variant angina is defined as transient ST elevation and organic or nonorganic stenosis. Compared with Caucasian patients with variant angina, Japanese patients with variant angina have less female, less organic stenosis, better survival at three-year follow-ups, and better myocardial infarction-free survival at three-year follow-ups. The widespread use of calcium channel blocker (CCBs) may have led to the attenuation of transient ST elevation. However, coronary spastic angina (CSA) is still prevalent in the clinic. Furthermore, there are few data regarding the differences between variant angina and non-variant angina.

In this article, we retrospectively investigated the clinical characteristics and clinical outcomes in patients with and without variant angina.

II. Methods

1. Study patients
From January 1991 to March 2019, we performed total 8,390 coronary angiography procedures: 2,381 percutaneous coronary intervention procedures and 6,009 diagnostic and follow-up cardiac catheterization procedures. During the same periods, we performed 1,854 acetylcholine (ACh) spasm provocation tests and 1,265 ergonovine (ER) spasm provocation tests. We tried to perform selective spasm provocation tests to examine the incidence of provoked spasms in patients who had undergone coronary angiography whenever possible. Subjects were excluded and the provocation test was not performed if patients had left main narrowing (>50%), triple-vessel disease, two-vessel disease with total occlusion, heart failure (New York Heart Association functional class III or IV), or renal failure (creatinine > 2.0 mg/dL); if spontaneous spasm was observed; or if isosorbide dinitrate was initially used to relieve spasm in the coronary artery tested.

2. The definition of positive spasm and variant angina
We defined positive spasm as ≥ 90% transient stenosis and usual chest symptom or ischemic ECG changes. Focal spasm...
was defined as discrete transient vessel narrowing ≥ 90% localized in the major coronary artery. Diffuse spasm was diagnosed when transient vessel narrowing was ≥ 90% compared to the baseline coronary angiography observed from the proximal to the distal segment in the three major coronary arteries. We defined variant angina as transient ST elevation and quick ST normalization after the administration of nitroglycerine, while we defined non-variant angina as all CSA except for variant angina.

The degree of ST-segment depression was measured 80 msec after the J point. We considered a result to be positive when at least 1 of the following ischemic ECG changes was demonstrated during and/or after the ACh test: (1) ST-segment elevation ≥ 0.1 mV in at least 2 contiguous leads; and (2) ST-segment depression of 0.1 mV in at least 2 contiguous leads. We also considered a negative U wave as a positive ischemic ECG change.

3. The definition of major cardiac events

Major cardiac events (MACEs) were defined as sudden cardiac death (SCD), acute coronary syndrome (ACS), ventricular fibrillation, percutaneous coronary intervention (PCI), heart failure, readmission due to angina pectoris, or coronary-aorta-bypass graft surgery.

4. Spasm provocation test

All drugs except for nitroglycerine were discontinued for ≥ 24 hours before the study, and nitroglycerine was also discontinued ≥ 4 hours before the study. Cardiac catheterization was performed from 9:00 am to 4:00 pm in the fasting state. After control coronary arteriograms of the left coronary artery (LCA) in the left anterior oblique with caudal projection and of the right coronary artery (RCA) in the right anterior oblique with caudal projection were obtained by injection of 8–10 ml of contrast medium, a temporary pacemaker was inserted into the right ventricle of each ACh testing patient and the pacing rate was set at 40–45 beats/min.

Provocation of coronary artery spasm was performed with an intracoronary injection of ACh, as previously reported. ACh chloride (Neucholin-A, 30 mg/2mL; Zeria Seiyaku, Tokyo, Japan) was injected in incremental doses of 20, 50 and 80 μg into the RCA and of 20, 50, 100 and 200 μg into the LCA over 20 seconds with at least a 3-minute interval between each injection. ER (ergometrine by injection F, 0.2 mg/mL; Fuji Seiyaku, Tokyo, Japan) in a 0.9% warm saline solution was injected at 10 μg/min for 4 minutes for a maximal dose of 40 μg into the RCA and 16 μg/min over 4 minutes for a total dose of 64 μg into the LCA, with at least a 5-minute interval between each injection.

Coronary arteriography was performed when ST-segment changes and/or, chest pain occurred or 1–2 minutes after the completion of each injection. When an induced coronary spasm did not resolve spontaneously within 3 minutes after the completion of ACh injections or when hemodynamic instability occurred as the result of coronary spasm, 2.5 to 5.0 mg of nitrate was injected into the involved vessel. A standard 12-lead electrocardiogram was recorded every 30 seconds. We used the ECG findings when ACh, saline and contrast medium were not injected into the responsible vessels for at least 60 seconds. After the spasm provocation tests were completed, an intracoronary injection of 5.0 mg isosorbide dinitrate was administered, and coronary arteriography was then performed in multiple projections.

