Incidence of spasm at the site of previous successful transluminal coronary angioplasty: effect of ergometrine maleate in consecutive patients

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SUMMARY The incidence of coronary artery spasm at the site of previous successful angioplasty and its importance in leading to subsequent restenosis or recurrence of symptoms are unknown. Fourteen consecutive patients with single vessel coronary artery disease who had undergone successful percutaneous transluminal angioplasty were studied. All patients were given ergometrine maleate (ergonovine maleate) intravenously during repeat cardiac catheterisation six weeks to three months after angioplasty. Five patients demonstrated excessive luminal reduction (spasm) at the site of previous angioplasty that led to luminal stenoses ranging from 50% to 79%. Two of these patients developed chest pain and ST segment changes during ergometrine maleate provocation and they also showed maximal vasconstriction. The remaining nine patients did not develop important luminal change at the site of angioplasty after ergometrine maleate. Ergometrine maleate administration resulted in \( \leq 20\% \) reduction in lumen diameter of adjacent apparently normal sections of the coronary arteries in all but two patients. At the site of previous angioplasty in the five patients with spasm, however, the lumen was constricted by a mean (SD) of 51 (12)%, whereas in the nine patients not demonstrating spasm mean reduction was 12 (7)%. Thus hypersensitivity to ergometrine maleate at the site of previous successful angioplasty was demonstrated in over a third of consecutive patients with single vessel coronary artery disease. The importance of this finding to long term results of coronary angioplasty needs to be investigated further.

Successful dilatation of coronary atheromatous lesions was first described by Gruentzig et al in 1979. Since then, several thousand patients have been successfully treated with percutaneous transluminal coronary angioplasty. Restenosis of a substantial proportion of successful dilatations occurs within a few months of operation. The reasons for restenosis and the type of patient in whom it is likely to occur remain obscure. In two recent reports, however, coronary artery spasm occurred several weeks after successful angioplasty in patients who had recurrence of anginal symptoms. The frequency of restenosis was higher in these patients and this raised the question of whether coronary spasm at the site of angioplasty was causing recurrence of a fixed stenosis. We studied consecutive patients with single vessel disease who had had successful angioplasty, and we used ergometrine maleate (ergonovine maleate) to provoke coronary spasm at the site of angioplasty.

Patients and methods

Patients Intravenous ergometrine maleate was given to fourteen patients (12 men and two women, mean (SD) aged 54 (5) years) who had repeat cardiac catheterisation between six weeks and five months after successful coronary angioplasty (Table). The 14 patients were selected from a total of 44 patients undergoing repeat cardiac catheterisation after
Characteristics of patients studied

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<th>Rest</th>
<th>Exercise test duration (min)</th>
<th>Angioplasty vessel</th>
<th>Drug treatment</th>
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<th>Angina Exertion</th>
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LAD, left anterior descending coronary artery; RCA, right coronary artery; Circ, circumflex coronary artery.

Angioplasty. They had no evidence of important coronary stenosis (>70%) either in the vessel in which previous angioplasty was performed or in another coronary artery.

Before angioplasty two patients complained of exertional angina, 12 patients complained of exertional and rest angina, and one patient (case 14) complained of angina only at rest. In 12 patients ST segment depression of >1 mm developed during stress testing before angioplasty; one patient (case 14) had a negative exercise test and one patient (case 12) was not exercised because he had frequent chest pain at rest which was accompanied by ST segment changes.

After angioplasty 11 patients were discharged on calcium antagonists (Table). Four patients complained of recurrence of chest pain typical of angina pectoris. Two of them had exertional pain only and two patients had rest and exertional angina. Treadmill exercise testing resulted in ST segment depression in only one patient (case 1). All other patients had negative exercise tests (Table). Informed written consent was obtained from all patients.

**CARDIAC CATHETERISATION**

During cardiac catheterisation a three lead electrocardiogram was recorded continuously. The left ventriculogram and multiple views of left and right coronary arteries were obtained before the infusion. Patients were then given 50 μg of ergometrine maleate intravenously, followed by 100 μg, 150 μg, 200 μg, and 300 μg at 2 minute intervals until chest pain or electrocardiographic changes supervened. Coronary arteriography was performed at whatever state these changes occurred and no further doses were given. If these changes did not occur in the earlier stages coronary arteriography was performed after a total dose of 800 μg of ergometrine maleate had been given. After this isosorbide dinitrate (2–3 mg) was given intra-arterially to 11 patients and the coronary arteriograms were repeated to ensure that any spasm that had occurred had been reversed.

