A 77-year-old white woman was referred for diagnostic coronary angiography after a 6-month history of exertional breathlessness and back pain. Her cardiovascular risk factors were hypercholesterolemia (low-density lipoprotein, 153 mg/dL) and a positive family history for cardiovascular disease (father died at 73 years of age because of a peripheral artery occlusive disease event). Furthermore, the patient was overweight (body mass index, 28.8 kg/m²). Exercise ECG stress testing had to be stopped after 75 W as a result of limiting symptoms (breathlessness) but without ST-segment depression.

Diagnostic coronary angiography revealed a 50% plaque in the distal circumflex coronary artery and diffuse minor irregularities in the remaining epicardial vessels (Figure 1). However, there was no flow-limiting epicardial stenosis. Left ventricular angiography showed normal left ventricular function without any wall motion abnormalities at rest, although left ventricular end-diastolic pressure was elevated at 25 mm Hg. To further investigate the cause of the patient’s symptoms, intracoronary acetylcholine (ACH) provocation testing was performed, together with simultaneous transthoracic myocardial contrast echocardiography (MCE), according to standardized protocols.1 During the ACH test, at the beginning of the 100-μg ACH injection into the left coronary artery, the patient started to experience shortness of breath. At this stage, MCE revealed subendocardial perfusion defects in the septum and the apex. After the 200-μg ACH dose, the patient had full reproduction of her usual symptoms, including back pain that had always been suspected to have a vertebral origin. Twelve-lead ECG showed ST-segment depression in leads V₄ through V₆, but no significant epicardial vasoconstriction was seen (Figure 2).

Subsequently, and in keeping with the ischemic cascade in
which perfusion abnormalities precede wall motion abnormalities, MCE at 200 μg ACH showed severe hypokinesia of the septum and apex (Figure 3 and Data Supplement Movies I–III). After intracoronary nitroglycerine injection, the pathological findings quickly reverted to normal.

In this case, we demonstrate for the first time myocardial hypoperfusion and hypokinesia, indicative of myocardial ischemia, in a patient with ACH-induced coronary microvascular dysfunction. Recently, we showed that patients with angina pectoris and angiographically unobstructed coronary arteries...
arteries often have microvascular coronary spasm/dysfunction during intracoronary ACH provocation testing. It is, however, unclear whether such a finding, despite reproduction of symptoms and ischemic ECG shifts during the ACH test, corresponds to myocardial ischemia. Currently, the coronary microcirculation cannot be visualized in vivo. Measurement of lactate extraction from the coronary sinus can be indicative of myocardial ischemia but is technically challenging. MCE has been shown to reliably detect perfusion defects and wall motion abnormalities at stress compared with baseline. However, to the best of our knowledge, an MCE examination has never been performed during intracoronary ACH testing. A strength of MCE is the portability of the technique, although future studies should assess whether noninvasive tools for provocation of microvascular spasm (eg, hyperventilation, cold pressor test) may be more practically suitable for simultaneous performance of MCE.

Our findings indicate that patients with microvascular dysfunction can develop not only ischemic ECG shifts and reproduction of symptoms during provocative testing with ACH but also more objective signs of myocardial ischemia such as hypoperfusion and hypokinesia during MCE. Thus, such patients truly belong to the group of patients with ischemic heart disease. Proof of wall motion abnormality in such patients may justify more intense initial pharmacotherapy (eg, with calcium channel antagonists, nitrates, ranolazine, and nicorandil) and closer follow-up because these patients may be at a higher risk for future cardiovascular events.

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**References**


**Key Words:** acetylcholine ▪ ischemic heart disease ▪ microvascular dysfunction ▪ myocardial contrast echocardiography
SUPPLEMENTARY MATERIAL

Legends for Online Supplementary Video Files

**Video 1.** Resting apical 4-chamber view showing normal wall motion and perfusion.

**Video 2.** 4-chamber view after 100µg intracoronary acetylcholine showing hypoperfusion in the septal and apical segments.

**Video 3.** 4-chamber view after 200µg intracoronary acetylcholine now showing a dilated cavity with wall motion abnormality in the apical segments.