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【 CASE REPORT 】

Vasospastic Angina Diagnosed by the Spasm Provocation Test with the Combined Use of the Acetylcholine and Ergonovine Provocation Tests

Mirai Matsumura[1], Chikage Oshita[2], Yuichi Fujii[2], Tomohiro Ueda[2] and Hiroki Teragawa[2]

Abstract:
The spasm provocation test (SPT) is important for diagnosing vasospastic angina (VSA), and acetylcholine (ACh) is usually used for this test in Japan. However, some patients with VSA have negative SPT results with the use of the standard ACh regimen alone. We herein report two cases in which VSA was diagnosed by the SPT with the combined use of ACh and ergonovine (EM). VSA could not be diagnosed in either case by the SPT using ACh infusions alone. For patients with negative SPT results, cardiologists should consider performing the SPT using a combination of ACh and EM.

Key words: vasospastic angina, coronary spasm, acetylcholine, ergonovine

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Introduction

Patients with vasospastic angina (VSA) present with chest pain during exertion and/or at rest; coronary spasms cause various cardiac diseases, such as acute myocardial infarction, cardiac arrest, and heart failure (1, 2). Thus, the exact diagnosis of VSA is extremely important in clinical settings.

The guidelines for coronary spasm (3) indicate that VSA can be diagnosed when patients with chest symptoms have a temporary ST deviation on an electrocardiogram (ECG). However, in clinical practice, a transient ST deviation is not always accompanied by anginal attacks. In such cases, the spasm provocation test (SPT) is usually performed to diagnose VSA. The SPT involves injecting acetylcholine (ACh) and/or ergonovine (EM) into the coronary artery to induce coronary spasm, and ACh as a provocative drug is commonly used in Japan. According to the guideline of VSA (3), the maximal ACh dose is 100 μg for the left coronary artery (LCA) and 50 μg for the right coronary artery (RCA). However, injecting ACh over the standard doses (4-6) and the combined use of ACh and EM during SPT (7, 8) can also be useful for provoking coronary spasm.

We herein report two patients with VSA who were diagnosed with the SPT using a combination of ACh and EM.

Case Reports

Case 1

A 60-year-old man presented with nausea and cold sweats once a month for 3 years. The symptoms usually persisted for 10-30 minutes and presented between 8 AM and 9 AM. He did not note any chest pain at these times. In mid-October 2015, he presented with nausea and cold sweats that lasted for 10-15 minutes and thus underwent a medical examination at our institution. His coronary risk factors were smoking (25 cigarettes per day for 38 years) and hypertension, which had not been treated.

Upon a medical examination, his height was 160 cm, weight 45 kg, and body mass index 17.6 kg/m^2. His blood pressure was 185/106 mmHg, while all other vital signs were stable, no cardiac murmur or abnormal respiratory sounds were noted, and no abnormal abdominal findings were observed. A blood examination revealed leukocytosis (12,300/μL). No significant increase in cardiac enzyme levels was noted. Chest radiography revealed a 43% cardiothoracic ratio and emphysema. An ECG revealed sinus and

[1]Department of Clinical Education, JR Hiroshima Hospital, Japan and [2]Department of Cardiovascular Medicine, JR Hiroshima Hospital, Japan
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Correspondence to Dr. Hiroki Teragawa, hiroteraga71@gmail.com

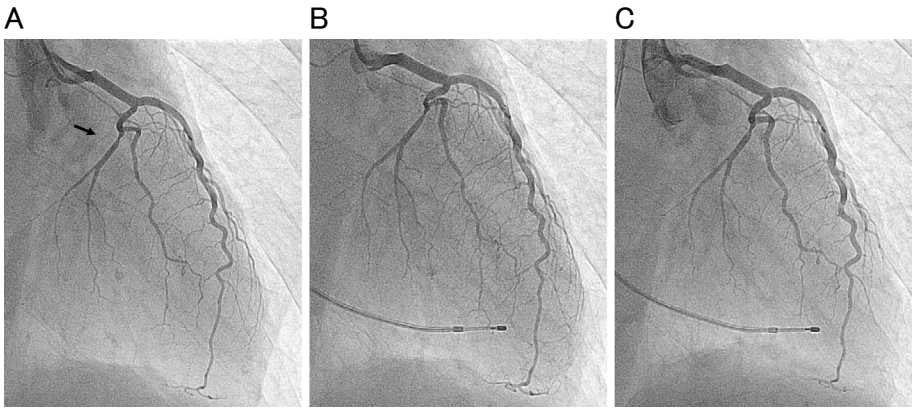

Figure 1. **Coronary angiography and the spasm provocation test in the left coronary artery in Case 1. A: Control angiography. Approximately 25% stenosis was observed in #13. B: After the injection of 200 μg of acetylcholine. C: After the administration of nitroglycerin.**

