'Coronary intimal fibrous stenosis' — early coronary atherosclerosis causing acute myocardial infarction

A case presentation and overview

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Summary

A 34-year-old Coloured man had typical angina pectoris which was unresponsive to medical therapy. There was no history of factors predisposing to atherosclerosis apart from moderate cigarette smoking. A resting ECG suggested a previous non-transmural anterolateral myocardial infarction, and a submaximal effort test was strongly positive for myocardial ischaemia. Serological investigation for syphilis was positive, and initially the possibility that coronary ostial stenosis was the cause of his symptoms was strongly considered. Cardiac catheterization and selective coronary angiography showed evidence of an anterolateral myocardial infarction and that there was no coronary ostial stenosis, but total occlusion of the left anterior descending coronary artery (LAD) proximally with retrograde filling from the right coronary artery was revealed. The left circumflex coronary artery also showed some insignificant internal luminal irregularities.

The patient was subjected to coronary artery bypass graft (CABG) surgery with saphenous grafts to the proximal LAD as well as its first diagonal branch. Proximally the LAD was a firm fibrotic cord; biopsy specimens were taken from this as well as part of the adjacent myocardium and aorta. The artery showed severe fibrous proliferation of the intima without any calcium or lipid deposits, which would have been expected with atherosclerosis, as well as an organized thrombus. There were no signs of cardiovascular syphilis.

The patient made quite a dramatic recovery with disappearance of the angina and improved results on submaximal stress testing. A month later cardiac catheterization showed improved segmental anterolateral contractility of the left ventricle as well as patency of both CABGs. Some 3 months postoperatively he again complained of angina, which gradually worsened on treatment. Stress testing again showed significant ischaemia and a second postoperative cardiac catheterization 10 months after surgery showed both CABGs to have occluded. The patient, who is on medication, is being followed up.

A pathological diagnosis of early coronary atherosclerosis was made. This lesion has been previously termed 'coronary intimal fibrous stenosis' as the authors concerned did not believe that it was due to coronary atherosclerosis. Ours is the third such case documented in the literature. Reference to earlier literature on coronary atherosclerosis confirms that this histological picture is in keeping with the early phase of this disease. The 'classic' features of coronary atherosclerosis may not have been evident on account of the patient's dietary habits, which may prove to be the important pathological differentiating feature in our White and Coloured population groups.

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Ischaemic heart disease (IHD) secondary to established coronary atherosclerosis is rife among White South Africans. The Black population is said to be rarely affected by this 'epidemic' except when they adopt a 'Westernized' lifestyle. The position as regards the Coloured population is accepted as falling between these two extremes.

Although atherosclerosis is virtually automatically incriminated in the spectrum of IHD as represented by angina pectoris, myocardial infarction and sudden death, other 'non-atheromatous' causes must be seriously considered in the differential diagnosis. Causes such as syphilis, involving the ascending aorta and subsequently leading to coronary ostial stenosis, are well known. The collagen diseases have also been incriminated, albeit rarely. Takayasu's disease ('pulseless disease') is well recognized as a possible underlying cause, especially when secondary to dissection of a thoracic aortic aneurysm. In fact, any arteritis can probably involve the coronary arteries and lead to one of the presenting features of IHD. Systemic emboli, whether they arise from a mural thrombus in the left atrium or in a left ventricular aneurysm, can give rise to a coronary embolus with subsequent acute myocardial infarction.

'Coronary intimal fibrous stenosis'[1] has been described as being an exceptionally rare clinicopathological entity. It was documented for the first time in 1971 by Brill *et al.*[1] These workers reported on acute myocardial infarction in 2 White sisters under the age of 20-years, neither of whom had been on oral contraceptives. Both these patients suffered acute anteroseptal myocardial infarctions, the younger girl having died following an attempt at a Vineberg operation. Postmortem examination revealed severe fibrous proliferation of the coronary intima, without any of the 'classic' accepted features of atherosclerosis, i.e. yellow calcified plagues, cholesterol clefts, foam cells or mucin.

The present case represents the third case of 'coronary intimal fibrous stenosis' known in the literature. The patient suffered an acute non-transmural anterolateral myocardial infarction and was subjected to coronary artery bypass grafting (CABG) for severe angina pectoris. However, we believe that this histological picture is that seen in early coronary atherosclerosis, and that it may have been influenced by the patient's race.

The short- and long-term fate of CABGs with reference to the pathogenesis of possible occlusion is outlined. The important pathogenetic role of cigarette smoking in this patient is stressed. Also, the possible incrimination of coronary vasospasm in the causation and progression of coronary atherosclerosis and its clinical sequelae is discussed.

Case presentation

The patient was a 34-year-old Coloured man referred to the Cardiac Clinic of Tygerberg Hospital on 10 March 1980 with a 2-year history of classic angina pectoris. Some 18 months previously he began taking long-acting nitrates and ß-blockers but this therapy was quite ineffective, and he had to discontinue working as a labourer because of severe angina which had also appeared at rest for some months. Apart from this disabling symptom he was asymptomatic. The patient had smoked some 10 cigarettes daily for many years, and there was no family history of IHD, diabetes mellitus, hypertension or hyperlipidaemia.

He was a rather thin young man, but there were no features of a systemic disease or hyperlipidaemia on examination. Examination of the cardiovascular system revealed a normal radial pulse, all peripheral pulses being present without evidence of radio-femoral delay. The jugular venous pressure was not elevated and the blood pressure was 120/80 mmHg in both upper limbs. The heart showed no abnormal signs. Ophthalmoscopy was also negative, as was examination of the respiratory, gastro-intestinal and central nervous systems.

A chest radiograph showed a normal cardiac silhouette and normal lung fields. A resting ECG (Fig. 1a) revealed sinus rhythm of 60/min, a mean QRS axis of −5°, and a PR interval of 0,13 second. There was possible left atrial enlargement and almost certain left ventricular hypertrophy. Anterolateral asymmetrical T-wave inversion was present, suggesting a previous non-transmural myocardial infarction or strain pattern secondary to the left ventricular hypertrophy. Poor R-wave progression over the anteroseptal leads could have been due to a 'pseudo-infarction pattern' secondary to left ventricular hypertrophy. Investigations for the presence of a collagen or autoimmune disease all proved negative but serological tests for syphilis (TPHA, RPR, WR and VDRL) were all positive, the last being positive to a titre of 1:32. The patient was therefore given a course of penicillin.

Both the fasting lipogram and glucose tolerance test were normal. The antistreptolysin O titre was 400 Todd units (normal). A full blood count was normal apart from an eosinophilia of 16% with an absolute value of 1 344/μl; stool investigation for parasitic or helminthic infestation proved negative, as did skin sensitivity tests, including the Mantoux test. The erythrocyte sedimentation rate was 5 mm/h (Westergren). Some weeks later the eosinophil counts were within normal limits. Pulmonary function tests showed features of a mild restrictive abnormality in that the vital capacity, lung compliance and total lung capacity were reduced and there was early peripheral airways obstruction, findings in keeping with the patient's smoking habits.

