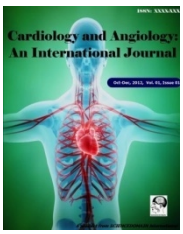

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Suspected Microvascular Coronary Spasm Diagnosed by Spasm Provocation Test with High Dose of Acetylcholine

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Authors' contributions

This work was carried out in collaboration between two authors. Two authors performed patient care together. Author SI wrote the first draft of the manuscript. Author TM read and approved the final manuscript.

Case Study

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ABSTRACT

A 71-year-old Japanese man was admitted to our hospital complaining of chest oppression on exercise, such as cycling uphill, which had continued for 9 years. We diagnosed him as having microvascular spasm according to the results of coronary angiography with an acetylcholine provocation test with a high dose (150μg) of acetylcholine administrated at a time during 20 seconds. Electrocardiographic changes during the spasm provocation test resembled that during exercise tests performed upon admission and 9 years previously. He was treated with a calcium channel blocker and partial symptom relief was obtained.

Keywords: Coronary vasospasm; microvascular dysfunction; cardiac syndrome X; acetylcholine; exercise.

1. INTRODUCTION

The acetylcholine (ACh) provocation test is useful for diagnosing coronary spasm including microvascular spasm, however, the appropriate dose has not yet been established. We present here a Japanese patient with a microvascular spasm who was diagnosed using a dose of ACh exceeding that recommended in the Japanese guideline.

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2. CASE

A 71-year-old man was admitted to our hospital in July 2013 complaining of chest oppression on strong effort, such as cycling uphill, which had continued for 9 years. Based on the results of the Master two-step test, he had undergone coronary angiography about 6 years earlier in May 2007 due to similar chest oppression on effort, however, no significant coronary stenosis was observed. A spasm provocation test was not performed at that time. No treatment was undertaken. Although the symptom had persisted, he was able to endure it until further worsening. On this presentation, the Master two-step test revealed ST level depression in leads V4-6 after exercise (Fig. 1). Left ventriculography showed no abnormal wall motion with a left ventricular ejection fraction of 78%. This result was quite similar to that obtained 6 years previously. Laboratory data values were within normal limits, with the exception of high total cholesterol (261 mg/dl). He had no other coronary risk factors. Thus, we recommended he undergo coronary angiography due to suspected coronary atherosclerosis and vasospastic angina pectoris. There was no significant coronary atherosclerotic stenosis and an acetylcholine (ACh) provocation test was performed. Usual doses of ACh (20μg followed by 50μg for the right coronary artery (RCA) and 50μg followed by 100μg for the left coronary artery (LCA)) showed negative results, however, 150μg for the LCA resulted in ST depression in leads V3-6 (Fig. 2) in association with severe chest oppression, which was quite similar to that during cycling but without any coronary arterial vasoconstriction or spasm (Fig. 3). Each dose was administrated at a time during 20 seconds. Intracoronary isosorbide dinitrate (ISDN) relieved the ST segment depression and symptom. ACh administration was performed according to a Japanese Circulation Society guideline [1]. Based on these results, we diagnosed him as having microvascular angina pectoris due to microvascular spasm. Benidipine hydrochloride 8mg per day was administered. Although the symptom could not be completely relieved, cycling uphill did become possible.

3. DISCUSSION

In this case report, we have described the importance of the appropriate dose (150μg) of acetylcholine in the diagnosis of microvascular spasm. We have also described that cardiac syndrome X, which is characterized by angina, a positive exercise test, and normal coronary angiogram, is an important clinical entity that should be differentiated from classic ischemic heart disease caused by coronary artery disease and should not be overlooked. Although the causes of this syndrome have not been conclusively defined, microvascular dysfunction and myocardial metabolic abnormalities have been implicated [2]. True myocardial ischemia, reflected in the production of lactate by the myocardium during exercise or pacing, has been observed in some of these patients; however, others have shown no metabolic evidence for ischemia as the cause of their discomfort. We have demonstrated the importance of the appropriate dose of ACh (150μg) at a time during 20 seconds for revealing the underlying endothelial dysfunction and microvascular spasm.

