Multiple coronary vasospasm: a cause of repeated myocardial infarction and symptomatic *'torsade de pointes'* (atypical ventricular tachycardia)

A case presentation and review

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Summary

A middle-aged Coloured man had a 6-year history of chest pain induced by effort and also experienced at rest. Quite dramatic episodes of associated arrhythmias, specifically *'torsade de pointes'* (atypical ventricular tachycardia) and syncope were experienced by the patient, despite the use of numerous anti-arrhythmic and anti-anginal agents. Transmural anteroseptal and non-transmural anterolateral myocardial infarctions were documented in the presence of a normal left coronary artery (LCA). Severe reversible vasospasm of the right coronary artery (RCA) was provoked with the use of ergonovine (ergometrine) maleate at cardiac catheterization. It is postulated that the cause of the previous myocardial infarctions was significant vasospasm of the LCA branches, and that he was subject to multiple coronary vasospasm, as was highlighted by the visualization of spasm superimposed on atheromatous plaque within the RCA. Furthermore, it is strongly suggested that the potentially lethal ventricular arrhythmias, including *'torsade de pointes'*, were a direct result of coronary vasospasm, which in turn gave rise to his presyncope and syncope attacks. No evidence of sinoatrial node disease could be found.

The only risk factor for ischaemic heart disease which applied in his case was heavy cigarette smoking. Control of his disabling symptoms seems to have been achieved by the use of maintenance nifedipine (a calcium-blocking agent), long-acting nitrates (isosorbide dinitrate) and quinidine gluconate, confirming the probable vasospastic aetiology of the *'torsade de pointes'*. At no stage was there dangerous prolongation of the QT interval, an oft-quoted prerequisite for this arrhythmia.

Some of the more important aspects of coronary vasospasm are discussed; as far as I am aware this is the first patient documented in the literature with *'torsade de pointes'* associated with angiographically demonstrated coronary artery spasm.

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Clinical presentation

The patient was a 57-year-old Coloured man who was initially admitted to the Coronary Care Unit of Tygerberg Hospital, Parowvallei, CP, in January 1976 with a few months' history of retrosternal pain on effort as well as at rest, and occasional dizziness related to physical exertion. At that stage an ECG (Fig. 1a) showed evidence of a possible old transmural anteroseptal myocardial infarction. The possibility of essential hypertension was considered (a blood pressure reading of 170/100 mmHg was recorded), and he was given propranolol and methyldopa, as well as sublingual isosorbide dinitrate when required. Later that year he complained of dyspepsia; barium studies were all negative.

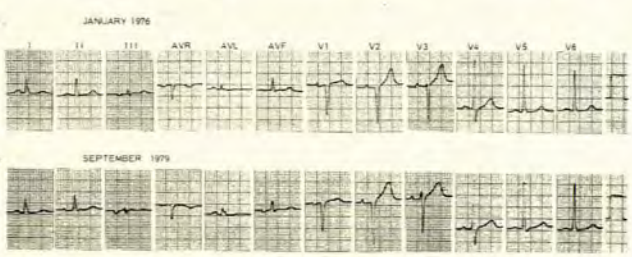

Fig. 1. a — ECG showing a possible old transmural anteroseptal myocardial infarction; b — ECG taken some 4 years later, showing no significant change.

I first saw the patient in October 1977 when he was admitted to the Coronary Care Unit of Tygerberg Hospital. His history was that of severe chest pain occurring at rest. Serial electrocardiographic and enzyme studies documented a non-transmural, anterolateral acute myocardial infarction (AMI). Clinical examination revealed no abnormal features apart from an apical grade 1/6 systolic murmur which did not alter with the Valsalva manoeuvre or with the patient squatting. The possibility of hypertrophic obstructive cardiomyopathy or mitral valve prolapse was considered, but this was not substantiated by normal echocardiographic findings. The patient was discharged without complications of the infarction and was advised to stop smoking (he had been smoking some 40 cigarettes daily for many years). Other possible risk factors such as hyperlipoproteinaemia and diabetes mellitus were excluded by appropriate investigations. There was no family history of heart disease.

The patient continued experiencing angina on effort despite receiving maintenance propranolol and sublingual isosorbide dinitrate. In addition, he complained of several episodes of palpitations related to effort, which were followed by angina and then by dizziness and syncope. Holter monitoring revealed numerous multifocal ventricular extrasystoles (only related to his symptom of angina), ventricular bigeminy and trigeminy, but no evidence

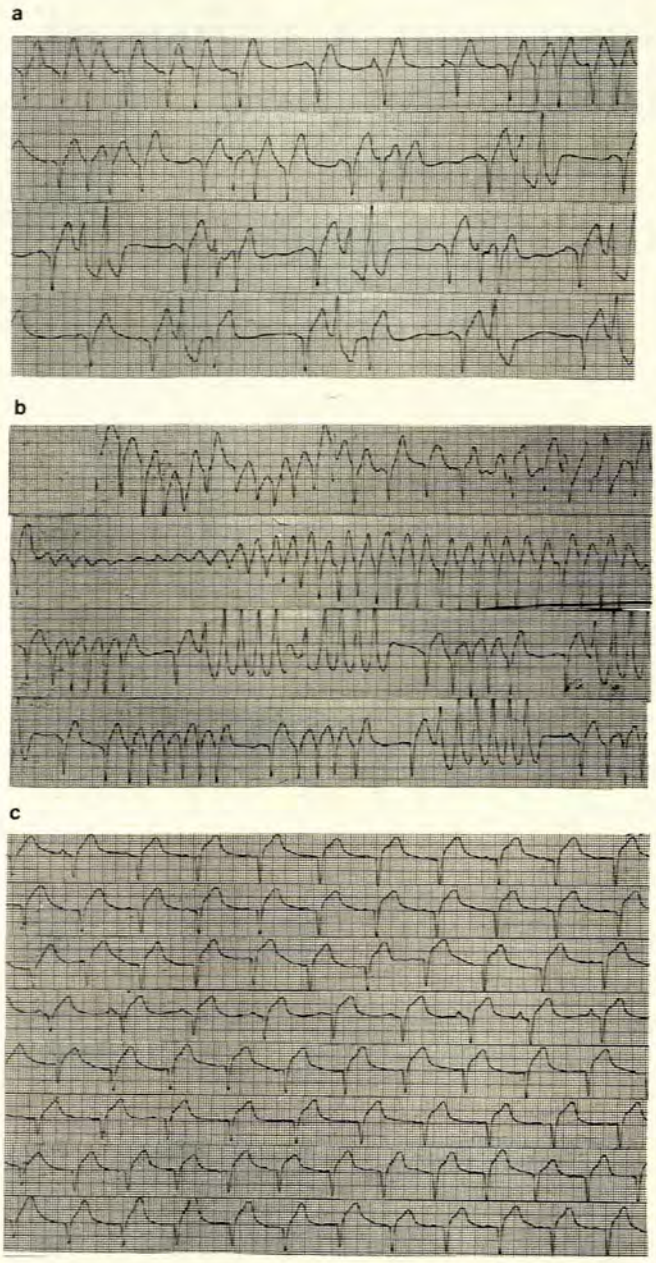

Fig. 2. Holter electrocardiographic tracings (modified standard lead II): a — multifocal ventricular extrasystoles, ventricular bigeminy and trigeminy is visualized; b — *'torsade de pointes'* (atypical ventricular tachycardia); c — most recent study, showing normal sinus rhythm.

of ventricular tachycardia or fibrillation (Fig. 2a). No supraventricular arrhythmias were recorded, but some 2 mm of horizontal ST-segment depression was noted during episodes of angina (Fig. 3).

A submaximal treadmill stress test induced no signs of ischaemia or any ventricular tachycardia or fibrillation. The patient was successfully treated with mexiletine and quinidine, and the dosage of ß-blocker was increased. However, he continued to experience effort angina and presyncope. The onset of frequent angina at rest and severe head injuries secondary to syncope prompted readmission in September 1979. Repeated electro-encephalographic recordings were unremarkable and neurological assessment was negative.

He was an exceptionally well-built, tall man with no evidence of hypertension or valvular heart disease. A chest radiograph was

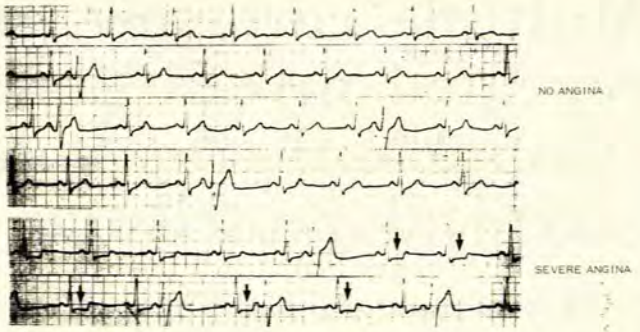

Fig. 3. Holter electrocardiographic tracings (modified standard lead II). Several unifocal ventricular extrasystoles are seen; significant (2 mm) horizontal ST-segment depression (arrowed) is present during severe angina.

entirely normal and a resting ECG (Fig. 1b) showed similar features to those of the ECG recorded in January 1976. The biochemical and haematological values were all within normal limits. M-mode echocardiography was again negative.