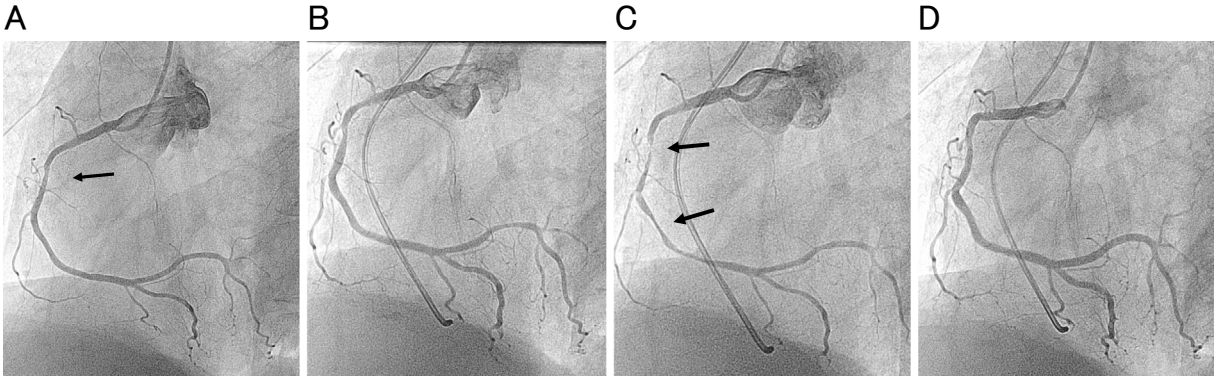

Figure 2. **Coronary angiography and the spasm provocation test in the right coronary artery in Case 1. A: Control angiography. Approximately 25% stenosis was observed in #2. B: After the injection of 80 μg of acetylcholine. C: After the injection of 50 μg of ergonovine. Spasm induced in #2 and #3. D: After the administration of nitroglycerin.**

poor progression of the R wave in V2 and V3; echocardiography showed no specific findings. He was admitted to our hospital because of suspected VSA and underwent coronary angiography (CAG).

CAG showed mild coronary stenosis at the mid-portion of the left circumflex coronary artery (LCX, Fig. 1A) and proximal portion of the RCA (Fig. 2A). First, we performed an SPT using ACh infusion. ACh was injected in incremental doses of 20, 50, 100, and 200 μg into the LCA and 20, 50, and 80 μg into the RCA, and CAG showed no significant coronary spasm in the LCA (Fig. 1B) or RCA (Fig. 2B). Second, we performed an SPT using EM infusion. When we injected 30 and 50 μg of EM into the RCA, the patient felt chest discomfort; this was accompanied by a slight ST depression from the inferior leads of the ECG. CAG showed subtotal narrowing at the proximal portion of the RCA and moderate narrowing at the mid-portion of the RCA (Fig. 2C). We then administered nitroglycerin (NTG) into the RCA, and CAG showed that the narrowing lesions in the RCA and LCA had dilated back to the initial condition (Fig. 2D and 1A, respectively).

This patient was placed on 40 mg of long-acting nifedipine per day. During his follow-up, he reported occasional chest pain when he forgot to take this medicine. We reminded him not to forget to take his medication, as this would allow him to live his daily life without experiencing chest pain, nausea, or cold sweats.

Case 2

A 30-year-old man presented with a tight feeling in his chest from night to early morning for 5 years. The symptoms occurred between once every two weeks and once a month. He visited our institution for an examination. He had been smoking three cigarettes a day for one year. Upon a medical examination, his height was 160 cm, weight 58 kg, body mass index 22.7 kg/m^2, and blood pressure 154/90 mmHg. All other vital signs were normal. No cardiac murmur or abnormal respiratory sounds were observed. No abnormal abdominal findings were noted. A blood examination revealed hyperalbuminemia (5.1 g/dL). Chest radiography, an ECG, and echocardiography showed no specific findings. He was admitted to our institution because of possible VSA and underwent CAG.

