Decreased coronary blood flow velocity in two patients with coronary microvascular spasm: case series†

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Introduction
Diagnostic criteria for coronary microvascular spasm (CMS) have not yet been fully established.

Case presentation
We present two cases of CMS in which decreased coronary blood flow velocities were observed during acetylcholine (ACH) provocation tests. The first patient suffered from chest pain occurring while at rest. The patient underwent coronary angiography (CAG), which revealed a decrease in the average peak velocity (APV) from 29 cm/s to 14 cm/s and a slow flow phenomenon following ACH injection. The second patient suffered from chest pain occurring during the night. The patient underwent CAG, which revealed a decrease in the APV from 17 cm/s to 7 cm/s with no significant epicardial coronary artery spasm following ACH injection. Both patients complained of chest pain, and electrocardiogram changes were observed in leads equivalent to the distal area of the vessel during an ACH provocation test. These findings were consistent with CMS, and their conditions improved under medical treatment.

Discussion
A transient decrease in coronary blood flow velocity following ACH administration might be a phenomenon specific to CMS. These cases may provide some insight into the underlying pathophysiology of CMS.

Keywords
Microvascular spasm • Angina pectoris • Doppler guidewire • Coronary blood flow • Acetylcholine • Case series

Learning points
• In clinical practice, coronary microvascular spasm (CMS) is often overlooked because diagnostic criteria for the disease have not yet been fully established.
• A transient decrease in coronary blood flow velocity following the intracoronary administration of acetylcholine (ACH) might be a phenomenon specific to CMS.
• Electrocardiogram changes observed in leads equivalent to the distal area of the vessel following the intracoronary administration of ACH might be a phenomenon specific to CMS.

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Introduction

Coronary microvascular spasm (CMS) is still not widely recognized despite it being nearly 20 years since the disease was first described in 1998. In this report, we present two cases of CMS, highlighting the alterations in coronary blood flow velocity (CBFV) observed during an acetylcholine (ACH) provocation test to clarify the underlying pathophysiology of this entity.

Timeline

| Time                        | Events                                                                                                                                 |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Case 1                      | Four years prior to admission<br>Four years prior to admission<br>Two months prior to admission<br>One day after admission | Medical history of dyslipidaemia (no medication)<br>Patient was suffering from chest pain occurring while at rest<br>99mTc-tetrofosmin myocardial single photon emission computed tomography showed normal results<br>Patient underwent coronary angiography (CAG)<br>• No obstruction<br>• Slow flow phenomenon after acetylcholine (ACH) injection<br>• Decreased coronary blood flow velocity (CBFV) from 29 cm/s to 14 cm/s after ACH injection |
| Case 2                      | Seven years prior to admission<br>Two years prior to admission<br>One day after admission | Medical history of dyslipidaemia (pravastatin: 5 mg/day)<br>Patient was suffering from chest pain occurring during the night<br>Patient underwent CAG<br>• No obstruction<br>• No significant epicardial coronary artery spasm after ACH injection<br>• Decreased CBFV from 17 cm/s to 7 cm/s after ACH injection |

Case 1

A 62-year-old woman was referred to our hospital suffering from chest pain occurring while at rest. She had been diagnosed with dyslipidaemia 4 years prior to visiting our hospital, but she had no history of medical treatment for any condition including dyslipidaemia. Her physical examinations were normal, and initial laboratory tests produced normal results, with the exception of a high low-density lipoprotein cholesterol level of 146 mg/dL (normal value <140 mg/dL). Although an electrocardiogram (ECG) and 99mTc-tetrofosmin myocardial single photon emission computed tomography showed normal results, she was admitted to our hospital with suspected vasospastic angina. She underwent a coronary angiography (CAG), which revealed no apparent epicardial coronary artery obstruction; an ACH provocation test was subsequently performed to the left coronary artery to assess coronary vasoconstriction. During the test, the patient reported the same chest pain that she had experienced previously, and an ECG showed ST-segment elevation in leads V2 to V6 (Figure 1). CAG performed at this time did not demonstrate an epicardial coronary artery spasm, but a slow flow phenomenon was observed in the left anterior descending (LAD) coronary artery; this phenomenon improved after the injection of nitroglycerin (see Supplementary material online, Videos S1 and S2). The CBFV as measured using a Doppler guidewire (Combowire); Philips Volcano, CA, USA) inserted into the LAD revealed a decrease in the average peak velocity (APV) from 29 cm/s to 14 cm/s within 60 s of the ACH injection (see Supplementary material online, Video S3).