At submaximal effort testing (following the modified Bruce protocol) carried out on 20 May 1980 in order to detect possible

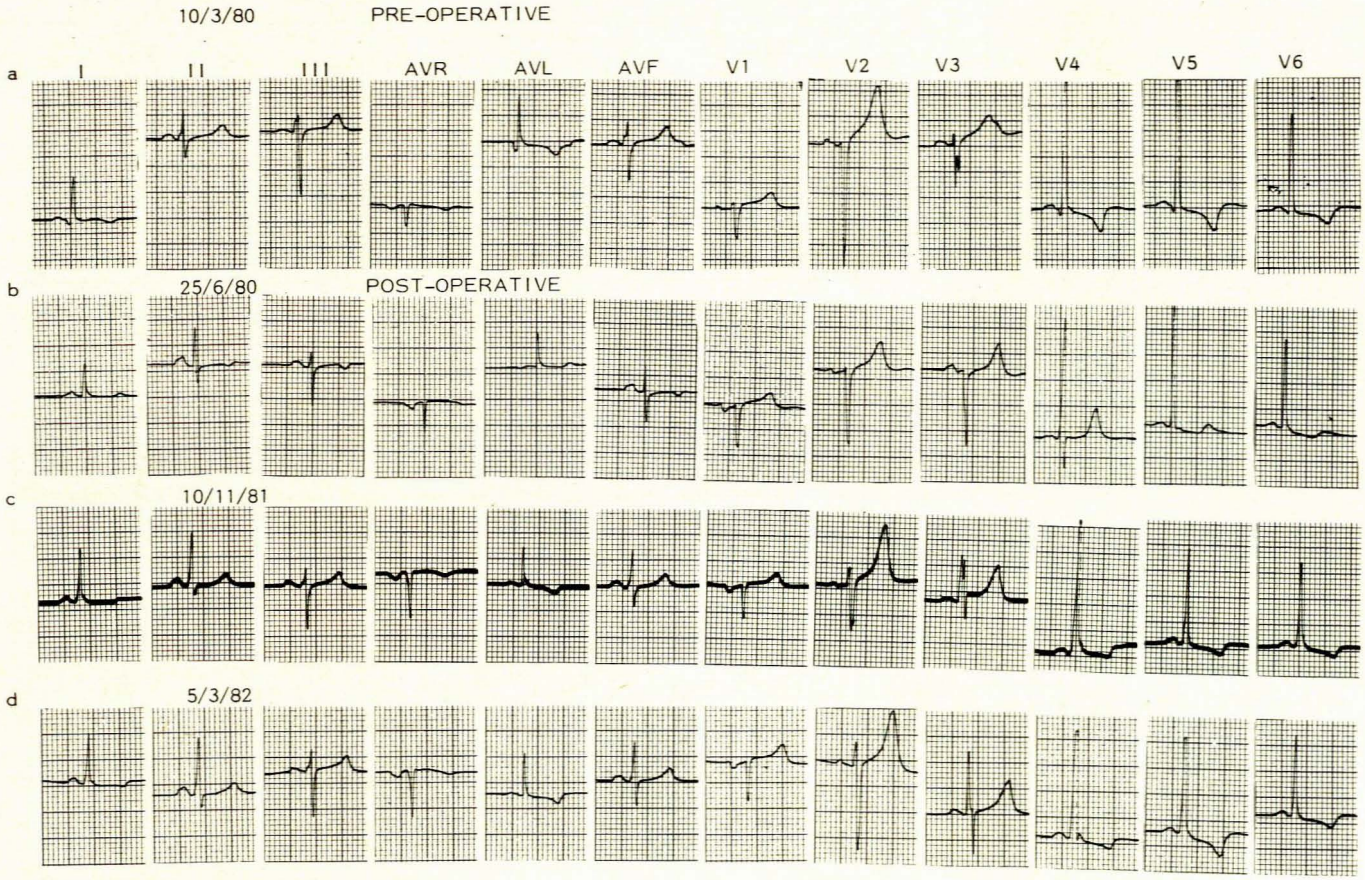

Fig. 1. a — Resting ECG showing possible old non-transmural anterolateral myocardial infarction. b — Postoperative resting ECG. Anterolateral abnormality no longer evident, but inferior ischaemia seen. c — Postoperative resting ECG. Similar to pre-operative tracing. d — Latest follow-up resting ECG. Possible old non-transmural anterolateral myocardial infarction is seen.

ischaemia the patient complained of severe chest pain 5 minutes after the onset of exercise, by which time he had reached a maximum heart rate of 95/min (target heart rate 170/min). Horizontal ST-segment depression of 1,6 mm was noted in the lateral leads 4,5 minutes into exercise (Fig. 2a). The test was interpreted as being positive for ischaemia.

M-mode echocardiography (Table I) revealed normal chamber size and function. There was no evidence suggestive of hypertensive heart disease or cardiomyopathy.

TABLE I. ECHOCARDIOGRAPHIC MEASUREMENTS

Parameter	Result	Normal (mean)
Left ventricular end-diastole	52 mm	35-56 (46 mm)
Left ventricular end-systole	36 mm	
Interventricular septum thickness (IVS)	11 mm	7-11 mm (9 mm)
Left ventricular posterior wall (LVPW)	11 mm	7-11 mm (9 mm)
IVS/LVPW ratio	1,0	<1,3
Left atrium dimension	33 mm	19-40 mm (29 mm)
Right ventricular end-diastole	21 mm	10-26 mm (17 mm)
Left ventricular end-diastolic volume	130 ml	130 ml/m^2
Left ventricular end-systolic volume	54 ml	25 ml/m^2
Ejection fraction	59%	>60%
Shortening fraction	31%	28-38%
Systemic isovolumic contraction time	29 ms	28-38 ms
Systemic pre-ejection period (PEP)	100 ms	
Left ventricular ejection time (LVET)	300 ms	
PEP/LVET ratio	0,33	<0,28-0,38

Since the patient was experiencing severe angina despite intensive medical therapy, and since the ECG suggested the likelihood of a possible previous myocardial infarction, the patient underwent full cardiac catheterization and coronary angiography.

Cardiac catheterization

This procedure was performed on 13 March 1980 using the standard percutaneous Seldinger technique via the right femoral vein and artery. A 7F Goodale-Lubin and pigtail catheter was

TABLE II. PRE-OPERATIVE INTRACARDIAC PRESSURES

Catheter position	Pressure (mmHg)	Comment
Right atrium	'a' wave 18 'v' wave 15 (mean 13)	Elevated pressures
Right ventricle	40/15-24	Raised systolic and diastolic pressures
Main pulmonary artery	40/19 (mean 25)	Mild pulmonary hypertension
Ascending aorta	126/80 (mean 102)	Normal pressures
Left ventricle	128/1-14	Raised end-diastolic pressure
Dp/dt (mm/s)	1 918	Normal
Pulmonary capillary wedge	'a' wave 22 'v' wave 27 (mean 21)	Elevated pressures