During the study, arterial blood pressure and ECG were continuously monitored on an oscilloscope by Nihon-Kohden polygraphy (Tokyo, Japan). In the present study, coronary arteriograms were analyzed separately by 2 independent observers. The percent luminal diameter narrowing of coronary arteries was measured using an automatic edge-counter detection computer analysis system. The size of the coronary catheter was used to calibrate the images in millimeters and the measurement was performed in the same projection of coronary angiography at each stage. Patients with catheter-induced spasms were excluded from this study. Significant organic stenosis was defined as > 75 percent luminal narrowing according to the American College of Cardiology/American Heart Association classification.

The study protocol complied with the Declaration of Helsinki. Written informed consent was obtained from all patients before performing the pharmacological spasm provocation tests and the protocol of this study was in agreement with the guidelines of the ethical committee at our institutions.

5. Statistical analysis

Data analysis was carried out with SPSS (version 22.0, IBM Japan, Ltd., Tokyo, Japan). All data are presented as the mean±SD. All data were analyzed with the Fisher’s exact test with correction or the Mann-Whitney U test. We investigated coronary risk factors and an independent cardiac event after the multivariate analysis between variant and non-variant angina. Event-free survival curves from sudden cardiac death, acute coronary syndrome, percutaneous coronary intervention, or readmission due to angina pectoris were constructed using the Kaplan-Meier survival method. Furthermore, the MACE-free survival curve was constructed using the Kaplan-Meier survival method with correction or Bonferroni test among four groups: variant angina and organic stenosis, variant angina and nonorganic stenosis, non-variant angina and organic stenosis, and non-variant angina and nonorganic stenosis. In all analyses, p<0.05 was regarded as statistically significant.

III. Results

1. Comparisons of clinical characteristics between variant and non-variant angina

As shown in Table 1, we diagnosed 902 patients with CSA including 105 patients with variant angina and 797 patients with
non-variant angina. The rate of organic atherosclerosis in patients with variant angina was approximately two times higher than that in patients with non-variant angina (37% vs. 16%, p<0.001). The administration of benzodiazepine-type CCBs, two-type CCBs, nitrates, and aspirin in patients with variant angina was markedly higher than that in patients with non-variant angina. Dihydropyridine-type CCBs were frequently observed in patients with non-variant angina. The mean number of coronary vasodilators in patients with variant angina was markedly higher than that in patients with non-variant angina (2.0±0.9 vs. 1.7±1.3, p < 0.01).

2. Comparisons of inducible spasm and pharmacological spasm provocation data

Table 2 shows that the distribution of inducible spasm in each coronary artery was not different between the two groups, while the incidence of one vessel spasm in patients with variant angina was lower than that in patients with non-variant angina, but the difference was not significant. The frequency of two-vessel spasm in patients with variant angina was higher than that in those with non-variant angina, but the difference was not significant, and there was no difference regarding the frequency of multiple spasms between the two groups. Furthermore, low-dose inducible spasm with ACh in patients with variant angina was not different from that in those with non-variant angina. The mean used ER dose for both coronary arteries in patients with variant angina was not different from that in patients with non-variant angina.

3. Comparisons of clinical outcomes between variant and non-variant angina

As shown in Table 3, the rate of coronary intervention therapy in patients with variant angina was significantly higher than in those without variant angina (33% vs. 3%, p<0.001). The frequency of readmission due to angina pectoris in patients with variant angina was markedly higher than in those with non-variant angina. Furthermore, the incidence of acute coronary syndrome, and ventricular fibrillation was markedly higher in patients with variant angina than in those with non-variant angina. Non cardiac death was observed in 3 patients with variant angina (2 malignancies and one pneumonia), while seven patients with non-variant angina (2 malignancies, 1 respiratory