The patient continued to experience unstable angina and it was therefore decided to carry out cardiac catheterization and selective coronary angiography. The procedure documented normal intracardiac pressures and parameters of left ventricular function. Left ventricular cine angiography (Fig. 4) identified a normally contracting chamber with a definite area of anterobasal dyskinesia secondary to myocardial infarction. There was no evidence of mitral valve prolapse, mitral insufficiency, calcification or hypertrophic cardiomyopathy. The right coronary artery (RCA) was dominant and displayed no obstructive lesions (Fig. 5). Likewise, the left coronary artery (LCA) was also seen to be normal on angiography (Fig. 6). The patient was therefore diagnosed as having 'angina pectoris with normal coronary arteries'. Ergonovine provocation was not carried out at this stage. Treatment with the calcium-blocking agent nifedipine was commenced, in addition to high dosage isosorbide dinitrate and quinidine gluconate. Propranolol was discontinued since coronary vasospasm was considered likely.

The patient was followed up regularly on an outpatient basis at the Cardiac Clinic of Tygerberg Hospital. He continued to complain of episodes of long-lasting, atypical and cyclical precordial pain at rest, which were poorly relieved by sublingual isosorbide dinitrate. In addition, he experienced bitemporal headaches associated with visual disturbance and nausea. These attacks were most suggestive of migraine. Several Holter monitoring sessions failed to document ventricular tachycardia or fibrillation. Furthermore, a possible 'sick sinus syndrome' could not be demonstrated. It was then decided to add sotalol hydrochloride to his calcium-blocker therapy in view of its additional class III anti-arrhythmic action. The quinidine gluconate and mexiletine were discontinued. Repeated neurological assessment revealed no abnormality, there being no sign of temporal lobe epilepsy in particular. Repeat barium studies of the upper gastro-intestinal tract were negative and the cervical spine was normal. His ECG reading remained unchanged from that taken in 1979.

The patient's symptoms then improved quite drastically, so much so that he was able to return to his work as a welder; however, this proved to be only a temporary relief. In January 1982 he was seen in the casualty department with severe facial injury secondary to syncope preceded by a peculiar epigastric sensation, palpitations and a crushing retrosternal pain. Again, a resting ECG was unchanged from previous tracings. He was then admitted to the Cardiac Unit for observation and Holter monitoring. On this occasion repeated Holter examinations revealed long episodes of ventricular bigeminy, trigeminy, complex ventricular extrasystolic activity, ventricular tachycardia and *'torsade de pointes'* (atypical ventricular tachycardia) (Fig.

2b). Supraventricular arrhythmias were also documented. The dosage of sotalol was increased and that of nifedipine continued. He had no syncope while hospitalized for a period of several weeks, and repeat M-mode echocardiograms were again normal. The patient was discharged, only to be readmitted within a few weeks with unstable angina pectoris, presyncope and syncope. All medication was then discontinued, apart from the frequently administered sublingual isosorbide dinitrate. Repeated serial enzyme estimations and resting ECGs were all within normal limits. Ventricular ectopic activity also appeared to have regressed. Submaximal treadmill stress testing was repeated but this failed to show any ischaemia or provoke ventricular arrhythmias. A thallium-201 exercise test was then performed, but this did not reveal features positive for myocardial ischaemia.

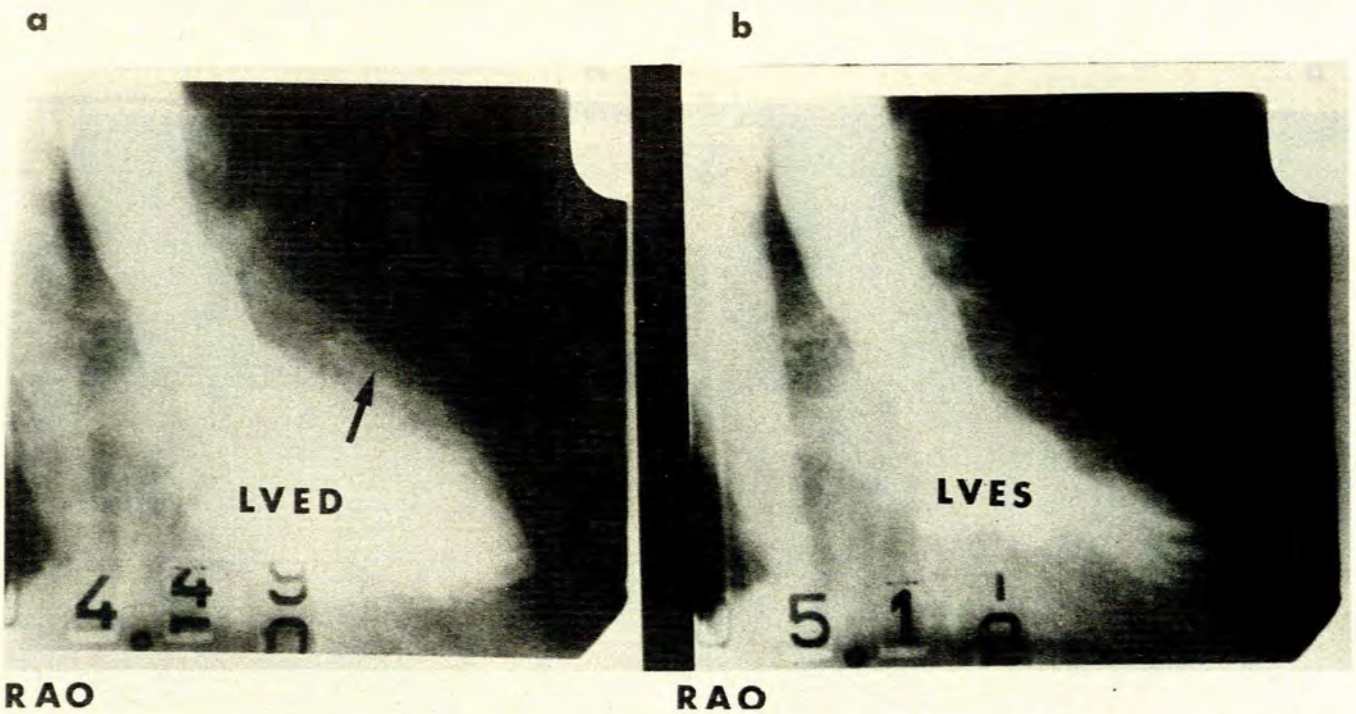

Fig. 4. Left ventricular cine angiograms demonstrating area of anterobasal dyskinesia (arrowed) due to previous myocardial infarction: a — right anterior oblique (RAO) view with left ventricle in end-diastole (LVED); b—RAO view with left ventricle in end-systole (LVES).

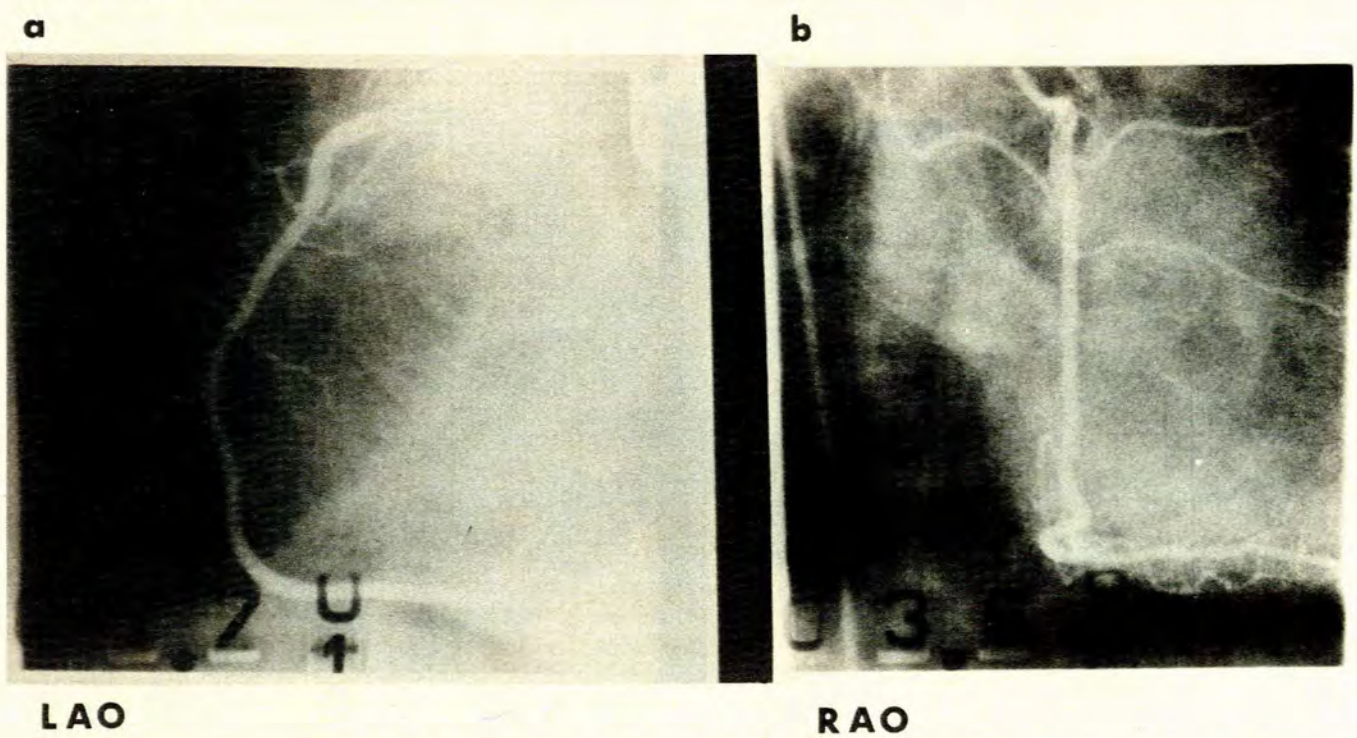

Fig. 5. Right coronary cine angiograms in the (a) left anterior oblique (LAO) and (b) RAO views. The artery is dominant and there are no visible lesions.