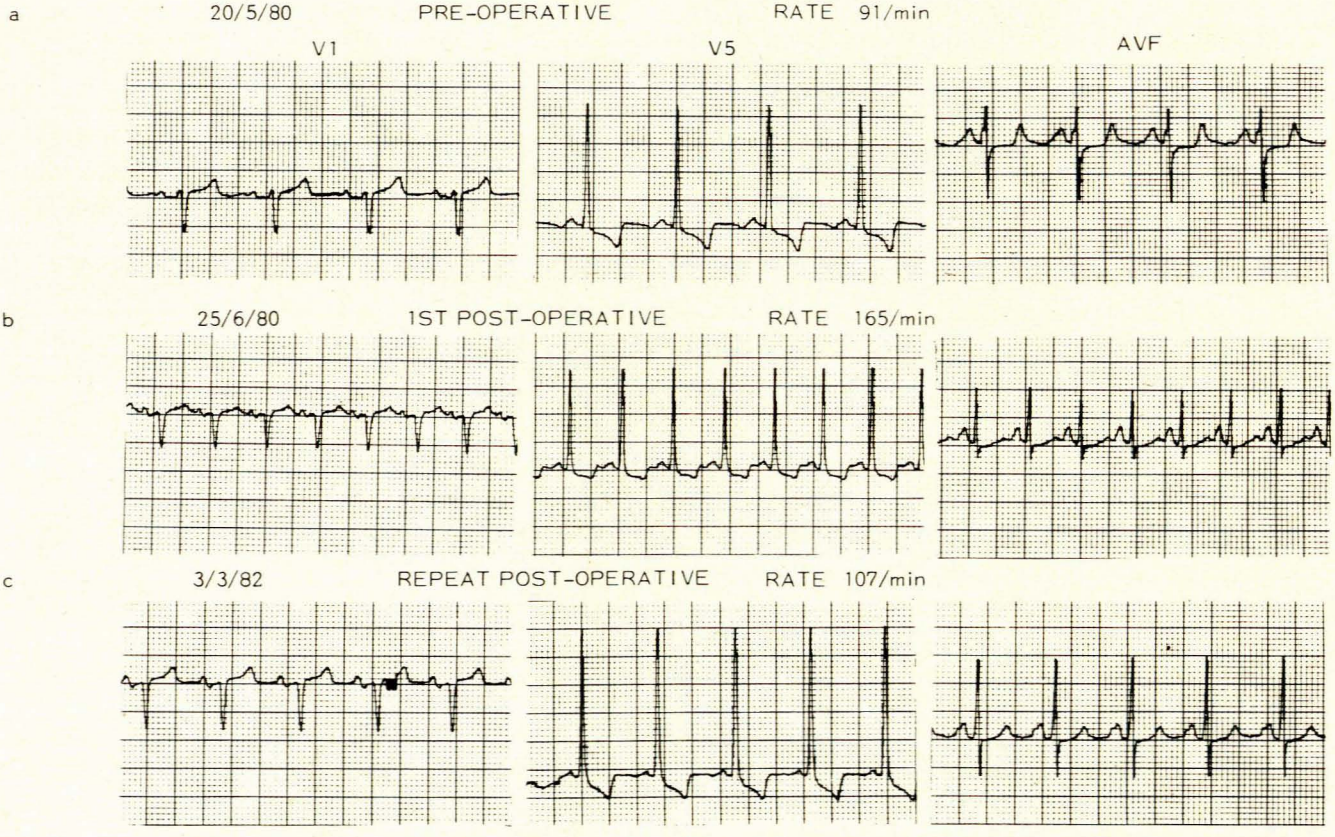

Fig. 2. a — Pre-operative submaximal stress ECG. Lateral subendocardial ischaemia (1,6 mm horizontal ST-segment depression) seen 4,5 minutes after onset of exercise. b — Postoperative submaximal stress ECG. Far less lateral ischaemia is seen with a longer period of exercise. c — Repeat postoperative strongly positive submaximal stress ECG showing 2,7 mm ST-segment depression laterally.

TABLE III. HAEMODYNAMIC CALCULATIONS

Parameter	Pre-operative (13 March 1980)	Postoperative 26 June 1980	Postoperative 4 March 1982
Oxygen consumption (ml/min)	**220**	**280**	**180**
Arteriovenous O_2 difference (vol %)	**3,0**	**3,9**	**4,3**
Cardiac output (Fick) (l/min)	**7,4**	**7,1**	**4,2**
Cardiac index (Fick) (l/min/m²)	**4,5**	**4,4**	**2,5**
Pulmonary vascular resistance (U)	**0,5**	**0,4**	**1,2**
Systemic vascular resistance (U)	**12,0**	**11,0**	**20,8**
Pulmonary/systemic resistance ratio (%)	**4,0**	**4,0**	**5,0**

used to measure intracardiac pressures on the right and left sides, as well as oxygen saturation in the main pulmonary artery and central aorta (Tables II and III). The right-sided pressures were moderately elevated, as were the mean capillary wedge and left ventricular end-diastolic pressures.

Left ventricular cine angiography in the right anterior oblique (Fig. 3) and left anterior oblique projections showed a somewhat hypokinetic anterobasal segment, but otherwise the left ventricle exhibited normal contractility. There was no evidence of mitral valve calcification, prolapse or insufficiency. Aortic cine angiography (left anterior oblique view) delineated a normal aortic valve and arch. Selective coronary angiography using 7F Judkin's catheters revealed striking features. Injection of contrast into the right coronary artery (RCA) in the left and right anterior oblique projections (Fig. 4) showed a normal dominant RCA with no ostial stenosis, but there was clear collateral filling of the left anterior descending (LAD) branch via septal perforators of the posterior descending artery of the RCA, filling the LAD as far proximal as its first septal perforator branch. Injection of dye into the left coronary artery in the left and right anterior oblique views (Fig. 5) identified a normal coronary ostium with total occlusion of the LAD just distal to its first septal perforator. In addition, haemodynamically insignificant lesions were present in the left circumflex coronary system. The procedure was completed without complication.

The LAD and its first diagonal branch were both considered to be suitable on angiography for saphenous vein CABG. At this stage it was accepted that anti-anginal medication had failed and that the patient was more likely to respond to surgical intervention. It was therefore decided to operate on the patient on 21 May 1980.

Operative findings and surgical correction

A median sternotomy approach was used. Moderate body hypothermia to 28°C was employed during cardiopulmonary bypass and cardioplegic solution was infused into the aortic root for myocardial protection. Proximally the LAD appeared as a firm fibrotic cord but there was no evidence of obvious myocardial infarction. A biopsy specimen was taken from this fibrotic section, as well as a small area of adjacent myocardium. A saphenous vein CABG was inserted into the LAD just distal to the origin of its first diagonal branch. The LAD had an internal luminal diameter of 1,5 mm, and a flow of 150 ml/min was registered via this CABG. A further CABG was inserted into the first diagonal branch of the LAD, and a similar satisfactory blood

