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Recurrent coronary artery spasm in the billowing mitral leaflet syndrome (primary mitral valve prolapse)

A case report and review of the literature

J. Z. PRZYBOJEWSKI

Summary

A 46-year-old White man had a 2-year history of frequent atypical chest pain associated with palpitations and presyncope. Clinical examination revealed an intermittent mid-systolic non-ejection click followed by a blowing mid-to-late systolic murmur indicative of the billowing mitral leaflet syndrome (BMLS) (primary mitral valve prolapse (MVP); Barlow's syndrome). This diagnosis was confirmed on cardiac catheterization, left ventricular cine angiography showing mild mitral insufficiency. M-mode and cross-sectional echocardiograms failed to show the MVP, although phonocardiography documented the intermittent non-ejection click and mid-systolic apical murmur. Ambulatory Holter monitoring showed symptomatic inferolateral myocardial ischaemia, and maximal stress-testing elicited asymptomatic ischaemia in the same zone. Selective coronary angiography delineated a normal left coronary artery and an insignificant fixed obstructive lesion in the second part of the dominant right coronary artery (RCA). Provocation with ergometrine (ergonovine) maleate gave rise to severe coronary vasospasm superimposed on the insignificant lesion in the RCA. This spasm provoked myocardial ischaemia resulting in symptomatic ventricular fibrillation which was successfully reversed. The patient's symptoms have been fairly well controlled by nitrates and nifedipine.

As far as I am aware this is the first documentation of coronary vasospasm in the BMLS. In this syndrome coronary artery spasm has often been postulated to be responsible for acute myocardial infarction with a normal appearance of the coronary arteries on angiography. This mechanism has also been incriminated in the genesis of ventricular arrhythmias in cases of primary MVP. These various contentious and important issues are reviewed.

S Afr Med J 1984; **66**: 138-143.

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Case report

The patient was a 46-year-old White man initially admitted to Tygerberg Hospital in April 1981 with a 2-week history of burning retrosternal pain radiating to the left shoulder and precipitated by tension and effort, although it often occurred when he was at rest and would wake him in the early morning. The pain would frequently last for several hours. He had no history of any disease apart from a previous psychiatric consultation for anxiety. The patient had once been a heavy smoker and his younger brother was hypercholesterolaemic and suffered from angina pectoris.

Clinical examination was negative. Repeated ECG showed sinus rhythm, a normal P-R interval and mean QRS axis but persistent ST-segment elevation in the inferior leads (Fig. 1a). Serial serum enzyme levels were normal, as was a fasting lipogram. A maximal treadmill effort test (Bruce protocol) failed to provoke angina, ST-segment deviation or arrhythmia. An M-mode echocardiogram was documented as normal with no features of mitral valve prolapse (MVP). At this admission the patient first underwent cardiac catheterization, which revealed normal intracardiac pressures and indices of cardiac function. A left ventricular cine angiogram in the right anterior oblique

(RAO) projection showed a normally contracting ventricle, but there was marked prolapse of the posterior leaflet of the mitral valve which was not calcified (Fig. 2), and mild mitral insufficiency. Selective coronary arteriography delineated a normal left coronary artery (LCA), but the right coronary artery (RCA) (a dominant vessel) had a 30% narrowing of the internal lumen in its second part, but otherwise appeared to be free of disease (Fig. 3). The patient did not experience any chest pain during this procedure. A diagnosis of MVP (billowing mitral leaflet syndrome (BMLS)) with insignificant coronary artery disease was made and the chest pain was interpreted as due to the prolapse. A barium meal test and follow-through study were negative. Therapy with long-acting nitrates, a ß-blocker and a calcium antagonist was started and the patient was discharged.

Some 2 months later he was admitted to the Intensive Coronary Care Unit at Tygerberg Hospital with a diagnosis of unstable angina. The chest pain was then occurring more frequently at rest and was not effectively relieved by sublingual isosorbide dinitrate. At this stage he was also taking high doses of a ß-blocking drug and a calcium antagonist. In addition, the patient noticed the onset of mild dyspnoea. Clinical examination was reported as negative apart from a loud fourth heart sound. Repeated studies of serum enzyme levels were all negative and

serial ECG tracings demonstrated intermittent symmetrical T-wave inversion in leads V2 - V6. Twenty-four-hour Holter monitoring sessions failed to show any possible arrhythmia or ST-segment deviation, and the patient did not experience any chest discomfort during these periods. A submaximal treadmill stress test was again negative. M-mode echocardiography did not delineate the MVP which had previously been demonstrated by left ventricular cine angiography. Two-dimensional echocardiography was also negative. The medication dosage was increased and the patient was discharged to be followed up by the author at the Cardiac Clinic.

