The role of coronary artery spasm in anginal syndromes

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Summary

The role of coronary artery spasm in the production of angina at rest is emphasized. Three case reports of variant angina are presented to illustrate the spectrum of presentation and to stress the principles underlying the therapy of coronary artery spasm. This entity should be suspected and diagnosed more frequently in order that patients may derive the benefit of relatively specific therapy which consists of calcium antagonists and long-acting nitrates.

While coronary artery spasm has long been known to be the mechanism causing the variant angina first described by Prinzmetal, it is only since more sophisticated diagnostic techniques have become readily available that interest in coronary artery spasm has been revived. In particular, it is the role of coronary artery spasm in stable angina, angina at rest and myocardial infarction that has received the closest attention.1,2

Variant angina is a well-defined entity in which angina occurs more frequently at rest than during exercise and is classically associated with marked ST-segment elevation. In contrast, it is usually ST-segment depression which accompanies typical effort-induced angina. Coronary angiography has demonstrated that variant angina is due to coronary artery spasm which occurs in people with underlying coronary artery disease (atherosclerotic) or, less frequently, in people with apparently normal coronary arteries.2,3 Attention was first drawn to the role of coronary artery spasm by Prinzmetal et al.4 who described anginal pain occurring at rest associated with ST-segment elevation in patients with underlying coronary artery disease. One of their 3 patients went on to develop myocardial infarction in the area that showed ECG changes during angina.

More recently, Maseri et al.5 emphasized the value of the term vasospastic angina to include the milder episodes of coronary spasm occurring frequently in patients with angina at rest and accompanied by less evident ECG changes including ST-segment depression. Because vasospastic angina, variant angina and Prinzmetal's angina all refer to angina due to coronary artery spasm which may occur in people with or without underlying coronary artery disease, the preferred terminology is, therefore, to indicate that a particular patient has angina due to coronary artery spasm (variant angina) and to state whether or not that patient has underlying coronary artery disease.

Prinzmetal et al.4 in their original article in 1959, suggested reasons why the variant form of angina pectoris was not diagnosed. It would seem that the same reasons hold true today. They stated: '(1) medical students are generally taught that angina pectoris occurs with exertion and recedes with rest. True angina pectoris, therefore, is generally regarded as only that pain which is provoked by exertion or excitement. (2) Electrocardiograms taken at the beginning or end of a severe attack of the variant form or during a mild attack may be unchanged or show spurious improvement. (3) If only one electrocardiogram is taken during pain, myocardial infarction is diagnosed almost inevitably. (4) Physicians are not aware of the complete syndrome, its diagnosis and treatment'.

This article presents three case reports of variant angina in which coronary spasm was treated by the calcium antagonist, nifedipine, and by nitrates. The therapy of angina at rest, in the light of the possible role of coronary spasm in causing or contributing to angina at rest, will then be considered.

Case reports

Case 1

This case illustrates the problem of a 38-year-old truck driver who presented to the emergency unit at Groote Schuur Hospital with an acute onset of severe retrosternal pain occurring while sitting in his truck. He sweated profusely, felt short of breath and only obtained relief an hour later when morphine was administered intravenously in hospital. He had not previously been known to have angina although he had been seen at the hospital 6 months earlier with an episode of chest pain, which was assessed as not being due to myocardial ischaemia. His only risk factor for ischaemic heart disease was cigarette smoking (20 per day).

The examination, apart from a bradycardia of 30/min, was unremarkable. The ECG on admission revealed a junctional...
Fig. 2. ECG 10 minutes later showing junctional rhythm with ST elevation inferolaterally and reciprocal ST depression in leads V1 - V4.

Ergonovine maleate 0.5 mg in doses of 0.1 mg/min was administered intravenously and 6 minutes later the patient developed chest pain and progressive ST-segment elevation. Angiography then revealed coronary artery spasm causing complete proximal occlusion of the circumflex artery and an 80% occlusion of the mid-portion of the left anterior descending artery (Fig. 5). Bradycardic rhythm occurred and responded to conventional therapy. The pain was rapidly relieved by isosorbide dinitrate (20 mg sublingually) and nifedipine (20 mg chewed) with return of the ECG to normal. His subsequent course was uneventful and he was discharged on nifedipine, isosorbide and sulphinpyrazone, an antplatelet agent (vide infra). The patient remains free of pain 2 years later.

Fig. 3. ECG 1½ hours later has returned to normal.

rhythm with ST-segment depression in the anteroseptal leads (Fig. 1). Ten minutes later he was in the same rhythm with marked ST elevation inferolaterally (leads 2, 3, AVF and V6) with reciprocal ST depression in leads V1-V4 (Fig. 2). He returned to normal sinus rhythm following intravenous atropine. An ECG taken 1½ hours later in the Coronary Care Unit was striking in that it was essentially normal, showing sinus rhythm and an axis of 0°, with a normal PR interval and iso-electric ST-segments (Fig. 3). The patient remained pain-free in the Coronary Care Unit where he was kept at strict bed rest. Therapy consisted of isosorbide dinitrate (Isordil) 20 mg 4-hourly and nifedipine (Adalat) 10 mg 8-hourly because of the clinical diagnosis of coronary artery spasm. Daily electrocardiography and cardiac enzyme estimations excluded an acute infarct.