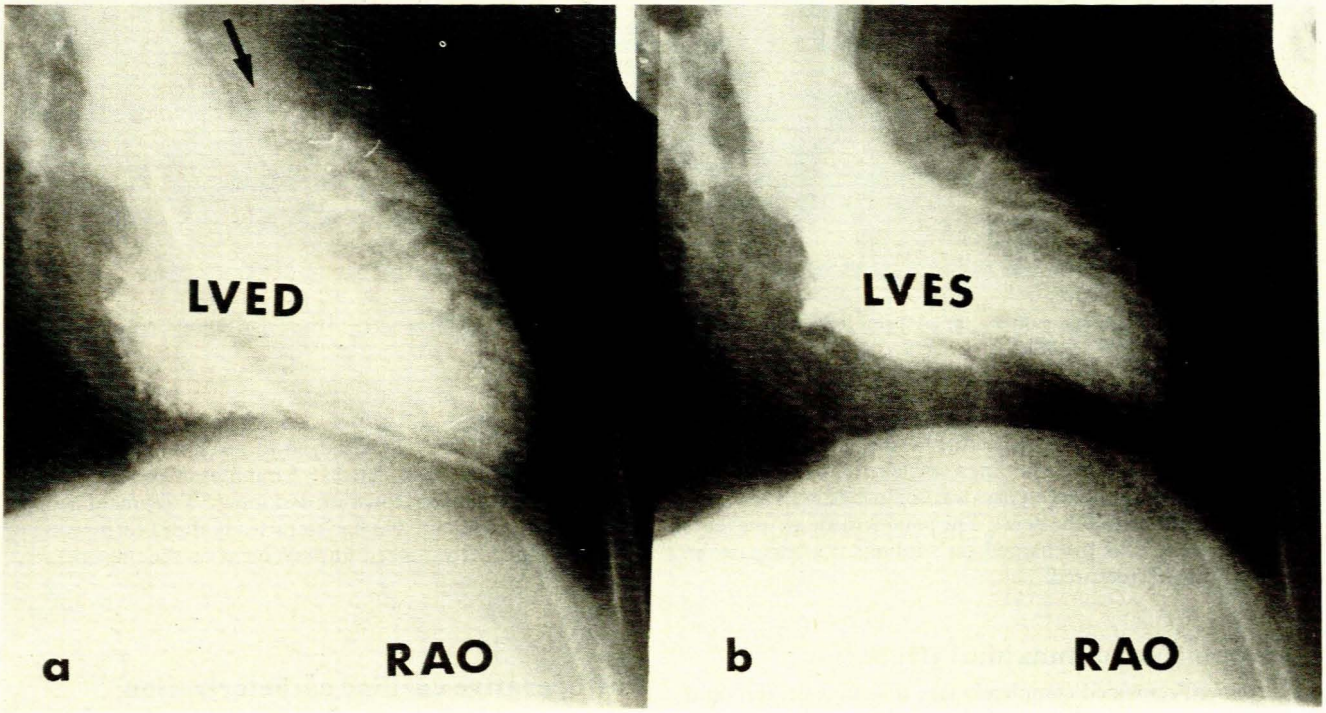

Fig. 3. Left ventricular cine angiograms (right anterior oblique (RAO) view) showing some anterobasal hypokinesia (arrowed): a — left ventricle in end-diastole (LVED); b — left ventricle in end-systole (LVES).

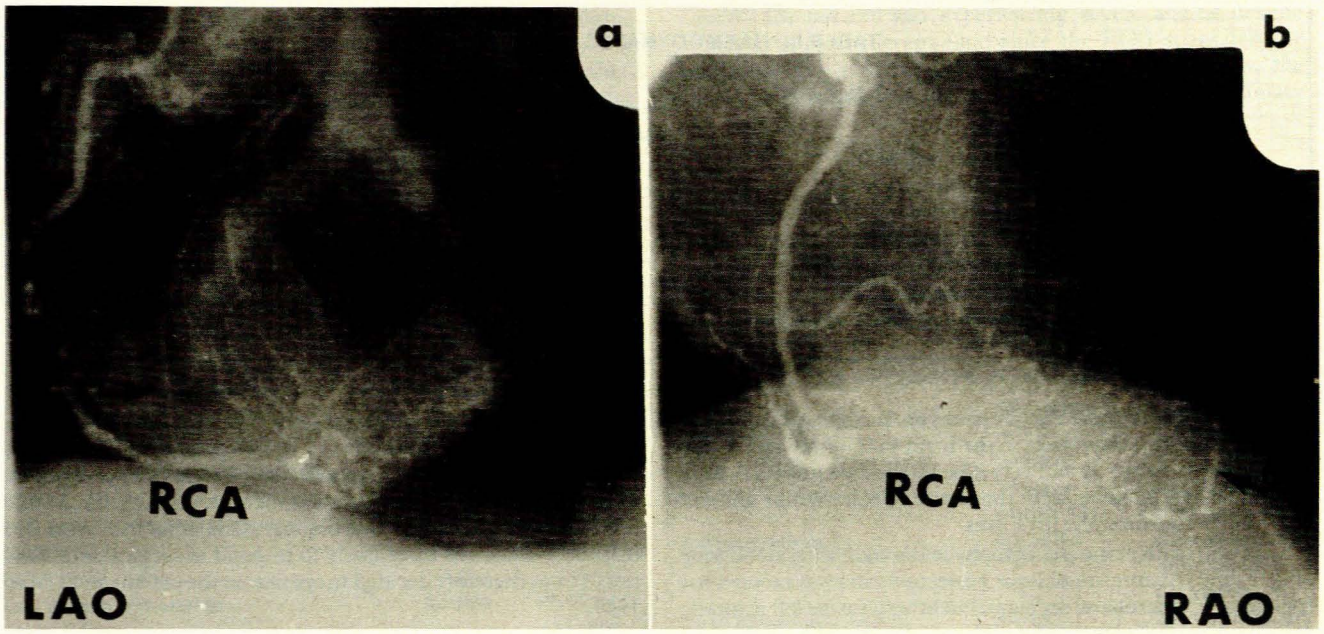

Fig. 4. Right coronary angiogram (RCA) taken in the (a) left anterior oblique (LAO) and (b) RAO projections. The RCA is normal with retrograde filling of the LAD (arrowed).

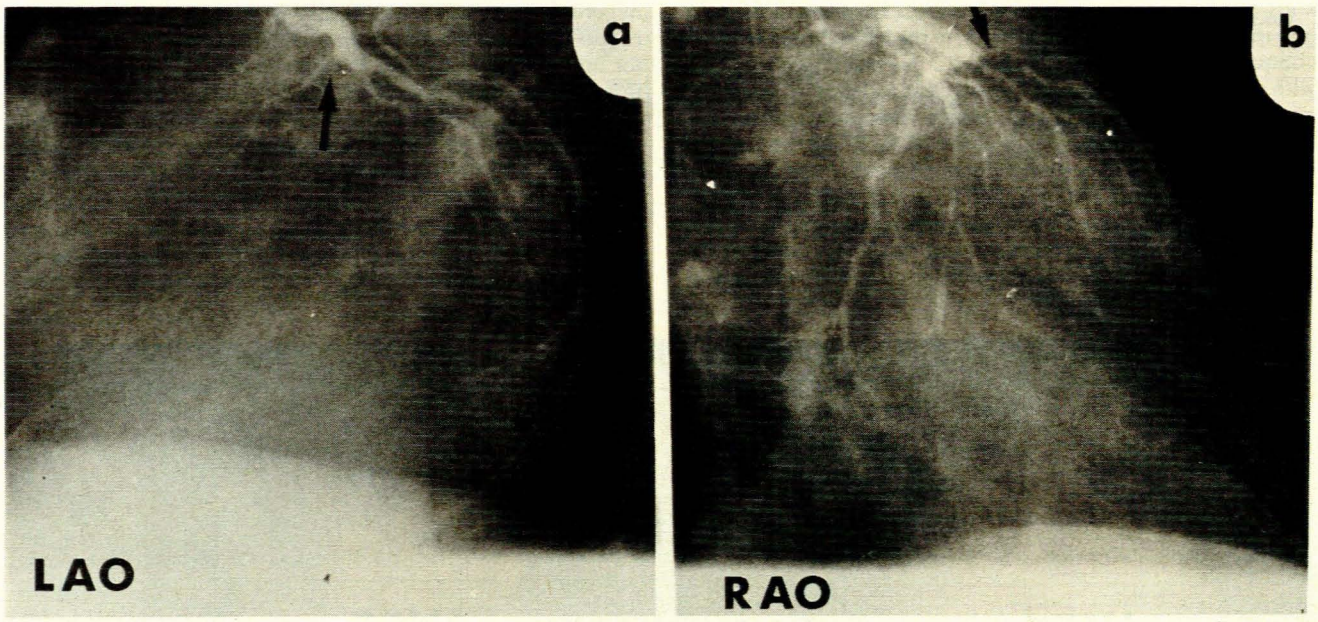

Fig. 5. Left coronary angiogram in the (a) LAO and (b) RAO projections. Total occlusion of the LAD is noted (arrowed). **A diffusely irregular left circumflex coronary artery is seen.**