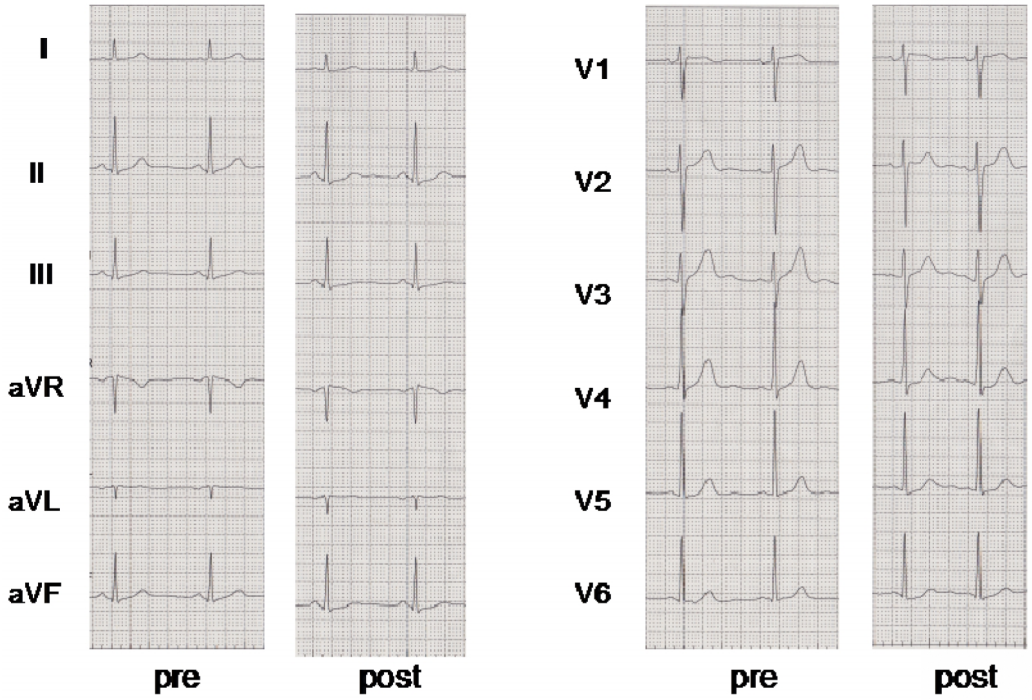

Fig. 1. Master two-step test on this presentation in July, 2013
The master two-step test showed ST level depression in leads V4-6 after exercise

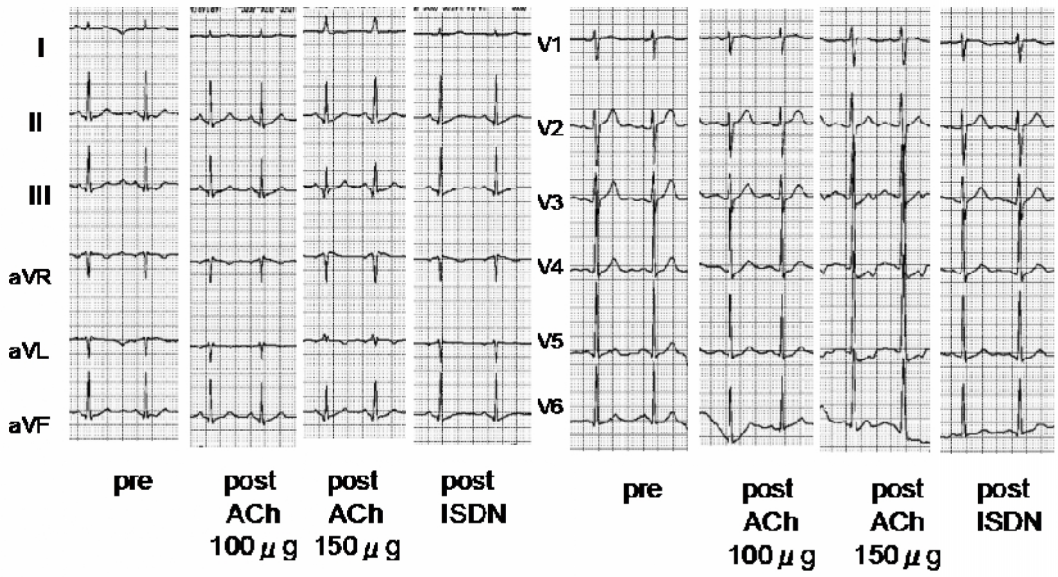

Fig. 2. Electrocardiographic changes during acetylcholine provocation test
usual doses of ACh (50μg for the right coronary artery and 100μg for the left coronary artery) showed negative results, however, 150μg for the left coronary artery resulted in severe chest oppression in association with ST depression in leads V3-6