Table 1 Patients’ clinical characteristics

|                         | VSA  | Variant | Non-Variant | p value |
|-------------------------|------|---------|-------------|---------|
| Total number of patients| 902  | 105     | 797         |         |
| Male                    | 737  | 92      | 645         | 0.0955  |
| Age (y)                 | 65 ± 10 | 64 ± 10 | 65 ± 10     | 0.8597  |
| Organic stenosis        | 165  | 39      | 126         | <0.001  |
| Hypertension            | 389  | 47      | 342         | 0.7188  |
| Dyslipidemia            | 445  | 54      | 391         | 0.6480  |
| Diabetes mellitus       | 221  | 23      | 198         | 0.5104  |
| History of smoking      | 721  | 92      | 629         | 0.0364  |
| Follow-up duration (days)| 1462 | 1537 | 1452 ± 905 | 0.8083  |
| Left ventricular ejection fraction (%) | 65 ± 10 | 67 ± 9 | 65 ± 10 | 0.8715 |
| Total cholesterol (mg/dL) | 191 ± 37 | 186 ± 33 | 192 ± 38 | 0.6908 |
| Triglyceride (mg/dL)    | 135 ± 84 | 127 ± 72 | 135 ± 85 | 0.3608 |
| HDL-cholesterol (mg/dL) | 49 ± 13  | 48 ± 12  | 49 ± 13    | 0.3739  |
| LDL-cholesterol (mg/dL) | 114 ± 32 | 114 ± 32 | 115 ± 32   | 0.9752  |
| Fast blood sugar (mg/dL) | 113 ± 41 | 109 ± 339 | 114 ± 42 | 0.5437  |
| Glycohemoglobin (%)     | 5.7 ± 1.0 | 5.7 ± 1.2 | 5.7 ± 1.0 | 0.6812  |

Medication

|                      | VSA   | Variant | Non-Variant | p value |
|----------------------|-------|---------|-------------|---------|
| CCB (dihydropyridine)| 641   | 65      | 576         | 0.0276  |
| CCB (benzodiazepine) | 311   | 50      | 261         | 0.0025  |
| CCB (both)           | 78    | 21      | 57          | <0.001  |
| Nitrate              | 416   | 76      | 340         | <0.001  |
| Nicorandil           | 136   | 16      | 120         | 0.9610  |
| Mean number of coronary vasodilators | 1.7 ± 1.2 | 2.0 ± 0.9 | 1.7 ± 1.3 | 0.0046 |
| Statin               | 213   | 23      | 190         | 0.6608  |
| Beta-blocker         | 81    | 9       | 72          | 0.8761  |
| Aspirin              | 318   | 54      | 264         | <0.001  |
| Anti-platelet        | 173   | 22      | 151         | 0.6235  |

VSA: vasospastic angina, HDL: high-density- lipoprotein, LDL: low-density-lipoprotein, CCB: calcium-channel-blocker, ARB: angiotensin receptor blocker, ACEI: angiotensin converting enzyme inhibitor
## Table 2  Comparisons of inducible spasm by pharmacological spasm provocation tests

|                   | Variant (n=84) | Non-Variant (n=797) | p value |
|-------------------|---------------|---------------------|---------|
| RCA               | 62 (74%)      | 592 (74%)           | 0.9255  |
| LCX               | 24 (29%)      | 263 (33%)           | 0.4102  |
| LAD               | 53 (63%)      | 559 (70%)           | 0.1825  |
| 1 vessel spasm    | 28 (33%)      | 353 (44%)           | 0.0538  |
| 2 vessel spasm    | 36 (43%)      | 270 (34%)           | 0.1001  |
| 3 vessel spasm    | 13 (15%)      | 174 (22%)           | 0.1754  |
| Multivessel spasm | 51 (61%)      | 446 (56%)           | 0.4032  |
| Number of ACh test| 78            | 678                 |         |
| ACh dose used in RCA (μg) |    |                     |         |
| 10                | 3 (4%)        | 10 (1.5%)           | 0.2865  |
| 20                | 16 (21%)      | 102 (15%)           | 0.2075  |
| 50                | 27 (35%)      | 203 (30%)           | 0.3954  |
| 80                | 21 (27%)      | 204 (30%)           | 0.5625  |
| ACh used dose in LCA (μg) |   |                     |         |
| 10                | 1 (1%)        | 4 (0.6%)            | 0.9813  |
| 20                | 14 (18%)      | 49 (7%)             | 0.8011  |
| 50                | 19 (24%)      | 124 (18%)           | 0.1948  |
| 100               | 31 (40%)      | 293 (43%)           | 0.5573  |
| 200               | 4 (5%)        | 80 (12%)            | 0.1129  |
| Number of ER test | 22            | 119                 |         |
| Mean ER dose in RCA (μg) | 37 ± 6   | 40 ± 12             | 0.0953  |
| Mean ER dose in LCA (μg) | 64 ± 1 | 61 ± 19             | 0.1262  |

