Pathological changes induced by repeated percutaneous transluminal coronary angioplasty

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SUMMARY The histopathological appearances of seven coronary arteries obtained from four patients after repeated percutaneous transluminal coronary angioplasty were analysed. A complex picture was found; typically there were ruptured atherosclerotic plaques, plaque dissection, and a fibrous tissue response. The histopathological appearance of older and more recent fibrous lesions was different. Older lesions contained more collagen and elastin fibres, whereas recent ones had more loosely arranged connective tissue containing abundant glycosaminoglycan and readily identifiable cells. The fibrous tissues tended to be damaged at the sites of previous injury and where the vessel wall was thinnest. In five of the seven arteries there was evidence of a repeated fibrous response to injury with partial or total rupture of the original media. In one instance a repair response within a pre-existing atherosclerotic plaque had caused restenosis.

The results indicate that restenosis after repeated percutaneous transluminal coronary angioplasty, like restenosis after a first procedure, is mainly the result of fibrocellular tissue response to injury of the wall tissues. Because older (that is more mature) repair tissue contains fewer cells and more connective elements than younger repair tissue (that is the loosely arranged connective tissue found soon after angioplasty), when it is disrupted by a further angioplasty procedure it is less capable of producing tissue that will obstruct the lumen. This may explain why in the majority of patients with restenosis repeated percutaneous transluminal coronary angioplasty is successful. The present study also showed that occasionally plaque haemorrhages may become organised and incorporated into the pre-existing atherosclerotic lesion.

Restenosis is a major complication of percutaneous transluminal coronary angioplasty. Follow up angiography showed a high frequency (33-6%) of restenosis in patients on a register of percutaneous transluminal coronary angioplasty procedures.1 Treatment of coronary restenosis by repeat percutaneous coronary angioplasty has a high immediate success rate and a low complication rate, but follow up angiographic examinations showed restenosis in 34% of these patients.2

Pathological changes underlying restenosis after a first coronary angioplasty procedure have been recognised.3-14 Although several questions still remain the consensus is that in most instances restenosis is caused by fibrocellular proliferation which is probably prompted by injury to the vascular smooth muscle cells. There are two reports of restenosis caused by atherosclerotic plaques in the absence of morphological lesions that were attributable to the angioplasty procedure.8 10

To the best of our knowledge the pathological changes found after repeated percutaneous transluminal coronary angioplasty have not been described before.

Patients and methods

The heart specimens were obtained from four patients. Table 1 gives the relevant clinical data. Repeated percutaneous transluminal coronary angioplasty of seven arteries had been performed because of recurrent angina pectoris and associated
restenosis. Patients had had from one to five percutaneous transluminal coronary angioplasty procedures. Table 2 shows the interval between the last percutaneous transluminal coronary angioplasty procedure and death.

Pathological examination

In each case the complete heart was available for study. After fixation in buffered formalin, the coronary arteries were removed from the epicardial surface and decalcified before sectioning. The arteries in which the percutaneous transluminal coronary angioplasty had been performed were sectioned serially every 1–2 mm for 8 cm from the origin of the vessels. The other coronary arteries were sectioned serially every 3 mm for 6 cm from the origin. All blocks were routinely processed and 5 μm thick sections were prepared. The sections were stained with haematoxylin and eosin, an elastic stain counter-

The numerals in parentheses indicate the arterial segment according to the American Heart Association Committee Report. Moderate atherosclerotic lesions, 50–75% stenosis; severe atherosclerotic lesions >75% stenosis. AMI, acute myocardial infarction; AP, angina pectoris; diag, diagonal; LAD, anterior descending coronary artery; LCA, main left coronary artery; LCx, left circumflex artery; OM, obtuse marginal artery; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; SMI, scarred myocardial infarct.

Table 1  Clinical data associated with pathological findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Clinical diagnosis</th>
<th>PTCA</th>
<th>Site of PTCA</th>
<th>No of PTCAs</th>
<th>Atherosclerosis of other coronary arteries</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>AP, SMI, AMI</td>
<td>Elective and emergency</td>
<td>RCA (1)</td>
<td>3</td>
<td>Moderate in distal part of RCA, LAD, and LCx</td>
<td>AMI</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>M</td>
<td>AP, SMI</td>
<td>Elective</td>
<td>LAD (6)</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>M</td>
<td>AP, chronic renal failure</td>
<td>Elective</td>
<td>LCx (11)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>M</td>
<td>AP, AMI</td>
<td>Elective and emergency</td>
<td>LAD (6, 7)</td>
<td>1</td>
<td>Moderate in RCA</td>
<td>AMI</td>
</tr>
</tbody>
</table>

*Segment(s) of the coronary arteries that were dilated are shown in parentheses (according to the American Heart Association Committee Report: RCA, right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex artery; OM, obtuse marginal artery; SMI, scarred myocardial infarct.*
stained with Van Gieson's stain, and a phosphotungstic acid haematoxylin stain. The blocks taken from the sites of the percutaneous transluminal coronary angioplasty were serially sectioned, whereas step sections were taken from the remaining blocks. When necessary additional sections were also mounted.