Because no adequate explanation was found for the symptoms and coronary vasospasm seemed a likely pathophysiological mechanism, it was decided to undertake repeat cardiac catheterization, selective coronary angiography and ergonovine provocation. All the intracardiac pressures and indices of left ventricular contractility were normal. Left ventricular cine angiography in the RAO projection still demonstrated the anterobasal dyskinesia shown previously, but no other abnormalities (Fig. 7). Baseline selective coronary angiography in multiple projections delineated a dominant RCA with a minor internal luminal irregularity in its second part (Fig. 8). This lesion was calculated as a 42% diameter stenosis and 67% area stenosis (Table I). The LCA appeared normal on angiography (Fig. 9). The patient did not complain of chest pain during the injections and there were no electrocardiographic changes in standard lead II and lead V5 on the oscilloscope. A 12-lead ECG was no different from the previously recorded tracings. The ergonovine provocation test was then carried out by the injection of an initial bolus of 0.025

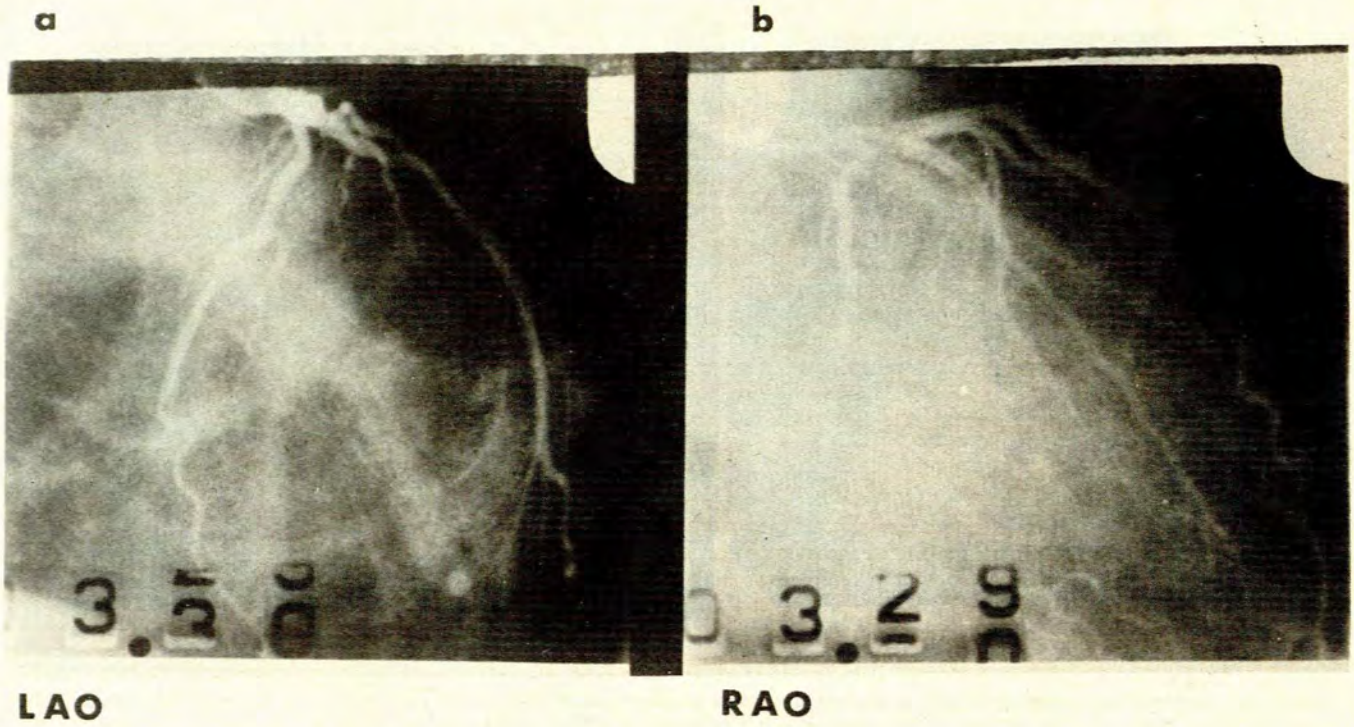

Fig. 6. Left coronary cine angiograms in the (a) LAO and (b) RAO projections, demonstrating normal vessels.

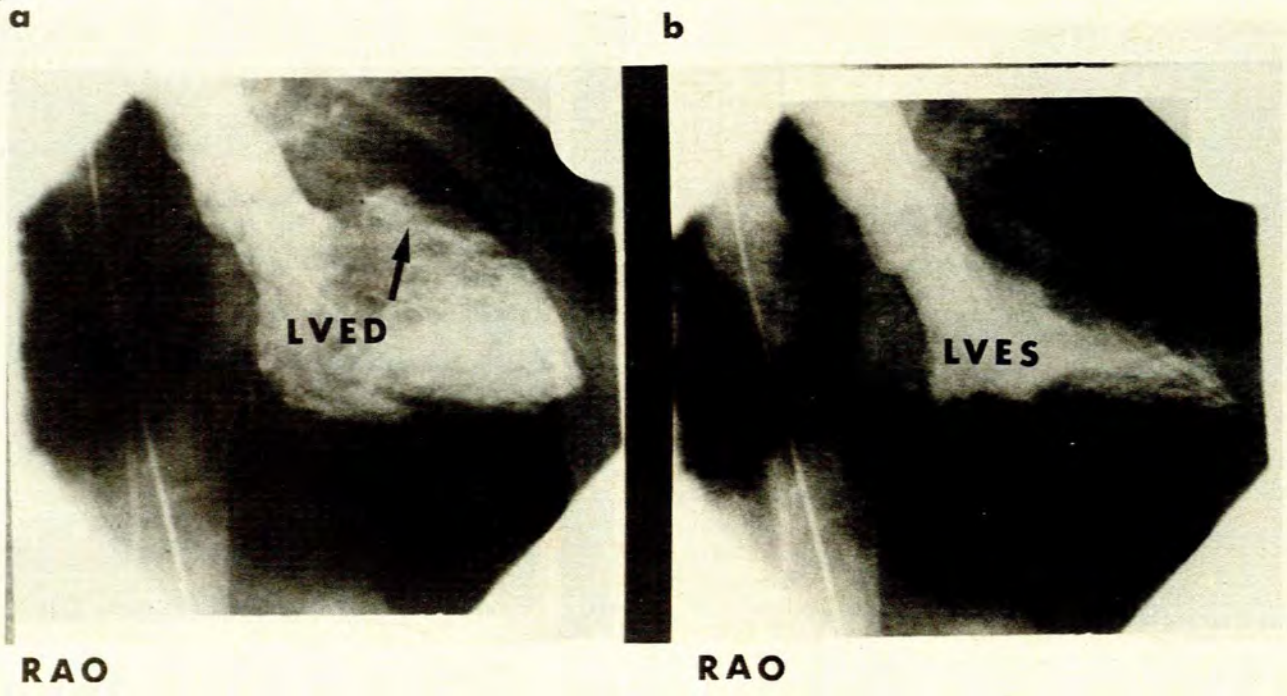

Fig. 7. Left ventricular angiograms demonstrating area of anterobasal dyskinesia (arrowed) due to past myocardial infarction. a — RAO view with LVED; b — RAO view with LVES.

mg into the main pulmonary artery while monitoring the aortic pressure and standard lead II and lead V5 on the oscilloscope. In addition, a 12-lead ECG was recorded every minute. A further bolus of 0,025 mg was given after a period of 4 minutes and the monitoring procedure repeated. Boluses of 0,05 mg were then administered to a total dosage of 0,4 mg of ergonovine maleate.