During the following 10 months the patient continued to complain of somewhat atypical chest pain, despite receiving high doses of anti-anginal drugs. Repeated resting ECG recordings were unchanged. A submaximal treadmill stress test carried out in April 1982 without provoking angina demonstrated 1 mm horizontal ST-segment depression in the lateral leads as well as 2 mm horizontal ST-segment depression in lead aVF which occurred soon after the patient attained the target heart rate. A resting ECG demonstrated small Q waves in the inferior leads. In view of continuing symptoms, the positive stress test and the possibility of a transmural inferior myocardial infarction since the patient's last admission, cardiac catheterization was repeated
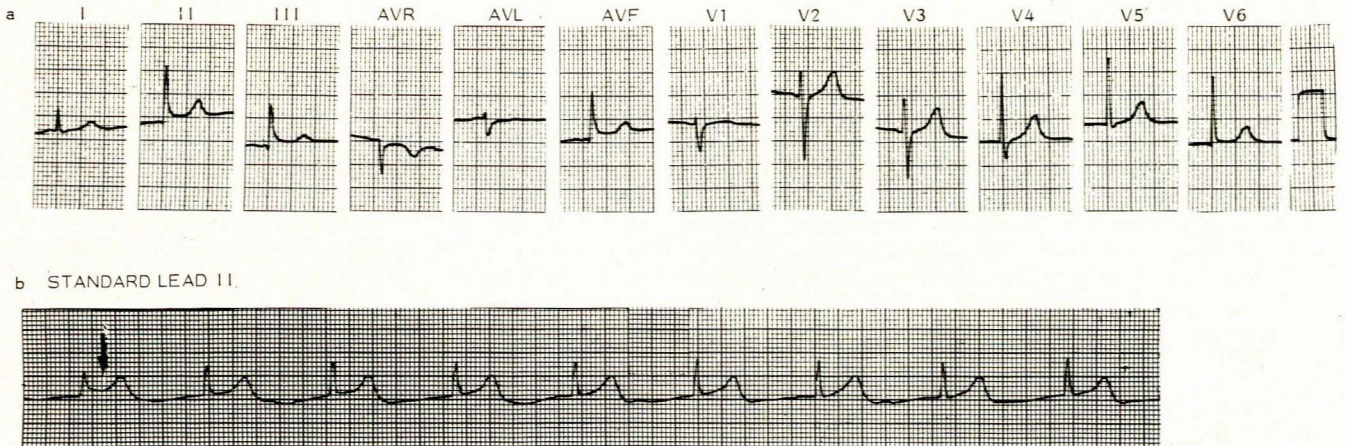

Fig. 1. a — resting 12-lead ECG (full standardization) showing ST-segment elevation in the inferior leads (April 1981); b — Holter monitor strip (standard lead II) showing the presence of intermittent ST-segment elevation (arrowed) which coincided with episodes of atypical chest pain (1982).
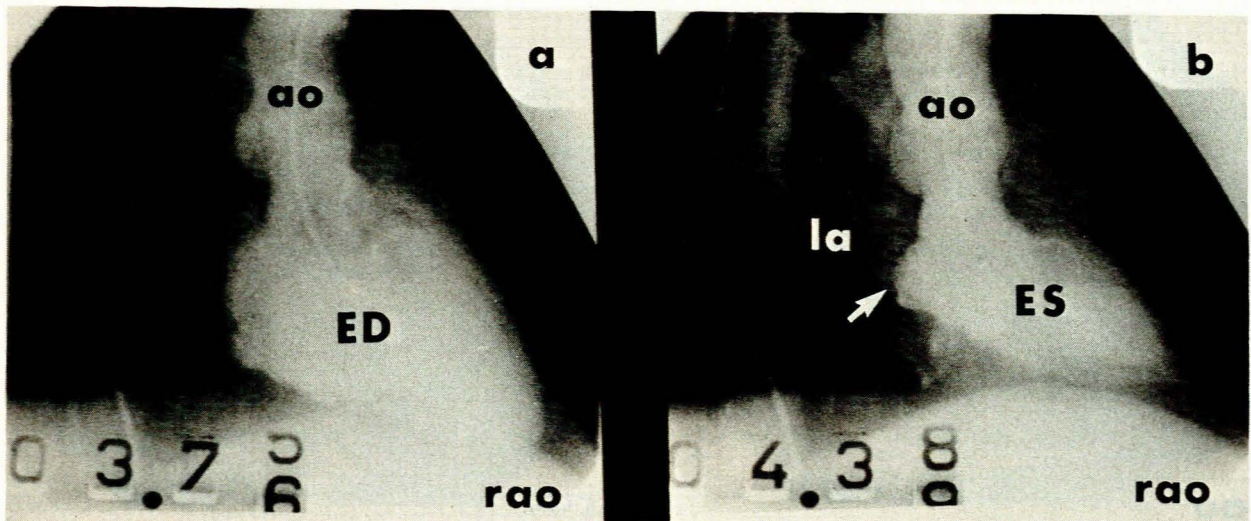

