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CASE SERIES
Coronary intervention

Do electrocardiographic changes induced during intracoronary vasospasm provocation testing reflect those during spontaneous angina episodes in patients with vasospastic angina?: a case series

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Background According to the Coronary Vasomotor Disorders International Study (COVADIS) group, the ECG criteria supporting the diagnosis of vasospastic angina (VSA) in spontaneous episodes or induced during intracoronary spasm testing are similar. However, it remains elusive whether acetylcholine-induced ECG changes during epicardial spasms reflect ECG changes that occur during the height of a spontaneous episode.

Case summary We present four patients diagnosed with VSA during intracoronary spasm testing, of whom the ECG characteristics during spasm testing and a spontaneous angina episode are described. All patients have >90% coronary epicardial vasoconstriction in one or more vessels during acetylcholine provocation. ECGs at the height of a spontaneous episode and during acetylcholine-induced coronary spasm are found to be different in three out of four patients.

Discussion In patients with VSA, the ECG at the height of a spontaneous episode and during acetylcholine-induced coronary artery spasm may differ substantially. In patients with symptoms suspicious of VSA, every effort should be undertaken to obtain ECGs during the height of a spontaneous episode of angina pectoris and there should be a low threshold to perform intracoronary function testing.

Keywords Vasospastic angina • Epicardial vasospasm • Electrocardiogram • Intracoronary spasm testing • Vasomotor dysfunction • Case report

ESC curriculum 3.3 Chronic coronary syndrome • 3.2 Acute coronary syndrome • 3.4 Coronary angiography

Learning points

- In patients with VSA, the ECG at the height of a spontaneous episode and during acetylcholine-induced coronary artery spasm may differ substantially.
- Every effort should be undertaken to obtain ECGs during the height of a spontaneous episode of angina pectoris in patients with symptoms suspicious of VSA.
- There should be a low threshold to perform intracoronary spasm testing in patients with symptoms suspicious of VSA.

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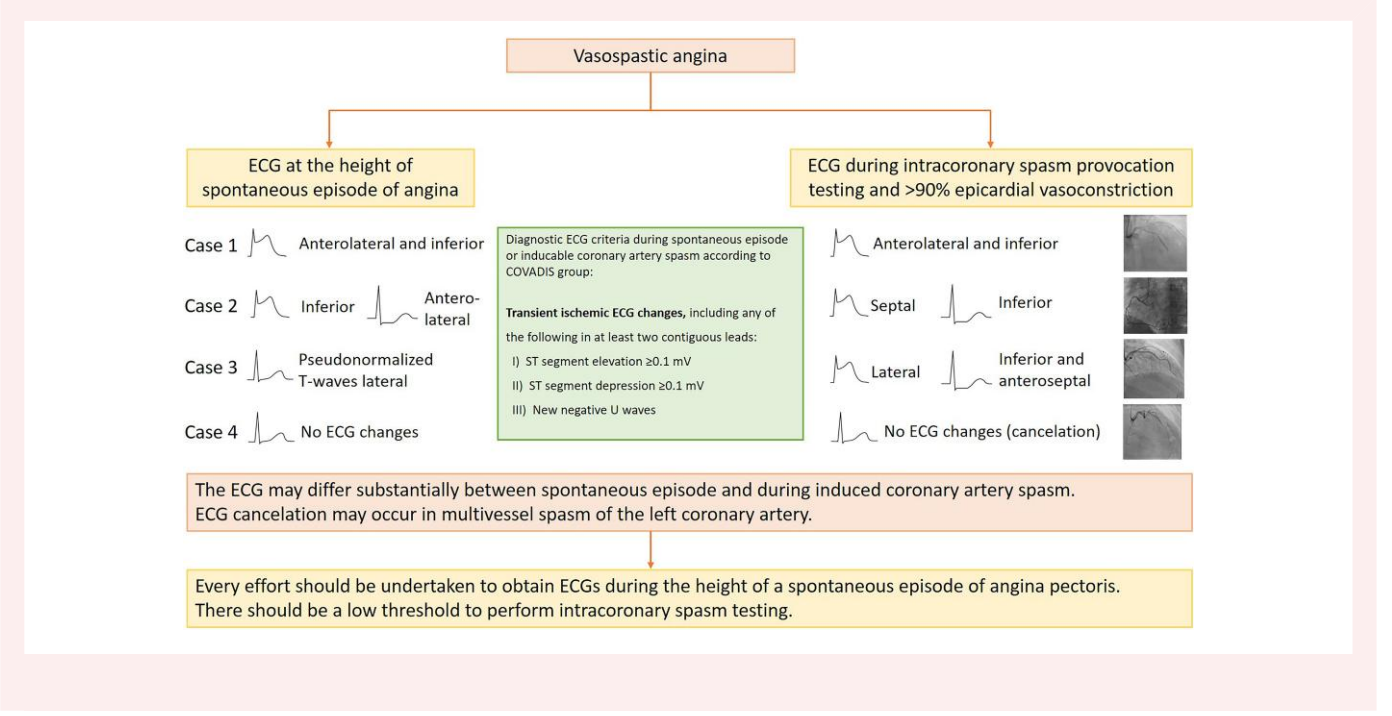
Introduction

