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Non-Invasive Evaluation of Coronary Vasospasm Using a Combined Hyperventilation and Cold-Pressure-Test Perfusion CMR Protocol

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ABSTRACT

Coronary vasospasm is a severe vasoconstriction of an epicardial coronary artery, which may lead to myocardial ischemia and cause symptoms of angina. The gold-standard for diagnosing coronary vasospasm is to perform an intracoronary provocation test and to demonstrate the epicardial vasoconstriction by coronary angiography. We report the case of a patient with coronary vasospasm in whom we succeeded to non-invasively provoke and subsequently non-invasively demonstrate myocardial ischemia by perfusion cardiovascular magnetic resonance (CMR).

INTRODUCTION

In patients presenting with unstable anginal symptoms, clinical work-up has to consider coronary artery disease (CAD), myocarditis (1), or coronary vasospasm (2) (apart from others) as possible underlying diagnoses. The clinical presentation of myocarditis comprises a wide range of symptoms including patients with angina pectoris or even acute myocardial infarction (3). CMR has been established as a routine tool for myocarditis work-up in the last years (4).

Coronary vasospasm is a severe vasoconstrictive response of an epicardial coronary artery with evidence of myocardial ischemia in response to various stimuli (5). It is involved in the pathogenesis of Prinzmetal's angina, acute myocardial infarction, and even sudden cardiac death (6). However, the precise cellular and molecular mechanisms of coronary vasospasm are still unknown (7). Previously, myocardial scintigraphy has been studied in order to non-invasively detect coronary vasospasm (8, 9). However, apart from using ionizing radiation, the disadvantages of scintigraphic techniques include limited functional evaluation and in-plane-resolution, respectively. By contrast, CMR offers the unique possibility of performing high-resolution functional studies without radiation exposure. Therefore, we explored methods of non-invasively provoking coronary vasospasm and detecting subsequent myocardial ischemia with perfusion CMR.

Here, we report a case of a patient with severe coronary vasospasm of the left anterior descending artery (LAD) who underwent cardiac catheterization in addition to comprehensive CMR analysis.

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CASE REPORT

A 37-year-old Caucasian male patient was admitted with acute chest pain and ST elevation in the ECG (Fig. 1). He was a current smoker (20 pack-years), and during the weeks prior to admission, he had already experienced several episodes of chest discomfort at work and at rest. The current episode of chest pain, which forced him to seek medical attention started a few hours before admission.

At immediate cardiac catheterization, ventriculography revealed a segmental wall motion abnormality of the mid-ventricular anterior wall (Fig. 2, full motion images can be viewed at http://217.160.89.38/rbk.de/yilmaz/images/). However, despite ST elevation, a troponin of 1.48μg/L (normal $<0.1\mu$g/L), and the presence of a wall motion abnormality, the coronary arteries showed no culprit lesion or ruptured plaque (Fig. 3, full motion images can be viewed at http://217.160.89.38/rbk.de/yilmaz/images/). There were diffuse, non-significant luminal irregularities without calcifications, and the diagnosis of diffuse coronary atheromatosis was made.