Fig. 2. Left ventricular cine angiograms in the RAO projection delineating prolapse of the posterior mitral valve leaflet (arrowed) with mild mitral insufficiency (ED = end-diastole (a); ES = end-systole (b); ao = ascending aorta; La = left atrium).

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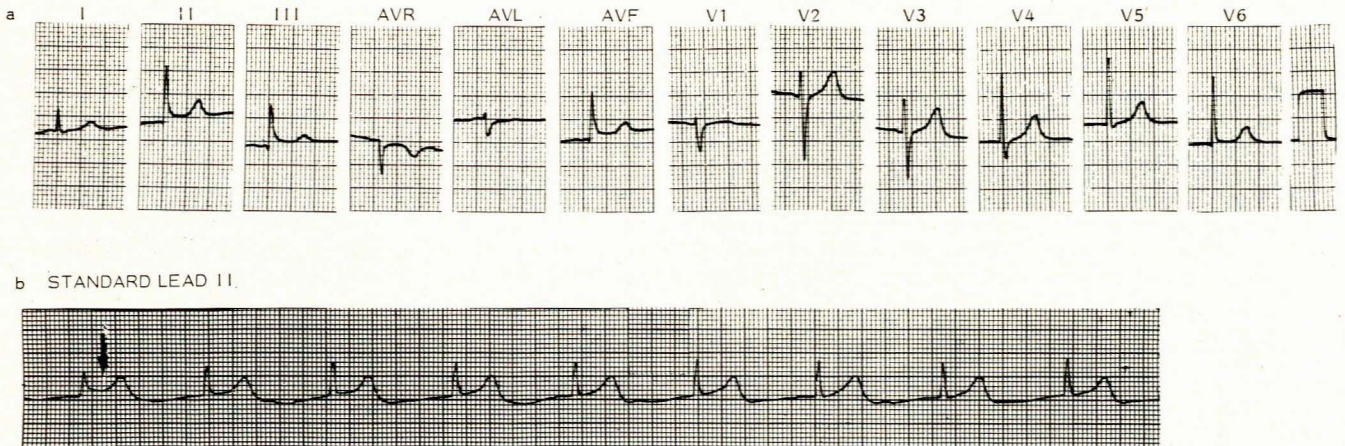

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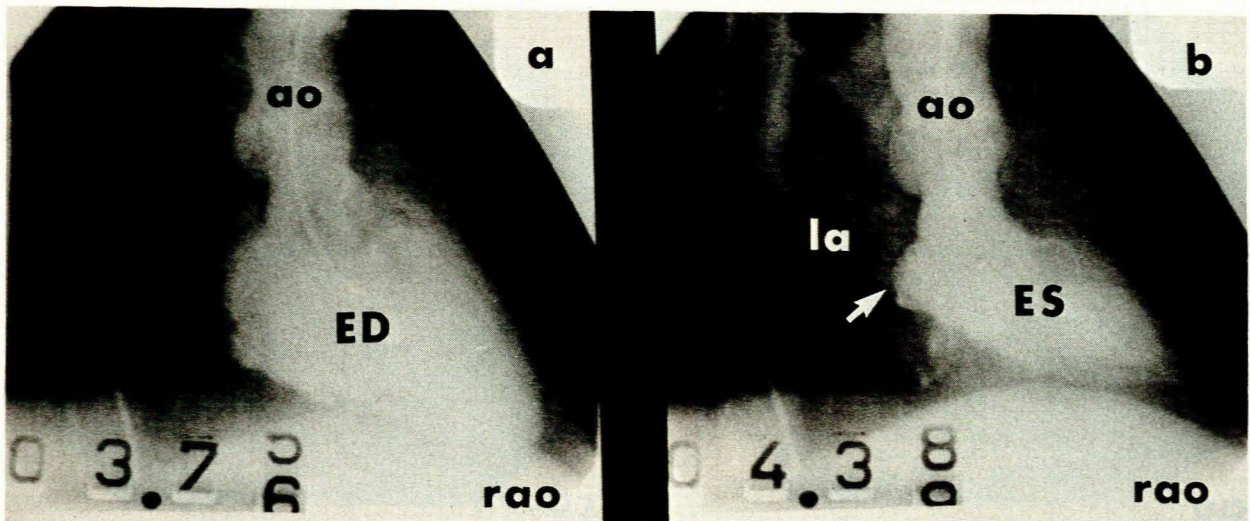