These findings were consistent with CMS. Diltiazem (200 mg/day) was prescribed to relieve the microvascular constriction but failed to improve her symptoms sufficiently. The treatment was supplemented with nicorandil (10 mg/day). Her condition improved and was good at the follow-up examination 2 years after discharge.

Case 2

A 62-year-old woman was referred to our hospital suffering from chest pain occurring during the night. She had been taking pravastatin (5 mg/day) for dyslipidaemia for 7 years; however, she had no other history of medical treatment. Initial laboratory tests produced normal results, and her physical examinations were also normal. She underwent CAG, which revealed no signs of atherosclerosis; an ACH provocation test was subsequently performed to identify vasospastic angina. After the administration of ACH into the left coronary artery, the patient complained of chest pain, and an ECG showed ST-segment elevation in leads V3 to V6 (Figure 2). CAG performed at this time revealed epicardial narrowing near the distal end of the LAD, but the reduction in diameter was 42%, which did not indicate significant constriction (see Supplementary material online, Videos S4 and S5). The CBFV as measured using a Doppler guidewire inserted into the LAD showed a decrease in the APV from 17 cm/s to 7 cm/s within 60 s of the ACH injection (see Supplementary material online, Video S6).

These findings were also consistent with CMS. Diltiazem (200 mg/day) was prescribed, and her condition improved and was good at the follow-up examination one year after discharge.

Discussion

Increasing attention has been given to decreased coronary flow reserve, which is one aspect of coronary microvascular dysfunction, because it frequently develops into cardiovascular events such as...
cardiac death, myocardial infarction, stroke, and congestive heart failure. However, CMS, which is known as another aspect of coronary microvascular dysfunction, is often overlooked because diagnostic criteria for the disease have not yet been fully established. In this case report, we measured CBFV during the ACH provocation test to evaluate coronary microvascular abnormalities for symptomatic women with unobstructed coronary arteries. To the best of our knowledge, this is the first report to describe decreased CBFV in response to ACH as a potential indicator of CMS. In patients with normal endothelial-dependent microvascular function, CBFV increases after ACH injection. Wei et al. conducted invasive coronary reactivity testing among 220 symptomatic women with evidence of myocardial ischaemia and unobstructed coronary arteries to evaluate microvascular dysfunction. In their study, they defined a less than 50% increase in CBFV in response to ACH as endothelial-dependent microvascular dysfunction and reported that this condition was present in 51% of the patients. Sara et al. also investigated the prevalence of coronary microvascular abnormalities among 1439 patients presenting with chest pain and unobstructed coronary arteries. Using the same criteria as Wei et al., they reported that endothelial-dependent microvascular dysfunction was present in

![Figure 1](image1.png)

**Figure 1** (A) An electrocardiogram showed normal results at baseline. (B) An electrocardiogram showed ST-segment elevation in leads V2 to V6 following the injection of acetylcholine into the left coronary artery.

![Figure 2](image2.png)

**Figure 2** (A) An electrocardiogram showed normal results at baseline. (B) An electrocardiogram showed ST-segment elevation in leads V3 to V6 following the injection of acetylcholine into the left coronary artery.
52% of the patients.7 Confirming these reports, since CMS is likely to develop as a result of the progression of endothelial-dependent microvascular dysfunction, the findings in the cases of this study suggest that a transient decrease in CBFV following ACH administration might be a phenomenon specific to CMS.