flow was documented. The ascending aorta appeared normal, on macroscopical examination, as did the ostia of the right and left coronary arteries. A biopsy specimen was taken from the ascending aorta. Cardiopulmonary bypass was completed after rewarming and defibrillation of the heart. The patient made an uneventful recovery and was discharged on sublingual nitrates to be taken when and if required.

Postoperative submaximal effort test

The patient remained completely free of angina pectoris and underwent a repeat stress test on 25 June 1980, some 6 weeks after surgery. On this occasion his resting ECG no longer showed the anterolateral ischaemic changes previously seen, but now showed inferior ischaemia (Fig. 1b) as well as left atrial hypertrophy, but an axis now of +40°. He managed to reach a maximum heart rate of 165/min and completed 16,5 minutes of exercise without angina or arrhythmias. Downward-sloping ST-segment depression of 0,9 mm was noted in the lateral leads after 14,0 minutes of exercise (Fig. 2b), a marked improvement on the pre-operative stress test.

Postoperative cardiac catheterization

This was carried out as before on 26 June 1980 in order to determine the patency of the CABGs. Tables III and IV show that both the right- and left-sided pressures were within normal

limits and evidence of improved left ventricular function.

Left ventricular cine angiography (right anterior oblique projection) demonstrated good left ventricular contractility in the area previously hypokinetic. There was no evidence of inferior wall abnormality as suggested by the stress test.

Selective coronary arteriography still showed a normal RCA and complete occlusion of the LAD just distal to its origin. The CABGs to the LAD and the first diagonal branch were patent (Fig. 6).

Clinical follow-up

The patient was discharged on 27 June 1980, and instructed to take sublingual nitrates when necessary. Investigations for possible collagen disease or other auto-immune abnormality were again all negative.

He was well for some 2 months after discharge, when he again began experiencing typical angina on effort; a moderately high dose of propranolol and long-acting nitrates were reintroduced with not much good effect. Even when nifedipine was added he continued complaining of angina at rest and on effort. He was seen every 3 months at the Cardiac Clinic, at which times he was normotensive and repeated resting ECGs were unchanged. A repeat resting ECG taken on 10 November 1981 showed no inferior ischaemia but a possible non-transmural anterolateral infarction (Fig. 1c). Because of his unresponsive angina despite intensive oral drug therapy, it was decided to readmit him for repeat stress testing, cardiac catheterization and coronary arteriography.

Repeat postoperative submaximal effort test

This was carried out on 3 March 1982 without discontinuing the ß-blocker or calcium-antagonist therapy. The patient could only reach a maximum heart rate of 110/min with a slight response in the blood pressure. Within 5 minutes he complained of typical angina, relieved by sublingual isosorbide dinitrate; the

TABLE IV. POSTOPERATIVE INTRACARDIAC PRESSURES

Catheter position	Pressures (mmHg) 26 June 1980	4 March 1982	Comment
Right atrium	**'a' wave 2 'v' wave 1 (mean 1)**	**'a' wave 3 'v' wave 4 (mean 2)**	**Normal**
Right ventricle	**12/0-2**	**20/0-2**	**Normal**
Main pulmonary artery	**12/3 (mean 5)**	**20/7 (mean 12)**	**Normal**
Ascending aorta	**91/66 (mean 79)**	**106/74 (mean 88)**	**Normal**
Left ventricle	**91/0-5**	**106/10-15**	**Raised (4 March 1982)**
Dp/dt (mm/sec)	**2 030**	**1 090**	**Low (4 March 1982)**
Pulmonary capillary wedge	**'a' wave 2 'v' wave 3 (mean 2)**	**'a' wave 9 'v' wave 12 (mean 6)**	**Normal**

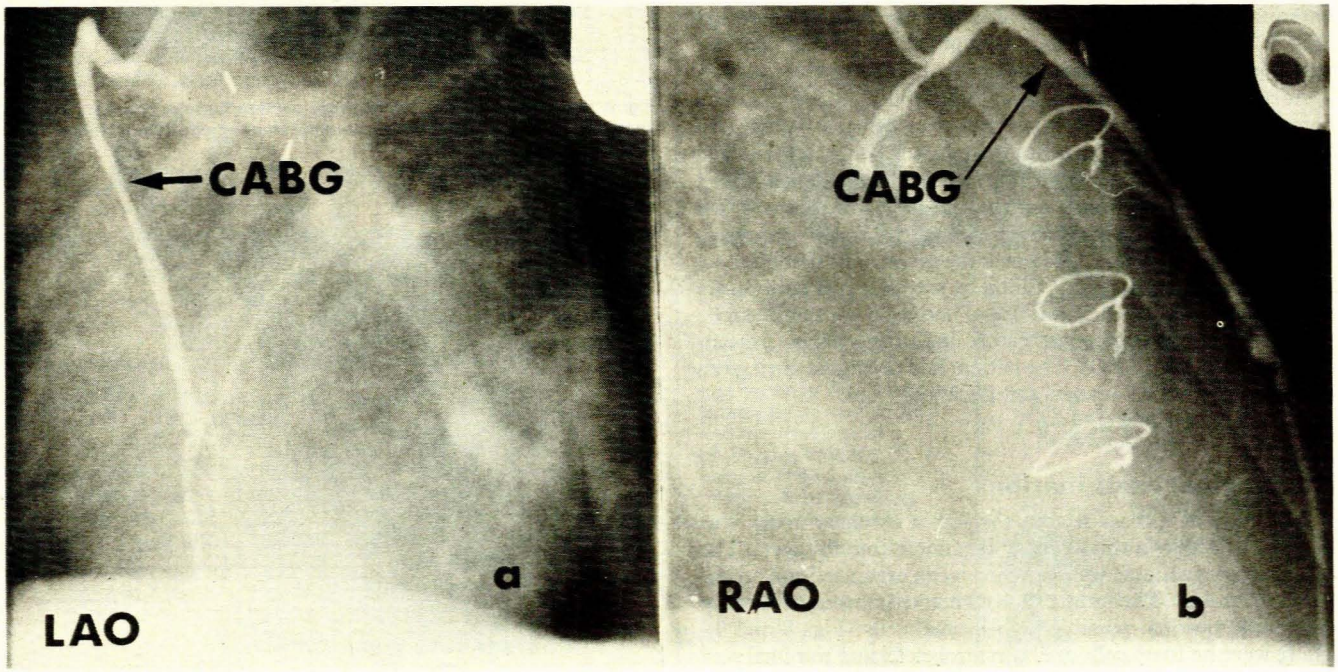

Fig. 6. Postoperative coronary cine angiograms showing (a) a patent CABG to the first diagonal branch of the LAD (arrowed) **and (b) a patent CABG to the LAD** (arrowed).