The RCA was then opacified with contrast medium in the LAO view, at which stage a severe, long-segment (7 mm) constriction was noted in the area previously delineated by an insignificant narrowing (Fig. 10a); this was calculated as causing an 80% diameter stenosis and 96% area stenosis (Table I). At this stage the patient complained of severe retrosternal pain accompanied by marked ST-segment elevation noted in standard lead II on the oscilloscope (unfortunately unrecorded). The patient was promptly given sublingual isosorbide dinitrate 5 mg and repeated right coronary cine angiograms were taken in the LAO projection (Fig. 10b). His chest pain subsided quite rapidly with return of the ST segment to the iso-electric line. Injection of intracoronary nitrate was not necessary, although this preparation was available. Repeat injections into the RCA demonstrated

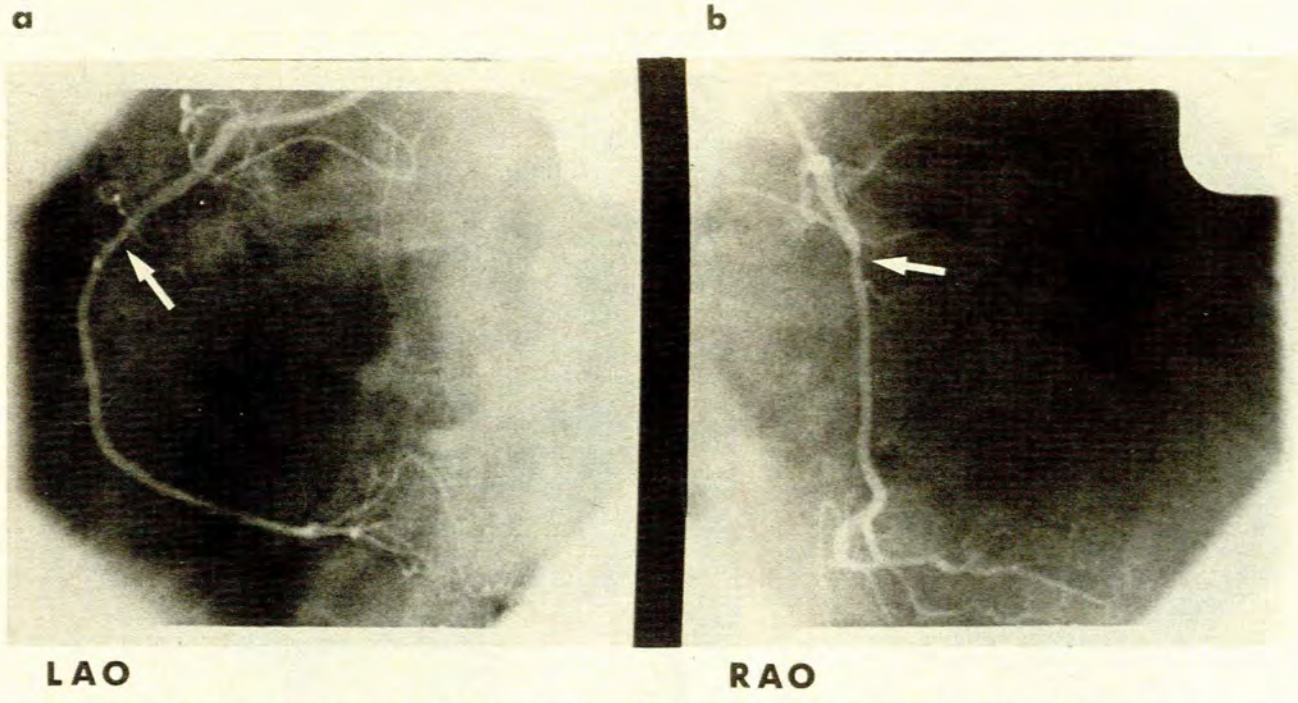

Fig. 8. Right coronary cine angiograms in the (a) LAO and (b) RAO views, taken before ergonovine provocation. A minor luminal irregularity (arrowed) is shown in (a).

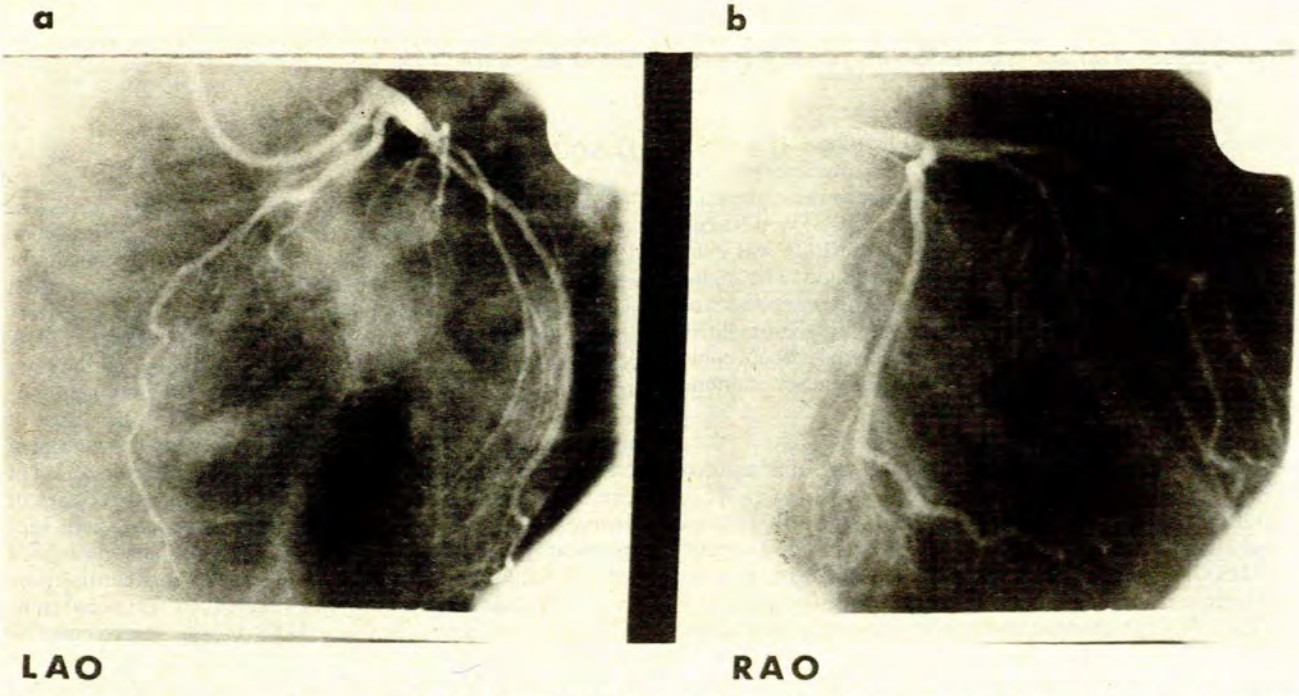

Fig. 9. Left coronary cine angiograms in the (a) LAO and (b) RAO projections, taken before ergonovine provocation. The vessels are angiographically normal.

TABLE I. CORONARY ANGIOGRAPHIC MEASUREMENTS

	Pre-ergo.	Post-ergo.			
	(LAO)	1(LAO)	2(LAO)	3(RAO)	4(RAO)
Minimum diameter (mm)	**1,40**	**0,52**	**1,14**	**1,80**	**1,55**
% diameter stenosis	**42**	**80**	**52**	**25**	**35**
Length of lesion (mm)	**6,0**	**7,0**	**7,0**	**2,0**	**4,0**
Minimum area (mm^2)	**1,54**	**0,22**	**1,01**	**2,55**	**1,88**
% area stenosis	**67**	**96**	**77**	**43**	**58**

Pre-ergo. = before ergonovine; post-ergo. = after ergonovine; LAO = left anterior oblique view; RAO = right anterior oblique view; 1, 2, 3, 4 = time sequence of coronary arteriogram after ergonovine injection.