CAG showed no significant coronary stenosis

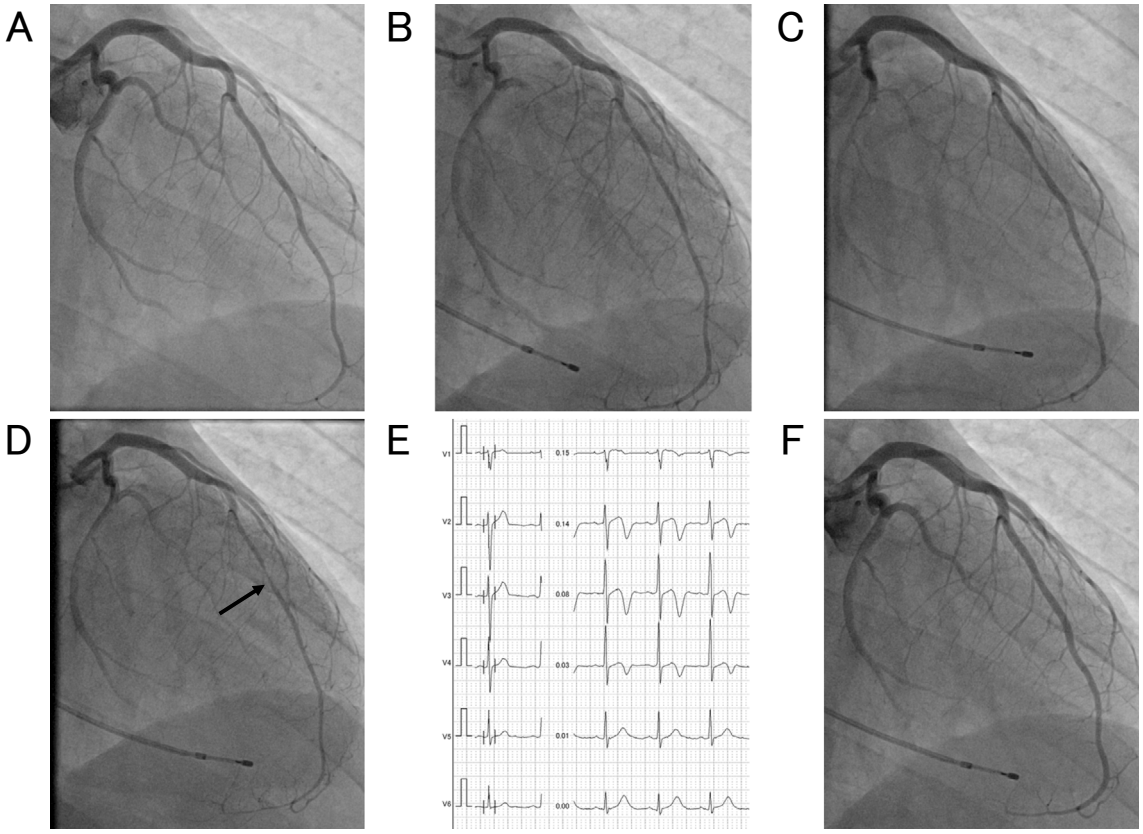

Figure 3. **Coronary angiography and the spasm provocation test in the left coronary artery in case 2. A: Control angiography. B: After the injection of 200 μg of acetylcholine. C: After the injection of 60 μg of ergonovine. D: After the injection of 200 μg of acetylcholine. E: The electrocardiogram with transient negative T waves after the injection of acetylcholine. F: After the administration of nitroglycerin.**

(Fig. 3A, 4A). First, we performed an SPT with ACh, injecting ACh at incremental doses of 20, 50, 100, and 200 μg into the LCA and 20, 50, and 80 μg into the RCA. During provocation, he experienced no symptoms, and an ECG and CAG showed no specific findings (Fig. 3B, 4B). We then performed an SPT with EM. Approximately 30 and 50 μg EM was injected into the RCA and 20, 40, and 60 μg into the LCA. However, no positive findings in response to EM were observed (Fig. 3C, 4C). Finally, we injected an additional 200 μg of ACh into the LCA following EM provocation of the LCA. He felt chest pain, the ECG showed negative T in V1-V4, and CAG showed severe narrowing at the mid-portion of the LCA (Fig. 3D and E). Upon injection of NTG, both coronary arteries were dilated (Fig. 3F, 4D).

He was diagnosed with VSA and began taking NTG tablets sublingually for the spasms because of low disease activity. He visited our institution and took sublingual NTG once every 2-3 months, which promptly improved his chest symptoms.

