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Late symptomatic exercise-induced coronary vasospasm after percutaneous transluminal coronary angioplasty

A case report and review

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Summary

A patient who underwent a successful double-vessel percutaneous transluminal coronary angioplasty (PTCA) had suffered from exercise-induced ST-segment elevation associated with angina pectoris (AP). This ECG pattern was present both before and 12 months after PTCA while nifedipine (Adalat; Bayer-Miles) therapy was electively discontinued. Reintroduction of calcium blockade with this drug eliminated the chest pain and resulted in normalization of the stress ECG. Cardiac catheterization at 6 and 12 months after PTCA demonstrated continuing angiographic improvement of the coronary stenoses of the left anterior descending and left circumflex (LCx) coronary arteries previously subjected to PTCA. It is believed that coronary artery spasm at the PTCA site on the LCx coronary artery was responsible for the AP and exercise-induced ST-segment elevation. Likely pathogenetic mechanisms of coronary vasospasm during and after the performance of PTCA, as well as the interrelationship with re-stenosis and the clinical implications of drug therapy, are discussed.

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Case report

A 58-year-old retired farmer smoked 30 cigarettes daily but had no other risk factors for ischaemic heart disease. For 3 months before admission to the Intensive Coronary Care Unit at Tygerberg Hospital he had suffered from effort-related angina pectoris (AP); 2 weeks before admission the AP became frankly unstable despite high doses of a combination of oral and transdermal nitrates, β-blockers and perhexiline maleate. Physical examination revealed nothing abnormal but a prominent left ventricular (LV) fourth heart sound was audible. The resting ECG and chest radiograph were both within normal limits, and results of routine biochemical and renal function tests were normal. The patient was heparinized, the β-blockade increased, and a calcium antagonist added to his therapeutic regimen. Serial ECGs and serum enzyme determinations excluded an acute myocardial infarction (MI). The patient's symptoms improved and he was gradually mobilized.

On 26 September 1983, 16 days after admission and while still on multiple anti-anginal medication, the patient underwent a submaximal treadmill exercise test. His resting heart rate was 50 and an age-predicted target heart rate of 162 was determined. After 5 minutes of exercise the heart rate was 85 with a poor blood pressure increment. He then complained of severe AP which was accompanied by inferolateral ST-segment elevation, a maximum of 9 mm being recorded in lead V5 (Fig. 1). During the recovery period the AP responded to sublingual nitroglycerin and the inferolateral ST-segment elevation had returned to the normal resting state by 6 minutes. An exercise technetium-99m gated blood pool scintiscan showed a resting ejection fraction of 62% which fell to 40% on exercise, eliciting a heart rate response of 85 accompanied by AP and obvious inferior akinesia.