Angina pectoris is the most common symptom of ischaemic heart disease and is a direct expression of a supply and demand mismatch of myocardial oxygen which results in myocardial ischaemia.[1] Historically, the pathological process of coronary artery disease (CAD) is solely attributed to atherosclerotic plaque leading to significant haemodynamic coronary obstruction. Nonetheless, up to 50% of patients with signs and/or symptoms of CAD or ischaemia undergoing coronary angiography (CAG) are found to have non-obstructive coronary arteries disease (NOCAD).[2,3] The underlying pathophysiology of anginal symptoms in NOCAD (ANOCA) or even ischaemia (INOCA) can be related to coronary vasomotor dysfunction, i.e. abnormal vasoconstriction, abnormal vasodilation or a combination of both and can be assessed by invasive coronary vasomotor function testing (ICFT). The gold standard to diagnose abnormal vasoconstriction, e.g. epicardial or microvascular vasospasm, is to perform intracoronary reactivity testing with acetylcholine (ACh) or ergonovine (ER).[4] Current European Society of Cardiology, American College of Cardiology/American Heart Association, and Japanese Circulation Society guidelines emphasize ICFT should be applied in routine practice in patients with ANOCA.[2,5,6]

The diagnostic criteria of vasospastic angina (VSA) are defined by the Coronary Vasomotor Disorders International Study (COVADIS) Group (*Table 1*) and differentiate between spontaneous episodes or inducible coronary artery spasms.[7] In spontaneous episodes definitive VSA is diagnosed when nitrate-responsive angina and transient ischaemic ECG changes occur while in inducible coronary artery spasm, all of the following criteria needs to be fulfilled: recognizable chest pain, transient ischaemic ECG, and >90% coronary vasoconstriction. However, it remains elusive whether ACh-induced changes on the ECG reflect those that occur during spontaneous attacks. This report describes ECG characteristics of four patients with epicardial vasoconstriction during vasospasm provocation and a spontaneous episode of vasospasm.

Summary figure



Case presentations

Case 1

A 75-year-old male with a history of anterior ST-elevation myocardial infarction (STEMI) treated with percutaneous coronary intervention (PCI) of the mid-LAD, re-PCI of the mid-LAD for in-stent restenosis, and paroxysmal atrial fibrillation (AF) presented with ongoing angina pectoris with ST-elevation in the precordial, lateral, and inferior leads on his ECG. (*Figure 1A*). Two weeks prior to admission he suffered multiple episodes of angina pectoris at night and early morning without triggering factors. Emergency CAG showed right dominance and no obstructive CAD. Hereafter, the patient was referred to our hospital for ICFT as INOCA was suspected. His cardiovascular risk factors were well controlled except that he was still an active smoker. Echocardiography demonstrated a mildly reduced left ventricular (LV) function with an akinetic apex and no heart valve pathology.

ICFT revealed at dose 3 of Ach infusion diffuse >90% vasospasm of the proximal and distal left anterior descending artery (LAD), the diagonal branches, and OM1 with recognizable anginal symptoms (*Figure 1D* and Supplementary material online, *Video 1*). Also, the ECG showed similar ST-elevation comparable to the ECG changes during a spontaneous episode of angina, both in the type of ECG abnormalities and in the affected myocardial area (*Figure 1B*). After intracoronary nitroglycerine his symptoms, ECG and CAG normalized (*Figure 1C and E*, and Supplementary material online, *Video 2*). The ICFT fulfilled the COVADIS criteria for VSA, and the patient was treated with a calcium antagonist and long-acting nitrates where he remained stable in the last 6 years with only occasionally mild angina pectoris.

Case 2

A 65-year-old male smoker with a history of hypertension was admitted after an out-of-hospital cardiac arrest due to ventricular fibrillation. Bystander cardiopulmonary resuscitation was started immediately and after defibrillation return of spontaneous circulation was achieved. Hereafter, the ECG showed ST-depression in the precordial and lateral

Table 1 Diagnostic criteria for vasospastic angina according to the COVADIS study group

1. **Spontaneous episode**
   a) **Nitrate-responsive angina,** with at least 1 of the following:
      i) Rest angina—especially between night and early morning
      ii) Marked diurnal variation in exercise tolerance—reduced in morning
      iii) Hyperventilation can precipitate an episode
      iv) Calcium channel blockers (but not b-blockers) suppress episodes

And

   b) **Transient ischaemic ECG changes,** including any of the following in at least two contiguous leads:
      i) ST-segment elevation ≥0.1 mV
      ii) ST-segment depression ≥0.1 mV
      iii) New negative U-waves

OR

2. **Inducible coronary artery spasm**, in response to provocative stimulus:
   a) Transient total or subtotal coronary artery occlusion (>90% constriction), **and**
   b) Chest pain provoked, **and**
   c) Transient ischaemic ECG changes provoked (as above)

COVADIS, Coronary Vasomotor Disorders International Study; ECG, electrocardiogram.

leads. Emergency CAG showed right dominance and mild atherosclerosis of the LAD and ramus circumflex (RCx). Echocardiography revealed a normal LV function and no valvular disease. At day 5 of admission, the patient experienced chest pain and ECG showed ST-segment elevation in the inferior leads and ST-depression in the precordial and lateral leads (*Figure 2A*). Within minutes, ventricular tachycardia developed for which successful cardiac defibrillation was performed.