RCA: right coronary artery, LCX: left circumflex artery, LAD: left anterior descending artery, ACh: acetylcholine, ER: ergonovine

## Table 3  Clinical outcome and pharmacological spasm provocation tests in patients with variant and non-variant angina

|                                   | Variant | Non-Variant | p value |
|-----------------------------------|---------|-------------|---------|
| Number of patients                | 105     | 797         |         |
| Spontaneous ST elevation          | 105     | 0           |         |
| Routine electrocardiogram         | 83 (79%)|             |         |
| Exercise test                     | 17 (16%)|             |         |
| Hyperventilation test             | 3 (3%)  |             |         |
| Holter electrocardiogram          | 2 (2%)  |             |         |
| ST elevation                      |         |             |         |
| Inferior                          | 60 (57%)|             |         |
| Anterior                          | 43 (41%)|             |         |
| Lateral                           | 4 (4%)  |             |         |
| Spasm provocation test            |         |             |         |
| Acetylcholine test                | 78 (74%)| 678 (85%)   | 0.0048  |
| Ergonovine test                   | 22 (21%)| 119 (15%)   | 0.1102  |
| Both test                         | 16 (15%)| 0           | < 0.001 |
| Not implemented                   | 21 (20%)| 0           | < 0.001 |
| Prognosis                         |         |             |         |
| Angina pectoris readmission       | 12 (11%)| 39 (5%)     | 0.0064  |
| Percutaneous coronary intervention| 35 (33%)| 20 (3%)     | < 0.001 |
| Cerebral infarction               | 2 (2%)  | 6 (0.8%)    | 0.5288  |
| Heart failure                     | 0       | 10 (1%)     | 0.5102  |
| Coronary-aorta-bypass graft surgery| 1 (1%)| 0           | 0.2314  |
| Ventricular fibrillation          | 5 (5%)  | 1 (0.1%)    | < 0.001 |
| Acute coronary syndrome           | 9 (9%)  | 6 (0.8%)    | < 0.001 |
| Sudden cardiac death              | 0       | 2 (0.3%)    | 0.5553  |
| Non cardiac death                 | 3 (3%)  | 7 (0.9%)    | 0.1853  |
failure, 1 renal failure, 1 Parkinson disease, and 2 pneumonias) had non cardiac death.

4. Kaplan-Meier survival curves

As shown in Fig. 1, there were no differences regarding the SCD-free survival curves between the two groups. In contrast, the ACS-free, PCI-free, and angina pectoris readmission-free survival curves were markedly lower in patients with variant angina than in those with non-variant angina. Furthermore, Fig. 2 shows that the MACE-free survival curve was remarkably lower in patients with variant angina and organic stenosis than other 3 groups. The MACE-free survival curve in patients with variant angina and nonorganic stenosis was remarkably lower than that in patients with non-variant angina and nonorganic stenosis. Furthermore, the MACE-free survival curve in patients with non-variant angina and organic stenosis was significantly lower than that in patients with non-variant angina and nonorganic stenosis.

5. Univariate and multivariate analyses regarding coronary risk factors and cardiac events between patients with and without variant angina

Table 4 shows that there were no differences regarding coronary risk factors between patients with and without variant angina. As shown in Table 5, ACS, PCI, readmission due to angina pectoris, and ventricular fibrillation were the significant factors after the univariate analysis, whereas PCI was the most determinant factor between the two groups after the multivariate analysis.

IV. Discussion

In this article, we showed the clinical and angiographical differences between variant angina and non-variant angina. Variant angina had higher rates of coronary spasticity and atherosclerotic stenosis. Although the administration of abundant coronary vasodilators including two types of CCBs, nitrates and aspirin, was observed in patients with variant angina compared with those...
with non-variant angina, the prognosis in patients with variant angina was unsatisfactory. Furthermore, clinical outcomes in patients with variant angina and organic stenosis was worse than other 3 groups. Cardiologists should pay more attention to treating patients with variant angina and especially those with organic stenosis.