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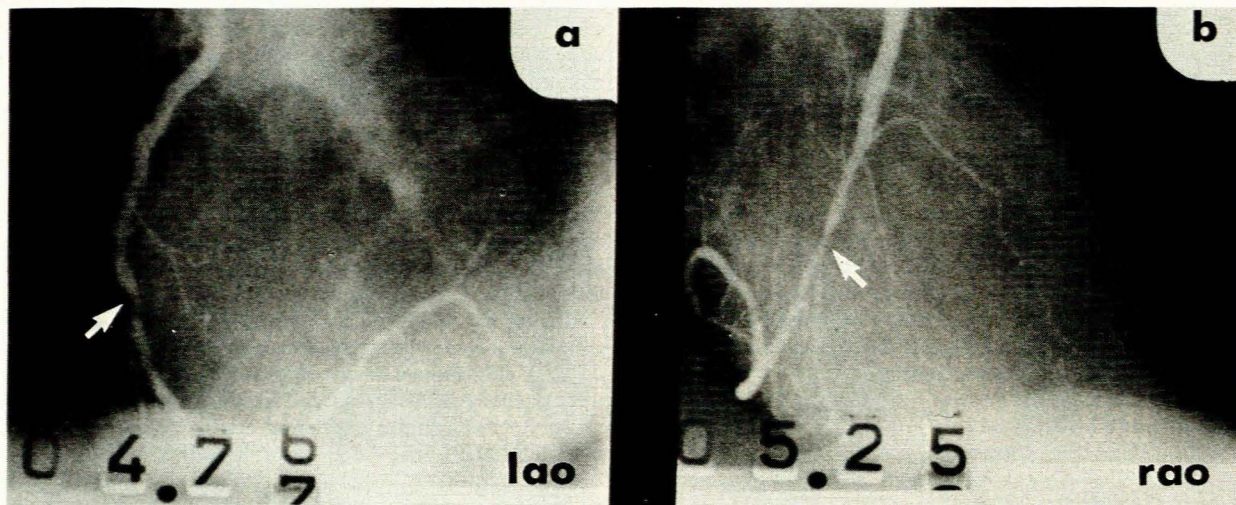
Fig. 3. Right coronary cine angiograms in the (a) left anterior oblique (LAO) and (b) RAO view. The vessel is dominant and there is an insignificant atherosclerotic narrowing (arrowed) in its second part.

in May 1982; this confirmed no change in left ventricular haemodynamics and there was no evidence of any inferior segmental contraction abnormality on left ventricular cine angiography. The significant MVP associated with mild mitral insufficiency was again demonstrated. Selective coronary cine angiography revealed no change in morphological appearances. The patient was not subjected to ergometrine (ergonovine) maleate stimulation since he was taking high doses of long-acting nitrates and a calcium antagonist, and the drugs might have masked any possible positive response. He was again discharged and medication was increased to a maximum level.

At frequent visits to the outpatients' Cardiac Clinic the patient complained of numerous episodes of atypical chest discomfort, some lasting as long as 3 hours and associated with dyspnoea. Poor relief was obtained with sublingual isosorbide dinitrate. In addition, he gave a history of frequent palpitations associated with chest discomfort which caused dizziness, almost ending in syncope. Raynaud's phenomenon and migraine as signs of an underlying generalized vasospastic disorder were absent. Holter monitoring demonstrated episodes of ST-segment elevation of some 1,5 mm in an inferior lead which was constantly associated

with atypical chest pain (Fig. 1b). At this stage, there was a strong likelihood that coronary vasospasm was responsible for the patient's symptoms. Clinical examination documented an intermittent, loud mid-systolic non-ejection click followed by a blowing mid-to-late systolic murmur at the mitral area displaying poor radiation. There were no further abnormal findings. Repeat M-mode and cross-sectional (two-dimensional) echocardiography again failed to show any characteristics of MVP but a phonocardiogram demonstrated an intermittent non-ejection click not always followed by a mid-systolic non-ejection murmur at the mitral area. The calcium antagonist and ß-blocker were gradually withdrawn, followed by a gradual reduction in the dose of oral isosorbide dinitrate.

