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# Importance of the Spasm Provocation Test in Diagnosing and Clarifying the Activity of Vasospastic Angina

**Hiroki Teragawa, Yuichi Fujii, Chikage Oshita and Tomohiro Ueda**

Department of Cardiovascular Medicine, JR Hiroshima Hospital, Hiroshima, Japan

**Corresponding author:** Hiroki Teragawa

hiroteraga71@gmail.com

Department of Cardiovascular Medicine, JR Hiroshima Hospital, Japan.

**Tel:** +81822621171

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## Abstract

**Background:** Some patients with Intractable Vasospastic Angina (i-VSA) have angina attacks, irrespective of vasodilator treatment. Despite the significance of the prediction of i-VSA in the clinical setting, the means to accomplish it remain unclear. Therefore, we investigated the relationship between i-VSA clinical parameters, including angiographic findings from the Spasm Provocation Test (SPT), and i-VSA to predict factors responsible for i-VSA.

**Methods:** We examined 155 patients (98 males and 57 females; mean age, 66 years) with VSA diagnosed using the SPT. We focused on the following two findings in the SPT: the positive SPT by a low dose of acetylcholine (L-ACh; 30 μg for the right coronary artery and 50 μg for the left coronary artery) and the total occlusion (TOC) due to coronary spasm. i-VSA was defined as uncontrollable angina even after the administration of two types of coronary vasodilators.

**Results:** There were 38 patients with i-VSA (25%). Positive L-ACh and TOC were more frequently observed in the i-VSA group (L-ACh, 78% vs. 19% in treatable VSA; TOC, 33% vs. 6% in treatable VSA; both $p<0.0001$). The logistic regression analysis demonstrated that L-ACh (odds ratio [OR] 26.54; $p<0.0001$) and TOC (OR, 8.36; $p=0.0038$) were significant predictors of i-VSA.

**Conclusions:** These results suggested that the occurrence of L-ACh and/or TOC during the SPT are predictive markers for i-VSA. The SPT may not only establish a diagnosis of VSA but also provide prognostic information in such patients.
**Keywords:** Vasospasm; Acetylcholine; Spasm provocation test

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## Introduction

Vasospastic Angina (VSA) is characterized by transient vasoconstriction of the epicardial coronary arteries leading to myocardial ischemia [1-3]. Calcium channel blockers are the first-line drug for VSA [4], and the attacks of VSA can usually be relieved or suppressed with coronary vasodilators such as calcium channel blockers and nitrates. However, there are some patients with VSA whose attacks are intractable, resistant to these drugs, and cannot be relieved or suppressed. This VSA is defined as intractable VSA (i-VSA) and is believed to be one of the problems related to VSA [4]. Although several studies are investigating the clinical characteristics of patients with i-VSA [5,6], it remains difficult to predict the presence of i-VSA. In the clinical setting, VSA is frequently diagnosed using the Spasm Provocation Test (SPT), and its findings may provide any information regarding the presence of i-VSA. Therefore, we investigated the relationship between clinical parameters, including angiographic findings from the SPT, and i-VSA to predict the factors responsible for i-VSA.

## Methods

### Study population

In this study, 155 patients (98 males and 57 females, average age, 66 years) with VSA, diagnosed based on the positive results of the SPT from 2011 to 2015 at our institution, were studied. Reportedly, coronary spasm can occur in patients who undergo Percutaneous Coronary Intervention (PCI) and such patients without obvious significant coronary stenosis with a positive SPT result were included in this assessment. However, patients with VSA who were diagnosed by only ST-T changes on Electrocardiography (ECG) during angina attacks were excluded

 

from the study. Besides, patients with moderate chronic kidney disease were also excluded from the study. The protocol was approved by the Ethics Committee of our institution and written informed consent was obtained from all patients.