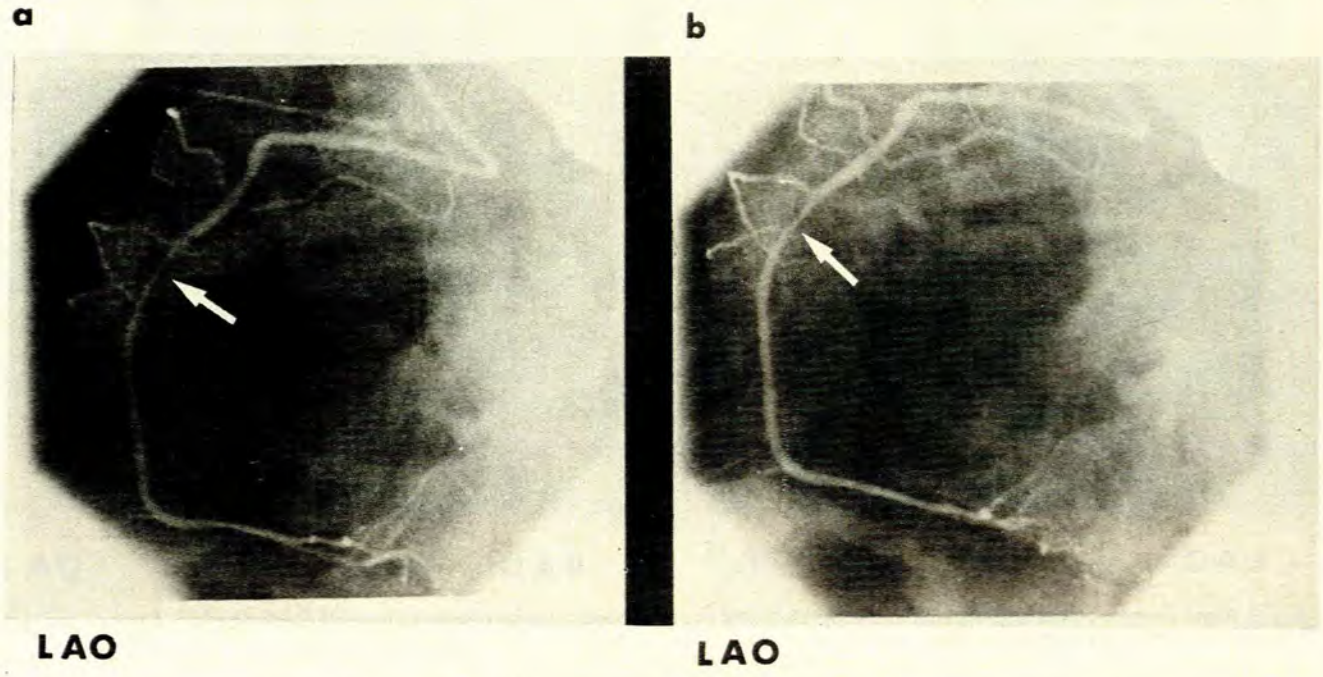

Fig. 10. Right coronary cine angiograms in the LAO projection immediately after ergonovine provocation. Severe vasospasm (arrowed) is seen in (a), which is less following sublingual isosorbide dinitrate (b) (see Table I).

a progressive decrease in severity of the obstruction (Fig. 10b); the vasoconstriction now amounted to a 52% diameter stenosis and 77% area stenosis, measurements similar to those obtained before the injection (Table I). The RCA in the RAO view had no significant vasospasm (Fig. 11). Similarly, the LCA was delineated in the RAO and LAO projections and found to be angiographically normal (Fig. 12). There were no further episodes of chest pain and no further electrocardiographic abnormalities could be visualized. The procedure was completed without complication. On subsequent days serial serum enzyme estimations and 12-lead ECGs showed no evidence of AMI.

A definitive diagnosis of coronary vasospasm superimposed on a probable atheromatous lesion in the second part of the RCA was thus established. The patient was then placed on a regimen comprising high doses of oral nifedipine and isosorbide dinitrate. In addition, oral quinidine gluconate 324 mg 8-hourly was administered. Repeated Holter monitoring failed to show any significant ST-segment elevation or depression, or any ventricular arrhythmias (Fig. 2c). The patient had no further episodes of chest pain and was discharged. He has remained asymptomatic. Numerous periods of Holter monitoring have documented normal sinus rhythm as well as no ischaemic ST-T-wave changes.

Discussion

The concept of coronary artery spasm in the pathogenesis of angina pectoris is not new since it was suggested by Heberden in 1792, although he is usually remembered for having defined the criteria for 'classic' angina pectoris, that is, effort-related chest pain. In 1876 Latham supported the concept of coronary artery spasm and this was later given more credibility by Osler in 1910. Nevertheless, following this the repeated finding of coronary artery thrombi in patients dying of myocardial infarction prompted support for the concept of an organic obstructive cause of angina pectoris rather than a functional one. Thus, the concept of coronary vasospasm lost popularity for a considerable period of time until 1955 when Prinzmetal *et al.*[1] documented cases of paroxysmal angina occurring at rest and associated with very significant, reversible ST-segment elevation. They postulated the superimposition of coronary artery spasm on atherosclerotic narrowing, thus reintroducing the concept of a functional component in symptomatic ischaemic heart disease as represented by angina, AMI and sudden death. In the succeeding years the work of such researchers as MacAlpin,[2] Oliva and Breckenridge,[3] Conti *et al.*,[4] Chahine *et al.*,[5] and Maseri *et al.*[6] firmly established the pivotal role of coronary vasospasm, not only in the presence

of coronary atheroma but also with underlying angiographically normal coronary arteries. The last few years have witnessed a flood of publications concerning coronary artery spasm, the implications of which are essential to the understanding of the rationale of current therapeutic practice in the clinical spectrum of ischaemic heart disease. Our case illustrates some of the important aspects of coronary vasospasm. In addition, the life-threatening arrhythmia termed *'torsade de pointes'* appears to be described for the first time in angiographically proven coronary artery spasm.

Atypical ventricular tachycardia

This arrhythmia was initially described by Dessertenne[7] in 1966. Various synonyms have been employed, e.g. polymorphous ventricular tachycardia, atypical ventricular tachycardia,[8] cardiac ballet,[9] repetitive paroxysmal tachycardia, transient ventricular fibrillation,[10] and *'torsade de pointes'*.[11] The mechanism of this potentially fatal arrhythmia is not clearly understood, but it is thought to be due to a re-entry mechanism secondary to impaired ventricular repolarization. Krikler[11] attempts to distinguish *'torsade de pointes'* from ventricular tachycardia by stating

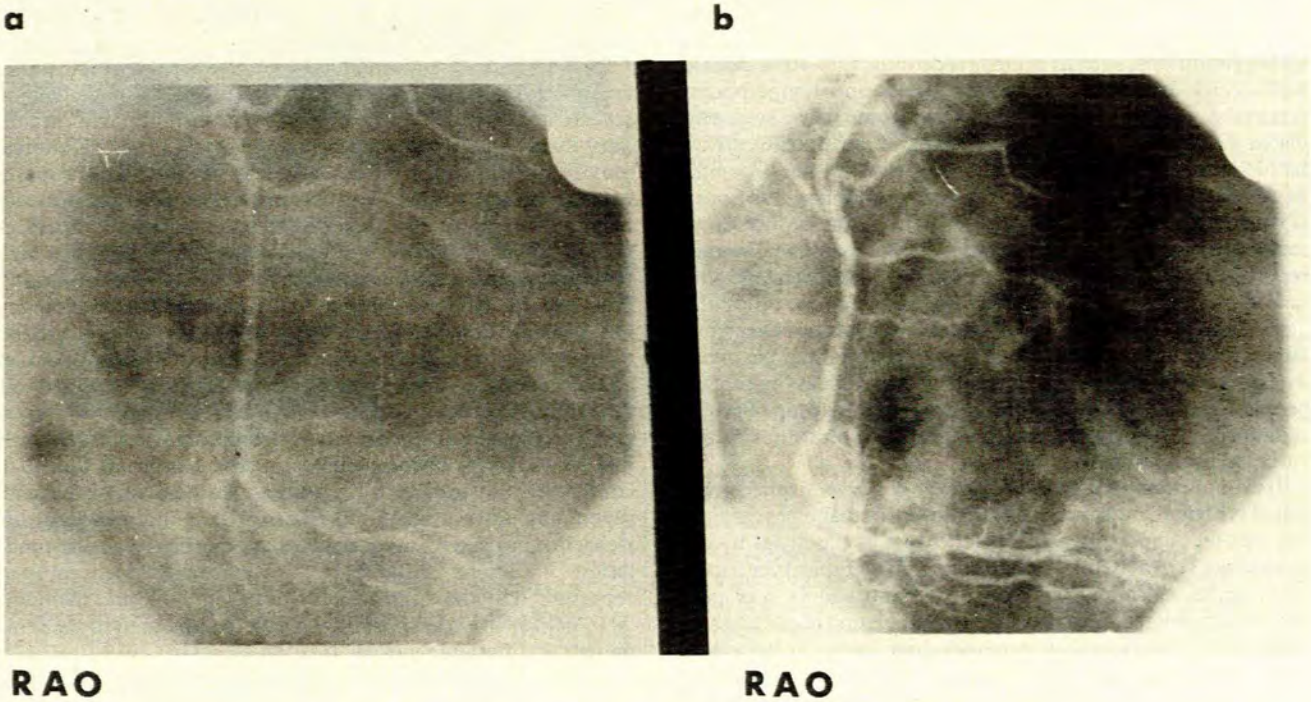

Fig. 11. Right coronary cine angiograms in RAO view showing no significant vasospasm.