Under the suspicion of ventricular arrhythmia due to coronary vasospasm, the patient underwent ICFT on day 9 of admission. After the third ACh dose, the RCA showed diffuse vasospasm with focal >90% vasospasm mid-RCA and at the ostium of the Ramus descending posterior (*Figure 2D* and Supplementary material online, *Video 3*). The patient experienced recognizable anginal symptoms and ECG during spasm showed mild ST-depression in the inferior leads and a mild ST-elevation in leads V1 and V2 with hyperacute T-waves (*Figure 2B*). After intracoronary nitroglycerine, his symptoms, ECG, and CAG normalized (*Figure 2C* and *E* and Supplementary material online, *Video 4*). However, ICFT fulfilled the COVADIS criteria for VSA, and the ECG during ICFT vs. spontaneous angina differed notably as ST-elevation occurred in another myocardial area.

The patient received a subcutaneous implantable cardioverter defibrillator (s-ICD) for secondary prevention and was treated with a calcium antagonist. He did have multiple s-ICD shocks for ventricular tachycardia in the first 3 months after implantation without preceding anginal symptoms for which amiodarone was started. He remained free of angina symptoms over the last 8 years.

Case 3

A 50-year-old female known with chronic depressive disorder, was admitted to our cardiac emergency department as she suffered typical chest pain with radiation to the left arm with a Visual Analogue Scale (VAS) score of 8. Her ECG showed sinus rhythm with pseudonormalization of T-waves in lead I, aVL, and V4 (*Figure 3A*). The negative T-waves in V1–3 remained unaltered during hospitalization. Sublingual nitroglycerin only shortly relieved her symptoms. In the previous year, she was admitted three times for angina pectoris with comparable ECG patterns and negative high-sensitive troponin T despite pharmacological treatment with aspirin, calcium antagonist, long-acting nitrates, angiotensin converting enzyme-inhibitor, and statins. A recent computed tomography coronary angiography showed an Agatston score of 0. Echocardiography demonstrated normal LV function and no valvular disease. Under the suspicion of coronary vasospasm, the patient was scheduled for a CAG with ICFT.

CAG revealed right dominance and no CAD. The fourth acetylcholine dose elicited recognizable anginal symptoms and angiography showed >90% spasm of the distal LAD (*Figure 3D* and Supplementary material online, *Video 5*). The ECG during spasm showed ST-elevation in leads I (only mild) and aVL and ST-depression in leads III, aVF, V1, V3, and V4 (*Figure 3B*). After intracoronary nitroglycerine, her symptoms, ECG and CAG normalized (*Figure 3C* and *E* and Supplementary material online, *Video 6*). Additional coronary flor reserve (CFR) measured 4.5 (normal). According to COVADIS, ICFT fulfilled the criteria for VSA; however, a remarkable difference was noted as the ECG during spontaneous angina pectoris during several hospitalizations did not show transient ischaemic changes.

Two years after ICFT the patient was hospitalized six times for angina pectoris, underwent cardiac rehabilitation, and still experienced angina pectoris at least once per week. Medical treatment was extended with ivabradine.

Case 4

A 52-year-old female treated for hypertension and dyslipidaemia was referred to our cardiac emergency department as she experienced chest pain early in the morning unresponsive to sublingual nitroglycerin. For the last year, she frequently experienced anginal symptoms which occurred only while in rest and mostly in the morning or evening. Sublingual nitroglycerin usually relieved her symptoms within minutes. ECG at admission showed sinus rhythm and was otherwise unremarkable (*Figure 4A*). Echocardiography demonstrated normal LV function and no valvular disease. A recent computed tomography coronary angiography showed an Agatston score of 0. The patient was scheduled for CAG and *ad hoc* ICFT in case of no obstructive CAD.