## Coronary angiography and SPT

All antianginal agents were discontinued at least 48 h before catheterization, except for sublingual Nitroglycerin (NTG) that was withheld 1 h prior to catheterization. We performed the SPT after a diagnostic coronary angiography using the standard percutaneous brachial approach. A 5-Fr transient pacing catheter (Bipolar Balloon Catheter, Bebrawn, Melsungen, Germany) was inserted into the right ventricle via the internal jugular vein is right? vein or median cubital vein, set at 50 beats/min. The arterial pressure, heart rate, and ECG readings were continuously monitored and recorded using a multichannel recorder (Polygraph 1600; Nihon Electric Corporation, Tokyo, Japan).

After baseline control conditions were established, incremental doses (30 μg and 50 μg) of Acetylcholine (ACh) were infused into the right coronary artery (RCA) for 20 s, with 3-min intervals between consecutive doses. If coronary spasms were expected to occur easily, according to patients' symptoms, 10 μg of ACh was adopted as the first dose. If coronary spasms were not induced by 50 μg ACh doses, 80 μg of ACh was infused into the RCA. When coronary spasms were induced or the infusion of the maximum ACh dose was completed, a coronary angiography was immediately performed. When coronary spasms were provoked but spontaneously relieved, we moved to the SPT of the Left Coronary Artery (LCA) without an NTG injection into the RCA. In such cases, after the SPT for the LCA was completed, we again performed coronary angiograms after an NTG injection into the RCA. When coronary spasms were prolonged or were significantly severe to cause unstable hemodynamics, 200 μg of NTG was administered by an intracoronary injection to relieve coronary spasms. Once coronary spasms were relieved, final coronary angiograms of the RCA were performed. Even after the intracoronary NTG injection into the RCA, we performed a subsequent SPT for the LCA because we have witnessed many patients with a positive spasm provocation for the LCA. If there was a small RCA on angiograms or if the catheter was not engaged into the ostium of the RCA, the SPT for the RCA was omitted.

After the baseline control conditions were established, incremental doses of 50 μg and 100 μg of ACh were infused into the LCA for 20 s with 3-min intervals between consecutive doses. If coronary spasms were expected to occur easily, according to patients' symptoms, 20 μg of ACh was adopted as the first ACh dose for the LCA. If coronary spasms were not induced by 100 μg of ACh, 200 μg of ACh and/or 20, 40 and 60 μg of ergometrine maleate was infused into the LCA. When coronary spasms occurred or provocation tests with the maximum ACh dose were completed, we immediately performed a coronary injection into the RCA. When coronary spasms were prolonged or were significantly severe to cause unstable hemodynamics, 200 μg of NTG was administered by an intracoronary injection to relieve coronary spasms. Once coronary spasms were relieved, final coronary angiograms of the RCA were performed. Even after the intracoronary NTG injection into the RCA, we performed a subsequent SPT for the LCA because we have witnessed many patients with a positive spasm provocation for the LCA. If there was a small RCA on angiograms or if the catheter was not engaged into the ostium of the RCA, the SPT for the RCA was omitted.

After the baseline control conditions were established, incremental doses of 50 μg and 100 μg of ACh were infused into the LCA for 20 s with 3-min intervals between consecutive doses. If coronary spasms were expected to occur easily, according to patients' symptoms, 20 μg of ACh was adopted as the first ACh dose for the LCA. If coronary spasms were not induced by 100 μg of ACh, 200 μg of ACh and/or 20, 40 and 60 μg of ergometrine maleate was infused into the LCA. When coronary spasms occurred or provocation tests with the maximum ACh dose were completed, we immediately performed a coronary angiography. After the intracoronary NTG injections of 200 μg, we performed the final coronary angiography for the LCA again. Each coronary angiogram was performed using an auto injection device (Zone Master, Sheen Man, Osaka, Japan) with contrast medium of 2.5 mL/s, up to a total 5 mL per injection.

During SPTs, if unstable hemodynamics (systolic blood pressure <90 mmHg) and/or a continuation of ST segment elevations on ECG occurred, we added another intracoronary NTG injection and increased the speed of the intravenous volume injection up to the maximum speed. Even after such countermeasures, if unstable hemodynamics and ST segment elevations on ECG continued, we infused small doses (2 μg to 10 μg) of adrenaline intracoronarily or intravenously [7].