Initial cardiac catheterization

Cardiac catheterization and selective coronary angiography was done by the Seldinger technique from the groin. LV cine angiography showed normal function. The right coronary artery (RCA) was dominant and displayed insignificant internal luminal irregularities, but the left coronary artery, excluding the mainstem, was significantly affected by atherosclerosis. There was asymmetrical subtotal obstruction in the left anterior descending (LAD) branch just distal to the origin of the first diagonal branch, with 60% stenosis in the left circumflex (LCx) artery proximal to the anterolateral branch origin (Fig. 2). Both these stenoses were considered suitable for percutaneous transluminal coronary angioplasty (PTCA), which was carried out on 27 September 1983.
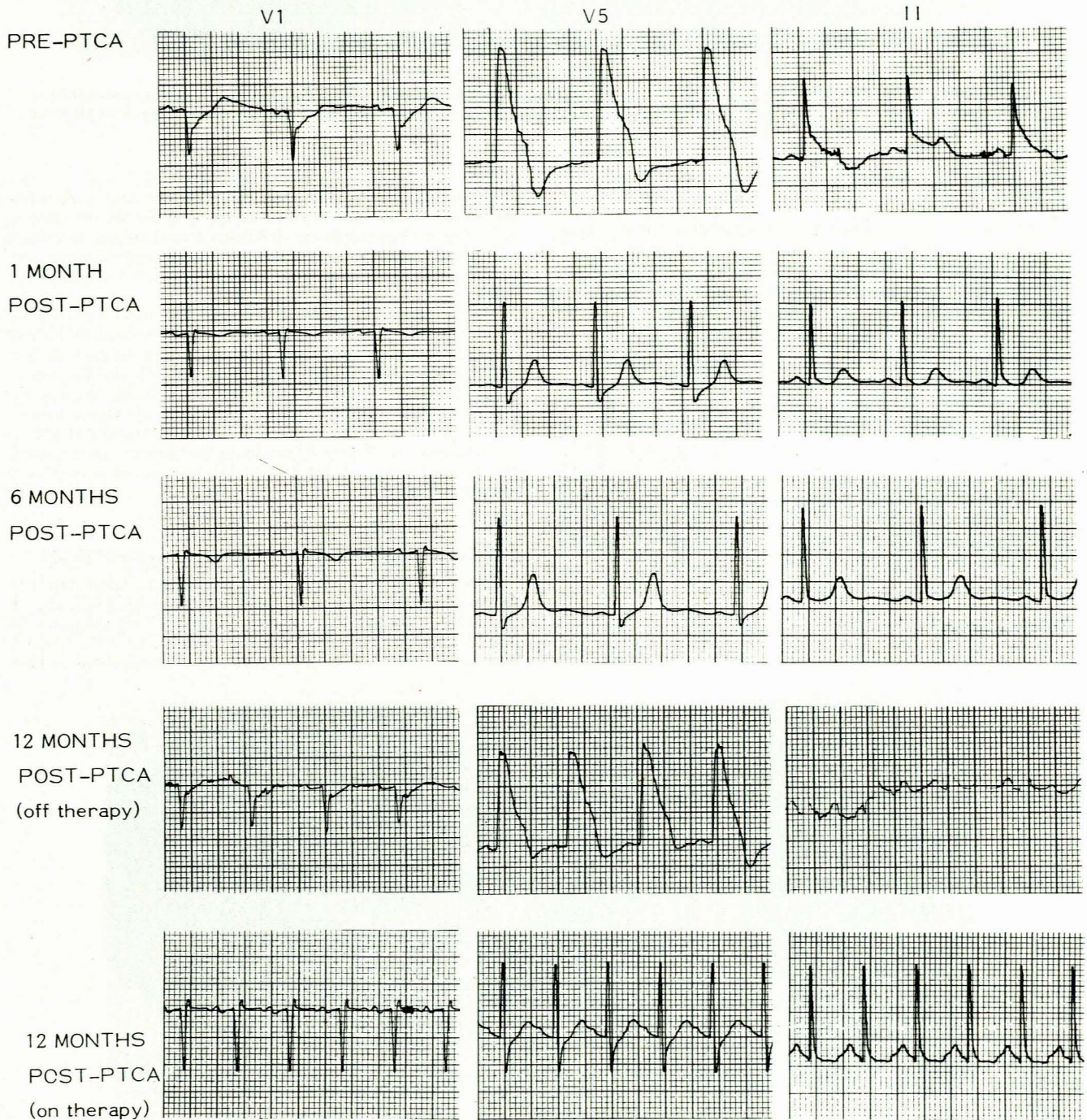

