Multifocal spasm with acetylcholine in Prinzmetal angina

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A 60-year-old female patient with Prinzmetal angina and a single non-critical (<50%) focal obstruction in the right coronary artery was referred for percutaneous coronary intervention. Coronary angiography with provocative testing using incremental doses of acetylcholine demonstrated diffuse mild vasoconstriction and multifocal hyperreactive vasoconstriction in apparently normal coronary segments but not at the site of the nonsignificant obstruction. We refrained from intervention and advised avoidance of β -blockade, and continuation of medical therapy with nitrates and calcium antagonists. (*Neth Heart J* 2008;16: 134-6.)

Keywords: Prinzmetal angina, acetylcholine, multifocal spasm

A 60-year-old female was awakened early one morning with extreme chest discomfort radiating to both her arms. She felt weak and light-headed and she fainted when she tried to get up. She regained consciousness quickly without sequelae. Upon arrival at the hospital she was without symptoms. The ECG was normal. Physical examination revealed no abnormalities. During her hospital stay she had two more early morning episodes of chest discomfort with inferior ST-segment elevation and second degree as well as complete AV block (figure 1). She is a cigarette smoker with no other classical risk factors. Coronary angiography in the absence of ischaemia revealed a

normal left coronary artery and a mild fixed coronary obstruction in the distal segment of the right coronary artery (RCA). The diagnosis of Prinzmetal angina was made.¹ She was treated with calcium antagonists and nitrates. She was referred for percutaneous coronary intervention (PCI) of the non-critical obstruction (figure 2A), but we decided to perform a provocative test with selective intracoronary infusions of acetylcholine in incremental doses.² Infusion of acetylcholine at the third dose level (50 μ g) induced diffuse mild vasoconstriction and multifocal hyperreactive vasoconstriction (spasm) in apparently normal coronary segments but not at the site of the alleged culprit lesion (figure 2B). The mild constriction and spasms were promptly resolved by intracoronary nitroglycerin (figure 2C). We refrained from PCI and advised an intensification of the therapy with calcium antagonists, nitrates, aspirin and statins, and avoidance of β -blockade and smoking.

Discussion

This patient presented with classical Prinzmetal (variant) angina. She is a cigarette smoker with no other classical risk factors.³ As with acute myocardial infarction, a circadian periodicity is present with attacks recurring at approximately the same time in the 24-hour period.⁴⁻⁶ The attacks are severe and are accompanied by syncope, inferior ST-segment elevation and transient AV block, suggestive of acute transient occlusion of the RCA, a frequent site in Prinzmetal angina.⁷ Coronary angiography showed a single non-critical obstruction in the distal part of the RCA. Intuitively we held spasm at this site responsible for the attacks, but later we realised that spasm may develop at sites other than the fixed lesion.⁸ We choose to perform a provocation test with acetylcholine. In intact endothelium stimulation of endothelial acetylcholine receptors produces uniform coronary dilation. Acetylcholine causes mild diffuse constriction in the presence of endothelial dysfunction. In patients with variant angina, acetylcholine has been shown to induce spasm and reproduce the clinical syndrome.⁹ We prefer acetylcholine over ergonovin because the frequency of provoked spasm with acetylcholine tests is significantly higher than with

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Figure 1. Twelve-lead ECG during ischaemic attack, showing massive ST-segment elevation in the inferior leads and 2:1 AV block.

ergonovine tests in patients without ischaemic heart disease, and in patients without (significant) fixed stenosis, and multiple spasms are more frequently observed with acetylcholine tests.¹⁰ A relatively low dose of acetylcholine induced diffuse mild constriction of the RCA with focal hyperreactive constriction in apparently normal coronary segments but not at the site of the non-critical obstruction. The effects of acetyl-

choline were promptly dissolved by intracoronary nitroglycerin. Nitrates and calcium antagonists are the mainstay of therapy. Beta-blockade may allow unopposed α -receptor-mediated vasoconstriction. The role of PCI is limited, as spasm may occur at sites other than the fixed stenosis.⁸ Prognosis is good in patients with no or mild fixed coronary obstruction who stop smoking.¹¹ ■

Figure 2. The right coronary artery A) before intracoronary provocative testing with acetylcholine, B) after the third dose level of acetylcholine, and C) after intracoronary nitroglycerin. The arrows indicate the alleged culprit lesion.

References

- 1 Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris. I. A variant form of angina pectoris. Preliminary report. *Am J Med* 1959;**27**:375-88.
- 2 Michels HR, van Hagen E, Pijls NJH. Endothelial dysfunction in patients with acute ischemia and apparently normal coronary arteries. *Cardiologie* 1999;**6**:115-22.
- 3 Kim HS, Lee MM, Oh BH, Song JM, Park SK, Yoo KY, et al. Variant angina is not associated with angiotensin I converting enzyme gene polymorphism, but rather with smoking. *Coron Artery Dis* 1999;**10**:227-33.
- 4 Cohen MC, Rohtla KM, Lavery CE, et al. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. *Am J Cardiol* 1997;**79**:1512-6.
- 5 Ogawa H, Yashue H, Oshima S, Okumura K, Matsuyama K, Obata K. Circadian variation of plasma fibrinopeptide A level in patients with variant angina. *Circulation* 1989;**80**:1617-26.
- 6 Sakata K, Hoshino T, Yoshida H, Ono N, Ohtani S, Yokoyama S, et al. Circadian fluctuations of tissue plasminogen activator antigen and plasminogen activator inhibitor-1 antigens in vasospastic angina. *Am Heart J* 1992;**124**:854-60.
- 7 Onaka H, Hirota Y, Shimada S, Kita Y, Sakai Y, Kawakami Y, et al. Clinical observation of spontaneous anginal attacks and multivessel spasm in variant angina pectoris with normal coronary arteries. Evaluation by 24-hour 12-lead electrocardiography with computer analysis. *J Am Coll Cardiol* 1996;**27**:38-44.
- 8 Tanabe Y, Itoh E, Suzuki K, Ito M, Hosaka Y, Nakamura I, et al. Limited role of coronary angioplasty and stenting in coronary spastic angina with organic stenosis. *J Am Coll Cardiol* 2002;**39**:1120-6.
- 9 Kugiyama K, Ohgushi M, Motoyama T, Sugiyama S, Soejima H, Matsumura T, et al. Enhancement of constrictor response of spastic coronary arteries to acetylcholine but not to phenylephrine in patients with coronary spastic angina. *J Cardiovasc Pharmacol* 1999;**33**:414-9.
- 10 Gueda S, Kohno H, Fukuda H, Ochi N, Kawada H, Hayashi Y, et al. Clinical impact of selective spasm provocation tests: comparison between acetylcholine and ergonovine in 1508 patients. *Coron Artery Dis* 2004;**15**:491-7.
- 11 Crea F. Variant angina in patients without obstructive coronary artery atherosclerosis: a benign form of spasm. *Eur Heart J* 1996;**17**:980-2.