Discussion

We encountered two cases of VSA that were able to be diagnosed by an SPT with ACh infusion. Coronary spasm was induced by ACh followed by EM in one patient (Case 1) and by adding ACh after provocation with both ACh and EM (Case 2). Negative SPT results may have been obtained in both cases if we had performed SPT using only ACh. These experiences show the importance of using both ACh and EM for an SPT.

VSA causes chest pain on exertion and/or at rest and several kinds of cardiac disease, including acute coronary syndromes and ischemic cardiac arrest (1, 2, 9-11). Thus, it is desirable to diagnose and treat patients with VSA (12). VSA can be diagnosed based on ischemic ECG changes during chest pain. However, patients with VSA sometimes do not present with any documented ECG changes during anginal attacks in clinical settings. Therefore, SPTs are usually performed to accurately diagnose VSA. We aggressively perform SPTs because we can obtain not only diagnostic information but also disease activity in this way (13).

The provocative drugs frequently used for SPT are ACh and EM, and these drugs should be used depending on the institution and doctors' experience. However, facilities in Japan usually use ACh alone for SPT (14). According to the guidelines for coronary spasm (14), ACh is injected in doses of 20, 50, and 100 μg into the LCA and 20 and 50 μg into the RCA, and CAG is performed after each injection of the provocative drug. Conversely, approximately 20-60 μg of EM is injected into the LCA and RCA. Of note, unlike an

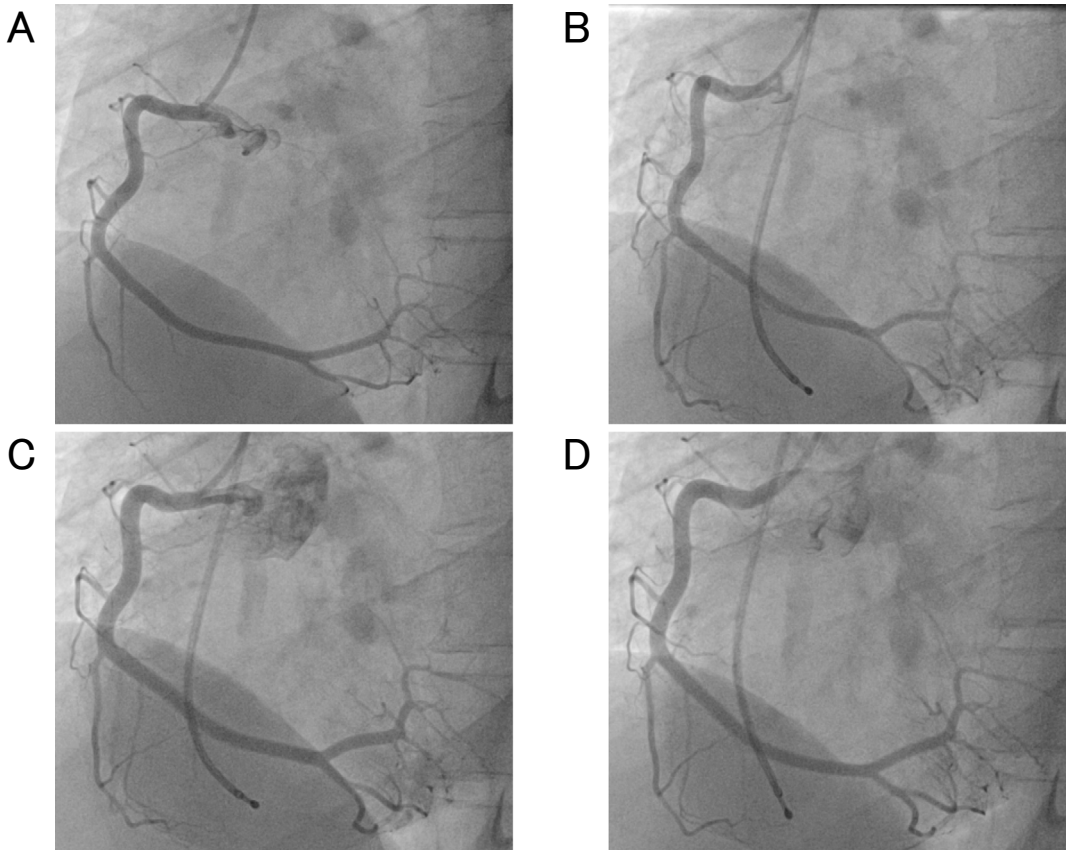

Figure 4. Coronary angiography and the spasm provocation test in the right coronary artery in Case 2. A: Control angiography. B: After the injection of 80 μg of acetylcholine. C: After the injection of 50 μg of ergonovine. D: After the administration of nitroglycerin.