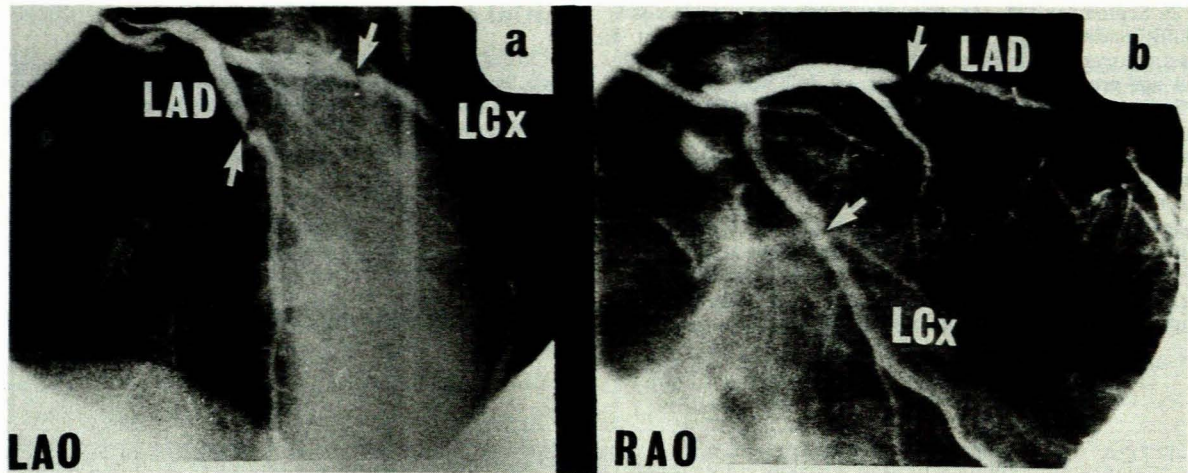**Fig. 1. Submaximal treadmill exercise tests performed at various intervals.**

Fig. 2. Left coronary cine angiograms before PTCA in the: (a) shallow left anterior oblique (LAO) and (b) right anterior oblique (RAO) view demonstrating an asymmetrical subtotal obstruction (arrowed) of the LAD coronary branch, as well as a 60% stenosis (arrowed) of the LCx coronary branch.

PTCA

This procedure was undertaken according to the technique previously reviewed by us.[1] A standard Schneider Medintag AG-Grüntzig Dilaca balloon catheter (2 cm long; 2,5 mm diameter balloon) and steerable guidewire was utilized for the PTCA of both the LAD and LCx. A maximum balloon inflation pressure of 8 atmospheres was applied. The LAD stenosis (initial gradient of 65 mmHg) was dealt with first, a final gradient of 10 mmHg being recorded. The LCx lesion gave rise to an initial gradient of 95 mmHg, reduced to a final gradient of 14 mmHg at the end of dilatation. Before PTCA, coronary angiography demonstrated the most significant lesions of both these major coronary vessels (Fig. 3); after PTCA results with both stenoses were considered acceptable on angiography (Fig. 4) as well as in the light of the final gradients recorded (a 'primary success'). The patient was soon discharged on nifedipine (Adalat; Bayer-Miles) 20 mg 3 times daily, atenolol (Tenormin; ICI) 100 mg/d, transdermal nitroglycerin (Nitradisc 10; Searle), dipyridamole (Persantin; Boehringer Ingelheim) 100 mg 3 times daily, and aspirin 75 mg/d.

Follow-up

The protocol outlined in our review article[1] was followed. A

repeat submaximal treadmill exercise test was carried out while the patient was on medication, 1 month after PTCA. The resting heart rate of 48 rose to a peak of 90 after 6 minutes and 30 seconds of exertion. AP did not occur and the test was now negative (Fig. 1). A few days later an exercise thallium-201 test was completely negative.

The patient continued to be asymptomatic and returned to an active life. Six months after PTCA a further submaximal treadmill stress test was completely negative (Fig. 1). The duration of effort achieved was 6 minutes and 30 seconds, with a peak heart rate of 90. However, a stress ^{201}Tl scintiscan on the folllowing day was frankly abnormal, demonstrating decreased uptake of isotope inferiorly at rest and after exercise. Reversible myocardial ischaemia not accompanied by any AP or ECG change was also reported. The possibility of a painless inferior MI sometime after the PTCA was entertained.

