INTRODUCTION

Coronary artery spasm is an established cause of angina (especially resting angina) in patients with or without obstructive coronary artery disease. Coronary artery spasm can affect either the epicardial arteries (diffuse or focal spasm), the microcirculation (microvascular spasm), or a combination of both. The current ESC guidelines for
the diagnosis and management of chronic coronary syndromes recommend intracoronary provocation testing (e.g., using acetylcholine [ACh]) with a class IIa recommendation for patients with unobstructed coronary arteries and suspected vasospastic angina. However, despite establishing the diagnosis of coronary spasm and institution of guideline-recommended pharmacotherapy we and others could recently show that sufficient symptom control often represents a challenge in these patients resulting in significant impairment of quality of life. Furthermore, our study could show that 64% of patients with stable angina and unobstructed coronary arteries undergoing intracoronary acetylcholine testing suffer from recurrent angina at long-term follow-up (7 years).

Thus, in the era of precision medicine individualized and targeted pharmacological therapies are urgently warranted. To achieve this goal, this study depicts a case in which we have used a modified protocol for ACh spasm testing including an additional invasive ACh provocation after pretreatment with potentially suitable drugs (e.g., nitroglycerine (NTG) and verapamil).

2 | CASE REPORT

A 55-year-old woman presented with recurrent angina at rest followed by presyncopal attacks and nausea. Her only cardiovascular risk factor was arterial hypertension. High-sensitive troponin T was 3 pg/ml ($n < 14$ pg/ml), and the 12-lead resting ECG was unremarkable. Differential diagnoses included stenosing coronary artery disease and coronary artery spasm. Thus, invasive coronary angiography was performed showing unobstructed coronary arteries (Figure 1).

Subsequently, ACh provocation testing in search of coronary spasm was carried out using incremental doses of ACh (2, 20, 100 and 200 µg) according to a standardized protocol (Figure 2). Continuous monitoring was ensured using a 12-lead ECG with radiopaque chest leads during the whole procedure to assess potential ischemic ECG changes such as ST-segment shifts, which represent one of the standardized diagnostic criteria of both epicardial and microvascular spasm. Moreover, the patient’s symptoms were ascertained in a continuous conversation between patient and operator to assess ACh-induced reproduction of the patient’s habitual pain. The interpretation of the provocation test results is based on the following criteria:

1. Reproduction of the patient’s habitual symptoms.
2. Development of ischemic ECG changes after administration of ACh (ST-segment depression $\geq 0.1$ mV, ST-segment elevation $\geq 0.1$ mV, negative T waves).
3. Epicardial coronary diameter reduction ($\geq 90\%$ focal or diffuse, compared with relaxed state after NTG administration).

Epicardial spasm is diagnosed when all of the previous criteria apply, and microvascular spasm can be diagnosed when a) and b) are fulfilled but the diameter reduction of epicardial arteries is $<90\%$ after the administration of ACh.

With the administration of 20 µg Ach, the patient reported a reproduction of her usual chest pain. At this time,
FIGURE 2  Flowchart of acetylcholine (ACh) testing including the ACh rechallenge after nitroglycerin (NTG) administration.

FIGURE 3  Acetylcholine (ACh) testing including the ACh rechallenge after NTG administration. Intracoronary administration of 20 µg ACh resulted in a full reproduction of the patients' usual chest pain. At this time, ischemic ECG changes (red arrows) and diffuse epicardial spasm of the left anterior descending artery (yellow arrows) and focal epicardial spasm of the distal left circumflex artery (green arrow) could be observed (A). Intracoronary administration of 200 µg NTG led to a normalization of the epicardial coronary artery diameters and resolution of ischemic ECG changes as well as the patient’s symptoms (B). In order to subsequently evaluate the protective effect of NTG on the vasoconstrictive potential of the coronary vasculature, 20 µg ACh was readministered 3 min after NTG injection. Strikingly, during this rechallenge no epicardial spasm could be elicited anymore (C), demonstrating that NTG had a pronounced protective anti-vasospastic effect on the epicardial arteries in this patient. Final administration of NTG resulted in normalization of the ECG but did not have an impact on the diameter of epicardial coronary arteries (D).
ischemic ECG changes and diffuse epicardial spasm of the left anterior descending artery (LAD) and focal epicardial spasm of the left circumflex artery (LCX) could be observed (Figure 3A). Intracoronary administration of 0.2 mg NTG led to normalization of the diameter of the epicardial arteries and resolution of ischemic ECG changes and symptoms (Figure 3B). In order to evaluate the protective effect of NTG on the vasoconstrictive potential of the coronary vasculature, 20 µg ACh was readministered. This rechallenge showed no more epicardial spasm (Figure 3C) suggesting that NTG has a protective anti-vasospastic effect on the epicardial arteries in this patient. Final administration of NTG did not change the diameter of epicardial coronary arteries no more (Figure 3D).

