

A rare but challenging condition

Paradoxical coronary spasm after intracoronary nitroglycerin injection

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Summary

Vasospastic angina is a clinical disorder primarily attributable to coronary artery spasm and typically characterised by a history of rest angina that promptly responds to short-acting nitrates. In this case report, we describe a 72-year-old man affected by vasospastic angina, who presented with asymptomatic transmural ischaemia during a routine exercise stress test and paradoxical subocclusive coronary spasm, superimposed on a non-significant coronary stenosis, following intracoronary nitroglycerin injection during coronary angiography. Other cases of paradoxical vasospastic response to nitrates during coronary angiography have been already described in literature. However, in these previously described cases, coronary spasm occurred in a portion of the vessel close to the catheter tip or following sublingual nitroglycerin administration, thus making it difficult to clearly assess the possible causative relation between nitrate administration and coronary spasm. This represents, to the best of our knowledge, the first described case of paradoxical coronary spasm occurring a few seconds after direct intracoronary nitroglycerin injection and in a portion of the vessel far enough from the catheter tip to exclude late-onset catheter-induced spasm in the absence of any catheter-tip drop-in or deep intubation. A paradoxical vasospastic response to nitrates in vasospastic angina patients represents a rare but very challenging condition. Thus, the best therapeutic approach in this subgroup of patients remains unclear. In our patient, because of the transmural ischaemia documented during the exercise stress test, a percutaneous coronary intervention (PCI) was performed and the clinical evolution was favourable. Therefore, we believe that PCI might represent an effective therapeutic option in vasospastic angina patients with a paradoxical response to nitrates and focal epicardial coronary spasm.

Keywords: vasospastic angina; coronary spasm; paradoxical response to nitrates

Introduction

Vasospastic angina is a clinical disorder primarily attributable to coronary artery spasm and typically characterised by a history of rest angina that promptly responds to short-acting nitrates [1].

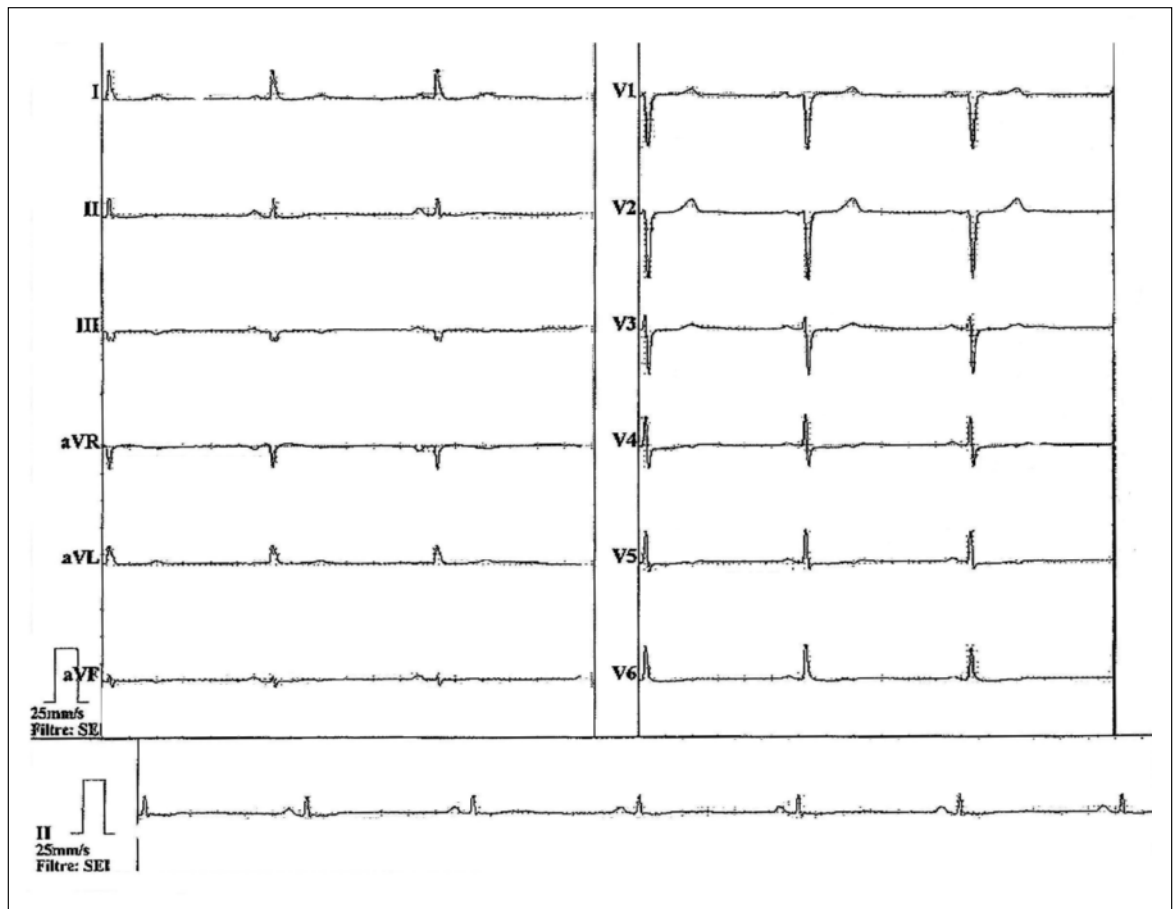
Coronary spasm usually occurs in patients without evidence of coronary atherosclerosis, but can also be superimposed on atherosclerotic lesions [2]. A paradoxical