## Quantitative coronary angiography

A method for measuring the coronary artery diameter has been previously described [8]. The spastic segments and atherosclerotic segments were selected for quantitative analysis. The luminal diameters of selected segments were measured by a single investigator blinded to the clinical data, using an end-diastolic frame by a computer-assisted coronary angiographic analysis system (CAAS II/QUANTCOR; Siemens, Berlin, Germany). All measurements were performed three times, and the average value was used for the analysis. The changes in the coronary artery diameter in response to ACh and NTG infusion were expressed as percentage changes from the baseline angiographic measurements obtained before the infusion. Both intraobserver and interobserver variability of this method were previously shown to be excellent [9]. Lesions with more than 20% stenosis were defined as atherosclerotic lesions. The myocardial bridging was defined as more than 20% reduction in coronary diameter during the systole.

## Definitions of VSA and parameters related to VSA

VSA is defined as ≥90% narrowing of the epicardial coronary arteries on an angiography during the SPT, presence of characteristic chest pain, and/or ST segment deviation on ECG [4]. A focal spasm is defined as >90% discrete transient vessel narrowing localized in the major and branch coronary arteries. A diffuse spasm is defined as 90% transient severe diffuse

vasoconstriction observed in more than two adjacent coronary segments of the epicardial coronary arteries and branches [10]. If a focal spasm occurred in one vessel and a diffuse spasm occurred in another vessel in the same patient, the focal spasm was defined for that patient. The presence of multivessel spasms is defined as coronary spasms that occur in more than two major coronary branches. When the SPT was not performed for the RCA because of a small RCA, inability to engage the catheter into the coronary ostium, or when NTG was intracoronarily infused to relieve coronary spasm and the following SPT was negative for a spasm, the presence of multivessel spasms was not assessed. In this study, we also focused on the following two conditions: the positive SPT induced by doses of ACh within 30 μg in the RCA and/or within 50 μg in the LCA (L-ACh) and the total occlusion due to coronary spasm (TOC).

Upon admission, we assessed chest symptoms via a detailed interview with patients and their family members, we estimated the duration (months) and the onset age of VSA and assessed the number of angina attacks before admission. After discharge, all patients were followed up by our institution (n=73) or by their primary care doctors (n=82), and they came to our institution 1 year after the discharge. At follow-up, we confirmed the contents of drugs from their medication notebook and assessed the number of coronary vasodilators as well as the number of angina attacks, which was the mean time of previous 3 months. Judging from the number of coronary vasodilators and angina attacks, the patients were divided into the following two groups: i-VSA group, whose angina cannot be controlled (the frequency of angina attack ≥ 1 time/month) even with the administration of two types of coronary vasodilators, and treatable VSA (t-VSA) group, whose angina can be controlled (the frequency of angina attack <1 time/month) by the administration of two types of coronary vasodilators. Although VSA patients had anginal attacks when they did not take regular medication or forgot to take vasodilators, they did not have any angina attacks under taking regular medication. We defined that such patients belong to the t-VSA.

Variant Angina (VA) is defined as angina that is documented with an ST elevation on ECG spontaneously. In addition, determining the prevalence of out-hospital cardiac arrest, smoking, angina at rest alone, significant organic stenosis, multivessel spasms, ST elevation, and beta-blocker use, the Japanese Coronary Spasm Association (JCSA) risk score [11] was calculated for each patient.

## Biochemical and other markers and assessment of coronary risk factors

Fasting blood samples were obtained on the day of the coronary angiography. All patients were questioned about their smoking status and classified as a current smoker, past smoker (who had stopped smoking for at least 1 month), or nonsmoker. The blood pressure was measured, and hypertension was defined as a systolic blood pressure of ≥ 140 mmHg, a diastolic blood pressure of ≥ 90 mmHg, and/or the patient was on antihypertensive drugs. The blood chemistry parameters, including the total cholesterol level, triglycerides, high-density lipoprotein cholesterol, fasting blood sugar, hemoglobin A1C, and creatinine, were also measured. The estimated glomerular filtration rate (mL/min/1.73 $m^2$) was calculated using the standard formula [12]. The low-density lipoprotein cholesterol was calculated using the Friedewald equation [13]. Hyperlipidemia was defined as low-density lipoprotein cholesterol of ≥ 120 mg/dL and/or the patient was on medication for the same. Diabetes mellitus was defined as a fasting blood sugar level of ≥ 126 mg/dL, hemoglobin A1C ≥ 6.5%, and/or the patient was on medication for the same. The frequency of having a family history of Coronary Artery Disease (CAD) and left ventricular ejection fraction on echocardiography was also evaluated.