Cardiac catheterization (6 months after PTCA)

This procedure was performed 2 days after the scintiscan, with the patient on his full drug regimen, asymptomatic and leading a normal life. Selective arteriography of the RCA demonstrated no change from that seen initially. The LAD and LCx stenoses subjected to PTCA 6 months previously now appeared to have
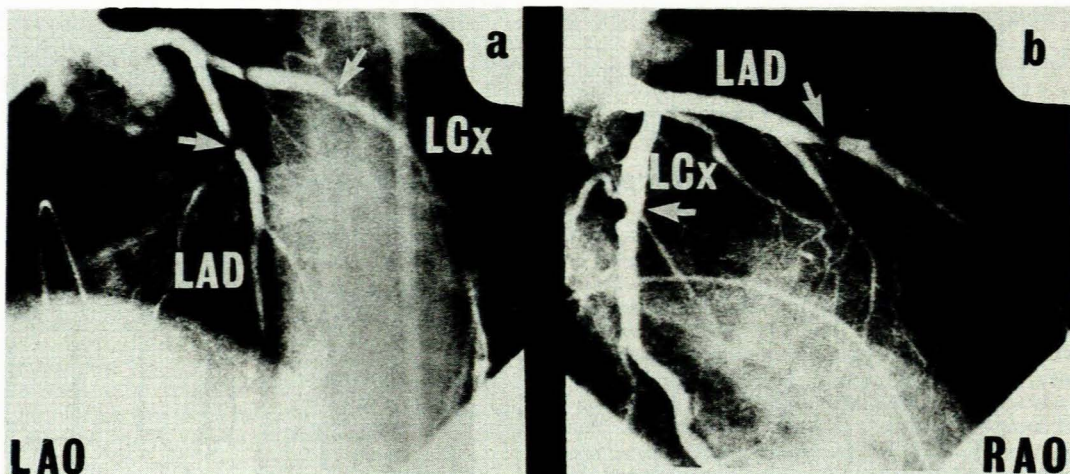

Fig. 3. Left coronary cine angiograms immediately before PTCA in the (a) LAO and (b) RAO view. The most significant lesions of the LAD and LCx are arrowed. A prophylactic temporary right ventricular pacemaker electrode is *in situ*.
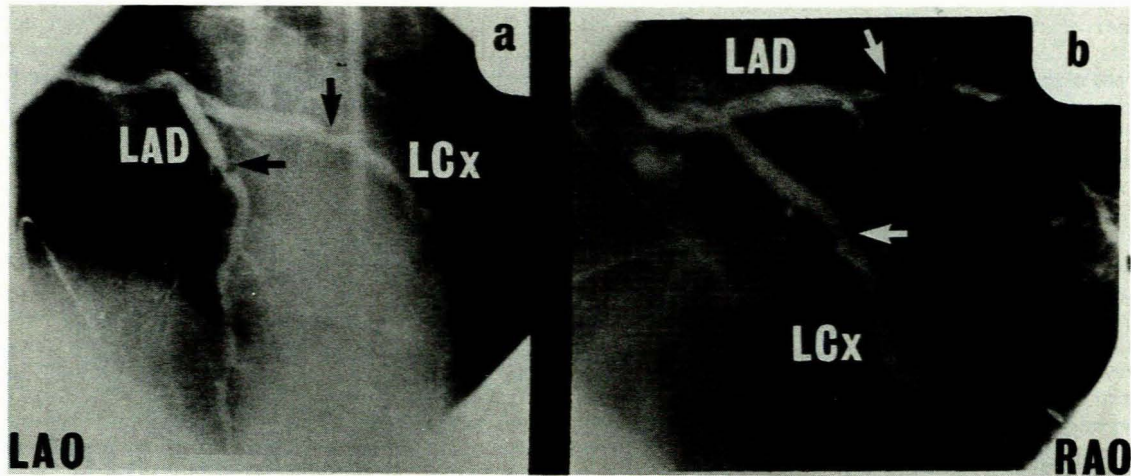
Fig. 4. Left coronary cine angiograms in the (a) LAO and (b) RAO projection after completion of PTCA. A satisfactory result has been achieved, as indicated by the arrows localizing the LAD and LCx stenoses.

improved (Fig. 5). In view of the patient's condition, the negative submaximal treadmill stress test and most favourable coronary angiographic features (despite the controversial ^{201}Tl exercise scintiscan), all medication, apart from transdermal nitroglycerin and low-dose aspirin, was discontinued the next day.