SPT with ACh infusions, the exact numerical dose of EM has not yet been defined (15).

The doses for ACh infusions described in the guidelines are based on the diagnosis of variant angina (16), which has been proposed as a type of VSA that exhibits the highest activity of all VSA (17). Thus, some patients with VSA present with negative spasms under the standard maximal dose of ACh (18). When the SPT using only standard ACh doses was negative, various other attempts have been reported to be performed. It may be useful to add EM after increasing the ACh dose (maximal dose: LCA, 200 μg; RCA, 80 μg) (4-6) or to perform ACh after infusion with both ACh and EM (7, 8, 19). If the standard doses stated in the guidelines were determined according to the results of SPT for variant angina, which exhibits a high activity, the adoption of higher doses of ACh (200 μg for LCA and 80 μg for RCA) for VSA with normal or decreased activity makes sense and should be attempted first in cases of negative SPT using standard doses of ACh. If an SPT with higher ACh infusions (up to 200 μg for LCA and 80 μg for RCA) shows negative results, as seen in some cases, an SPT with the combined use of ACh and EM may provide diagnostic information because of the difference in the acting receptors between ACh and EM. The combination of ACh and EM has two steps: 1) EM provocation when it is negative, based on the ACh test, and 2) adding the maximal ACh infusion again after the first ACh and second EM tests. These methods have been called "sequential methods" by Sueda et al., who reported that these approaches did not increase the risk of SPT-related complications (8).

In the two cases reported here, coronary spasm could not be provoked at the standard doses of ACh, as described in the guidelines. Therefore, we injected ACh at the maximal doses of 200 μg into the LCA and 80 μg into the RCA. However, the SPT showed negative findings in each case. In Case 1, we injected EM after ACh, and positive findings at the proximal and mid-portion of the RCA were observed. In Case 2, we added an ACh dose of 200 μg after the first ACh and second EM infusions, and coronary spasm was induced at the mid-portion of the LAD. In other words, coronary spasm was not induced following the SPT with ACh infusion only, in either case, whereas the SPT with the combined use of the two drugs was able to elicit a reaction that resulted in the diagnosis of VSA, allowing us to begin treatment for VSA. Many papers have reported such aggressive SPTs (4-8), although these methods have not yet been widely accepted as routine approaches. The accumulation of evidence concerning the usefulness of these aggressive SPTs from many institutions and areas is important if this approach is to be widely accepted; to this end, we have presented two cases to demonstrate the effectiveness of these aggressive SPTs. However, careful attention should be paid

to the possibility of false positive results using an aggressive SPT with a combination of ACh and EM. In the present cases, it was not false positive to diagnose them as VSA using such an aggressive SPT, because chest pain occurred repeatedly in one patient who forgot to take his medicine (Case 1), and taking sublingual nitroglycerin promptly improved chest symptoms in another patient (Case 2).

A positive finding for coronary spasm based on SPT is related to the disease activity of VSA, medication before admission, time of examination, and a patient's stress level. Neither of these two patients was taking any coronary dilators. We had to perform SPTs in the afternoon because we could not perform them in the morning due to an insufficient number of staff members at our institution. In addition, physiological saline at 37℃ was not used to dissolve ACh, as recommended in the guidelines (3). These factors might also have influenced our results. Furthermore, it is challenging to provoke spasm by an SPT using a single drug in patients with VSA (20). In Case 2, the patient was younger than 40 years old. Younger individuals have fewer coronary risk factors and less coronary endothelial dysfunction than elderly individuals. For young individuals with suspected VSA, it may be necessary to consider performing an SPT using two drugs or in a sequential method, as in this study.

Conclusion

In this study, two patients with VSA were diagnosed by an SPT with the combined use of ACh and EM but not ACh infusion alone. Coronary spasm may not be induced by SPT with ACh infusions only; as such, an SPT using only ACh may not lead to a definite diagnosis. Thus, an SPT with the combined use of ACh and EM is important in clinical settings, and cardiologists should consider performing SPT using a combination of these two drugs, particularly in patients with low-activity VSA.

The authors state that they have no Conflict of Interest (COI).

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