In order to confirm the diagnosis of coronary artery spasm he was submitted to coronary angiography 3 days after admission. Normal coronary vasculature was demonstrated (Fig. 4).

Case 2

A 57-year-old female was admitted to a medical ward with a history suggestive of unstable angina for the preceding week. There was no previous history of angina pectoris. She was a heavy smoker and had symptoms attributable to obstructive airways disease. Examination was unremarkable. The admission ECG showed inferior T-wave changes only and serial daily cardiac enzyme values were normal. She was managed by strict bed rest, sedation (diazepam), isosorbide and propranolol. The patient experienced occasional chest pain in the ward, obtaining prompt relief with nitroglycerin. On two occasions she was observed by the nursing staff to become pulseless and apnoeic, requiring resuscitation on the second occasion. ECGs were not taken during these episodes. She was transferred to the Coronary Care Unit where the propranolol was withdrawn because of the probability of a conduction disturbance.

Soon after transfer to the Coronary Care Unit, the patient again complained of chest pain, lost consciousness and her monitoring ECG lead showed that she had developed a transient 2:1 atrioventricular block with marked ST elevation (Fig. 6). A temporary transvenous pacemaker was inserted and nifedipine 20 mg 8-hourly was prescribed, in addition to isosorbide dinitrate 20 mg 6-hourly, because of the clinical diagnosis of coronary artery spasm (vide infra).

The patient remained free of pain, acute myocardial infarction was excluded and 6 days later she underwent coronary angiography. Two atherosclerotic lesions in the proximal right
The patient to angina as the result of spontaneous coronary artery spasm. Specific therapy with the calcium antagonist, nifedipine, and isosorbide dinitrate was commenced and the patient became free of pain. He was perhaps spared months of discomfort, inconvenience and the ill-advised use of agents such as antacids and β-blockers (see Discussion).

The second patient, who presented with unstable angina, had transient ST-segment elevation during pain with associated conduction disturbances causing syncope, and had two atheromatous lesions of the right coronary artery. The combination of intermittent typical ischaemic chest pain with transient ST-segment elevation led to the clinical diagnosis of coronary artery spasm. Despite therapy with nifedipine and nitrates, she developed infarction in the territory of the diseased coronary artery.

The third patient was demonstrated to have normal coronary arteries in which spasm could be produced by ergonovine. The presence of normal coronary arteries in the absence of conditions such as aortic stenosis or hypertrophic cardiomyopathy excludes increased myocardial oxygen demand as a cause of his pain and illustrates that a local factor reducing myocardial oxygen supply (such as coronary artery spasm) must be implicated. It is suggested that the trigger for coronary artery spasm was emotional stress (side infra). It is highly probable that the presentation of this patient to the hospital with chest pain over a year earlier was due to coronary artery spasm. Had the correct diagnosis been made and appropriate treatment instituted, he would have been spared a year of severe pain at rest.

Discussion

Clinical picture

Variant angina typically occurs at rest, as it did in all our patients. The haemodynamic differences between typical effort angina pectoris and variant angina are reviewed by Hillis and Braunwald. In variant angina there is a sudden reduction in the supply of oxygenated blood to the myocardium, whereas in typical effort angina there is an increase in myocardial oxygen demand rather than a decrease in myocardial perfusion. In variant angina there is characteristically transmural ischaemia which is manifested electrocardiographically by ST-segment elevation, whereas in typical angina the ischaemia is usually not so severe, being mainly subendocardial and manifested by ST-segment depression. In some patients with vasospastic angina there is also ST depression rather than elevation, caused by generalized subendocardial rather than transmural ischaemia.

The role of coronary artery spasm, however, is not limited to variant angina. A patient with variant angina at rest may have numerous attacks of vasospasm, many occurring without the patient experiencing pain. Sometimes vasospasm may even be precipitated by physical exertion and cause chest pain on effort. Thus the separation of typical angina from variant angina becomes less distinct.

An important hypothesis, stressed by Maseri’s group, is that coronary artery spasm may develop into acute myocardial infarction. Spasm may be superimposed on pre-existing coronary artery disease as in Prinzmetal’s original description, but coronary artery spasm may sometimes cause myocardial infarction even without any organic stenosis. In industrial workers who are exposed to nitroglycerin, angina pectoris, myocardial infarction and sudden death may occur when they are moved from their work environment. In that study all the patients had angiographically normal coronary arteries. The proposed mechanism for development of myocardial ischaemia in this group is that coronary artery blood flow diminishes once the vasodilator effect of nitroglycerin is withdrawn.