Follow-up after repeat cardiac catheterization

Approximately 12 months after PTCA, and while receiving only a small dose of nitrate and aspirin, the patient again began experiencing unstable AP and was readmitted on 18 September 1984. A resting ^{99m}Tc gated blood pool scintiscan demonstrated normal LV function with an ejection fraction of 75%, a finding which did not correlate with the suggested previous inferior MI. During a submaximal treadmill stress test the resting heart rate of 78 rose to a peak of 110 after 4 minutes of exercise. The resting ECG was normal. Immediately after completion of effort the patient complained of severe AP, accompanied by marked antero-lateral ST-segment elevation (maximum of 7 mm in lead V5). Morphine and sublingual nitrate relieved the AP and the ECG returned to normal in 3 minutes. Therapy with nifedipine 20 mg 3 times daily and transdermal nitroglycerin was resumed. Serial ECGs and serum enzyme levels remained normal, thus excluding acute MI.

Cardiac catheterization performed 2 days after admission showed normal left-sided cardiac pressures; LV cine angiography demonstrated normal contractility, thus failing to corroborate the results of the previous ^{201}Tl stress test. Right coronary cine angiography failed to outline any significant obstructions. Left coronary arteriography demonstrated that the LAD and LCx PTCA sites (Fig. 6) had improved further. Ergometrine maleate provocation testing for possible coronary vasospasm was not carried out.

Four days after cardiac catheterization with the patient on full medication, he was submitted to repeat submaximal stress testing. The resting heart rate of 103 rose to a peak of 162. The patient exercised for 7 minutes and 20 seconds without experiencing any AP or there being evidence of myocardial ischaemia on the ECG. A repeat ^{201}Tl stress scintiscan 2 days later now appeared normal, a heart rate of 138 being achieved without AP.

No further investigation seemed indicated and the patient was discharged with scintigraphic and angiographic evidence of a persisting satisfactory PTCA result. Nevertheless, repeated sub-maximal stress testing had delineated the presence of myocardial ischaemia and poor effort tolerance when calcium-blocker therapy had been discontinued, with features almost identical to those before PTCA (Fig. 1). Reinstitution of nifedipine and an increase in the maintenance nitrate therapy caused the patient's AP to disappear and effort tolerance to improve, and the stress ECG abnormalities to normalize. We postulate that exercise-induced
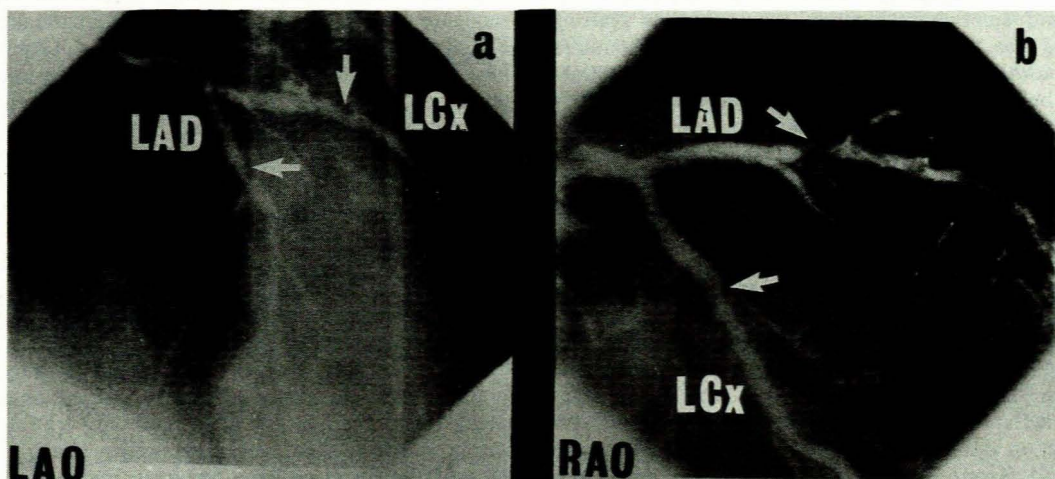