Nine patients had percutaneous angioplasty of the left anterior descending coronary artery, three of the right coronary artery, and two of the circumflex coronary arteries. All 14 patients had a successful dilatation of a stenosis that had increased the lumen diameter by >40% and reduced the trans-stenosis pressure drop.

**CALCULATIONS**

Views of the coronary arteries were obtained in similar positions before and after ergometrine maleate and isosorbide dinitrate. Cineangiograms were projected from an identical distance and coronary artery diameters were measured to the nearest mm with a ruler. Cineangiograms were obtained at the site of previous angioplasty where the lumen appeared to be narrowest and also at an adjacent site where the artery appeared to be normal. All measurements were made blindly in one projection by an independent radiologist.

Luminal narrowing at the site of the previous angioplasty is expressed as a percentage of the diameter at an adjacent apparently normal section of the coronary artery (Figs. 1 and 2).

To compare the effect of ergometrine maleate at the site of previous angioplasty with its effect on the adjacent normal section of the coronary artery we calculated the percentage change in lumen diameter for each section before and after ergometrine maleate (Fig. 3).

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\text{Percentage change in lumen diameter} = \frac{\text{Diameter after ergometrine maleate} - \text{Diameter before ergometrine maleate}}{\text{Diameter before ergometrine maleate}} \times 100\%
\]
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Results

**EFFECT OF ERGOMETRINE MALEATE AT THE ANGIOPLASTY SITE**

After intravenous ergometrine maleate (mean (SD) dose 607 (240) μg) two patients had typical anginal chest pain which was associated with ST segment elevation in one (case 1) (Fig. 4) and ST segment depression in the other (case 2). In these two patients the narrowing of the lesion changed from 41% and 46% before to 73% and 79% respectively with intravenous ergometrine maleate. After isosorbide dinitrate the narrowing was reduced to 31% and 41% respectively, and this was accompanied by relief of chest pain and resolution of the electrocardiographic ST segment changes (Fig. 4). In three other patients (cases 3–5) intravenous ergometrine maleate caused narrowing of the lumen down to ≥50% (50–60%) compared with a narrowing of 31 (11)% before ergometrine maleate. None of these
patients, however, complained of chest pain or had reversible ST segment changes during the procedure. One patient (case 6) had no evidence of spasm at the site of angioplasty during ergometrine maleate stimulation, but two hours after the procedure he developed chest pain at rest which was accompanied by ST segment elevation in lead V5.

Nine patients (cases 6–14) had a mean lumen narrowing of 34 (10)% (range 14–43%) after ergometrine maleate compared with a narrowing of 34 (8)% (range 27–45%) before ergometrine maleate (Fig. 2).

**EFFECT OF ERGOMETRINE MALEATE AT THE ANGIOPLASTY SITE COMPARED WITH EFFECT AT AN ADJACENT NORMAL SECTION OF CORONARY ARTERY**

In each patient we studied the change in lumen diameter at an adjacent apparently normal section of the coronary artery in response to ergometrine maleate and compared it with the change in diameter at the site of the previous angioplasty (Fig. 3). Only two patients (cases 5 and 12) demonstrated a change in luminal narrowing of $\geq 20\%$ in the apparently normal sections of the coronary arteries after
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Ergometrine maleate. The remaining 12 patients had smaller reduction of the diameter of these sections (mean 12 (7)%, range 0–20%). At the site of previous angioplasty, however, the mean diameter narrowing with ergometrine maleate was 29 (21)%, ranging from 0 to 79%. Two fairly distinct responses were discernible. In five patients (case 1–5) ergometrine maleate resulted in a pronounced change in lumen diameter with a mean reduction of 51 (12)% (range 33–63%), whereas in the remaining nine patients the reduction resembled that seen in the adjacent normal sections of the coronary arteries (mean 12 (7)%, range 0–20%).

Discussion

Two previous studies have reported on the occurrence of variant angina after percutaneous transluminal coronary angioplasty.3 4 In both of these studies patients were investigated for coronary artery spasm only after anginal symptoms has recurred. Spasm occurred spontaneously during post-angioplasty cardiac catheterisation in some patients, whereas in others it was provoked by ergometrine maleate.3 4 Our study is unique in that we prospectively investigated the possibility of spasm occurring at the site of angioplasty in consecutive patients irrespective of their clinical state. To minimise the risks of intravenous ergometrine maleate we selected a group of 14 patients with single vessel disease who had no evidence of important narrowing in other coronary arteries.