The patient continued to receive the sublingual preparation of isosorbide dinitrate and noted more frequent episodes of chest discomfort. A third cardiac catheterization and selective coronary cine angiography were carried out in August 1982 with the express purpose of demonstrating induced vasospasm of the RCA in the area where the obstructive lesion had previously been located. All intracardiac pressures and indices of left ventricular contractility were normal. Left ventricular cine
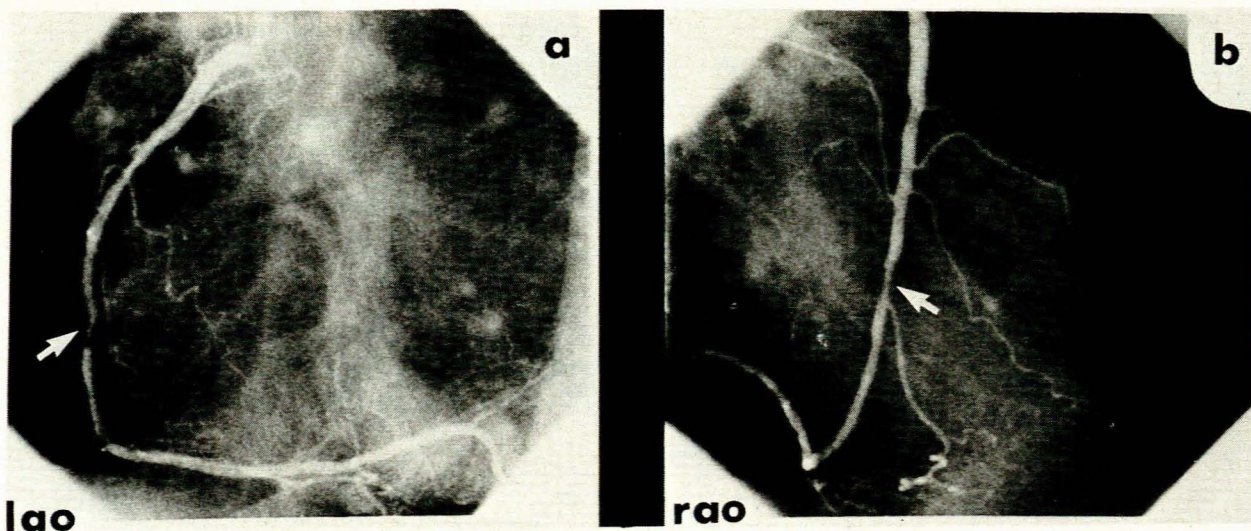

Fig. 4. Right coronary cine angiograms in the (a) LAO and (b) RAO views prior to ergometrine maleate provocation. A 27% diameter stenosis (arrowed) is visualized in the second part.

angiography in the RAO projection still showed prolapse of the posterior mitral leaflet associated with mitral insufficiency. Baseline selective coronary angiography in multiple projections delineated a normal non-dominant LCA, and the RCA had an obstructive lesion unchanged in severity (Fig. 4). The patient did not complain of any chest pain during the procedure and no ECG changes were noted in standard lead II on the oscilloscope. A 12-lead ECG at this stage was no different from previous tracings. The ergometrine maleate provocation test was carried out by injection of an initial bolus of 0,025 mg into the main pulmonary artery while monitoring the aortic pressure and standard lead II on the oscilloscope (Fig. 5a). In addition, a 12-lead ECG was recorded every minute. A further bolus of 0,025 mg was given after 4 minutes and the monitoring procedure was repeated. After this, boluses of 0,05 mg were administered until a total of 0,4 mg ergometrine maleate had been given. Within 2 minutes of injecting the last bolus the patient complained of severe precordial pain similar to his usual episodes. Right coronary cine angiography in the LAO view demonstrated that the previous obstructive lesion (27% diameter, 47% area stenosis) had become more severe (66% diameter and 89% area stenosis) (Fig. 6a and Table I). Almost immediately the patient developed ventricular fibrillation (Fig. 5b) with loss of consciousness. Electrical defibrillation was immediately successful (Fig. 5c), the patient regaining consciousness but still complaining of severe chest pain. Nitroglycerin solution was then injected directly into the RCA via the angiography catheter and the patient was also given sublingual isosorbide dinitrate. Repeat cine angiography of the RCA in the LAO projection showed the lesion to be less severe (38% diameter and 62% area stenosis) (Fig. 6b and Table I), and the pain was much reduced.
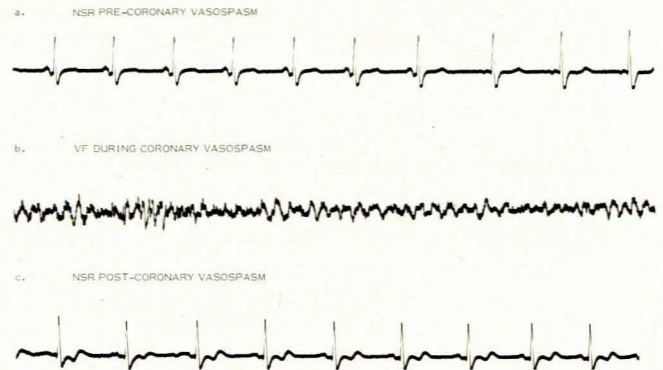