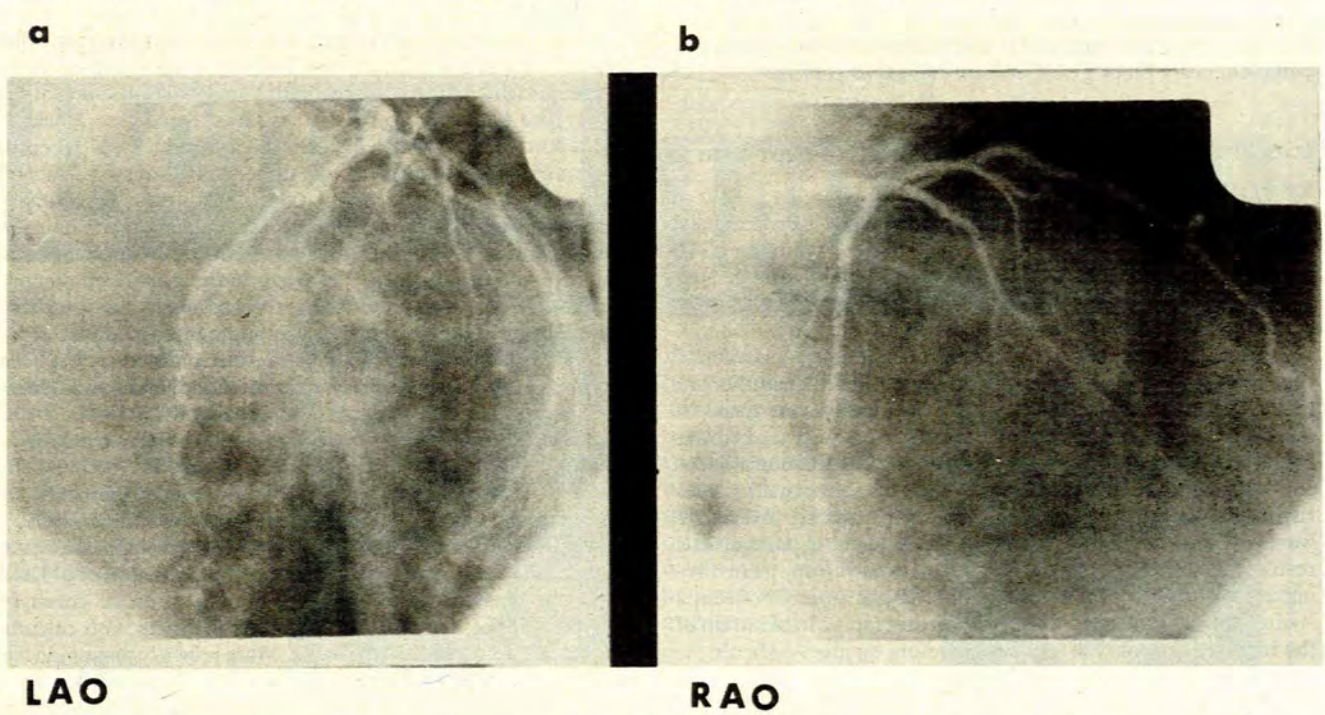

FIg. 12. Left coronary cine angiograms in the (a) LAO and (b) RAO projections after ergonovine provocation. No vasospasm is evident.

that in the latter a prolonged QT interval is present, and that a late ventricular extrasystole initiates the arrhythmia which has the form of 'twisting complexes' due to undulation of the QRS axis. The episodes may be short or prolonged, and a very real danger is that of degeneration into ventricular fibrillation with ensuing sudden death. Difficulty often arises in distinguishing this arrhythmia from 'bidirectional ventricular tachycardia'.[12]

Classically, *'torsade de pointes'* has been described in the setting of QT prolongation. Thus, drugs such as quinidine,[13] procainamide, lignocaine, prenylamine, disopyramide,[14] mexiletine, and amiodarone[15] have been incriminated, as have tricyclic antidepressants and the phenothiazines.[16] Electrolyte disturbances such as hypokalaemia (Conn's syndrome; familial periodic paralysis) and hypomagnesaemia are also well-known causes. Other conditions, such as acute myocarditis, sino-atrial disease, high-degree atrioventricular block, Jervell and Lange-Nielsen syndrome, and the Romano-Ward syndrome, have been associated with this arrhythmia. In 2 cases paroxysmal atrioventricular block causing syncope was associated with *'torsade de pointes'* as well as angina pectoris attributed to coronary vasospasm (Prinzmetal's variant angina),[17] but vasospasm was not documented by coronary arteriography. I was unable to find any report in the literature of proven coronary vasospasm and *'torsade de pointes'*, so our case may be unique. Very rarely this arrhythmia has complicated AMI due to asynchrony of ventricular repolarization. Atypical ventricular tachycardia, occurring over a period of many years, has been reported in asymptomatic people. The use of anti-arrhythmic drugs in this group of people is uniformly ineffective, and they appear to suffer from a benign variation of this abnormality.

It is important to distinguish *'torsade de pointes'* from conventional ventricular tachycardia and idioventricular tachycardia, as the treatment and prognosis differ. Most of the drugs used to counteract ventricular tachycardia can cause atypical ventricular tachycardia. Correction of electrolyte disturbances is of paramount importance, as well as the discontinuation of the causative drug. Direct-current countershock may convert *'torsade de pointes'* to ventricular fibrillation. Krikler[11] and Krikler and Curry[12] suggest the emergency use of intravenous isoprenaline infusion in an attempt to shorten the period of repolarization and thus counteract the defect of asynchronous depolarization. Overdrive temporary transvenous cardiac pacing has been documented as life-saving, and is also indicated in the presence of complete heart block giving rise to *'torsade de pointes.'*

Electrocardiographic spectrum of coronary vasospasm

The classic prototype of coronary artery spasm is Prinzmetal's variant angina, originally described with marked temporary ST-segment elevation (indicative of subepicardial injury) associated with recurrent episodes of atypical chest pain, often occurring at rest.[1] This electrocardiographic change is manifest in transmural myocardial ischaemia and is often secondary to total occlusion of the involved coronary artery, the anatomical distribution of which is accurately localized by the ECG. Less severe forms of myocardial ischaemia due to vasospasm causing incomplete occlusion of a coronary artery give rise to non-transmural (subendocardial) myocardial ischaemia. This latter abnormality gives rise to 'pseudonormalization' of T waves (previously inverted T waves become upright) or transient ST-segment depression as a result of distal collateral blood supply, or even vasospasm involving a small coronary artery branch.[18] Non-transmural ischaemia is often diffuse, and accurate electrocardiographic localization of the involved coronary artery can therefore be most difficult.

More recently, coronary vasospasm has also been implicated in effort-induced angina pectoris.[19,20] Thus, stress-testing has shown transient ST-segment elevation which often correlates with significant obstructions delineated by coronary arteriography. ST-segment depression occurring on exercise has also been attributed to coronary vasospasm, and is more frequently associated with underlying significant atherosclerotic obstructive lesions. Nevertheless, Boden *et al.*[21] have demonstrated exercise-induced ST-segment depression due to coronary vasospasm of an angiographically normal coronary artery. This important observation raises the exciting possibility that vasospasm may well be more commonly responsible for effort-induced angina pectoris, as well as a 'positive stress ECG'. The concomitant use of thallium-201 in patients with coronary vasospasm at rest and/or on exercise has more clearly localized the area of myocardial ischaemia and the coronary artery involved.[18] Cases of multiple coronary artery spasm have also been documented, but are rather rare.[22]

In some patients transient Q waves have been reported during an episode of coronary vasospasm, but this electrocardiographic feature usually signifies the presence of transmural AMI secondary to vasospastic subendocardial ischaemia. The QT interval may be prolonged during an episode of coronary artery spasm causing variant angina. This electrophysiological abnormality may well be important as regards the precipitation of *'torsade de pointes'* (as in our patient) and other arrhythmias, some of which may prove fatal and thus account for cases of 'sudden death'. However, the Holter recordings of this patient failed to show any QT prolongation before the onset of the atypical ventricular tachycardia (*'torsade de pointes'*) associated with episodes of angina experienced at rest. Also, this investigation revealed significant ST-segment depression during the angina attacks at rest, this being indicative of non-transmural myocardial ischaemia secondary to 'incomplete' coronary vasospasm. This is in contrast to the marked ST-segment elevation associated with severe angina resulting from transient transmural myocardial ischaemia provoked by ergonovine (ergometrine) maleate stimulation. Variations in the severity of myocardial ischaemia, as represented by the differing electrocardiographic and thallium-201 ('cold spot') scans, have been well documented in the same patient at different times.[18]

Aetiology and provocation of coronary vasospasm

It has been appreciated for a long time that the epicardial coronary arteries are innervated both by α-adrenergic and ß-adrenergic fibres. Constriction is attributed to stimulation of the former and dilatation to the latter. Thus, ß-receptor blockade would tend to negate vasodilatation and unmask the α-receptor vasoconstrictor action. Some researchers have stressed an actual increase in α-adrenergic stimulation as manifested by coronary vasospasm occurring frequently at night and in the early hours of morning (circadian rhythm), as well as during cold weather and rapid eye movement sleep.[23] More recently it has been demonstrated that underlying coronary atherosclerosis, and probably altered serum cholesterol levels, may augment α-mediated coronary vasospasm. Intrinsic smooth-muscle contractility has been clearly shown in the coronary arteries of explanted and denervated hearts known to be dependent on calcium ion fluxes.[24] The thromboxane A_2-prostacyclin counteraction has also been considered to be important in coronary vasospasm. The former substance is released by platelets and is a potent smooth-muscle constrictor, while the latter is synthesized by intima and is a powerful vasodilator. Possible underlying pathophysiological mechanisms are further complicated by the influence of pH and blood gas tensions, alkalosis being said to provoke coronary vasospasm since hydrogen ions directly compete with calcium ions for entry into myocardial cells. More recently histamine has been implicated.[25] Furthermore, Maseri *et al.*[6] favour the concept of 'hypersensitive' coronary smooth muscle. It would therefore seem highly likely that the cause of coronary vasospasm is multifactorial.