Yamamoto et al.8 described two types of CBFV patterns in Thrombolysis In Myocardial Infarction flow grade 2 (TIMI-2 flow) in patients with acute myocardial infarction: (i) systolic flow reversal followed by forward diastolic flow with a rapid deceleration, implying a lack of tissue perfusion because of capillary damage and (ii) slow forward systolic and diastolic flow, implying an increase in coronary arterial resistance because of an increased thrombus burden. They reported that intracoronary thrombus was frequently observed in patients with the second flow pattern and suggested that coronary arterial resistance might be increased by a massive distal embolism in such cases. The decreased CBFV observed in our cases resembled this second flow pattern. The coronary microvascular resistance, calculated as the mean distal coronary artery pressure divided by the coronary microvascular resistance following ACH administration, which is theoretically quite consistent with the mechanism that Yamamoto et al. described in patients with the second flow pattern.

Case 2 exhibited epicardial constriction during the ACH provocation test. Even though the degree of constriction was not significant and TIMI-3 flow was maintained, whether the decreased CBFV in this case was caused by epicardial spasm seems open for discussion. In a recent study, Yamanaga et al.11 measured the APV during the ACH provocation test in 29 patients with significant epicardial constriction (reduction in diameter >90%) and found that the mean APV increased from 25.0 cm/s to 47.2 cm/s following ACH injection. This finding that an increase in CBFV following ACH administration is possible even when severe epicardial constriction is present suggests that the alterations in CBFV observed during the ACH provocation test may be more dependent on microvascular function. In addition, from our own experience, patients with epicardial spasm without CMS show coronary haemodynamic changes following ACH administration, such as an increased APV followed by an epicardial coronary artery pressure gradient. Therefore, we believe that CMS was a more likely cause of the decreased CBFV following ACH administration in Case 2 of this study. Furthermore, a decreased CBFV in response to ACH, which might be specific to CMS, can be observed not only in patients exhibiting a slow flow phenomenon, but also in those exhibiting TIMI-3 flow.

Additionally, an evaluation of the ECG changes that occurred during the ACH provocation test in these cases is likely to be important in understanding the pathophysiology of CMS. Case 1 showed ST-segment elevation in leads V2 to V6 and Case 2 showed ST-segment elevation in leads V3 to V6. Although ST-segment depression is considered to be a common ECG change observed in CMS,13 ST-segment elevation, which indicates a more severe condition and might arise as a result of transmural myocardial ischaemia, might also be observable in this disease. Another important observation of these ECG changes is that the leads in which the changes developed are equivalent to the distal area of the LAD. This finding can be explained by the hypothesis that the coronary microvasculature exhibits a denser distribution in apical areas than in basal areas. Moreover, this hypothesis is also supported by the recent discussion that Takotsubo cardiomyopathy (TC), which demonstrates a unique abnormal apical and midventricular wall motion, might be a form of microvascular acute coronary syndrome.13 Several researchers have reported impaired coronary microcirculation during the acute phases of TC, which normally improves naturally within a relatively short period of time.14–16 A case of TC that developed 3 weeks after a diagnosis of CMS had also been reported.15 Even though CBFV measurement using a Doppler guidewire is relatively safe and is associated with a low rate of adverse events during testing,6 it would be useful for patients with chest pain and unobstructed coronary arteries if a diagnosis of CMS could be made using less invasive modalities. Further studies to determine whether ECG changes observed in the distal area of the vessel during the ACH provocation test are specific to CMS are needed.

CMS is often difficult to diagnose because coronary microcirculation cannot be observed using angiography. The findings described in these cases, such as the alterations in CBFV, ECG, and microvascular resistance, may provide insight into the underlying pathophysiology of this entity.

**Conclusion**

In contrast to an increase in CBFV, which is the normal response to ACH, a transient decrease after ACH administration might be a phenomenon specific to CMS. Further consideration should be given to the assessment of CMS, and further research is needed to establish criteria for the efficient diagnosis of this entity.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.

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**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

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