## Statistical analysis

All data are expressed as mean ± SD. The baseline characteristics of the two groups were compared using the Student's unpaired *t*-test or $\chi 2$ analysis as appropriate. The logistic regression analysis was used to clarify factors associated with a presence of i-VSA. A p value of <0.05 was considered statistically significant.

# Results

## Patient characteristics, blood chemical parameters, and echocardiographic parameters

There were 38 patients (25%) in the i-VSA group and 117 patients (75%) in the t-VSA group **(Table 1)**. The body mass index was lower in the i-VSA group than in the t-VSA group (p=0.0481). Regarding the conventional coronary risk factors, the frequency of lipid disorder was significantly lower in the i-VSA group than in the t-VSA group (p=0.036), whereas other risk factors, including smoking status, were not different in the two groups. The history of PCI was similar in the two groups (5% in the i-VSA group vs. 5% in the t-VSA group), and the use of drug-eluting stents was not different in the two groups (0% in the i-VSA group vs. 3% in the t-VSA group).

Regarding blood chemical and echocardiographic parameters, there were no significant differences in the two groups **(Table 2)**.

## VSA-related parameters and medications

Regarding VSA-related parameters, the duration of VSA was longer (10.7 ± 14.5 vs. 6.4 ± 7.9 months, p=0.0222) and the

**Table 1** Patients' characteristics.

| | t-VSA | i-VSA | p |
|---|---|---|---|
| **Numbers (%)** | **117 (75)** | **38 (25)** | |
| Age (yrs) | 67 ± 10 | 64 ± 12 | 0.1609 |
| Male/Female | 72/45 | 26/12 | 0.4446 |
| Body mass index | 24.5 ± 3.9 | 23.1 ± 3.7 | 0.0481 |
| **Coronary risk factors (%)** | | | |
| Smoking Current | 33 (28) | 10 (26) | 0.8212 |
| Smoking Current/past | 34/34 | 10/12 | 0.9334 |
| Hypertension (%) | 76 (65) | 19 (51) | 0.1378 |
| Lipid disorders (%) | 66 (56) | 14 (37) | 0.036 |
| Diabetes mellitus (%) | 27 (23) | 5 (13) | 0.1894 |
| Family history of CAD | 10 (9) | 5 (13) | 0.4036 |

CAD-Coronary Artery Disease; VSA-Vasospastic Angina

estimated age of onset of VSA was younger (62 ± 16 vs. 66 ± 10 years, p=0.0407) in the i-VSA group, whereas the number of angina attacks did not differ in the two groups (5.0 ± 4.9 vs. 5.2 ± 6.8 in the t-VSAgroup). The frequency of VA tended to be higher in the i-VSA group (13% vs. 5% in the t-VSA group, p=0.094), whereas the JCSA score did not differ in the two groups (4.4 ± 2.1 in the i-VSA group vs. 3.9 ± 1.7 in the t-VSA group). All data are summarized in **(Table 3)**.

At follow-up, the number of patients taking coronary vasodilators was significantly higher in the i-VSA group (2.1 ± 0.8 vs. 1.3 ± 1.0 in the t-VSA group, p<0.0001). The frequency of taking calcium channel blockers was also higher in the i-VSA group (87% vs. 70% in the t-VSA group, p=0.0403), whereas other drugs, including statins and beta-blockers, were not different between the two groups. The numbers of angina attacks were significantly higher in the i-VSA group (2.9 ± 2.7 vs. 0.7 ± 1.2 in the t-VSA group, p<0.0001).