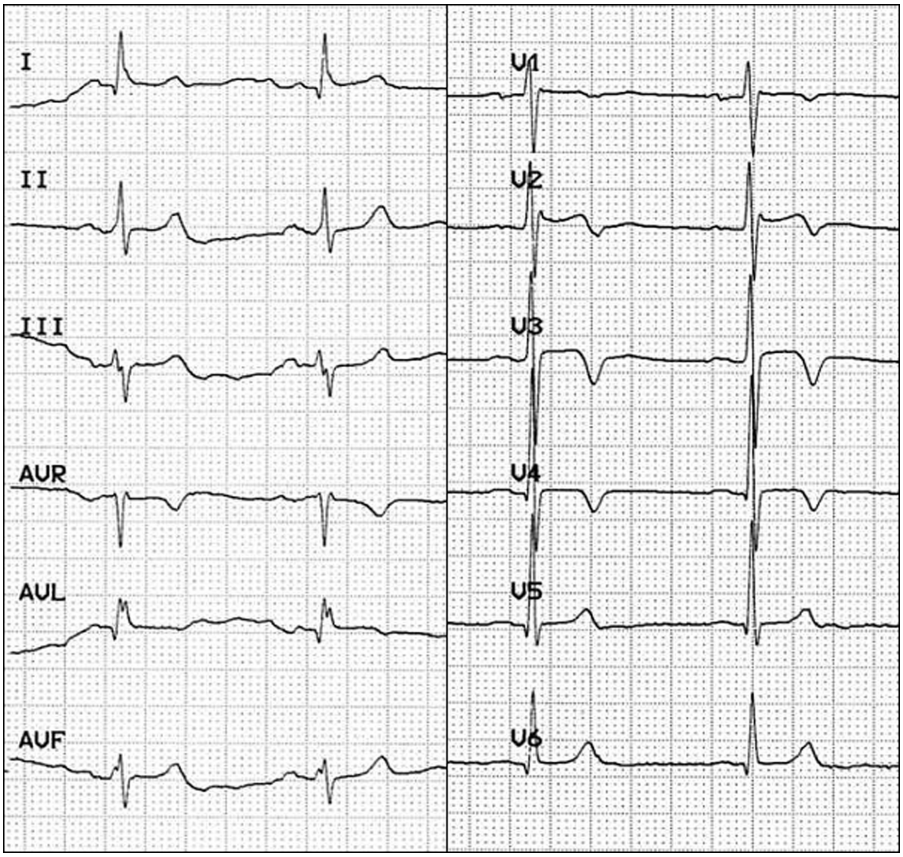

Figure 1. Resting ECG recorded on admission showing ST-segment elevation in leads V2 and V3 with concomitant negative T-waves in leads V1-V5.

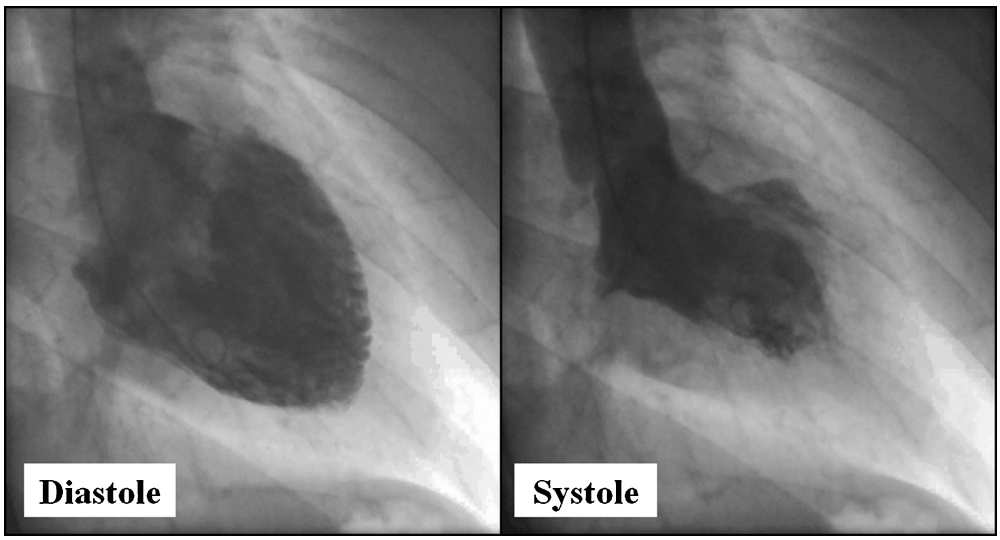

Figure 2. Ventriculography demonstrating a segmental hypokinesia in the midventricular anterior wall.

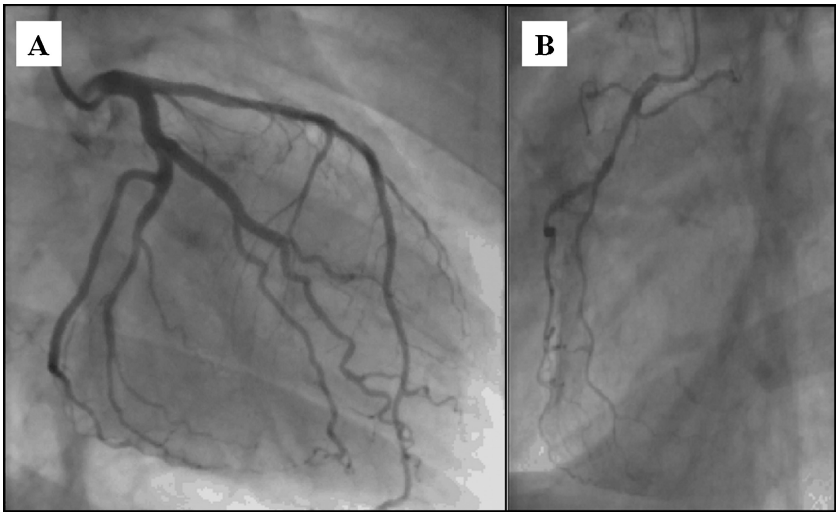

Figure 3. Panel A, Baseline coronary angiogram of the LCA demonstrating some luminal irregularities but no significant coronary artery disease. **Panel B**, Baseline coronary angiogram of the RCA demonstrating some luminal irregularities but again no significant coronary artery disease.