CAG demonstrated a balanced coronary system without atherosclerosis and ICFT was performed directly after. After the fourth ACh dose diffuse vasospasm was observed of the left coronary artery (LCA) with >90% stenosis mid-LAD and distal RCx (*Figure 4D* and Supplementary material online, *Video 7*). The patient had recognizable chest pain without ECG changes (*Figure 4B*). After intracoronary

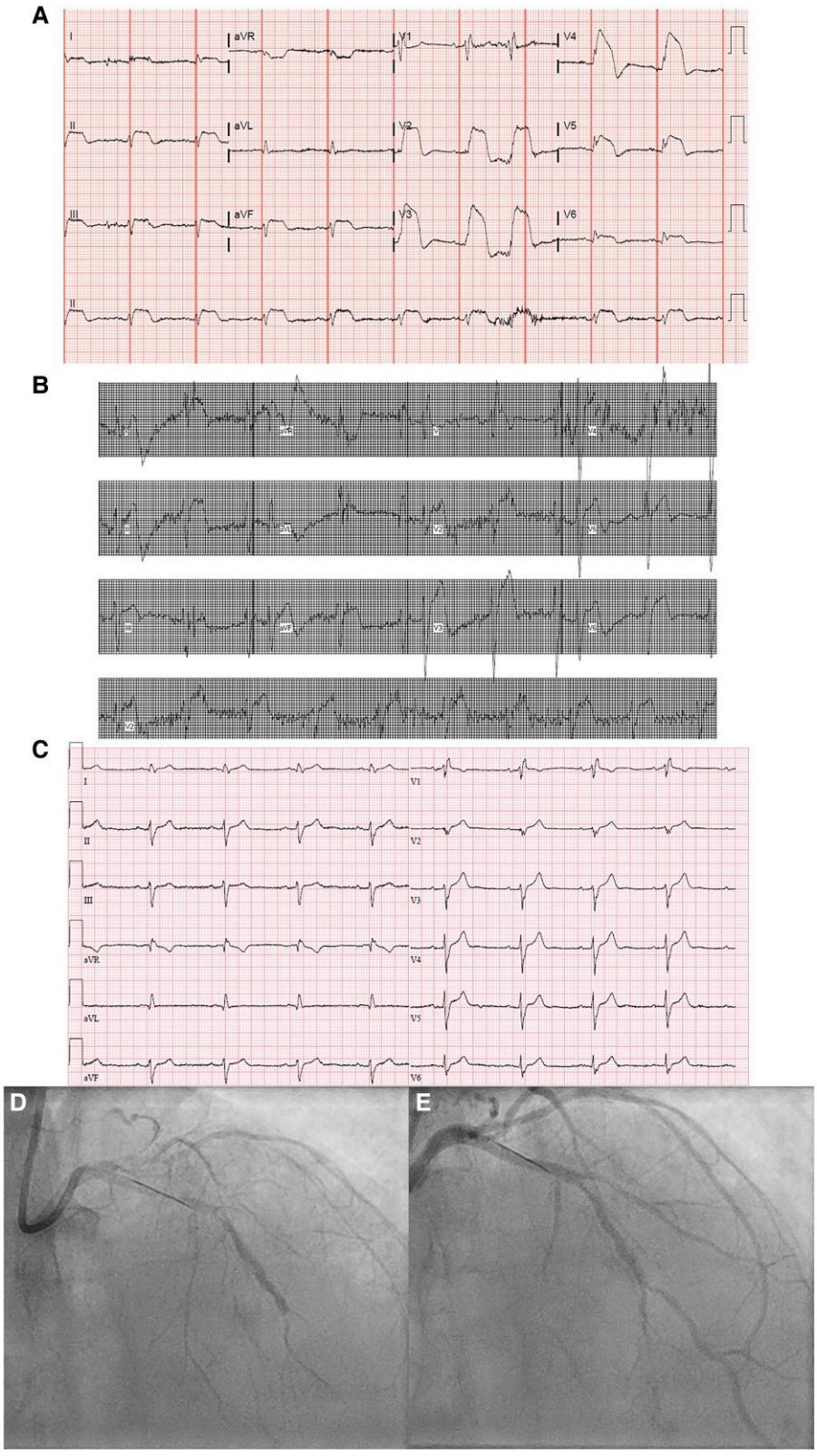


Figure 1 Case 1: (*A*) ECG at the height of a spontaneous episode of angina. (*B*) ECG during maximal coronary spasm. (*C*) ECG at rest. (*D*) Angiography of left coronary artery during maximal epicardial spasm. (*E*) Angiography of left coronary artery after intracoronary nitroglycerine.