## Findings of coronary angiography and SPT

The presence of angiographic atherosclerotic change and MB was not different between the two groups **(Table 4)**. The types of focal and diffuse spasms were similar in the two groups. The frequencies of L-ACh (76% in the i-VSA group, 19% in the t-VSA group, p<0.0001) and TOC (34% in the i-VSA group, 5% in the t-VSA group, p<0.0001) were significantly higher in the i-VSA group. Although the prevalence of multivessel spasms was higher in the i-VSA group (83% vs. 59% in the t-VSA group, p=0.0397), multivessel spasm could be assessed in 28 of 38 patients (71%) in the i-VSA group and in 76 of 117 patients (65%) in the t-VSA group. The assessment of multivessel spasms could not be performed because of a small RCA, disengagement of the catheter into the RCA, and the use of NTG because of severe spasm, and we excluded the factor of multivessel spasms from the subsequent analyses.

## Factors associated with the presence of i-VSA

Using the factors associated with the presence of i-VSA, such as the body mass index, absence of lipid disorder, duration of VSA, onset age of VSA, presence of L-ACh, and presence of TOC, the logistic regression analyses revealed that L-ACh (odds ratio [OR], 26.54, p<0.0001) and TOC (OR, 8.36, p=0.0038) were significant factors associated with the presence of i-VSA **(Table 5)**.

**Table 2** Blood chemical and echocardiographic parameters.

| Blood chemical parameters | | | |
|---|---|---|---|
| Total cholesterol (mg/dL) | 195 ± 36 | 197 ± 35 | 0.8063 |
| Triglyceride (mg/dL) | 131 ± 7 | 135 ± 12 | 0.7874 |
| HDL-cholesterol (mg/dL) | 59 ± 15 | 59 ± 17 | 0.9839 |
| LDL-cholesterol (mg/dL) | 112 ± 32 | 112 ± 32 | 0.9157 |
| Fast blood sugar (mg/dL) | 106 ± 26 | 104 ± 26 | 0.6917 |
| Hemoglobin A1C (%) | 6.0 ± 1.1 | 5.9 ± 0.6 | 0.5741 |
| C-reactive protein (mg/dL) | 0.21 ± 0.59 | 0.17 ± 0.32 | 0.7509 |
| eGFR (mL/min/1.73m2) | 69.5 ± 15.2 | 74.1 ± 16.3 | 0.3674 |
| **Echocardiographic parameters** | | | |
| LVEF (%) | 66 ± 11 | 68 ± 9 | 0.3674 |
| LV asynergy (%) | 8 (7) | 2 (5) | 0.7229 |

**Table 3** Medications at follow-up and VSA-related parameters.

| Taking medications at follow-up | | | |
|---|---|---|---|
| Numbers of coronary vasodilators | 1.3 ±1.0 | 2.3 ± 0.8 | <0.0001 |
| Calcium channel blocker (%) | 82 (70) | 33 (87) | 0.0403 |
| Beta blocker (%) | 14 (12) | 3 (8) | 0.4853 |
| Statin (%) | 37 (32) | 10 (26) | 0.4782 |
| **VSA-related parameters** | | | |
| VA (%) | 6 (5) | 5 (13) | 0.094 |
| JCSA risk score | 3.9 ± 1.7 | 4.4 ± 2.1 | 0.1687 |
| Duration of VSA (months) | 6.3 ± 7.9 | 10.7 ± 14.5 | 0.0222 |
| Age of onset of VSA (yrs) | 66 ± 10 | 62 ± 16 | 0.0407 |
| No. Anginal attacks (/month) before admission | 5.2 ± 6.8 | 5.0 ± 4.9 | 0.8913 |
| No. Anginal attacks (/month) at follow-up | 0.7 ± 1.2 | 2.9 ± 2.7 | <0.0001 |

**Table 4** Findings of coronary angiography and spasm provocation test.

| Coronary angiography | | | |
|---|---|---|---|
| Myocardial bridge (%) | 17 (15) | 9(24) | 0.2053 |
| Atherosclerotic change (%) | 34 (29) | 9(24) | 0.5022 |
| **Spasm provocation test** | | | |
| Diffuse/focal spasm | 86/31 | 29/9 | 0.1255 |
| Multi-vessels spasm (%) | 45/76 (59) | 19/27 (83) | 0.0397 |
| L-ACh (%) | 22(19) | 29(76) | <0.0001 |
| TOC (%) | 6(5) | 13(34) | <0.0001 |

# Discussion

We investigated the relationship among the clinical factors, including the findings of coronary angiography and SPT, and the presence of i-VSA, to predict i-VSA. We demonstrated that the presence of L-ACh and TOC, which were observed during the SPT, are significant factors associated with the presence of i-VSA.