On the following day, after the patients symptoms had subsided, a repeated ECG demonstrated ST-segment normalization together with increased deep T-waves (Fig. 4). He underwent CMR to exclude myocarditis as the cause of his symptoms. CMR was performed using a 1.5T Magnetom Sonata (Siemens Medical Solutions, Erlangen, Germany) after obtaining written informed consent. Cine images revealed that the wall motion abnormality demonstrated by angiography one day earlier had nearly resolved (Fig. 5, A-B). Contrast and T2-weighted CMR could not detect any signs of myocarditis (Fig. 5C, full motion images can be viewed at http://217.160.89.38/rbk.de/yilmaz/images/).

In order to find out whether the patient's symptoms were caused by coronary artery vasospasm, we performed the following combined hyperventilation and cold-pressure test perfusion CMR protocol; fifteen minutes after a normal resting perfusion

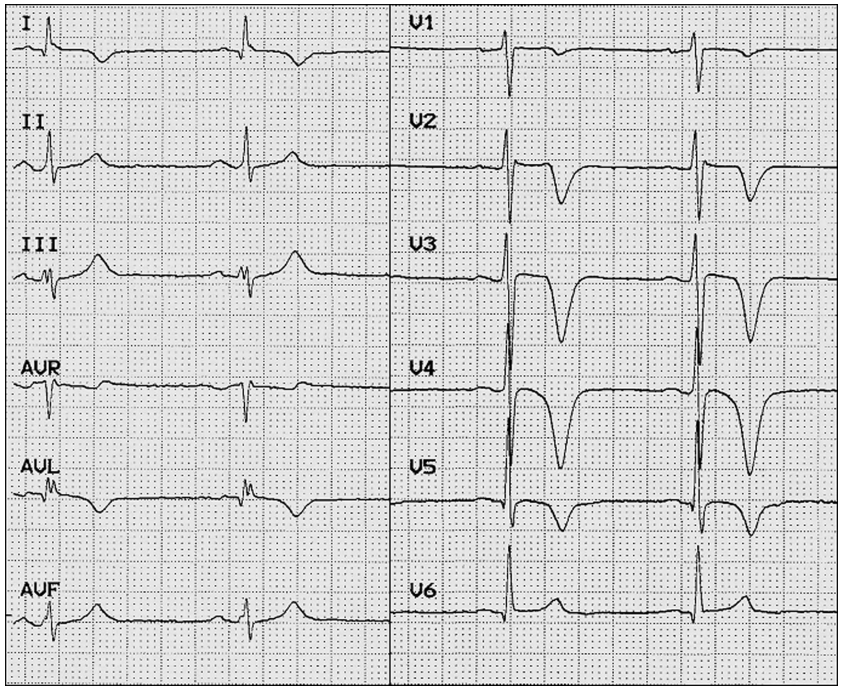

Figure 4. Resting ECG recorded the following day after admission showing ST-segment normalization in leads V2 and V3 with concomitant increased negative T-waves in leads V1-V5.