Fig. 5. Left coronary cine angiograms in the (a) LAO and (b) RAO view at the 6-month follow-up after PTCA. The lesions (arrowed) in the LAD and LCx are still both satisfactory.
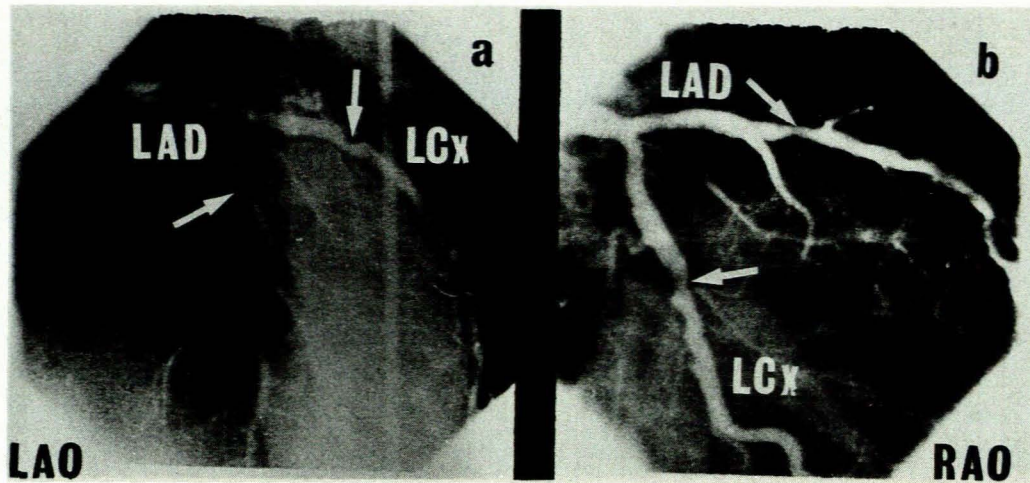
Fig. 6. Left coronary cine angiograms in the (a) LAO and (b) RAO projection at 12 months after PTCA. The stenoses (arrowed) in both the LAD and LCx are still insignificant with no increase in severity compared with previous catheterization.

coronary vasospasm, superimposed on the PTCA site of either the LAD or LCx lesion, was responsible for these findings some 12 months after 'primary success'.

Discussion

PTCA has now been accepted as a therapeutic procedure, but in common with other recently introduced techniques, it still has to display its full potential in a disease of great importance in South Africa. Perhaps two of the most perplexing questions remaining unanswered are those regarding the role of coronary artery spasm and the pathogenetic mechanism of re-stenosis after 'primary success'. An even greater challenge is the possible interrelationship between coronary vasospasm and re-stenosis after PTCA. Furthermore, the role of maintenance drug therapy with antiplatelet agents, long-acting nitrate preparations and calcium-channel-blocking agents is under close scrutiny.

Coronary vasospasm during PTCA

The frequency of coronary artery spasm during the PTCA procedure itself has been recorded as 4,2%.[2] This complication is also known to predispose to such major complications as acute MI, and emergency coronary artery bypass grafting (CABG), and also death. It has therefore become standard practice to administer prophylactic intracoronary nitrate preparations before PTCA and for the patient to take coronary vasodilator drugs orally for at least a few days previously. The additional intracoronary nitrate is administered because coronary vasospasm can be resistant to sublingual nitrate administration.[3] Calcium-channel-blockers, specifically nifedipine and verapamil, can also be utilized by the intracoronary route if nitrates are ineffective. The possibility of coronary vasospasm affecting the contralateral artery and causing continuing AP during the procedure must also be contemplated.[4] There is much debate about the mechanism of coronary spasm during PTCA since simple balloon inflation of the coronary stenosis usually gives rise to AP, which disappears after balloon deflation. Disruption of the coronary intima with platelet activation and release of vaso-active substances may be the cause and is one reason why antiplatelet drugs are administered.

