Case reports
Transient microvascular vasoconstriction: a possible cause of unstable angina

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We report the case of a 65-year-old woman who developed unstable angina 2 months after successful coronary angioplasty of the left anterior descending coronary artery. Coronary angiography failed to show angiographic restenosis, but intracoronary ergonovine caused ST segment elevation and her habitual chest pain in the absence of epicardial coronary spasm and important pressure changes in the distal left anterior descending coronary artery assessed by a pressure wire, thus suggesting that distal vessel constriction was responsible for unstable angina.

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Case report

A 65-year-old woman with family history of sudden death was admitted to our hospital because of typical angina at rest. Her recent medical history was characterized by the onset of typical angina on exertion which had remained stable for 3 months. Few days prior to admission she noted a worsening of symptoms with the onset of angina at rest. On admission the physical examination was unremarkable; ECG and chest X-rays were within normal limits. Blood tests showed hypercholesterolemia; the remaining parameters including cardiac enzymes were within normal limits. Immediately after admission she developed her habitual chest pain which promptly responded to sublingual nitrates; an ECG recorded during chest pain showed transient ST segment depression in antero-lateral leads. She was given aspirin, intravenous heparin and nitrates, calcium antagonists and beta-blockers with immediate resolution of her anginal symptoms. She remained asymptomatic for 3 days; the administration of intravenous nitrates was then discontinued and the patient underwent bicycle exercise testing which was stopped at 50 W because of angina and severe ST segment depression in antero-lateral leads. Due to evidence of inducible myocardial ischemia at low workload she was submitted to coronary angiography which showed a severe stenosis of the proximal left anterior descending coronary artery (LAD) and of the first diagonal. She underwent coronary angioplasty of both stenoses with good angiographic results (residual stenosis < 20%). The patient remained asymptomatic for 2 months on aspirin, beta-blockers and statins. Then she developed recurrence of exertional angina with occasional episodes at rest and, for the first time, at night always promptly reponsive to sublingual nitrates. Therefore, the patient was readmitted to our hospital. On admission physical examination, ECG and blood tests were normal. The patient remained asymptomatic for 2 days and was submitted to a treadmill exercise test which was stopped at the end of stage II of the Bruce protocol because of angina and ST segment depression in antero-lateral leads at a heart rate-pressure product of 22 800 b/min ٠ mmHg. Due to the high probability of restenosis she underwent repeat coronary angiography which showed an intermediate LAD stenosis. In order to assess its functional severity, a 0.014" pressure wire (RADI) was passed through the stenosis. Distal/proximal coronary pressure gradient was 0.93 at baseline and 0.83 following intracoronary injection of a bolus of adenosine (24 μg), thus confirming that the stenosis was not hemodynamically critical. In order to understand the mechanisms responsible for the recurrence of angina in this patient, scalar doses of ergonovine were administered into the left coronary artery at intervals of 3 min starting with 2 μg; proximal and distal coronary pressure and lead V_5 were contin-

uously monitored throughout the infusion. Following the administration of 32 μg of ergonovine the patient developed ST segment elevation and her habitual chest pain in the absence of detectable spasm of the LAD with only a modest decrease in distal/proximal coronary pressure ratio (from 0.93 to 0.91). Symptoms and signs of ischemia were promptly relieved by intracoronary administration of 2 mg of isosorbide dinitrate (Fig. 1). A treadmill exercise test carried out following 5 mg of sublingual isosorbide dinitrate was stopped at the end of stage III of the Bruce protocol (heart rate-pressure product 20 960 b/min × mmHg) in the absence of angina and ECG signs of myocardial ischemia. The patient was discharged on aspirin, calcium antagonists, oral nitrates and statins and remained asymptomatic for the following 6 months.

Discussion

It is well known that an alteration of coronary microcirculation plays an important role in the pathogenesis of myocardial ischemia in syndrome X[1], in patients with stable angina[2] and in the "no-reflow" phenomenon[3]. It is still controversial, however, whether a severe constriction of distal coronary vessels can be a primary cause of ischemia in patients with unstable angina. In our patient with unstable angina and a non-critical LAD stenosis, ergonovine caused transient ST segment elevation and angina, similar to her habitual chest pain in the absence of spasm of proximal coronary vessels. These findings strongly suggest that both ergonovine-induced and spontaneous angina were caused by distal vessel constriction. Our results are consistent with those of