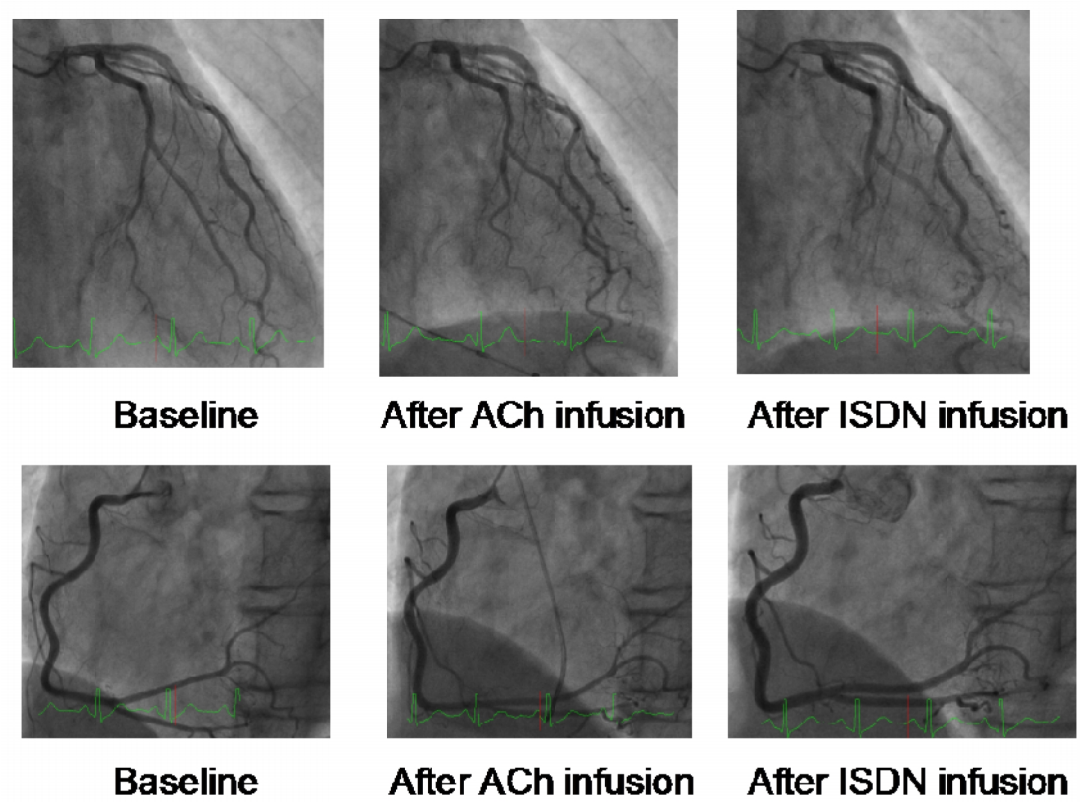

Fig. 3. Coronary angiograms during acetylcholine provocation test
There was no coronary arterial vasoconstriction after acetylcholine provocation even using 150μg for the left coronary artery. Upper panel shows ACh provocation test for the left coronary artery and lower panel for the right coronary artery

In this case, we diagnosed the patient as having microvascular spasm based on the results of the ACh provocation test. Although transcardiac lactate could not be measured, ST depression during provocation was observed. Electrocardiographic changes recorded during the provocation tests and exercise test resembled each other. Furthermore, similar ST depression after exercise could be observed in Master two-step test performed 6 years ago. Thus, we speculated that exercise may have induced microvascular dysfunction due to spasm. Although microvascular spasm is not a rare clinical entity, it can be easily overlooked, like in this case. If we had stopped the test with only the usual dose of ACh as recommended in the Japanese guideline [1], a diagnosis would not have been made. Thus, in patients who are strongly suspected of having microvascular spasm, a dose of ACh higher than the usual one could be an important option to try. Even in patients with "epicardial" coronary spasm, in Japan there is some debate about the maximum dose of ACh to provoke coronary spasm. Although the Japanese Circulation Society guideline recommends a maximal dose of 100μg for the left coronary artery, in a report by Ong et al. incremental ACh doses of 2, 20, 100, and 200μg were used to induce coronary spasm [3] without any adverse effects. Thus, we used 150μg before 200μg taking into consideration the physical differences between Japanese and caucasian patients.

For the definition of microvascular spasm, we used the criteria established by Mohri et al. [4]. Hence, in this case, we diagnosed microvascular spasm when the injection of ACh reproduced the symptoms usually experienced by the patient and triggered ischemic ECG changes (i.e., ST-segment depression or ST-segment elevation of ≧0.1mV or T-wave peaking in at least 2 contiguous leads), in the absence of epicardial spasm (≧75% diameter reduction). It is known that calcium channel blockers are not as effective as they are in coronary vasospastic angina but should be used as a first line drug. Matsumoto et al. reported that the angina status was improved in only 16 of 33 patients treated with calcium channel blockers alone among patients with microvascular spasm [5]. In contrast, it was improved in 18 of 21 patients treated with the combination of calcium channel blockers and angiotensin converting enzyme inhibitors ($P<0.05$). Other potential drugs for microvascular spasm include nicorandil and rho kinase inhibitors. However, the studies were only performed in small populations and have not provided any concrete evidence. In this patient, benidipine was fortunately effective and decreased the symptom. No other drugs have been administered thus far. We were unable to ascertain whether this patient had microvascular spasm based on the Master step test alone. However, in patients who are strongly suspected of having coronary spasm or microvascular spasm, empiric medical therapy with calcium channel blockers, as recommended in Japanese guidelines, could be also a reasonable solution than performing coronary angiography and using higher doses of ACh. The reasons why we performed invasive aangiography in this case are as follows.

The coronary atherosclerotic stenosis might have developed during the 6 years following the previous coronary angiography. Despite the high probability of coronary spasm, we wanted to evaluate the severity of coronary spasm (total occlusion or multivessel spasm or microvascular spasm) by ACh provocation test in order to determine the treatment strategy and evaluate the prognosis.

4. CONCLUSION

In this case report, we have described the importance of the appropriate dose (150μg at a time during 20 seconds) of acetylcholine in the diagnosis of microvascular spasm.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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