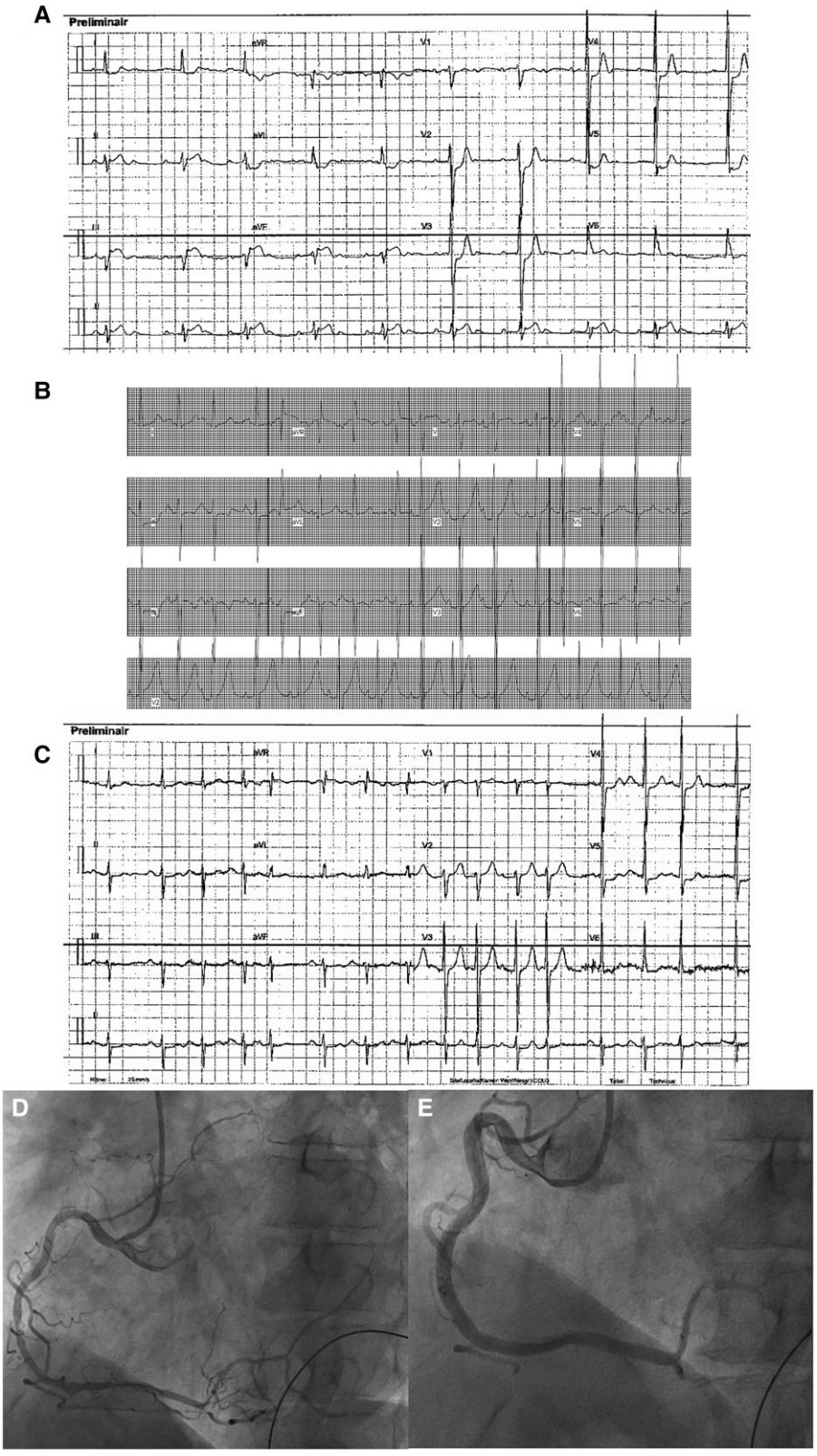


Figure 2 Case 2: (*A*) ECG at the height of a spontaneous episode of angina. (*B*) ECG during maximal coronary spasm. (*C*) ECG at rest. (*D*) Angiography of right coronary artery during maximal epicardial spasm. (*E*) Angiography of right coronary artery after intracoronary nitroglycerine.