It has recently been suggested by Schiffer et al. that emotion can cause coronary artery spasm. Equivalent degrees of ST-segment depression, i.e. the same amount of ischaemia, were present with psychological stress.
induced by exercise and by emotion in the same group of patients. In emotionally induced ischaemia the index of myocardial oxygen consumption was lower than in exercise-induced ischaemia, the postulation thus being that the ST-segment changes in emotion were largely due to a decreased oxygen supply. It is suggested, therefore, that coronary artery spasm could be an operative mechanism.

It may thus be concluded that coronary spasm contributes to a wide variety of clinical ischaemic syndromes, but in particular to angina at rest.

**Therapy of variant angina**

**Nitrates and calcium antagonists**

Nitrates can relieve spasm, as shown angiographically.

Coronary vasodilators, which act by decreasing the slow calcium currents, play an important role in the therapy of coronary artery spasm. Nifedipine and verapamil are particularly effective. Verapamil, however, has the theoretical disadvantage that it may cause heart block, particularly when used in combination with other agents such as digoxin or β-blockers. Combined therapy with nitrates and nifedipine (or verapamil) is usually used. Our second case was unusual in that infarction developed, despite this standard therapy.

**Alpha-antagonists**

Alpha-adrenergic stimulation of coronary arteries causes vasoconstriction and thus α-blockade (phenolamine, phenoxybenzamine and prazosin) theoretically is effective in preventing coronary artery spasm. In practice, α-blockade is used only if nitrates and calcium antagonists are ineffective.

**Beta-blockade**

Beta-blocking agents, which are the cornerstone of treatment of typical angina pectoris, may be hazardous in the treatment of coronary artery spasm because the resulting unopposed α-effect may aggravate the spasm. In theory, β-blockers combined with an α-blocking effect (labetalol) should be more effective than agents with only a β-blocking action. Therapeutic trials to prove this point are still awaited.

Vasodilation of the arterial vascular bed is generally held to be mediated by β1-receptors. Thus, cardioselective agents (β1-antagonists) should cause less coronary vasoconstriction by unopposed α-activity than non-selective agents. However, the receptor status of the human coronary vascular bed is in doubt; some evidence implicates the β2-receptors. According to this information, both selective and non-selective β-blockers could contribute to coronary artery spasm, which would explain why the cardioselective agent practolol gave no advantage over the non-selective agent, propranolol. Beta-blockers are, therefore, best avoided.

**Anti-platelet agents**

There is speculation that anti-platelet drugs (aspirin, dipyridamole, sulphinpyrazone) may be useful for two reasons. Firstly, they may prevent mechanical obstruction by platelets and, secondly, they may inhibit the release of thromboxane A2, a powerful vasoconstrictor, from aggregated platelets. In practice, anti-platelet agents are frequently used on the supposition that they may help and will not harm.

**Coronary artery bypass grafting**

Coronary artery bypass grafting is contraindicated in those patients with coronary artery spasm and 'normal' coronary arteries as they almost inevitably develop spasm in the coronary artery distal to the site of anastomosis. There is no contraindication to coronary artery bypass grafting in patients with coronary artery spasm superimposed on significant occlusive (> 70% stenosis) underlying atherosclerotic coronary artery disease, the decision being made on the suitability of the coronary artery anatomy.

**Therapy of angina at rest**

Maseri et al. estimated that about 10% of angina at rest may be due to coronary artery spasm. Clinically, it is usually not possible to distinguish patients with significant spasm from those without, unless transient ST-segment deviations are found during repeated ECGs. Spasm must be suspected in all patients with angina at rest, and agents that are effective against angina at rest with or without spasm should be selected. Therefore, all patients with angina at rest are given long-acting nitrates (such as isosorbide dinitrate) which have sustained haemodynamic effects and give prolonged relief from coronary artery spasm.

When coronary spasm is strongly suspected, or if nitrates alone are not effective, a calcium antagonist such as nifedipine or verapamil should be added. Such agents are of proven value in variant angina and also in angina at rest.

The role of β-blockers is contentious. In their original study on angina at rest, Fischl et al. successfully used β-blockade, in the form of propranolol, together with nitrates. Possible mechanisms for the effectiveness of β-blockade are the relief of reactive hypertension and tachycardia arising from the chest pain, and an anti-platelet effect. More recently, two observations have cast doubts on the efficacy of β-blockade in the treatment of angina at rest. Firstly, β-blockade has usually failed in the therapy of angina at rest due to coronary artery spasm. Secondly, several studies show that the primary event in angina at rest is neither a rise in blood pressure nor a tachycardia, but a 'spontaneous' fall in coronary blood flow such as is caused by spasm. The role of β-blockade in spasm has already been discussed. In angina at rest, where there may be a variable spastic component, the addition of a β-blocking agent could be either helpful or harmful.

In our practice, β-blockers are used if the patient is experiencing both typical effort-induced angina and angina at rest; conversely, β-blockers are avoided if the angina occurs only at rest, the treatment then consisting of nitrates and calcium antagonists.

The importance of appropriate therapy for vasospastic angina is highlighted in a report in which long-term follow-up of patients with coronary artery spasm demonstrated a favourable prognosis.