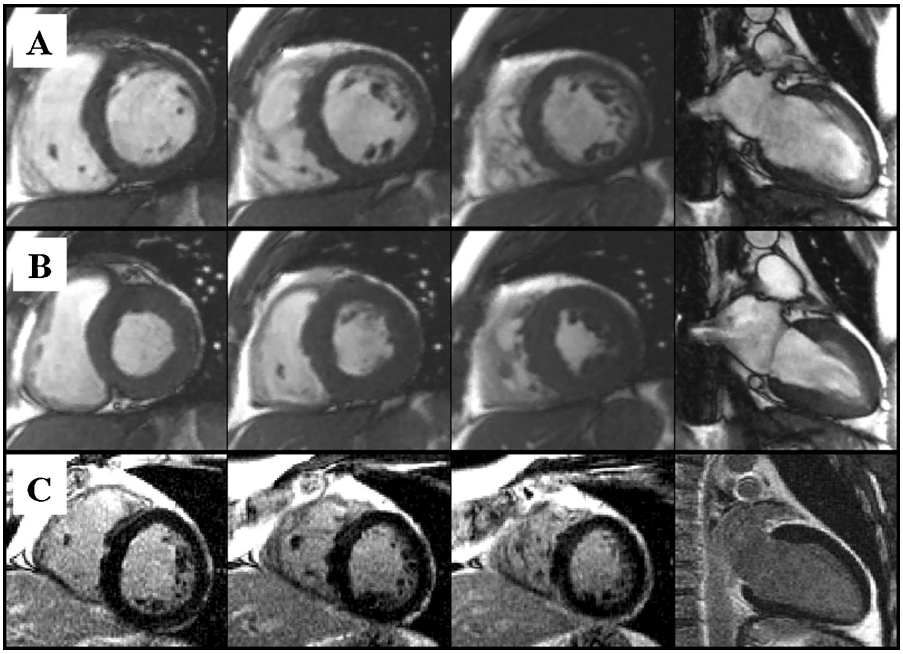

Figure 5. Panel A/B, Cine images at diastole (A) and systole (B) demonstrating nearly total resolvement of the segmental hypokinesia in the midventricular anterior wall. **Panel C,** Basal, mid and apical short-axis views and 2-chamber long-axis view after administration of gadolinium ruling out late gadolinium enhancement of ischemic or non-ischemic origin.

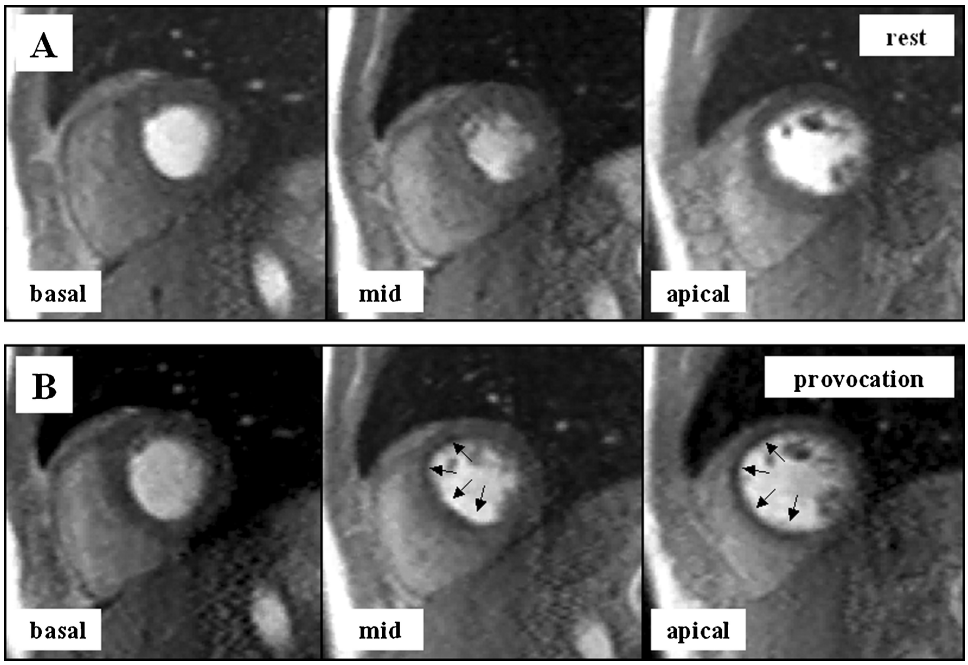

Figure 6. Panel A, Perfusion MRI at rest in three short-axis views (basal, mid and apical) showing no perfusion defect. **Panel B**, Repeated perfusion MRI after performing a non-invasive spasm provocation with a combination of hyperventilation and cold-pressure-test. An extensive subendocardial perfusion defect in the anterior septal wall (mainly in the mid and apical short-axis) is detectable compared to the resting images.