Fig. 5. Oscilloscope tracings (standard lead II) taken during right coronary cine angiography after ergometrine maleate provocation: a — normal sinus rhythm (NSR) before coronary vasospasm; b — ventricular fibrillation (VF) during coronary vasospasm; c — NSR after defibrillation and relief of coronary vasospasm with intra-coronary nitroglycerin administration.
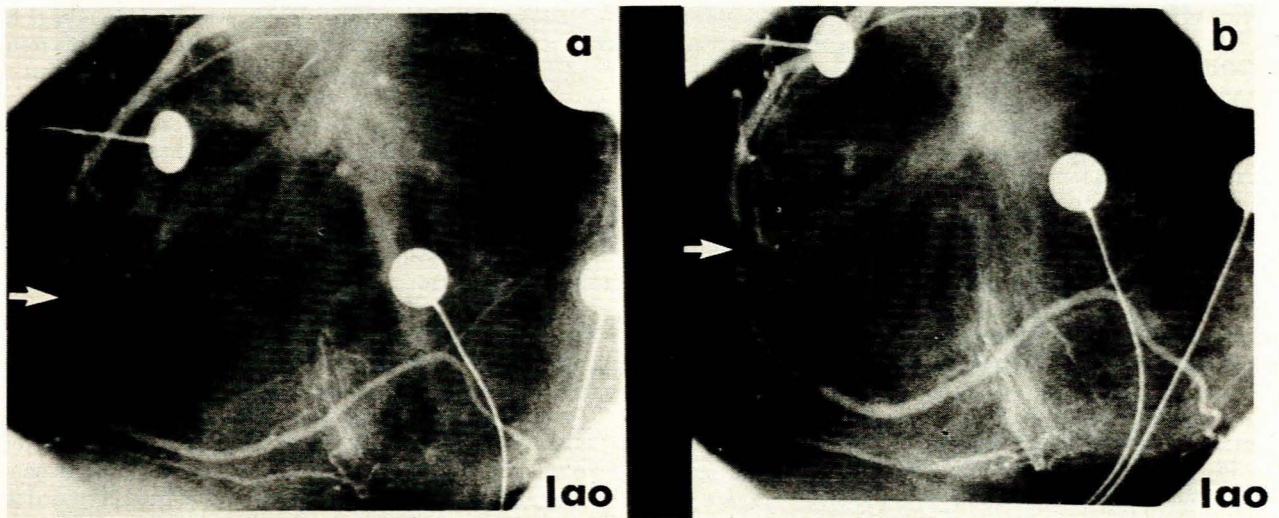

Fig. 6. Right coronary cine angiograms in the LAO view. a — 66% diameter stenosis (arrowed) after ergometrine maleate provocation and before intracoronary nitroglycerin administration; b — 38% diameter stenosis (arrowed) after intracoronary nitroglycerin administration.

TABLE I. RIGHT CORONARY ANGIOGRAPHIC MEASUREMENTS*

			August 1982				
			Pre-ERGO	Post-ERGO			
					Post-NG		
	May	April			1	2	3
	1981	1982					
Minimum diameter (mm)	1,91	1,88	1,80	0,66	1,73	1,91	2,17
% diameter stenosis	31	24	27	66	38	29	26
Length of lesion (mm)	3,0	4,0	3,0	5,0	5,0	4,0	4,0
Minimum area (mm^2)	2,87	2,77	2,55	0,34	2,34	2,86	3,70
% area stenosis	53	42	47	89	62	50	45