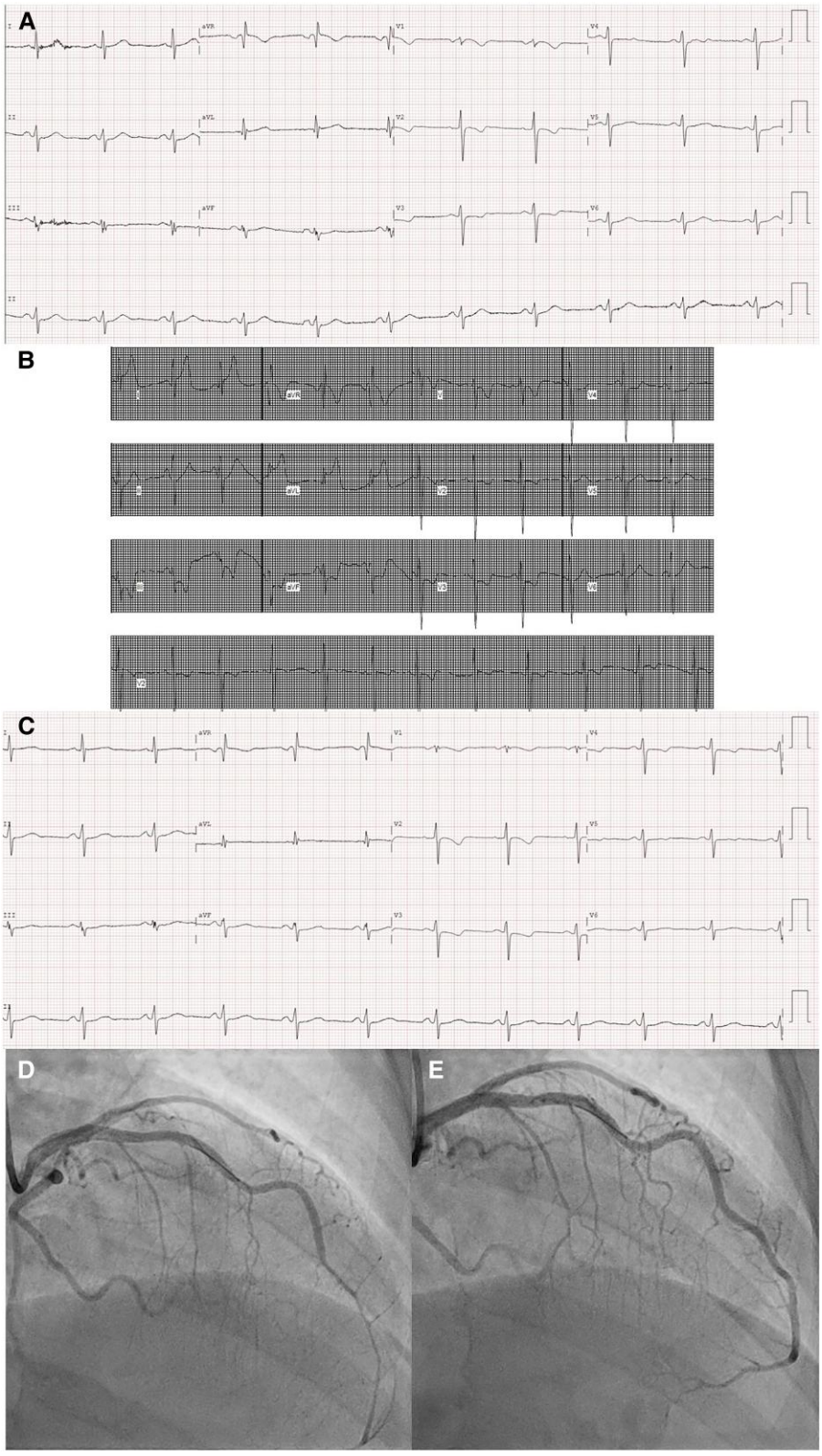


Figure 3 Case 3: (*A*) ECG at the height of a spontaneous episode of angina. (*B*) ECG during maximal coronary spasm. (*C*) ECG at rest. (*D*) Angiography of left coronary artery during maximal epicardial spasm. (*E*) Angiography of left coronary artery after intracoronary nitroglycerine.