vasospastic response to nitrates in vasospastic angina patients represents a rare but very challenging condition and the best therapeutic approach in this particular subgroup of patients remains unclear [3–4]. We describe the case of a patient affected by vasospastic angina, presenting with asymptomatic transmural ischaemia during a routine exercise stress test and a paradoxical subocclusive coronary spasm, superimposed on a non-significant coronary stenosis, following intracoronary nitroglycerin injection during coronary angiography. This represents, to the best of our knowledge, the first described case of a paradoxical coronary spasm occurring few seconds after direct intracoronary nitroglycerin injection and in a portion of the vessel far enough from catheter tip to exclude late-onset catheter-induced spasm in the absence of any catheter-tip drop-in or deep intubation.

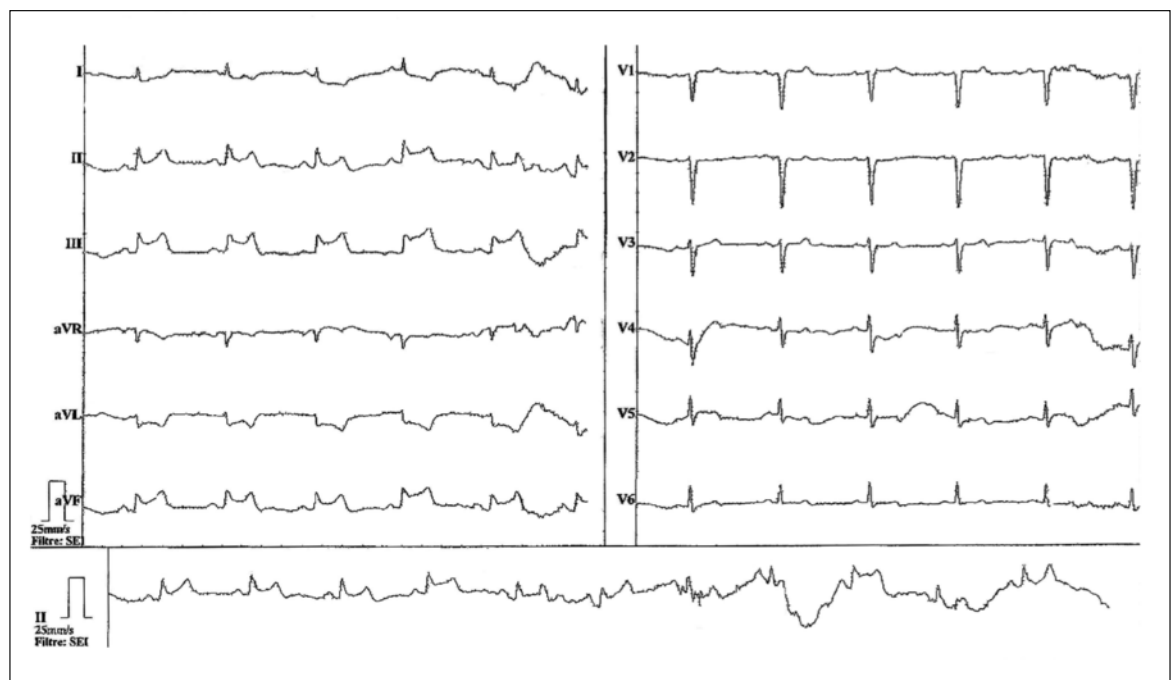
Case description

A 72-year-old man, known for hypertension and dyslipidaemia, was treated with implantation of a bare metal stent in the proximal portion of the left anterior descending artery 10 years ago. One year ago he experienced a symptomatic very late in-stent restenosis of the left anterior descending artery stent, treated with drug eluting balloon.