*All measurements taken in LAO projection at the time of diastole. Measurements derived by utilizing the A2D Prodical 1101 Programmable Digital Caliper and the Vanguard Cineangiographic Viewer.
Pre-ERGO = before ergometrine maleate; post-ERGO = after ergometrine maleate; post-NG = after intracoronary nitroglycerin; 1, 2, 3 = time sequence of coronary arteriograms after intracoronary nitroglycerin.
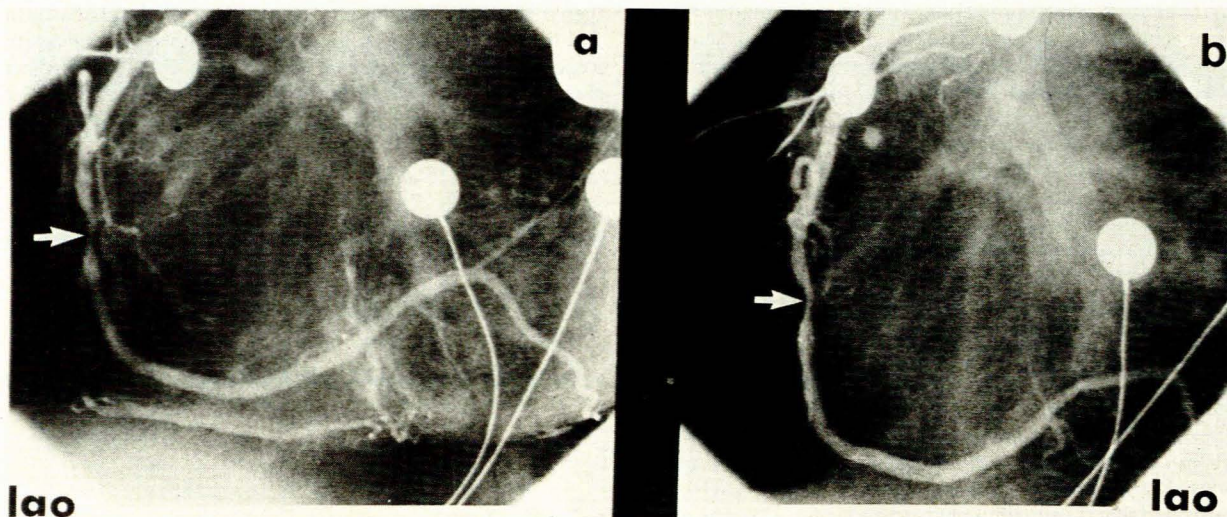
Fig. 7. Right coronary cine angiograms taken in the LAO projection after intracoronary nitroglycerin administration showing diffuse coronary dilatation. a — 29% diameter stenosis (arrowed) now less severe; b — 26% diameter stenosis (arrowed), the same as before performance of the ergometrine maleate provocation test.

A RCA cine angiogram indicated further relief of the vasospasm (29% diameter stenosis and 50% area stenosis) (Fig. 7a and Table I). There were no further runs of ventricular fibrillation and the last cine angiogram (Fig. 7b) delineated a 26% diameter stenosis and 45% area stenosis (Table I), similar measurements to those obtained before the ergometrine test. Selective LCA cine angiography demonstrated that the left anterior descending and left circumflex branches were free of obstructive lesions and were diffusely dilated secondary to nitrate administration.

After cardiac catheterization the patient was transferred to the Intensive Coronary Care Unit and given high doses of oral nitrates and nifedipine; ß-blockers were withheld in the light of the provoked vasospasm. Continuous ECG monitoring failed to show any further arrhythmia and there was no further chest pain. Serial serum enzyme estimations and 12-lead ECG examinations excluded a possible acute myocardial infarction. After 1 week the patient was discharged on high dosages of oral nitrates and nifedipine.

After discharge the patient felt reasonably well apart from occasional palpitations and nonspecific chest pain. However, early in 1983 he was admitted to another hospital with severe chest pain, at which stage an acute myocardial infarction was excluded. The patient was then advised that there was nothing wrong with his heart and that all his symptoms were due to achalasia, for which he was given medication. Nevertheless, his symptoms continued and he returned to Tygerberg Hospital for follow-up. When last seen in June 1983 he had minimal symptoms and clinical examination revealed the intermittent mid-systolic non-ejection click followed by a blowing mid-to-late systolic murmur at the apex. A resting ECG was unchanged from that taken in August 1982. Holter monitoring did not detect any ventricular arrhythmia. Oral isosorbide dinitrate therapy was replaced by Nitradisc 10 mg for improved patient compliance. In addition, nifedipine was continued and the patient was advised to try to lead a normal life.