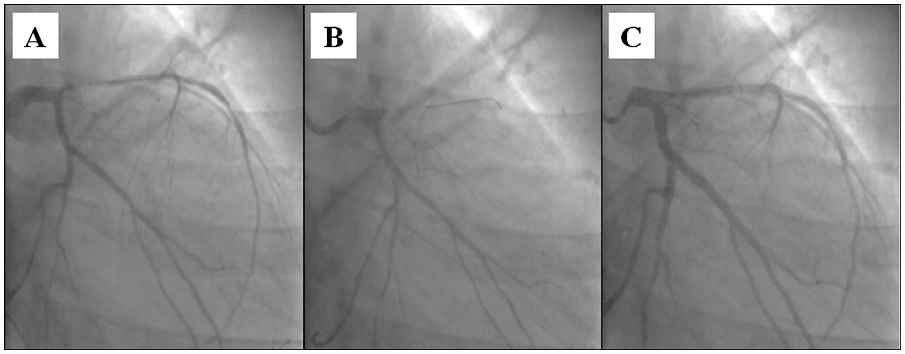

Figure 7. Panel A, Baseline coronary angiogram of the LCA before acetylcholine-testing demonstrating minor vasoconstriction in the proximal segment of the LAD after placement of the catheter. **Panel B**, Coronary angiogram immediately after low-dose acetylcholine application (2 μg) provoking total occlusion of the LAD. **Panel C**, Coronary angiogram immediately after nitroglycerin application demonstrating re-dilation of the LAD.

CMR study (Fig. 6A), the patient was asked to hyperventilate inside the scanner for six minutes with 30 breaths per minute. In addition, his feet were put into ice water for the last two minutes of hyperventilation. During the first minutes of hyperventilation, the patient experienced similar chest discomfort as in the weeks prior to admission and finally had reproduction of the same severe symptoms that lead to hospital admission one day earlier. A second perfusion CMR study ("provocation"), which was performed during the reproduction of symptoms, revealed a significant subendocardial perfusion defect in the anterior septal wall when compared to rest perfusion images (Fig. 6B, full motion images can be viewed at http://217.160.89.38/rbk.de/yilmaz/images/). At the end of the scan, the patient's chest pain remained constant and normal sinus rhythm changed to ventricular bigeminus. However, after application of sublingual nitroglycerin (0.8 mg), the pain resolved immediately and the ECG returned to normal sinus rhythm with negative T-waves.

Based on this indirect confirmation of coronary artery vasospasm by the combined hyperventilation and cold-pressure test perfusion CMR protocol, invasive acetylcholine-testing was performed two days later to confirm the diagnosis of LAD spasm. Selective intracoronary infusion of low-dose acetylcholine (2 μg) into the LAD, which was already preconstricted in its proximal segment after placement of the probing catheter, triggered a spastic proximal total LAD occlusion (Fig. 7, full motion images can be viewed at http://217.160.89.38/rbk.de/yilmaz/images/) as well as reproduction of the symptoms leading to hospital admission a few days earlier. Due to this severe LAD spasm and reproduction of symptoms, the test was terminated without testing of the other coronary arteries. Consequently, the patient was diagnosed with troponin-positive acute coronary syndrome due to coronary artery vasospasm and discharged a few days later on calcium-antagonists, long-acting nitrates and short-acting nitrates as needed.

DISCUSSION

It has been shown previously that patients presenting with troponin-positive acute coronary syndrome have a high incidence of coronary vasospasm (2), which was the underlying pathophysiology in our patient as well. The clinical history of this patient, however, also was suggestive of myocarditis (positive troponin, ECG changes in the anterior leads, transient segmental hypokinesia in the anterior wall). However, contrast and T2-weighted CMR revealed no signs of myocarditis.

As an alternative to intracoronary provocation testing using acetylcholine or ergonovine (10), several non-invasive methods of spasm testing were described, which often use hyperventilation as a trigger (11). Based on these studies, we designed a combined hyperventilation and cold pressure test perfusion CMR protocol. This new technique was not only capable of triggering coronary vasospasm non-invasively but also to demonstrate the hemodynamic link between epicardial coronary vasospasm and subendocardial ischemia.

However, it should be kept in mind that a hyperventilation combined with cold-pressure test perfusion CMR protocol as described in the present report may potentially lead to severe ventricular arrhythmias and ventricular fibrillation in rare instances if severe multivessel spasm occurs. As spasm may be more common in patients with diffuse coronary disease and subcritical stenoses, coronary anatomy should be known by the investigator to ensure that there is no critical stenosis before any provocative test for searching a coronary spasm. Future investigators wanting to reproduce this test must be aware of potential risks when performing spasm provocation testing in the CMR environment. Furthermore, emergent invasive cardiac catheterization must be available on site in case of refractory coronary spasm requiring coronary intervention. However, similar test settings were previously reported using nuclear perfusion imaging and echocardiography as imaging techniques without complications (8, 9).

Further investigations are needed to assess the sensitivity and specificity of this new diagnostic procedure. Combining non-invasive spasm provocation with perfusion imaging and work-up for myocarditis by CMR may become clinically useful in patients with acute coronary syndromes but normal coronary arteries.

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