A routine 1-year follow-up exercise stress test was performed while the patient was asymptomatic and without interruption of β -blocker therapy. His treatment at the moment of the exercise stress test included aspirin (100 mg 1 \times /day), lisinopril (20 mg 1 \times /day), pravastatin (40 mg 1 \times /day) and atenolol (25 mg 1 \times /day). During the exercise stress test the patient was pain free. However, as shown in figure 1, significant ST-segment elevation occurred in all inferior leads. This ST-segment elevation appeared during the effort phase and persisted throughout the recovery phase. The patient was then referred for coronary angiography, which showed a non-significant stenosis (less than 50% of the reference vessel diameter) in the proximal-mid portion of the right coronary artery. During diagnostic coronary



A



B

Figure 1: Panel A. Basal electrocardiogram (ECG), showing no significant ST-segment modifications. Panel B. ECG recorded during the stress test. A significant ST-segment elevation occurred in inferior leads. These ECG modifications persisted throughout the recovery phase.

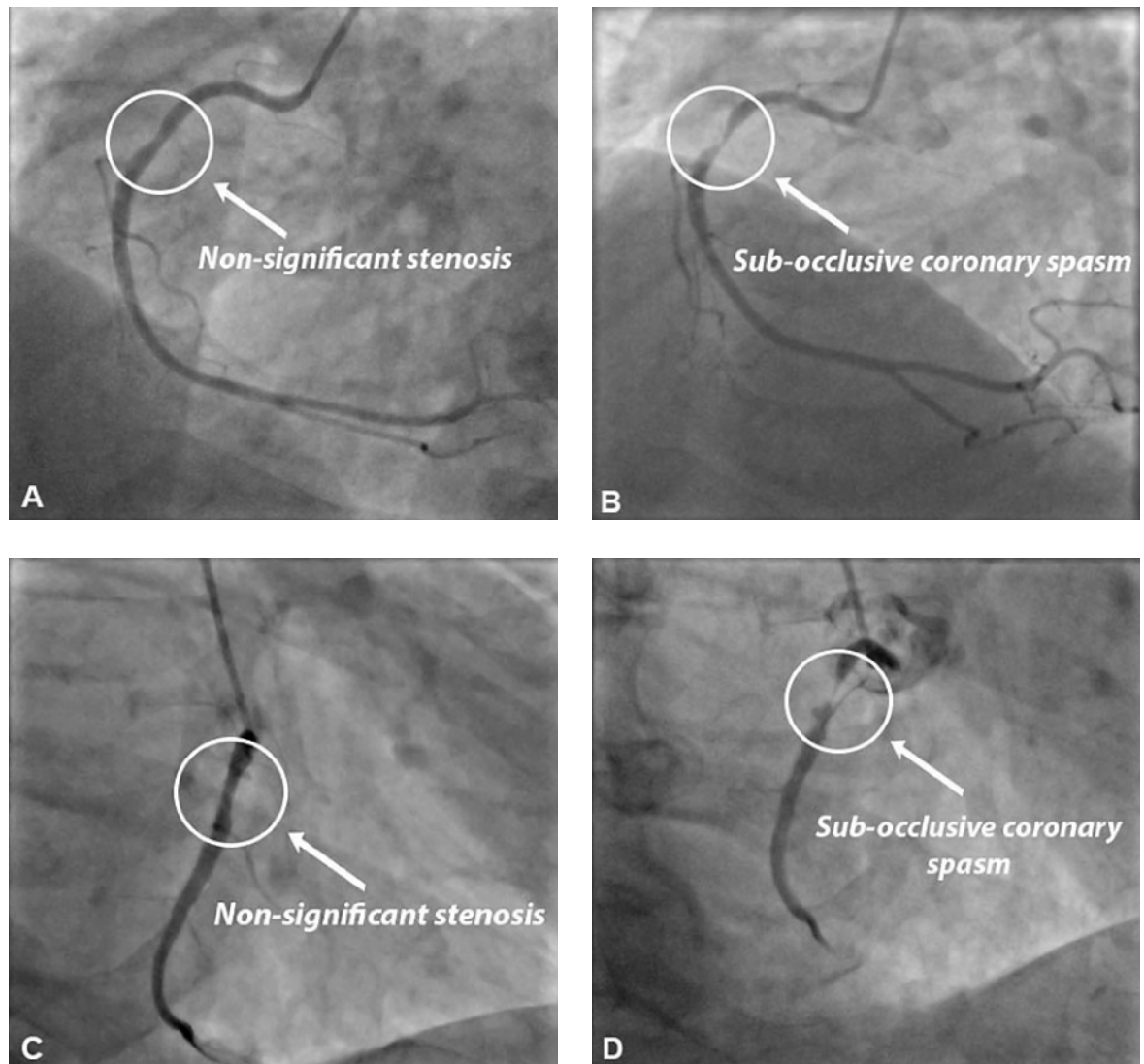


Figure 2: Panel A: Basal coronary angiography, showing a non-significant (less than 50% of the reference vessel diameter) stenosis in the proximal-mid portion of the right coronary artery. Panel B: Following intracoronary nitroglycerin injection, sub-occlusive coronary spasm, superimposed on the previously described coronary plaque, was observed. Panel C and D: Basal angiography and focal coronary spasm observed in another projection.

angiography, a 1000 μ g intracoronary nitroglycerin bolus was administered in order to better assess reference vessel diameter and stenosis severity. A few seconds after intracoronary nitroglycerin injection, asymptomatic paradoxical subocclusive coronary spasm, superimposed on the previously described plaque, was observed (fig. 2), suggesting a diagnosis of vasospastic angina for this patient. Of note, no drop-in of the catheter tip, which is quite common during right coronary artery cannulation and frequently associated with coronary spasm, was observed during coronary angiography. No deep intubation of the right coronary artery occurred. Because of the transmural ischaemia documented on the exercise stress test, a drug-eluting stent was implanted in the right coronary artery. Inter-

estingly, the spasm was sustained and lasted until stent implantation. The clinical evolution was favourable and a 1-month follow-up exercise stress test was clinically and electrically negative. Holter monitoring did not show any transient ST-segment elevation and the patient did not experience any episodes of chest pain during 6 months of follow-up.