Discussion

The BMLS (MVP; Barlow's syndrome) has provoked a great deal of controversy which is unlikely to be resolved in the near future. The present case illustrates some of these crucial aspects. Definitive diagnosis by echocardiography, whether M-mode or cross-sectional, is not always straightforward. Neither method of

echocardiography could demonstrate the BMLS in our case, although one could argue that this deformity was intermittent and only by chance demonstrated on two occasions by left ventricular cine angiography. If the auscultatory findings had not been so convincing the negative echocardiographic results might well have misled us, although it is well known that the echocardiogram can be totally normal in the presence of an isolated non-ejection mid-to-late systolic click (as demonstrated on the phonocardiogram in this case) in patients with documented MVP. It is fairly well known that M-mode echocardiograms show characteristic features,[1] but a spectrum of abnormalities has also been appreciated.[2] However, overdiagnosis of the BMLS has often been blamed on over-enthusiastic echocardiographers. Over the past few years two-dimensional (cross-sectional) echocardiography has been utilized in an attempt to make a more convincing diagnosis.[3-5] Various 'provocative' manoeuvres, such as making the patient stand or inhale amyl nitrite, have also been applied,[6] but doubt still exists.

Theories to explain the pathophysiological mechanisms underlying the numerous symptoms in the BMLS have been numerous. This applies particularly to the atypical angina pectoris, dyspnoea, palpitations, presyncope and syncope. It has been proposed that the abnormal tension that the chordae tendinae exert upon the papillary muscle causes 'ischaemia' of this muscle which in some way causes the chest pain and initiates supraventricular or ventricular arrhythmias.[7,8] Some authors have even reported ventricular tachycardia and ventricular fibrillation as a complication.[9-11] A 'cardiomyopathy' has been invoked, but with doubtful general support.[12,13] The presyncope and syncope have therefore often been believed to be an expression of the arrhythmia, particularly if this is ventricular.

Myocardial infarction as a complication of 'primary' MVP has been described by Chesler et al.,[14] who found normal coronary angiograms in their patients and suspected that coronary vasospasm was responsible but did not carry out ergometrine tests. Painless myocardial infarction in the presence of normal coronary arteries and a negative ergometrine provocation test has been described, this perhaps being due to coronary embolization.[8] The present case report is the first in the literature in which coronary artery spasm has been identified in the BMLS and shown to give rise to life-threatening ventricular fibrillation. Provocation of coronary vasospasm by ergometrine maleate in susceptible individuals is now generally accepted as most reliable,[15-19] but this test can be dangerous if intracoronary

nitroglycerin is not available.[20,21] Coronary vasospasm in Prinzmetal's angina is known to cause ventricular fibrillation[20] and to give rise to 'torsade de pointes' with resultant syncope.[21] Coronary vasospasm with ventricular fibrillation has also been reported in 4 out of 1 089 patients undergoing ergometrine maleate provocation.[22] It is therefore reasonable to assume that coronary vasospasm plays an important role in the genesis of serious ventricular arrhythmias in MVP and could account for puzzling symptoms.

That coronary angiography caused the ventricular fibrillation in our patient is highly improbable since coronary artery spasm was seen to precede the ventricular fibrillation. Selective coronary angiography is known to give rise to ventricular fibrillation in a small percentage of patients. Davis et al.[23] reported an incidence of 0,63% among a total of 7 553 patients, Adams et al.[24] an incidence of 1,41% (percutaneous route) and 1,15% (Sones' method), and Bourassa and Noble[25] a total of 0,34% among 5 250 cases. However, in none of these studies did coronary vasospasm precede the episodes of ventricular fibrillation.

Sudden death as a complication of the BMLS is now generally thought to result from ventricular arrhythmia, although the exact pathogenetic mechanism is not fully understood. Chesler et al.[11] found a total of 39 patients in the literature and reported on a further 14 patients, some of whom were shown to have had ventricular fibrillation before death. None of Chesler et al.'s cases had a prolonged Q-T interval (which might have predisposed to a ventricular tachyarrhythmia with subsequent death), although this prolongation has popularly been believed to be an important forerunner of sudden death in MVP since ventricular fibrillation has been found in such cases.[7,14]

If the atypical chest pain in the BMLS is really due to coronary vasospasm, and if the ventricular tachyarrhythmia with resultant presyncope and syncope is secondary to vasospasm, then serious consideration must be given to the prophylactic use of long-acting nitrate preparations and calcium-antagonist drugs rather than ß-blocking drugs aimed at controlling the ventricular arrhythmias. Our patient appears to be reasonably asymptomatic on this medication, which will probably have to be continued long-term. Most recently, Subramanian et al.[26] have quite convincingly demonstrated the existence of a 'calcium antagonist withdrawal syndrome' in patients with ischaemic heart disease. Their observation may have an important practical application in the treatment of patients with MVP suspected of having coronary artery spasm in whom abrupt calcium-antagonist withdrawal might precipitate fatal coronary spasm. There is much potentially fruitful and challenging research being carried out in this controversy-filled area and the answers have yet to be found.

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