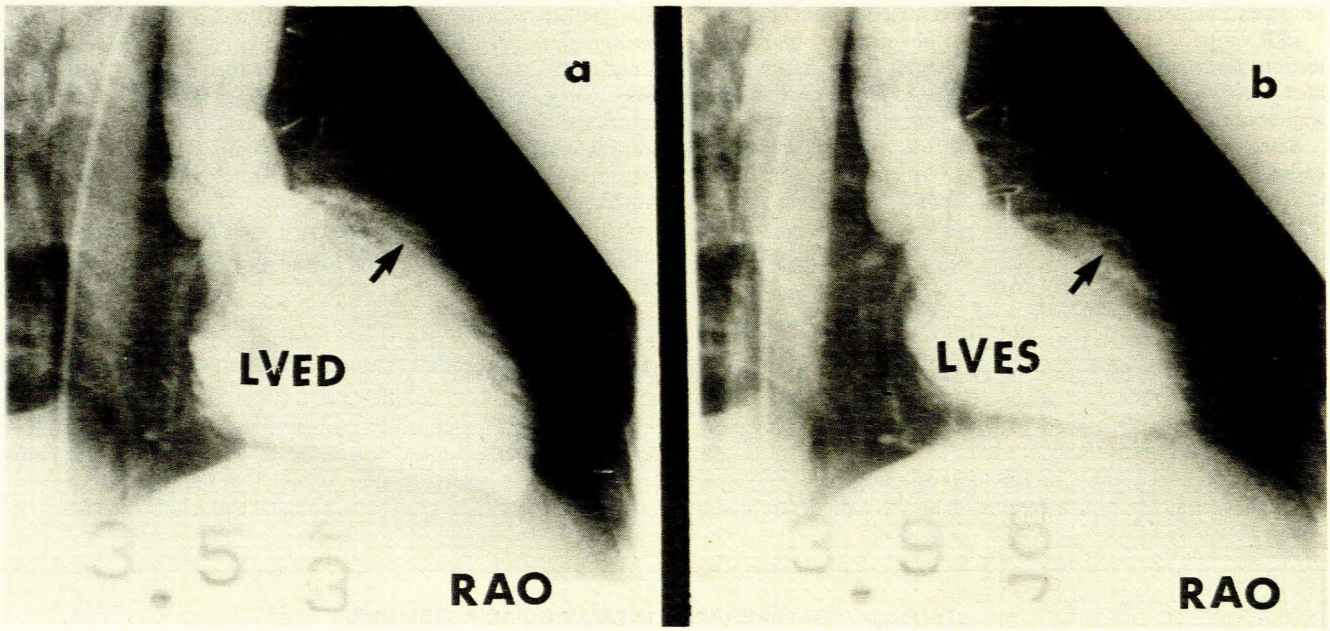

Fig. 7. Repeat postoperative left ventricular cine angiograms (RAO view) showing anterolateral akinesia (arrowed): a — left ventricle in end-diastole (LVED); b — left ventricle in end-systole (LVES).

exercise was then terminated, at which time down-sloping ST-segment depression of 2,7 mm was noticed in the lateral leads (Fig. 2c). This stress test was assessed as positive for ischaemia. It was then decided to reinvestigate his cardiac function and the status of his coronary arteries and the CABGs to the LAD and its first diagonal branch.

Repeat postoperative cardiac catheterization

This procedure was performed on 4 March 1982; the pressures were mostly normal apart from a slight increase in the left ventricular end-diastolic pressure and reduced left ventricular dp/dt (Tables III and IV). Left ventricular cine angiography (right anterior oblique projection) now demonstrated an area of anterolateral akinesia probably due to a myocardial infarction (Fig. 7). The rest of the ventricle contracted normally and no mitral insufficiency could be seen.

Aortic cine angiography (left anterior oblique view) showed a competent aortic valve but there was obvious occlusion of both CABGs at the proximal aortosaphenous anastomoses. Selective coronary arteriography in multiple projections demonstrated that the RCA anatomy was unchanged, but the left circumflex coronary artery still showed irregular, insignificant obstructions. The LAD was totally occluded near the origin of its first diagonal branch and some retrograde filling by way of septal perforators of the RCA was noticed. Wash-out of undyed blood could not be seen in the LAD system, a feature indicating almost certain occlusion of both CABGs. The patient had no angina during the procedure and there were no complications.

Histological examination

A portion of a cross-section through a coronary artery was received as well as a small biopsy specimen from the aorta. The coronary artery lumen was occupied by an organized and recanalized thrombus. The intima showed marked fibrous thickening with some residual possible myo-intimal cells (Figs 8 and 9). There were no foam cells or cholesterol clefts and minimal acid mucopolysaccharides in the intima in contrast to the organized thrombus, which showed abundant acid mucopolysaccharides with Alcian blue staining. The internal elastic membrane

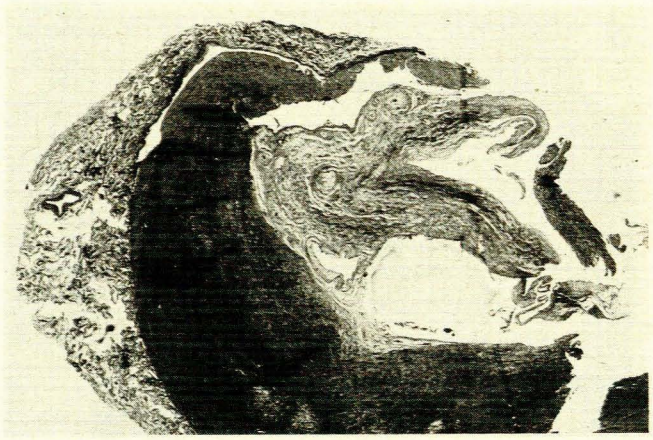

Fig. 8. Low-power view of partial cross-section through coronary artery showing organized and canalized luminal stenosis and intimal thickening (Verhoeff X 45).

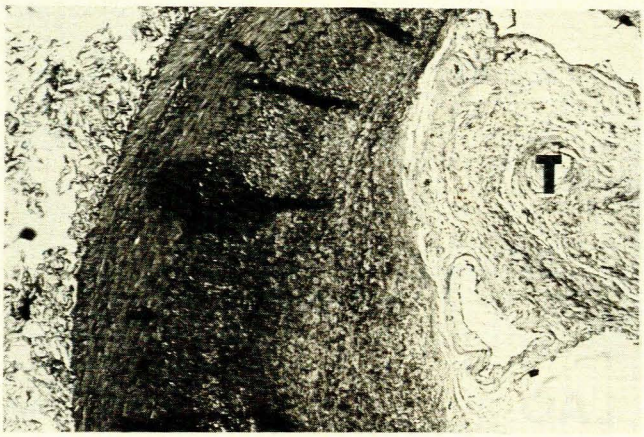

Fig. 9. Somewhat higher magnification through coronary artery showing luminal thrombus (T), the arrows indicating internal elastic lamina and greatly thickened and proliferated intima (Verhoeff X 90).

appeared slightly split but was otherwise not remarkable. The media appeared normal.