Discussion

Vasospastic angina is a clinical disorder primarily attributable to coronary artery spasm and typically characterised by a history of rest angina that promptly responds to short-acting nitrates. During chest pain episodes, the electrocardiogram usually shows tran-

sient ST-segment elevation. Ischaemic episodes often occur in the night or early in the morning and are rarely triggered by physical activity [1]. Smoking represents a significant risk factor for vasospastic angina and Asian ethnicity patients seem to have a higher risk of developing vasospastic angina [5]. Hyperventilation represents a common trigger for coronary spasm in vasospastic angina patients [5]. Moreover, coronary spasms seem to be more frequent during the cold season, probably a result of an increase in systemic sympathetic tone [6]. The prognosis of patients with vasospastic angina is favourable. However, complications can occur, including acute myocardial infarction, malignant ventricular arrhythmias, high-grade atrioventricular blocks, syncope and sudden cardiac arrest [5].

The pathophysiology of epicardial coronary spasm is complex and multifactorial, the major determinants being endothelial dysfunction and enhanced contractility of vascular smooth muscle. Endothelial dysfunction essentially leads to deficient basal release of nitric oxide, which induces smooth muscle relaxation. Epicardial coronary spasm can be defined as focal when it is confined within the borders of a coronary segment and diffuse when adjacent coronary segments are involved [2].

Coronary spasm usually occurs (almost 70% of reported cases) in patients without evidence of coronary atherosclerosis. However, as in our case, coronary spasm can be superimposed on atherosclerotic lesions, with a potential risk of plaque rupture and acute myocardial infarction [2]. In clinical practice, provocative tests are usually necessary to confirm the diagnosis of vasospastic angina. The gold standard diagnostic approach involves invasive coronary angiography with intracoronary acetylcholine or ergonovine used as provocative pharmacological stimulus [5]. In our patient, coronary spasm was paradoxically induced by intracoronary nitroglycerin injection, which suggests severe coronary hyperreactivity. Interestingly, hyperventilation, which represents a well-known trigger for coronary spasms in vasospastic angina patients, was not observed during either the exercise stress test or coronary angiography. However, the exercise stress test and coronary angiography were both performed during the cold season; therefore, an influence of meteorological conditions cannot be excluded in the present case.