We already reported that variant angina pectoris has the same clinical characteristics as those with non-variant angina pectoris, although variant angina tends to cause greater spasmodilic activity and more organic stenosis\(^{11}\). Variant angina requires more PCI therapy. In this study, we also achieved the same results regarding clinical characteristics, but the clinical outcomes in patients with variant angina were worse than in those with non-variant angina. Cardiologists should reconsider medical or mechanical therapy to suppress catastrophic events due to coronary spasm. In this study, the administration of nitrates in pa-

Table 4 Univariate and multivariate analysis regarding coronary risk factors between patients with variant and non-variant angina

|                      | Univariate analysis | Multivariate analysis |
|----------------------|---------------------|-----------------------|
|                      | p value             | Odds ratio            | 95% lower  | 95% upper  | p value  |
| Sex                  | 0.107               | 0.873                 | 0.3440     | 2.210      | 0.775    |
| History of smoking   | 0.019               | 2.320                 | 0.8940     | 6.010      | 0.0835   |
| Hypertension         | 0.754               | 1.080                 | 0.7100     | 1.640      | 0.725    |
| Diabetes mellitus    | 0.548               | 0.796                 | 0.4820     | 1.320      | 0.373    |
| Dyslipidemia         | 0.679               | 1.130                 | 0.7410     | 1.720      | 0.572    |

Table 5 Univariate and multivariate analysis regarding cardiac events between patients with variant and non-variant angina

|                      | Univariate analysis | Multivariate analysis |
|----------------------|---------------------|-----------------------|
|                      | p value             | Odds ratio            | 95% lower  | 95% upper  | p value  |
| Acute coronary syndrome | 0.000007            | 1.29                  | 0.3140     | 5.330      | 0.721    |
| Congestive heart failure | 0.616              | 0.0000003            | 0.0000     | inf        | 0.983    |
| Percutaneous coronary intervention | 0.0000000 | 16.8                 | 8.6000     | 32.700     | 0.000000 |
| Sudden cardiac death | 1                   | 0.0000000            | 0.0000     | inf        | 0.993    |
| Readmission due to angina pectoris | 0.0118 | 1.49                 | 0.6490     | 3.430      | 0.346    |
| Ventricular fibrillation | 0.000107           | 11.8                  | 0.9180     | 153.000    | 0.0582   |

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tients with variant angina was remarkably higher than in those with non-variant angina. We administered nitrates and nicorandils when patients with CSA were in refractory state. According to previous reports, chronic nitrate therapy in patients with CSA may aggravate prognosis\(^\text{12,13}\). Although the administration of nitrates in patients with variant angina may influence the worse clinical outcomes, the condition of variant angina itself may lead to a worse clinical prognosis. Variant angina has not only greater spasticity but also severe grade of disease activity.

The occurrence of variant angina may become less likely due to the widespread use of CCBs. However, CSA is still prevalent in the clinical grounds. Cardiologists in the western countries, except for those in some special institutions, do not perform spasm provocation tests to diagnose coronary artery spasm routinely in the cardiac catheterization laboratory\(^\text{14,15}\). A small portion of western institutions perform spasm provocation tests in patients with myocardial infarction without obstructive coronary arteries\(^\text{16}\). However, coronary artery spasm may be associated with various cardiac disorders, such as fatal ventricular arrhythmia, SCD, ACS, syncope, heart failure, and stable or unstable angina pectoris\(^\text{17,18}\). Cardiologists in the western countries should reconsider to perform intracoronary ACH or ER tests in cases where the cause of the above disorders is unknown in the cardiac catheterization laboratory.

V. Limitations

This study has several limitations. First, it was a retrospective, single-center study with a small sample size. Second, it had a long study design. Lifestyle changes and medication changes may have contributed to some of the results. Third, we could not perform spasm provocation tests in all variant angina patients. Fourth, we could not perform 24-hour Holter monitoring in all variant angina patients. Finally, we could not perform spasm provocation tests in all variant angina patients. We administered nitrates and nicorandils when patients with CSA were in refractory state. According to previous reports, chronic nitrate therapy in patients with CSA may aggravate prognosis\(^\text{12,13}\). Although the administration of nitrates in patients with variant angina may influence the worse clinical outcomes, the condition of variant angina itself may lead to a worse clinical prognosis. Variant angina has not only greater spasticity but also severe grade of disease activity.

VI. Conclusions

There were no differences regarding the clinical and angiographical characteristics between patients with and without variant angina. However, variant angina had greater spasticity and more atherosclerotic stenosis. Although the mean number of coronary vasodilators in patients with variant angina was significantly higher than that in those with non-variant angina, the clinical outcomes in patients with variant angina were unsatisfactory, especially in patients with variant angina and organic stenosis. Medical and mechanical therapy in patients with variant angina should reconsider in the clinical situation.

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None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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