Patients showed two distinct responses to the administration of ergometrine maleate. In nine there was no excessive narrowing at the site of angioplasty, but in the remaining five excessive constriction occurred which caused a narrowing down to 50% to 79%. Two of these five patients had recurrence of angina after angioplasty and both had pain and ST segment changes at the time of ergometrine maleate provocation. They also had the most severe stenoses (mean narrowing 73%). The other three patients did not complain of recurrent angina and did not have pain or electrocardiographic changes associated with ergometrine maleate. Mean luminal narrowing after ergometrine maleate was, however, less severe in these patients (<60%) and was clearly insufficient to precipitate ischaemia at rest. These three patients were treated with verapamil after successful angioplasty and this may have prevented the recurrence of symptoms.

Ergometrine maleate, an ergot alkaloid, has a powerful direct stimulating action on smooth muscle.5 Use of this agent became widespread after it was demonstrated that in patients with variant angina intravenous ergometrine maleate precipitated focal coronary narrowing that was associated with electrocardiographic narrowing and chest pain.5–8 In these patients the angiographic appearance during spasm was identical with that during spontaneous episodes of pain. Various studies have investigated the response to ergometrine maleate of coronary arteries where they are apparently normal and at sites of important and unimportant stenosis in patients with and without a history of variant angina.5–7 In symptom free patients or those with classic angina the mean luminal narrowing of “normal” sections of coronary arteries produced by ergometrine maleate was about 15%.5 6 In patients with variant angina, mean luminal narrowing of “normal” sections of arteries was 24% and there were other discrete areas of more profound subtotal or total luminal occlusion, ranging from 75% to 100%.5 7 Freedman et al arbitrarily defined excessive spasm as narrowing of the lumen by 55%.7 Using these criteria, three of the five patients whom we regard as demonstrating spasm had excessive narrowing. There is evidence that vasomotion of medial smooth muscle within the normal range could obstruct pliable vessels at the sites of previous obstructive lesions.9 A supranormal increase in the medial smooth muscle tone has been suggested to account for the luminal occlusion caused by ergometrine maleate that occurs at sites of minimal or no luminal narrowing in patients with variant angina.5 7 The underlying mechanism for spasm at the site of previous angioplasty in our patients remains unclear.

Patients who had excessive vasoconstriction at the site of previous angioplasty after ergometrine maleate may have had this tendency before the provocation test; however, none of them had ergometrine maleate provocation before angioplasty. By restricting the use of ergometrine maleate to patients with single vessel disease and severe symptoms before angioplasty, we may well have selected out a population of patients in which underlying coronary artery spasm may have been an important pathophysiological mechanism for precipitating ischaemia even before angioplasty. The patient's history did not clarify the issue either. Three of the five patients demonstrating spasm had rest and exertional pain, whereas the other two had exertional pain only; however, a patient not demonstrating spasm also gave a history of rest and exertional pain.

The usual delay between angioplasty and recurrence of symptoms may be due to the time required for the smooth muscle to recover after the trauma incurred during angioplasty.3 10 11 Equally, there is evidence that smooth muscle cell stimulation leading to fibrocellular proliferation may also occur at sites of medial damage12 and this may be responsible for excessive spasm at the sites of angioplasty; however,
other pathological studies have not fully supported this view.\textsuperscript{9,13} Unless ergometrine maleate stimulation is carried out before and after successful angioplasty, this question cannot be satisfactorily answered.

Restenoses occurs at the site of previous angioplasty in 25–30\% of cases.\textsuperscript{2,14} In variant angina, however, the recurrence rates appear to be much higher.\textsuperscript{4} It has also been suggested that repeated spasm at the site of the previous intimal damage may delay healing and exacerbate the tendency towards atheromatous deposition.\textsuperscript{15} In our limited follow up of these patients, recurrence of fixed lesions has not occurred. This may be due to the use of calcium antagonists in our patients. If spasm is an important mechanism of restenosis, then the use of calcium antagonists after angioplasty may well reduce the rate. The results of prospective trials investigating the role of calcium antagonists will therefore be very important.

We are indebted to the British Heart Foundation for their support.

References