The exact mechanism of coronary vasospasm in general is still controversial and the subject of much basic research.[5]

Gertz et al.[6] demonstrated that thrombus formation followed experimental coronary artery constriction which in turn resulted in endothelial damage. This sequence of events is therefore crucial when considering the onset of acute MI after coronary vasospasm during PTCA. The interrelationship between coronary artery spasm and thrombosis was recently reviewed,[7] as was the role of coronary vasospasm in the pathogenesis of acute MI.[8] However, acute MI during PTCA may well be a result of coronary artery dissection, which in itself can stimulate coronary vasospasm and may be very difficult to differentiate from the latter on angiography. We believe that the frequency of coronary artery spasm acutely complicating PTCA is far higher than has hitherto been accepted.

Coronary vasospasm after PTCA

The frequency of this complication either in hospital or later is extremely difficult to determine. Attempts to prevent it by the use of maintenance coronary vasodilators, antiplatelet drugs and anticoagulants have probably decreased its frequency. Some recent clinical research is pertinent. Mehta et al.[9] demonstrated that exercise stimulated a far greater release of the vasoconstrictor substance thromboxane A_2 than of the vasodilator prostacyclin in patients with atherosclerosis. This sequence of events may be magnified in the few days after PTCA on account of endothelial disruption. Grüntzig et al.[10,11] have advocated the use of submaximal bicycle ergometer stress testing 2 days after PTCA, a recommendation probably influenced by economic factors, but this policy has recently been criticized, especially after a report by Dash,[12] who was the first to document the occurrence of an acute MI associated with a fresh thrombus overlying the site of PTCA in a patient who had undergone stress testing 2 days after successful PTCA. Dash[12] suggested the possibility of effort-induced turbulence disrupting a freshly exposed endothelial area with possible dissection or coronary vasospasm, possibly aggravated by increased platelet activity due to strenuous exercise.[13] Przybojewski and Weich,[14] as a result of experience of a similar clinical sequence of events, elected to delay routine stress testing for 1 month after successful PTCA. This policy has been substantiated by a report by Cragg et al.[15] of an alteration in vessel-wall arachnidonate metabolism after PTCA which could be responsible for vasospasm.

Bentivoglio et al.[16] further emphasized the important role of coronary artery spasm in their series of 74 patients undergoing

single-vessel PTCA; 14 had this mechanism superadded to significant fixed obstruction. This incidence of 15% is higher than usual and was believed to be due to the frequency of unstable AP in their patient population. They thought that 3 of the 14 patients had catheter-induced coronary vasospasm while in the remaining 11 it was unprovoked, and emphasized the importance of the availability of intracoronary nitroglycerin. However, coronary vasospasm in their cases did not cause more complications at follow-up, a puzzling finding. Bentivoglio et al.[16] concluded with a crucial statement: 'coronary spasm may outlast the relief by PTCA of the fixed component of the mixed stenosis and requires long-term vasodilator therapy', that would appear to be relevant to our patient since we clearly demonstrated that the two lesions subjected to PTCA remained a 'success' on angiography, whereas myocardial ischaemia occurred on stress-testing when all vasodilator therapy was withdrawn. That this myocardial ischaemia was consequent upon coronary vasospasm is suggested by the marked ST-segment elevation.

David et al.[17] documented coronary artery spasm unrelated to exercise after successful PTCA. Among their group of 83 patients, coronary vasospasm was demonstrated before PTCA in 5 patients, and within 4 months afterwards in another 6 patients. Variant AP (vasospastic angina) recurred in 3 of the 5 patients with vasospasm before PTCA, and in a further 2 with vasospastic AP before successful repeat PTCA. Coronary re-stenosis at the PTCA site developed in 5 of the 9 patients with variant AP after PTCA.