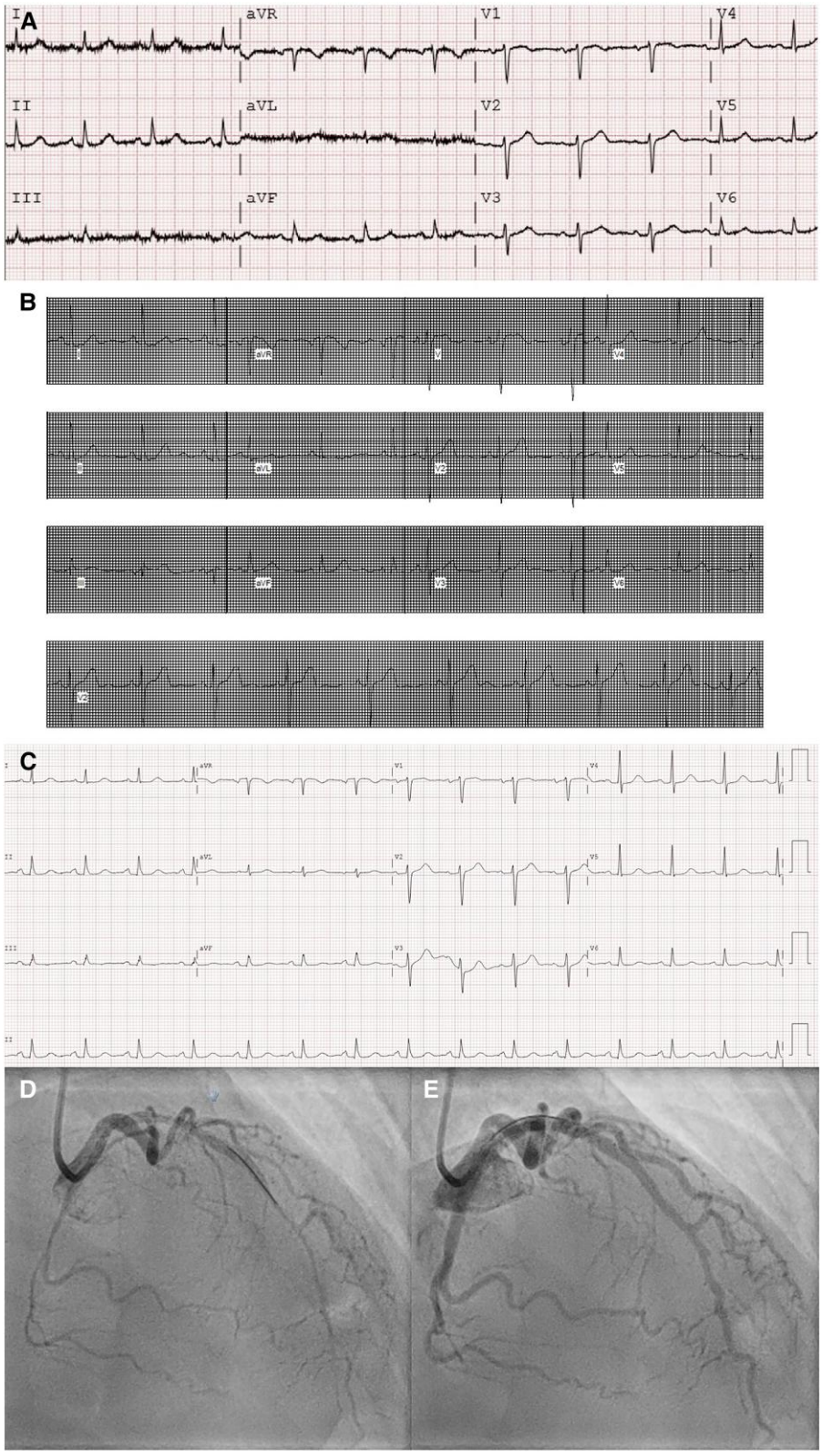


Figure 4 Case 4: (*A*) ECG at the height of a spontaneous episode of angina. (*B*) ECG during maximal coronary spasm. (*C*) ECG at rest. (*D*) Angiography of left coronary artery during maximal epicardial spasm. (*E*) Angiography of left coronary artery after intracoronary nitroglycerine.

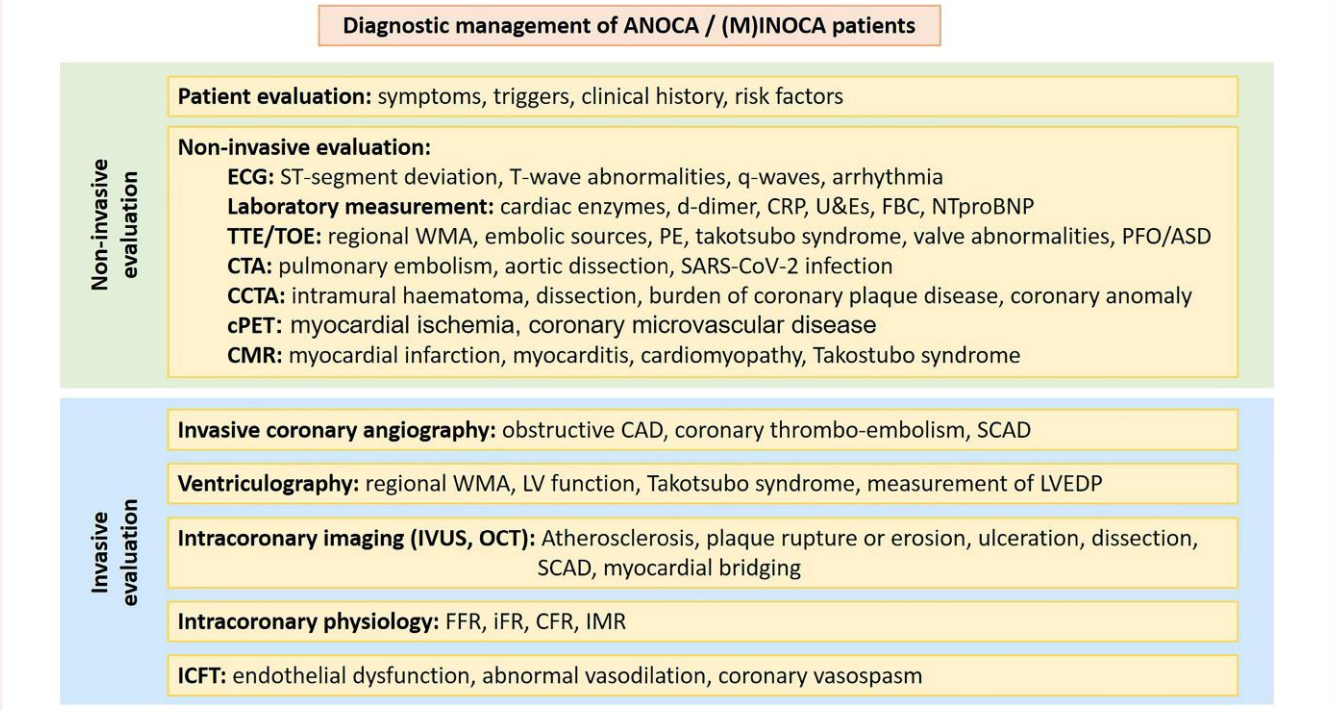


Figure 5 Diagnostic management of (*M*)INOCA patients.

nitroglycerine, her symptoms and CAG normalized (*Figure 4C* and *E* and Supplementary material online, *Video 8*). Additional CFR measured 3.0 (normal).

According to COVADIS, the criteria for VSA are not met as there are no transient ischaemic ECG changes observed despite obvious epicardial vasospasm of >90%.