It has been accepted that the prognosis of patients with VSA is relatively good with coronary vasodilators [14-16], however, there have been several residual problems related to VSA, and i-VSA is presumed to be one of them [4]. The presence of i-VSA varies from 11.4% to 42% [4-6], and in the present study, the frequency of i-VSA was 25%, which was appropriate, compared with those in the previous reports [4-6]. There are several reports investigating the clinical characteristics in patients with i-VSA [5,6], such as younger age at onset, smoking status, normotension, eNOS-786C allele, longer history of chest pain, and the presence of diffuse spasm. Among these factors, two factors, younger age at onset and longer history of chest pain, were also recognized in the univariate analyses of the present study. Other factors, such as smoking status, normotension, and diffuse spasm, were not coincident with the results of this study. The differences in patient characteristics, definition of focal/diffuse spasm, and duration and timing of follow-up may contribute to the different results. Particularly, the assessment of chest symptoms at 1-year follow-up after discharge was adopted in this study, and the assessment at longer follow-ups may cause variation in results. Despite several factors associated with i-VSA on univariate analyses, including younger age at onset and longer history of chest pain, the logistic regression analyses

**Table 5** Logistic regression analysis for the presence of i-VSA.

| Factors | Odds ratio | p value |
|---|---|---|
| Presence of L-ACh | 26.54 | <0.0001 |
| Presence of TOC | 8.36 | 0.0038 |
| Duration of VSA | 1.81 | 0.1782 |
| Body mass index | 1.06 | 0.3031 |
| Age of onset of VSA | 0.51 | 0.4731 |
| Absence of lipid disorder | 0.05 | 0.8303 |
| R2=0.3202 | | |

demonstrated only two factors: L-ACh and TOC observed during the SPT. In the present study, L-ACh and TOC were the significant factors associated with the presence of i-VSA. These two factors may imply the presence of easiness in the vasoconstriction of the epicardial coronary artery, leading to the higher activity of coronary spasm. The presence of multivessel spasms was also recognized as a factor for i-VSA; however, this finding was not obtained from all patients who underwent the SPT because of the use of an intracoronary injection of NTG during the SPT. Although we omitted it from the analyses, this finding may be one of the predictors for the presence of i-VSA.

The present study has the following clinical implications. The proposition that two or more coronary vasodilators will be needed to control the chest symptoms soon from the present examination, is important information for patients as well as doctors. Such patients can understand their disease activity, leading to the high compliance of taking coronary vasodilators. In addition, based on these findings, doctors, including the primary care doctors, can easily add another coronary vasodilator.

## Conclusion

We demonstrated that the presence of L-ACh and TOC, observed during the SPT, were factors for the presence of i-VSA, which is refractory VSA. The SPT may be an important examination, not only in making the final diagnosis of VSA but also in providing information regarding the VSA activity.

## Limitations

There were several limitations in the present study. First, this study was performed retrospectively at only one institution, and the number of patients with VSA was small. Second, the assessment of follow-up was performed 1 year after the discharge. Conversely, an assessment at a longer follow-up may be needed. Many patients were followed up by their primary care doctors and, unavoidably, such follow-up after 1 year was adopted in the present study. Third, angina attacks were assessed by only chest symptoms. However, such symptoms were not always due to myocardial ischemia and some no ischemic symptoms may be involved in the results of this study, and the frequency of i-VSA may be overestimated. Fourth, i-VSA itself may not show prognosis of VSA. Thus, the results of this study did not demonstrate any prognosis in patients with VSA.

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