The patient showed a pathological response toward ACh testing and was thus diagnosed with epicardial coronary artery spasm. However, since injection of NTG prior to acetylcholine readministration prevented ACh-induced epicardial coronary artery spasm, we suggested that NTG may have a protective anti-vasospastic effect on the epicardial coronaries in this patient.

3 | OUTCOME AND FOLLOW-UP

The patient reported almost complete relief of symptoms under continuous treatment with amlodipine and an oral short-acting nitrate in case of symptoms at 18 months follow-up supporting the efficacy of oral nitrates to achieve satisfactory symptom control during acute attacks.

4 | DISCUSSION

The comprehensive assessment of changes in coronary diameter, resistance, and blood flow in response to ACh and adenosine is of great importance to identify coronary vasomotor disorders. If coronary artery spasm is observed during ACh testing, adding the ACh rechallenge is a simple tool to directly evaluate the anti-vasospastic effect of a drug potentially leading to a more individualized and targeted pharmacotherapy. In this patient, epicardial spasm could be diagnosed with ACh testing and strikingly prior administration of NTG inhibited the elicitation of epicardial coronary artery spasm. We can thus assume that testing the individual responsiveness of the coronary vasculature to the vasodilatory effect of NTG is helpful to distinguish responders to NTG from nonresponders in order to achieve satisfactory symptom control in this patient.

Importantly, the ACh rechallenge may also be performed using verapamil instead of NTG. The common dose that is injected into the coronary arteries is 1 mg over a period of 2 min. This strategy could avoid ineffective treatment approaches in symptomatic patients with coronary artery spasm who are often highly symptomatic and difficult to treat. However, even though this approach proved to be helpful in this patient, the clinical usefulness of this approach (e.g., reduction in readmissions and repeated coronary angiographies) and the influence of drug administration route (oral vs. intracoronary) yet need to be proven in future clinical trials. Furthermore, a comprehensive invasive diagnostic workup of coronary vasomotor disorders includes not only spasm provocation testing but also measurements of coronary flow reserve and microvascular resistance and should be considered in clinical practice.

5 | CONCLUSIONS

Patients with recurrent angina despite unobstructed coronary arteries frequently suffer from coronary artery spasm. In this patient, ACh testing revealed diffuse epicardial spasm of the LAD and focal spasm of the LCX, which could be resolved by intracoronary administration of 0.2 mg NTG. To evaluate the effect of NTG, ACh provocation testing was repeated after NTG injection. This rechallenge showed no more epicardial spasm, suggesting that NTG has a protective antispastic effect on the epicardial arteries. Furthermore, this case shows that the effect of NTG in an individual patient can be assessed by ACh rechallenge after NTG administration. The proposed advanced diagnostic workup including the direct assessment of the anti-vasospastic effects of a potentially suitable drug, which can be carried out as part of the routine diagnostic procedure, may be considered in selected patients with recurrent vasospastic angina in whom there is uncertainty regarding the efficacy of pharmacological treatments.

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CONFLICT OF INTEREST
Nothing to disclose.

AUTHOR CONTRIBUTIONS
PO, AS, and US conceived the idea of the study and contributed to the write-up of the manuscript. PO managed the patient in the cardiology department and performed the procedure. VMP interviewed the patient, collected the data, reviewed the literature, and drafted the manuscript. All authors discussed and approved the final version of this manuscript.
ETHICAL APPROVAL
We confirm that our research complies with current ethical guidelines.

CONSENT
Witten informed consent was obtained from the patient to publish this report in accordance with journal’s patient consent policy.

DATA AVAILABILITY STATEMENT
PO confirms that he had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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