The section through the aortic biopsy specimen showed medial smooth-muscle and elastic lamellae obliquely sectioned with some acid mucopolysaccharides in the interstices. The section did not include the intimal surface. Despite the absence of atheroma formation the appearances in the coronary artery were considered consistent with the spectrum of lesions seen in coronary atherosclerosis.

Follow-up

It was decided that re-operation would not be in the best interest of the patient, who was against it anyway. He was discharged on high doses of long-acting nitrates, propranolol 160 mg/d and nifedipine 20 mg three times daily. A resting ECG taken on 5 March 1982 still showed features in keeping with a possible previous non-transmural anterolateral myocardial infarction (Fig. 1d). The patient claimed that his angina was much relieved and that he could cope with his daily responsibilities. He will be followed up regularly at the Cardiac Clinic outpatients' department.

Discussion

Histogenesis of coronary atherosclerosis

There has been much controversy regarding the precise definition of the terms 'hyperplastic arteriosclerosis' and 'atherosclerosis'. Moschcowitz[2] firmly believed that these were two histopathological entities, the former consisting of hyperplasia of the media, internal elastic lamina and intima secondary to 'normal' ageing, and the latter being indicative of a 'disease' process since lipid infiltration could be identified. However, he was also in agreement with the known fact that the presence of hypercholesterolaemia is not essential for the development of atherosclerosis.[3,4] Moon and Rinehart[5] made the following definitions: 'early coronary arteriosclerosis' — intimal hyperplasia (fibroblastic proliferation) with the appearance of mucoid ground substance in the media and intima, as well as focal degeneration of the internal elastic lamina, usually with the absence of any lipid deposition — they called 'moderately advanced coronary arteriosclerosis'; more significant fragmentation and reduplication of the internal elastic lamina in addition to the presence of lipid was called 'far advanced coronary arteriosclerosis', with addition of hyalinization (usually positive for mucopolysaccharide), lipid-laden macrophages, calcification and frequently thrombosis.

The World Health Organization (WHO) has defined atherosclerosis as 'a variable combination of changes of the intima of arteries (as distinguished from arterioles) consisting of the focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits and associated with medial changes'.[6] Platelet action on the intima has been strongly advocated as the initiating stimulus to early inflammation with subsequent progression to the fully-developed histological picture of coronary atherosclerosis as defined by the WHO.[3,7]

Most recently, Marzilli *et al.*[8] have postulated a coronary vasospasm-injury-vasospasm mechanism as the basic underlying cause of all the pathological manifestations of coronary atherosclerosis. However, this general hypothesis has been accepted with much reservation since the incidence of proven coronary vasospasm is so low, despite smooth-muscle cell proliferation being crucial to the development of artherosclerosis.

Aetiology of aortocoronary saphenous vein graft occlusion

The use of reversed autogenous saphenous veins in CABG surgery has been exceedingly popular since the operation was first described by Favaloro in 1968.[9] This has provided much information as regards the fate of these grafts, which is so important to the patient's postoperative course. Progressive intimal fibrous hyperplasia ('phlebosclerosis'[2]) of the saphenous grafts ensues within the first month.[10-13] Absence of intimal fibroelastosis in some CABGs removed early after operation but the presence of concentric intimal thrombus converted to fibrous plaque has indicated that this is not just 'arterialization' of the saphenous graft or a simple reaction to increased intraluminal pressure.

Early CABG occlusion is generally accepted as being due to technical factors such as the angle of the aortic anastomosis[14,15] or inadequate distal 'run-off' in the bypassed coronary artery,[11] and is invariably associated with thrombosis. Compression of the intrinsic coronary artery, coronary dissection and thrombus formation have also been implicated.[10] However, late CABG occlusion is usually secondary to progressive intimal fibromuscular proliferation and is not often associated with occlusive thrombosis.[11] This intimal hyperplasia is frequently seen in conjunction with atheromatous plaque formation and greater internal luminal narrowing, especially in the presence of hyperlipidaemia.[16] Walts *et al.*[17] described atheromatous plaque rupture with superimposed occlusive thrombosis as an unusual mechanism of late CABG occlusion, and stated that these lesions were undistinguishable from those of atherosclerosis in the native coronary arteries. The importance of the mechanism described by Walts *et al.*[17] is that these patients may be amenable to non-surgical correction by percutaneous transluminal coronary angioplasty[18] or intracoronary thrombolysis.[19,20] Bulkley and Hutchins[21] documented a case of acute postoperative CABG occlusion consequent upon bacterial (*Pseudomonas aeruginosa*) saphenous phlebitis.

Progression of the underlying coronary atherosclerosis is considered most significant in determining the outcome of CABG surgery. Patency of CABGs 1 year postoperatively has been reported as between 15% and 30%.[22-24] Cardiac catheterization studies[23] have suggested that the most significant obstructions in the bypassed coronary artery are located immediately adjacent to the proximal and distal ends of the anastomosis rather than within the anastomosis itself.

A most unique and fascinating patient was recently documented by Victor *et al.*[25] This 66-year-old man had multiple CABGs for severe angina pectoris. Surgery was effective until significant angina recurred some 2 months postoperatively. Recatheterization demonstrated the presence of coronary vasospasm in the sequential CABG to the obtuse marginal branch of the left circumflex coronary and the posterior descending branch of the RCA. This was associated with severe chest pain but no significant ECG changes. Complete angiographic resolution of the coronary vasospasm was achieved with nitroglycerin injection, and the patient remained angina-free on a combination of calcium antagonists and nitrates. The authors then proceeded to postulate that early closure of CABGs may be due to spasm followed by platelet aggregation with ensuing release of powerful vasoconstrictors causing eventual thrombosis. This theory is further substantiated by the strong probability of coronary vasospasm occurring in a totally denervated heart.[26]

The role of cigarette smoking

Our patient had no known risk factors for coronary atherosclerosis — hyperlipidaemia, hypertension, diabetes mellitus and a family history of the condition —but he had smoked some 10 cigarettes daily for as long as he could recall. Another factor in his favour was that he was Coloured — the incidence of atheromatous IHD is known to be low in this population group in the absence of the other risk factors.

The Framingham study[27] has clearly shown that fatal coronary episodes occur much more frequently in cigarette smokers. Furthermore, when these do occur they are more likely to end in sudden death. The incidence of angina has also been shown to be increased, particularly among heavy smokers.[28] The relative effect of cigarette smoking on IHD is less significant with increasing age, but more significant in men than in women. Interestingly, cigarette smoking seems to be less of a risk factor for IHD in those countries in which mortality from IHD is low. It has also been shown that stopping smoking decreases the risk of mortality from IHD.

Pathophysiological mechanisms attributed to cigarette smoking are quite numerous. Nicotine stimulates catecholamine production with a subsequent increase in heart rate, blood pressure and cardiac output, giving rise to greater myocardial oxygen consumption.[29] This effect is particularly important in the presence of underlying coronary atherosclerosis because myocardial ischaemia may be precipitated. Another effect of nicotine is elevation of the serum free fatty acid level via noradrenaline stimulation, which also raises the serum triglyceride level. As a result of these actions arrhythmias, especially ventricular fibrillation, may ensue with subsequent sudden death. The increase in catecholamines also increases platelet adhesiveness and aggregation which may accelerate thrombus formation, especially since fibrinolysis is inhibited.