An understanding of the possible underlying mechanisms of coronary artery spasm has prompted the use of various 'provocative tests'. Much discussion has also centred around the argument that these tests may not be truly representative of the operational mechanism in the patient subjected to the provocation. The 'cold pressor test' has been utilized for some years now, the rationale for its use being the resulting sympathetic stimulation with predominant α-adrenergic action.[26] Thus, an increase in coronary resistance occurs, accompanied by a reduction in coronary blood flow in arteries affected by atherosclerotic obstruction. On occasion this stimulus has proved so potent that actual myocardial infarction has resulted.[27] However, generalized rather than focal vasoconstriction ensues, making it a somewhat unreliable provocative test. The 'hyperventilation test' has also been employed, either alone or in combination with the former test, with varying reliability.[28] Thus, these stimuli have mostly been abandoned in favour of the use of the 'ergonovine stimulation test'.[29-31] Ergonovine maleate has been shown to be highly specific and sensitive in patients with Prinzmetal's variant angina, and has therefore become the standard test for the provocation of coronary vasospasm. Its safety has been firmly established, although (rarely) complications such as ventricular fibrillation, complete heart block, AMI and death have been documented, especially when the test was not carried out with all the caution required. Some centres use this provocation test on outpatients,[32] relying on the patient developing chest pain accompanied by ST-segment elevation or depression, or even pseudonormalization of T waves, for 'positivity'. However, Conti *et al.*[4] are strict in their definition of a positive ergonovine test, insisting on 'any reduction in coronary artery lumen, with or without chest pain, accompanied by objective parameters of myocardial ischaemia, in the absence of increased heart rate and markedly increased blood pressure'. They therefore imply that selective coronary angiography is mandatory in the performance of this provocative procedure. The diagnostic test has become so reliable that workers are employing it in the assessment of the effectiveness of medical therapy. Provoked coronary vasospasm can usually be rapidly relieved by isosorbide dinitrate given sublingually, or nitroglycerine injected either intravenously or directly into the affected coronary artery.[33] Very recently, sublingual nifedipine has been successfully employed for this purpose.[34]

The coronary vasospasm - myocardial infarction link

Oliva and Breckenridge[3] were the first to convincingly demonstrate the importance of coronary artery vasospasm in the causation of AMI. These workers documented dilatation of a significant coronary lesion in response to intracoronary nitroglycerine in 40% of 15 patients who were catheterized within 12 hours of having suffered an AMI. Furthermore, the fact that obstructive coronary thrombi are absent in some 73 - 100% of patients dying from non-transmural AMI, and in some 46% dying from transmural AMI, makes the (likely) role of coronary vasospasm more attractive. In fact, many researchers firmly believe that coronary thrombosis only occurs subsequent to the onset of AMI.

The incrimination of coronary vasospasm as the initiating factor in the development of AMI is strengthened by the knowledge that 15 - 20% of patients suffering from Prinzmetal's variant angina sustain both non-transmural and transmural myocardial infarctions. Maseri *et al.*[35] have demonstrated AMI in the same area in which transient reversible ischaemia (attributed to coronary artery spasm) had been noted on thallium-201 scintigrams. It is believed that most episodes of coronary artery spasm are too shortlived to result in myocardial infarction, although the late intracoronary injection of nitrates may fail to reverse the spasm. Gersh *et al.*[36] reported that vasospasm of angiographically normal coronary arteries might cause transmural AMI on an 'allergic' basis since one of their patients had asthma, hypereosinophilia and systemic disease, probably of immunological aetiology. This concept appears to be further supported by the recent documentation of coronary artery spasm as part of an anaphylactoid reaction to iodine-containing contrast material.[37]

An exceptionally fine study by Gertz *et al.*[38] demonstrated the production of coronary artery endothelial cell damage with subsequent thrombus formation after partial experimental coronary constriction, claiming that vasospasm was important in the causation of AMI. Recently Waters *et al.*[39] reported on the frequent appearance of AMI within 1 month of the demonstration of variant angina, and noted that this would take place in the absence of significant fixed atherosclerotic coronary lesions and despite the apparent improvement of symptoms after administration of calcium blockers. The real possibility that coronary vasospasm could cause an extension of an AMI was recently documented by Koiwaya *et al.*[40] These authors showed that ST-segment elevation frequently occurred in areas represented by new Q waves and in patients in whom the anatomical supply was confirmed by angiographically documented and provoked coronary vasospasm, and that life-threatening arrhythmias ensued.

With the tremendous enthusiasm displayed in attempts to reduce infarct size by acute intracoronary thrombolysis with streptokinase, the incidence of coronary vasospasm has been estimated. In a series of 30 patients, Leinbach and Gold[41] showed that the main pathogenetic mechanism was that of coronary thrombosis rather than coronary vasospasm. However, more experience will be needed to determine the true incidence of coronary vasospasm before, during, and after an AMI.

As regards the present case, there appear to be sufficient data to suggest that previous transmural anteroseptal and non-transmural anterolateral myocardial infarctions were due to vasospasm of the LCA, since this was found to be patent on two separate cardiac catheterization procedures. Also, coronary vasospasm was clearly provoked in the RCA in the absence of an inferior myocardial infarction. Thus, multiple coronary artery spasm almost certainly took place. In addition, the frequent episodes of '*torsade de pointes*' were more than likely secondary to AMI precipitated by significant coronary artery spasm.

Therapeutic considerations

The most effective drugs for coronary vasospasm appear to be either the long-acting nitrates[42] or calcium-channel blockers,[43] or a combination of these two, although some authors have reported improvement in only 50% of patients treated with long-acting nitrates, perhaps because of the short pharmacological half-life of these drugs. Nevertheless, nitroglycerine ointment has proved most efficacious in the coronary care unit,[44] and will probably be used more extensively in the future. The various calcium-blocking drugs, such as nifedipine,[45] diltiazem,[46] verapamil[47] and amiodarone[48] have also been used with exceptionally good results and would certainly seem to offer the most ideal form of medical therapy to date.

A surgical approach to therapy consists of plexectomy (partial denervation of the heart), combined with coronary artery bypass if haemodynamically significant atherosclerotic obstructive lesions are also present.[49] A more drastic form of surgery is that of complete denervation of the heart (autotransplantation), which has been employed successfully in severe refractory coronary vasospasm.[50] The effectiveness or otherwise of treatment has been assessed by the use of repeat ergonovine provocation tests, as well as hyperventilation in some patients.

On theoretical grounds the use of ß-adrenergic blocking drugs would be contraindicated in proved coronary vasospasm because they unmask the α-adrenergic action stimulated by endogenous

catecholamines. Worsening of variant angina has been clearly documented,[51] and these drugs should therefore be employed only as a last resort. However, the use of selective $ß_1$-receptor blockade should lessen this adverse action.

So far, the therapeutic response of my patient is most satisfactory. He has denied any further rest- or effort-related angina, and has had no more episodes of presyncope or syncope. Repeated Holter monitoring has failed to detect any ectopic ventricular activity, specifically episodes of *'torsade de pointes'*.