Recently, further clinical data have been published by Hollman et al.;[18,19] they reported coronary vasospasm at the site of previously successful PTCA in 5 patients within 2 months. This group has performed over 1 000 successful PTCA procedures, and the incidence of coronary vasospasm is much lower than that encountered by David et al.,[17] a difference probably accounted for by the fact that the latter group employed additional ECG criteria for the diagnosis of coronary vasospasm. One of the patients documented by Hollman et al.[18] died 2 months after PTCA and soon after CABG surgery. They believed that 'the angioplasty-induced balloon injury may have damaged the muscular media sufficiently so that temporarily the media was incapable of coronary spasm. After healing, however, spasm was again possible.' Four of the 5 patients with coronary artery spasm reported by Hollman et al.[18] were unresponsive to calcium-antagonist and nitrate medication and went on to develop re-stenosis at the PTCA site.

Effort-induced ST-segment elevation

The usual exercise-induced ischaemic response in significant coronary atherosclerosis is that of varying degrees of ST-segment depression, an expression of subendocardial or non-transmural ischaemia. However, more recent clinical research[20] has demonstrated that coronary vasospasm at rest or precipitated by exercise can also cause ST-segment depression as an indication of 'incomplete vasospasm' with resulting non-transmural myocardial ischaemia. Thus, a too-simplistic approach must not be applied to interpretation of the ECG during episodes of myocardial ischaemia.

Przybojewski and Thorpe[21] recently documented exercise-induced ST-segment elevation possibly due to coronary artery spasm; Chahine et al.[22] and several other workers[23-35] have also reported on the meaning of ST-segment elevation precipitated by effort in patients with Prinzmetal's or variant angina, and a study correlating ECG and coronary arteriographic findings has been published recently.[36] The influence of various drugs on effort-related ST-segment elevation and other parameters of myocardial ischaemia secondary to coronary vasospasm has also been assessed.[37-39] ST-segment elevation after effort may be related to abnormal ventricular contractility rather than myocardial ischaemia.[22-26] Weiner et al.[40] and other workers[31,32,41] showed that ST-segment elevation in the recovery phase, particularly if preceded by ST-segment depression during exercise, was a poor prognostic sign in variant (vasospastic) angina. There is no doubt that exercise-induced ST-segment elevation does occur in rare instances in the absence of coronary vasospasm in patients with severe fixed coronary atherosclerotic lesions.[22,42-44]

Our patient undoubtedly had significant fixed lesions before PTCA but the fact that the effort ECG reverted to normal after PTCA and the angiographic demonstration of a far lesser degree of coronary stenosis strongly indicated the absence of haemodynamically significant fixed coronary stenosis, as did the disappearance of AP. The return of AP and reversion to positivity of the stress ECG at 12 months with the patient off most medication, and in the absence re-stenosis on angiography, is against a pure fixed coronary stenosis, as is the return to negativity of the stress ECG and scintiscan and disappearance of pain after reintroduction of nifedipine therapy. We therefore believe that coronary vasospasm was responsible for the late recurrence of symptoms and signs.

Coronary re-stenosis after successful PTCA

The antagonists of PTCA support their argument by the worrying fact that re-stenosis usually occurs within 6 months in some 13 - 47% of patients after 'primary success'.[45-48] Despite this, it is now known that repeat PTCA is much easier in these cases, complications are fewer and the recurrence rate is approximately the same as after initial PTCA.[48] The exact pathogenetic mechanism responsible for re-stenosis is still controversial. Of importance, and an observation requiring more clinical research, is the increased tendency of patients displaying coronary artery spasm during PTCA to have re-stenosis later (R. K. Myler — personal communication). This would explain the higher incidence of re-stenosis in patients with documented variant angina.

Conclusions

Our experience substantiates the need for careful follow-up of patients after PTCA. The mechanisms responsible for recurrence of symptoms and objective signs of myocardial ischaemia are obscure, but the possible role of coronary artery spasm must always be entertained, particularly when there is no deterioration in coronary stenosis on angiography. Re-introduction of maintenance drug therapy late after 'primary success' in PTCA may well be indicated in the prophylaxis of coronary vasospasm and possibly re-stenosis.

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