This paradoxical response to nitroglycerin was surprising, since nitrates usually induce vasodilatation, even in endothelium-deficient coronary arteries, due to their direct effect on smooth muscle cells in the media. However, a paradoxical vasoconstrictor response

to nitrates has already been described in literature. A few clinical reports described a paradoxical increase in frequency and intensity of chest pain episodes in vasospastic angina patients treated with long-acting nitrates. Moreover, in these cases, the clinical evolution was favourable after nitrate discontinuation [3–4]. The mechanisms explaining this paradoxical response to nitrates in patients chronically treated with long-acting nitrates are mostly unknown, but are likely to involve the same mechanisms that account for the well-known phenomena of nitrate tolerance and rebound angina [7]. The first cases of paradoxical coronary spasm occurring during coronary angiography following nitrate administration were reported by Feldman et al. They described two focal coronary spasms occurring in the right coronary artery a few minutes after sublingual nitroglycerin administration during diagnostic coronary angiography. However, both epicardial spasms involved the ostial portion of the vessel and coronary angiography was performed with the Sones technique, which is no longer routinely used in the catheterisation laboratory [8]. A few other cases of paradoxical coronary spasm occurring during coronary angiography following nitrate administration were reported in the Judkins era. Once again, the coronary spasm involved a portion of the vessel close to the catheter tip, thus making it difficult to exclude late-onset catheter-induced spasm [9–10]. Hamirani et al. recently described the first case of mid-vessel coronary spasm following nitrate administration during diagnostic coronary angiography performed with Judkins technique. In this case, focal coronary spasm, superimposed on a non-significant epicardial stenosis, was observed in the mid-portion of the left anterior descending artery 5 minutes after sublingual administration of nitroglycerin. Of note, a few minutes after the spontaneous resolution of the epicardial coronary spasm, an intracoronary nitroglycerin bolus was administered, but no subsequent coronary spasm was observed [11].

In our patient, coronary spasm occurred a few seconds after direct intracoronary nitroglycerin injection and in a portion of the right coronary artery far enough from the catheter tip to exclude late-onset catheter-induced spasm in the absence of any catheter-tip drop-in or deep intubation during right coronary artery cannulation, thus further strengthening the possible causative relation between nitrate administration and the occurrence of coronary spasm. This represents, to the best of our knowledge, the first described case of paradoxical coronary spasm occurring a few seconds after direct intracoronary nitroglycerin injection and in a portion of the vessel far

enough from catheter tip to exclude a late-onset catheter-induced spasm in the absence of any catheter tip drop in or deep intubation. Mechanisms explaining this paradoxical response to nitrates are mostly unknown. Our patient did not report a history of previous exposure to long-acting nitrates, so the mechanisms that account for the well-known phenomena of nitrate tolerance and rebound angina are unlikely to explain the vasospastic response to nitrates reported in our paper. It could be hypothesised that in the coronary plaque microenvironment (in which endothelial dysfunction is known to occur) and in adjacent coronary segments, rapid-acting vasoconstrictor agents, such as endothelin-1 and acetylcholine (which is known to have a vasoconstrictor effect in the presence of endothelial dysfunction), are released in response to nitroglycerin injection. These vasoconstrictor agents could drive the vasospastic response once levels of nitroglycerin and of its active metabolites in the plaque microenvironment significantly decrease. However, this mechanism is speculative.

Some limitations of the present case should be highlighted. First of all, the dose of the intracoronary nitroglycerin bolus (1000 µg) was high. However, at high doses, nitroglycerin usually shows an enhanced vasodilator effect via both nitric oxide-dependent and nitric oxide-independent pathways [7]. There is no evidence in literature for a dose-dependent paradoxical vasoconstrictor effect of nitroglycerin. Therefore, it is unlikely that the vasospastic response to nitroglycerin observed in our patient is related to the high dose of the intracoronary bolus. Moreover, injectable nitroglycerin preparations contain some excipients, such as alcohol and propylene glycol. Therefore, a hypersensitivity reaction against excipients cannot be formally excluded.

Conclusion

Paradoxical vasospastic response to nitrates in vasospastic angina patients represents a rare but challenging condition. Indeed, rapid acting nitrates are usually effective for a rapid control of anginal episodes, which were proven to be a trigger for trans-mural ischemia in

our case. After percutaneous coronary intervention (PCI), the clinical evolution of our patient was favourable, with a 1-month follow-up exercise stress test not showing recurrence of transmural ischaemia and an uneventful 6-month clinical follow-up. Therefore, in this clinical setting and in the presence of focal coronary spasm, PCI may represent an effective treatment strategy. However, stent implantation has been associated with endothelial dysfunction even with second-generation drug eluting stents [12]. Considering that other pharmacological options are available for vasospastic angina patients [5], any firm conclusion about the best treatment strategy in this situation would be speculative.

Disclosure statement

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