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REFERENCES

1. Prinzmetal M, Kennamer R, Merliss R *et al.* A variant form of angina pectoris; preliminary report. *Am J Med* 1959; **27:** 375-388.
2. MacAlpin RN. Relation of coronary arterial spasm to sites of organic stenosis. *Am J Cardiol* 1980; **46:** 143-153.
3. Oliva PB, Breckenridge JC. Acute myocardial infarction with normal and near normal coronary arteries. Documentation with coronary arteriography within 12½ hours of the onset of symptoms in two cases (three episodes). *Am J Cardiol* 1977; **40:** 1000-1007.
4. Conti CR, Feldman RL, Pepine CJ. Coronary artery spasm; prevalence, clinical significance, and provocative testing. *Am Heart J* 1982; **103:** 584-588.
5. Chahine RA, Raizner AE, Ishimori T, Luchi RJ, McIntosh HD. The incidence and clinical implications of coronary artery spasm. *Circulation* 1975; **52:** 972-978.
6. Maseri A, Chierchia S, L' Abbate A. Pathogenetic mechanisms underlying the clinical events associated with atherosclerotic heart disease. *Circulation* 1980; **62:** supp V, 3-13.
7. Dessertenne F. La tachycardie ventriculaire à deux foyers opposés variables. *Arch Mal Coeur* 1966; **59:** 263.
8. Meltzer RS, Robert EW, McMorrow M *et al.* Atypical ventricular tachycardia as a manifestation of disopyramide toxicity. *Am J Cardiol* 1978; **42:** 1049-1053.
9. Smirk FH, Ng J. Cardiac ballet: repetitions of complex electrocardiographic patterns. *Br Heart J* 1969; **31:** 426-434.
10. Tamura K, Tamura T, Yoshida S, Inui M, Fukuhara N. Transient recurrent ventricular fibrillation due to hypopotassemia with special note on the U wave. *Jpn Heart J* 1967; **8:** 652.
11. Krikler DM. A fresh look at cardiac arrhythmias. *Lancet* 1974; **i:** 913-918.
12. Krikler DM, Curry PVL. *Torsade de pointes,* an atypical ventricular tachycardia (Editorial). *Br Heart J* 1976; **38:** 117-120.
13. Seltzer A, Wray HW. Quinidine syncope. Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. *Circulation* 1964; **30:** 17-26.
14. Nicholson WJ, Martin CE, Gracey JG, Knoch HR. Disopyramide-induced ventricular fibrillation. *Am J Cardiol* 1979; **43:** 1053-1055.
15. Keren A, Tzivoni D, Gottlieb S, Benhorin J, Stern S. Atypical ventricular tachycardia (*torsade de pointes*) induced by amiodarone. *Chest* 1982; **81:** 384-386.
16. Schoonmaker FW, Osteen RT, Greenfield JC. Thioridazine (Mellaril) induced ventricular tachycardia controlled with an artificial pacemaker. *Ann Intern Med* 1966; **65:** 1076-1078.
17. Chiche P, Haiat R, Steff P. Angina pectoris with syncope due to paroxysmal atrioventricular block: role of ischaemia. Report of two cases. *Br Heart J* 1974; **36:** 577-581.
18. Parodi O, Uthurralt N, Severi S *et al.* Transient reduction of regional myocardial perfusion during angina at rest with ST-segment depression or normalization of negative T waves. *Circulation* 1981; **63:** 1238-1247.
19. Chaitman BR, Waters DD, Theroux P, Hanson JS. S-T segment elevation and coronary artery spasm in response to exercise. *Am J Cardiol* 1981; **47:** 1350-1358.
20. Waters DD, Chaitman BR, Dupras G, Theroux P, Mizgala HF. Coronary artery spasm during exercise in patients with variant angina. *Circulation* 1979; **59:** 580-585.
21. Boden WE, Bough EW, Korr KS *et al.* Exercise-induced coronary artery spasm with S-T segment depression and normal coronary arteriography. *Am J Cardiol* 1981; **48:** 193-197.
22. Dunn RF, Kelly DT, Sadick N, Uren R. Multivessel coronary artery spasm. *Circulation* 1979; **60:** 451-455.
23. Yasue H. Pathophysiology and treatment of coronary arterial spasm. *Chest* 1980; **78:** 216-223.
24. Ginsburg R, Bristow MR, Harrison DC, Stinson EB. Studies with isolated human coronary arteries: some general observations, potential mediators of spasm, role of calcium antagonists. *Chest* 1980; **78:** 180-186.
25. Bristow MR, Ginsburg R, Harrison DC. Histamine and the heart; the other receptor system. *Am J Cardiol* 1982; **49:** 249-251.
26. Raizner AE, Chahine RA, Ishimori T *et al.* Provocation of coronary artery spasm by the cold pressor test· haemodynamic, arteriographic and quantitative angiographic observations. *Circulation* 1980; **62:** 925-932.
27. Shea DJ, Ockene IS, Greene HL. Acute myocardial infarction provoked by a cold pressor test. *Chest* 1981; **80:** 649-651.
28. Girotti LA, Crosatto JR, Messuti H *et al.* The hyperventilation test as a method for developing successful therapy in Prinzmetal's angina. *Am J Cardiol* 1982; **49:** 834-841.
29. Heupler FA, Proudfit WL, Razavi M, Shirey EK, Greenstreet R, Sheldon WC. Ergonovine maleate provocative test for coronary arterial spasm. *Am J Cardiol* 1978; **41:** 631-640.
30. Heupler FA. Provocative testing for coronary arterial spasm: risk, method and rationale. *Am J Cardiol* 1980; **46:** 335-337.
31. Waters DD, Theroux P, Szlachic J *et al.* Ergonovine testing in a coronary care unit. *Am J Cardiol* 1980; **46:** 922-930.
32. Ginsburg R, Lamb IH, Bristow MR, Schroeder JS, Harrison DC. Application and safety of outpatient ergonovine testing in accurately detecting coronary spasm in patients with possible variant angina. *Am Heart J* 1981; **102:** 698-702.
33. Pepine CJ, Feldman RL, Conti CR. Action of intracoronary nitroglycerine in refractory coronary artery spasm. *Circulation* 1982; **65:** 411-414.
34. Schwartz T, Halon D, Gotsman MS. Angiographic relief of coronary artery spasm with sublingual nifedipine. *Chest* 1982; **81:** 127-128.
35. Maseri A, L'Abbate A, Baroldi G *et al.* Coronary vasospasm as a possible cause of myocardial infarction. In: Mason DT, Neri Serneri GG, Oliver MF, eds. *International Meeting on Myocardial Infarction* (International Congress Series No. 491). Amsterdam: Excerpta Medica, 1979: 67-74.
36. Gersh BJ, Bassendine MF, Forman R, Walls RS, Beck W. Coronary artery spasm and myocardial infarction in the absence of angiographically demonstrable obstructive coronary disease. *Mayo Clin Proc* 1981; **56:** 700-708.
37. Druck MN, Johnstone DE, Staniloff H, McLaughlin PR. Coronary artery spasm as a manifestation of anaphylactoid reaction to iodinated contrast material. *Can Med Assoc J* 1981; **125:** 1133-1135.
38. Gertz SD, Uretsky G, Wajnberg RS, Navot N, Gotsman MS. Endothelial cell damage and thrombus formation after partial arterial constriction: relevance to the role of coronary artery spasm in the pathogenesis of myocardial infarction. *Circulation* 1981; **63:** 476-486.
39. Waters DD, Szlachicic J, Miller D, Theroux P. Clinical characteristics of patients with variant angina complicated by myocardial infarction death within 1 month. *Am J Cardiol* 1982; **49:** 658-664.
40. Koiwaya Y, Torii S, Takeshita A, Nakagaki O, Nakamura M. Post-infarction angina caused by coronary arterial spasm. *Circulation* 1982; **65:** 275-280.
41. Leinbach RC, Gold HK. Coronary angiography during acute myocardial infarction: a search for spasm. *Am Heart J* 1982; **103:** 768-772.
42. Ginsburg R, Lamb IH, Schroeder JS, Hu M, Harrison DC. Randomized double-blind comparison of nifedipine and isosorbide dinitrate therapy in variant angina pectoris due to coronary artery spasm. *Am Heart J* 1982; **103:** 44-48.
43. Gunther S, Muller JE, Mudge GH, Grossman W. Therapy of coronary vasoconstriction in patients with coronary artery disease. *Am J Cardiol* 1981; **47:** 157-162.
44. Salerno JA, Previtali M, Medici A *et al.* Treatment of vasospastic angina pectoris at rest with nitroglycerine ointment: a short-term controlled study in the coronary care unit. *Am J Cardiol* 1981; **47:** 1128-1133.
45. Hill JA, Feldman RL, Pepine CJ, Conti CR. Randomized double-blind comparison of nifedipine and isosorbide dinitrate in patients with coronary arterial spasm. *Am J Cardiol* 1982; **49:** 431-438.
46. Kimura E, Kishida H. Treatment of variant angina with drugs: a survey of 11 cardiology institutes in Japan. *Circulation;* 1981; **63:** 844-848.
47. Johnson SM, Mauritson DR, Willerson JT, Cary JR, Hillis D. Verapamil administration in variant angina pectoris: efficacy shown by ECG monitoring. *JAMA* 1981; **245:** 1849-1851.
48. Rutitzky B, Girotti AL, Rosenbaum MB. Efficacy of chronic amiodarone therapy in patients with variant angina pectoris and inhibition of ergonovine coronary constriction. *Am Heart J* 1982; **103:** 38-43.
49. Bertrand ME, Lablanche JM, Tilmant PY. Treatment of Prinzmetal's variant angina: role of medical treatment with nifedipine and surgical coronary revascularization combined with plexectomy. *Am J Cardiol* 1981; **47:** 174-178.
50. Bertrand ME, Lablanche JM, Tilmant PY, Ducloux G, Warembourg H, Soots G. Complete denervation of the heart (autotransplantation) for treatment of severe, refractory coronary spasm. *Am J Cardiol* 1981; **47:** 1375-1378.
51. Robertson RM, Wood AJJ, Vaughn WK, Robertson D. Exacerbation of vasotonic angina pectoris by propranolol. *Circulation* 1982; **65:** 281-285.