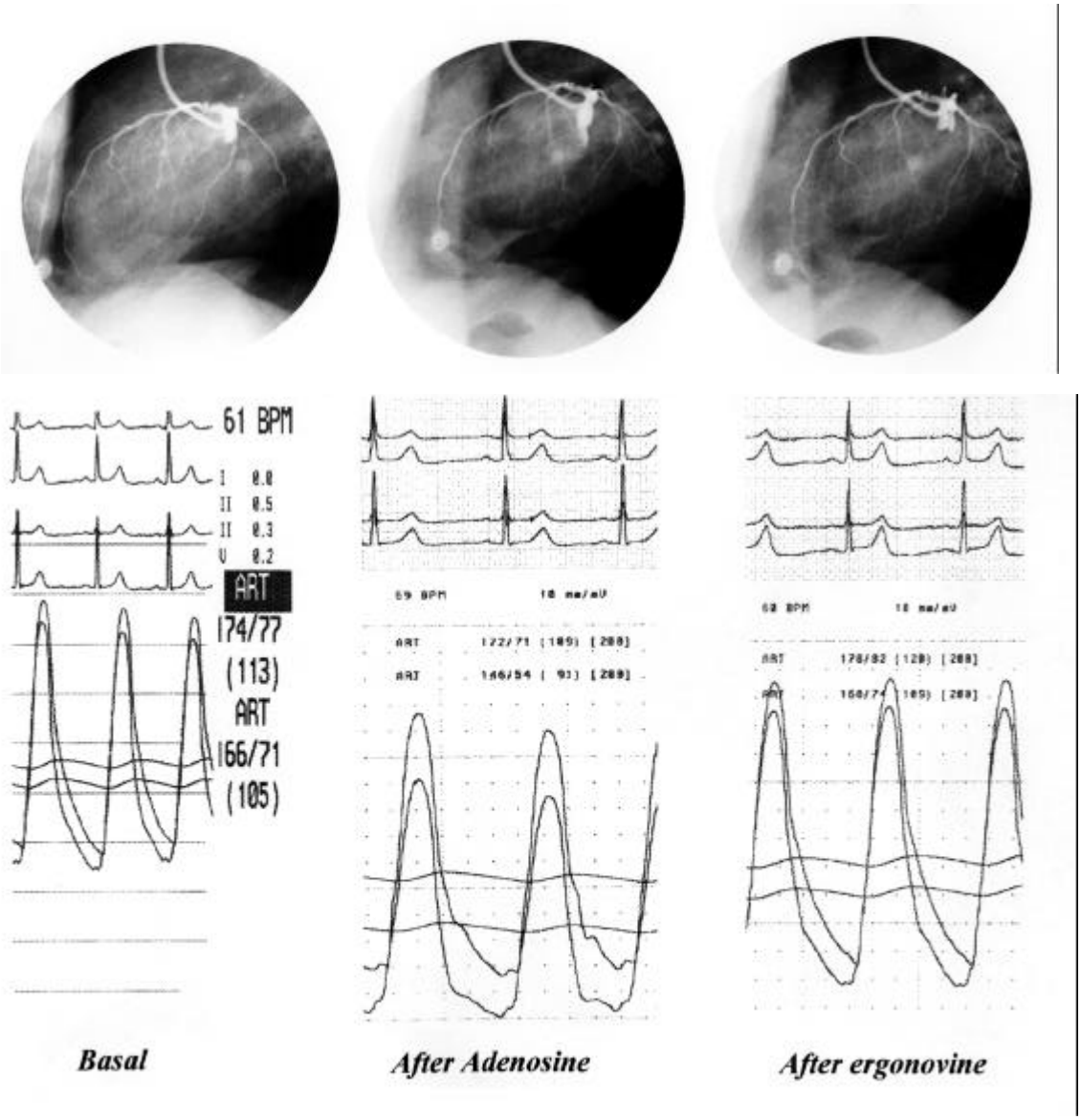

Figure 1. *Top panel: coronary angiograms of the left anterior descending coronary artery (LAD) showing a proximal intermediate stenosis at baseline, following adenosine and ergonovine (from left to right). Bottom panel: ECG and pressures (proximal and distal to LAD intermediate stenosis) at the same times. At baseline the distal/proximal pressure ratio is small (0.93); following adenosine the ratio shows a modest decrease (0.83) indicative of a functionally non-significant stenosis in the absence of ECG changes and chest pain; following ergonovine, despite a distal/proximal pressure ratio higher than that observed with adenosine and the lack of epicardial coronary spasm at angiography, the patient exhibited ST segment elevation and her habitual chest pain.*

Murakami et al.[4] who demonstrated that angina and transient ST segment elevation occurred spontaneously in the absence of proximal coronary artery spasm in 3 patients who underwent coronary angiography because of unstable angina. They are also consistent with the recent study of Marzilli et al.[5] who documented a marked increase in distal coronary vessel resistance during spontaneous transient myocardial ischemia in patients with unstable angina and obstructive atherosclerosis of epicardial coronary arteries.

The mechanisms responsible for distal coronary vessel constriction during spontaneous angina in our patient can be multiple; indeed it might be due to endothelial dysfunction, primary smooth muscle hyperreactivity, enhanced sympathetic stimulation, raised concentrations of blood borne constrictors or to a combination of these mechanisms. Endothelial dysfunction in coronary microcirculation has been found in patients with syndrome X[6] and in patients with obstructive atherosclerosis[7]. Furthermore, endothelin released by activated endothelial cells in unstable angina is a much more powerful constrictor of distal than proximal coronary vessels[8]. Distal coronary vessel constriction can also be due to primary smooth muscle hyperreactivity similar to that observed in proximal coronary arteries in patients with coronary spasm[9]. Distal coronary vessel constriction, finally, can be caused by enhanced sympathetic constriction or an increased release of blood borne constrictors. Interestingly neuropeptide Y[8] released by cardiac sympathetic and serotonin released by aggregating platelets are more powerful constrictors of distal than proximal coronary vessels[10,11].

Regardless of the mechanisms this case report shows that distal coronary vessel constriction can be primarily responsible for unstable angina. In this particular case the lack of significant proximal coronary stenosis made it possible for us to highlight the important pathogenetic role of distal coronary vessels. In patients with unstable angina and obstructive atherosclerosis the potential pathogenetic role of distal coronary vessels is more difficult to detect because it requires the demonstration that transient myocardial ischemia occurring at the time of coronary angiography is not associated with a reduction of the pressure gradient across the stenosis.

In conclusion, this case report further confirms that unstable angina is a complex syndrome caused by mechanisms operating both at proximal and distal coronary vessels; the prevailing mechanisms of instability are likely to be different in different patients. In our patient distal vessel abnormality responded remarkably well to an appropriate dosage of calcium antagonists.

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