The role played by carbon monoxide (CO) may be less important than that of nicotine. The former substance is known to shift the oxygen-dissociation curve to the left and thus interferes with oxygen release to the tissue, and more importantly, leads to a potentially ischaemic myocardium. It has been proved experimentally that CO increases endothelial permeability, with increasing deposition of lipids in the arterial wall and subsequent atherosclerosis. Increased platelet adhesiveness has also been shown, possibly contributing to thrombus formation. Angina is known to occur at lower levels of exercise in those exposed to cigarette smoke or after exposure to air pollution in heavy traffic. Ischaemic ST-segment depression also appears earlier and is more severe after inhalation of CO compared with the findings after inhalation of compressed purified air. This also occurs when the product of the heart rate and systolic blood pressure is lower.

The combination of nicotine and CO in cigarette smoke would therefore seem to be lethal. CO decreases the oxygen available to the myocardium when the cardiac work is significantly increased by nicotine, and is especially detrimental in the presence of underlying atherosclerotic coronary artery narrowing. By differing mechanisms, these two substances may also accelerate thrombus formation with subsequent atherosclerosis. Also deleterious is the association of cigarette smoking with decreased levels of high-density lipoprotein, which is normally somehow protective.

It is well known that patients suffering an acute myocardial infarction (AMI) are usually heavy smokers,[30] particularly those in younger age-groups. The incidence of repeat AMI and cardiovascular deaths is also higher in patients who continue to smoke after their first AMI.[30] Interestingly, patients who discontinue smoking have higher blood pressures and need antihypertensive medication more frequently than those who continue the habit after AMI.

It was shown recently that cigarette smoking diminishes the beneficial actions of propranolol treatment in patients receiving this drug for the control of angina pectoris.[31] Thus, exercise-induced blood pressure elevation and heart rate increases are more significant in patients taking propranolol and who smoke, as is the total ST-segment depression at peak exercise and the number of leads showing these ischaemic changes. Smoking was also documented as directly reducing plasma propranolol concentration by hepatic enzyme induction.

In the USA the reason for the decline in mortality from cardiovascular disease over the past decade is unknown. Nevertheless, it has been suggested that 50% of this decline can be attributed to the decreased incidence of smoking, 25% to a reduction in serum cholesterol and 25% to better control of hypertension.[27]

The possible role of coronary vasospasm

The recent literature has provided some interesting publications which attempt to associate the known pathophysiological entity of coronary artery spasm and the development of atherosclerosis resulting in AMI. Hellstrom[32] advocated his 'injury-vasospasm hypothesis' as a possible explanation of the progression of coronary atherosclerosis and was subsequently supported in this by Marzilli *et al.*[8] Coronary artery thrombosis was then attributed to possible coronary vasospasm by Hellstrom[33] who noted that large transmural myocardial infarctions were more often associated with coronary thrombi than were non-transmural (subendocardial) infarctions. This theory was then clearly verified by Maseri *et al.*[34]

Workers have also postulated that coronary atherosclerosis *per se* can precipitate coronary vasospasm, thus completing the pathophysiological cycle. Oliva and Beckinridge[35] suggested that the release of platelet vasoconstrictors by these abnormal coronary arteries can evoke vasospasm. Hellstrom[32,36] proposed that obstructive coronary atherosclerosis could cause severe ischaemia and therefore myocardial injury, which in turn could precipitate coronary vasospasm in the small intramural coronary arteries leading to eventual spasm of the large epicardial coronary arteries. Hellstrom also postulated that, irrespective of the initial cause of the infarction, myocardial infarction tissue can precipitate coronary artery spasm and give rise to the so-called 'no-reflow phenomenon'.[32] Most recently Gertz *et al.*,[37] carrying out experimental work with dogs and rabbits, showed that endothelial damage with ensuing thrombus formation may take place at an area of localized arterial narrowing even though the decrease in transmural diameter is not severe enough to significantly alter the rate of blood flow. These experiments strongly supported the primary role of coronary vasospasm in initiating thrombus formation with myocardial infarction.

Our patient may well have had repeated episodes of coronary vasospasm causing the early appearance of coronary atherosclerosis which, with the added risk factor of cigarette smoking, progressed with further coronary spasm intervening to terminate in AMI with subsequent thrombosis within the proximal LAD. His further clinical course may well provide the answer to this most complicated interrelationship, which will be important in determining the most effective therapeutic approach, especially if his angina becomes debilitating.

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Nuus en Kommentaar/News and Comment

Physical activity, thinness and menarche

It is well known that girls who indulge in intensive physical activity will also experience a delay in menarche. However, it is difficult to distinguish this effect from the finding that thinner girls tend to begin menstruation at a later date. To disentangle the potential effects of thinness and physical activity on girls in a Dutch suburb, Vandenbrouche *et al.* (*Br Med J* 1982; **284:** 1907) studied the records of 648 girls aged 10 - 14 years. They divided the girls into four classes, thin or not thin, and intensely active or not. Their findings suggest that either thinness or intensive sport activity tends to delay menarche, and that a combination of both factors has a synergistic effect in delay.

Teofillien in swangerskap

Die farmakologiese uitwerking van die xantienderivate insluitende teofillien, kafeïen en teobromien bestaan uit sentrale-senustelselstimulasie, kardiale-spierstimulasie, verslapping van gladdespier en diurese. Die gebruik van serum-teofillienvlakke is waardevol om potensiële toksiese reaksies te monitor sowel as om 'n riglyn vir die geneesheer aan te dui by die behandeling van omkeerbare obstruktiewe lugwegtoestande. Volgens Labovitz *et al.* (*JAMA* 1982; **247:** 786) verhoog die risiko van toksiese teofillienreakies wanneer die serum-teofillienvlak bo 20 μg/ml styg. Die simptome en tekens van toksisiteit mag van hoofpyn, mislikheid en vomering tot dodelike stuiptrekkinge, sonder waarskuwing varieer. Alhoewel teofillien met veiligheid gedurende swangerskap gebruik kan word, is daar min data beskikbaar betreffende die oordrag van teofillien deur die plasentale verskansing na die baba en die effekte op pasgeborenes. Teofillien kan ook in premature babas na kafeïen omgeset word sodat kafeïentoksisiteit ook moontlik is in die pasgeborene wie se moeder teofillienbehandeling ontvang het.

Labovitz *et al.* het die pasgeborene se potensiaal om toksiese reaksies van plasentale oordrag van teofillien, of kafeïenoorsetting van teofillien te kry, in 12 pasgeborenes van asmatiese moeders bestudeer. Hulle resultate toon aan dat moederlike en koord-teofillien vlakke nie baie verskil het nie, maar dat hakskeenbloed van die pasgeborene 'n hoër vlak getoon het. Hierdie vlak het tussen 2,3 en 19,6 μg/ml, met 'n gemiddelde van 10,5 μg/ml, gevarieer. Daar was geen tekens van omsetting van teofillien na kafeïen nie. Die hartspoed, Apgartelling en ander parameters het nie statisties verskil van dié van babas wie se moeders nie teofillien ontvang het nie. Die newe-effekte by 3 babas wie se serumvlakke van teofillien hoër as 10 μg/ml was, was tagikardie en bewerigheid van verbygaande aard.