The patient was treated with a calcium antagonist and long-acting nitrates. Two years after ICFT, she still suffered from intermittent anginal complaints but to a lesser extent.

Discussion

This case series reports four patients with VSA diagnosed with ICFT in whom ECGs during the height of a spontaneous episode of angina pectoris are available. We show that the ECG may differ substantially between spontaneous episodes and inducible coronary artery spasms.

In general, patients presenting with ANOCA/MINOCA require further investigation to establish the underlying pathophysiology (*Figure 5*) to prevent inadequate or inappropriate treatment. Patients with VSA have a high risk of major adverse cardiovascular events (MACE) therefore early diagnosis is crucial, as these major adverse events can be prevented with appropriate treatment.[8,9] Patients with symptoms suspicious of vasomotor disorder should undergo ICFT to establish the diagnosis by assessing the underlying pathophysiology; abnormal vasodilation, exaggerated vasoconstriction or both.[2] Although both endotypes can initially be treated with a calcium antagonist, additional pharmacotherapy differs. Testing both domains during ICFT should be considered in particular when patients remain symptomatic despite pharmacotherapy to guide further treatment.[10]

Whether induced ECG changes during ICFT reflect those of during spontaneous episodes of VSA remains largely unknown. According to the COVADIS, the ECG criteria supporting the diagnosis of VSA in spontaneous episodes or induced are similar, i.e. transient ST-segment deviation ≥0.1 mV or new negative U-waves.[7] Nevertheless, obtaining an ECG during the height of spontaneous episodes can be challenging due to the transient nature of the diagnostic ECG changes, the use of nitroglycerin before an ECG is performed when they present to an emergency room, or the attack has subsided before an ECG was performed.[11] In the four cases presented, we were able to obtain an ECG at the height of spontaneous episode (VAS score of ≥ 8) but only two patients fulfil the COVADIS criteria for VSA. In contrast, ischaemic ECG changes in reaction to acetylcholine provocation during ICFT are induced in three out of four patients. Notably, only in one patient identical ECGs are seen during a spontaneous episode and during ICFT. In patient two, the spontaneous ECG shows ST-segment elevation in the inferior leads. Therefore, the RCA was tested during ICFT and despite the focal spasm provoked, the induced ECG is remarkably different. Anatomically, epicardial spasms may be focal or diffuse within a vessel, may affect multiple vessels, and may migrate from site to site.[12] The current report suggests that anatomical differences between spontaneous episodes and induced coronary artery spasms may exist within the same patient.

Since the COVADIS ECG criteria only comprise ST-segment deviation and/or new negative U-waves, other ECG changes like T-wave alterations [i.e. isolated T-waves inversion or hyperacute (symmetric) T-waves] are not included but are known to be suggestive for acute ischaemia that may precede ST-segment deviation.[13–15] Moreover, Ter Haar *et al.* show that coronary artery occlusion of >1 min is needed before ST-segment deviation is at least ≥0.1 mV.[16] Although patient three suffered chest pain (VAS score 9) for more than 1 h, the spontaneous ECG only showed mild changes (pseudonormalization of T-waves in leads I, aVL, and V4) while during ICFT the distal LAD showed > 90% spasm resulting in ST-elevation in the lateral leads and ST-depression in the inferior and anteroseptal leads. The ECG changes are in the same territory but as the patient was prescribed anti-anginal medication, this may have affected the spontaneous ECG changes.

Some patients do not have transient ischaemic ECG changes during spontaneous episode or induced coronary artery spasm, although an evident coronary artery spasm of ≥90% is present during ICFT. Typically, in patients with multivessel spasm, such as in patient four, the absence of transient ischaemic ECG changes can be observed that may be explained by so-called ECG cancellation. This occurs when ischaemic ECG abnormalities from one coronary artery counterpoise ischaemic ECG abnormalities from other coronary arteries, due to the opposite direction of ischaemic vector.[17,18] To refine the ECG criteria within the COVADIS, intracoronary ECG could be useful when changes are minimal or not present, such as in the case of ST-segment cancellation when concurrent ischaemia of regions supplied by the LAD and RCx occurs or in patients where ECG interpretation is hampered due to pre-existing bundle branch block.

Conclusion

This case series shows that in patients with VSA, the ECG during spontaneous episode and during induced coronary artery spasm may differ substantially. In patients with symptoms suspicious of VSA, every effort should be undertaken to obtain ECGs during the height of a spontaneous episode of angina pectoris, and there should be a low threshold to perform ICFT.

Lead author biography

Rutger Feenstra is a physician at the Amsterdam University Medical Center in Amsterdam, the Netherlands. After graduating from the University of Amsterdam he completed 4 years of research focused on the diagnosis and treatment of coronary vasomotor disorder in patients with angina with no obstructive coronary artery disease.

Supplementary material

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

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Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patients in accordance with COPE guidelines.

Conflict of interest: None declared.

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Data availability

The data that support the findings of this study are available from the authors upon reasonable request.

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