The myocardium was studied by cutting the heart in parallel slices, perpendicular to the left ventricular long axis. Full thickness slices were then taken for histological examination, at different levels, to include both the left and right ventricles.

Results

Table 2 shows the most important pathological features found in the coronary arteries.

Dissection and rupture of pre-existing atherosclerotic plaques was detected in all seven arteries. There was plaque rupture with recent haemorrhage and mural thrombosis in three arteries (case 1: right coronary artery, diagonal branch; left anterior descending coronary artery), which had been dilated two hours before death.

Pre-existing eccentric atherosclerotic plaques were damaged where the plaque was attached to the underlying media and pre-existing concentric lesions were damaged at their thinnest part (fig 1). Rupture sites and dissection clefts were filled with fibrous tissue, which indicated the stage of healing. Laceration of repair tissue was clearly indentifiable. Older repair tissue contained more collagen and elastin fibres than more recently formed tissue which had a looser texture and contained abundant glycosaminoglycans and readily identifiable cells. Disruption of fibrous tissue tended to occur at the site of earlier injury, generally where the vessel wall was thinnest. In five of seven arteries evidence of a repeated fibrous response to injury was accompanied by partial or total rupture of the original media (fig 2). In one instance (case 1: left anterior descending coronary artery) cholesterol filled the dissection cleft between a pre-existing atherosclerotic plaque and the media (fig 3).

In three arteries attenuation and separation of smooth muscle cells had disrupted the media at the site that initially was considered to be plaque free (fig 4).

In one instance (case 4) there was massive dissection of the coronary arteries. The first attempt to dilate the left circumflex artery (10 months and 13 days before death) probably caused plaque dis-

<table>
<thead>
<tr>
<th>Media</th>
<th>Medial smooth muscle cells attenuation/disruption</th>
<th>Thrombosis</th>
<th>Restenosis</th>
<th>Fibrocellular proliferation</th>
<th>Atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Attenuation</td>
<td>Recent thrombus</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Partial and total rupture</td>
<td>(Rupture)</td>
<td>Recent thrombus</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Partial and total rupture</td>
<td>Attenuation/disruption</td>
<td>Recent thrombus</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(Rupture)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Laceration of plaque-free wall</td>
<td>Attenuation, disruption of plaque-free wall</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Partial and total rupture</td>
<td>(Rupture)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Partial and total rupture; dissection</td>
<td>(Rupture)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
erosclerotic plaque (fig 6). The artery showed several surface irregularities that were covered by recent thrombosis; these were considered to be an effect of the most recent attempt at dilatation (two hours before death). Within pre-existing atherosclerotic plaques there were highly disorganised and cellular areas caused by proliferation of fibroblasts intermingled with many lipid laden macrophages and the occasional lymphocyte and dispersed iron deposits. In one artery (case 1: left anterior descending coronary artery) we found both a repair process within an atheroma and a fibrocellular tissue proliferation.

The myocardium of each of the four patients showed features of healed and acute myocardial infarction. In each of these instances death was considered to be related either directly to the last procedure or to pre-existing generalised obstructive coronary atherosclerosis (see table 1).

Discussion

We studied four hearts obtained from patients who died after repeated percutaneous transluminal coronary angioplasties for coronary artery restenosis in whom the initial procedure had been successful. Histological examination of the seven arteries showed a complex structure, dominated by arterial wall laceration involving both pre-existing atherosclerotic plaques and fibrous repair tissue that was considered to have been produced in response to the initial injury. Indeed, in all instances the changes found at microscopy were in accord with the clinical history of repeated percutaneous transluminal coronary angioplasties. There was plaque rupture with dissection and damage to the underlying media in each instance. Laceration usually occurred at the end of the plaque in eccentric lesions and at the thinnest part of the arterial wall in concentric atherosclerotic lesions. There was fibrous tissue at the injury site characterised by well formed collagen and elastin fibres. Subsequent laceration of the arterial wall had caused further injury to the repair tissues and these newer sites were covered by a fibrocellular tissue rich in glycosaminoglycans that contained fewer collagen and elastin fibres. The history of each percutaneous transluminal coronary angioplasty procedure could be followed almost step by step.

In one artery cholesterol deposits were embedded within fibrous tissue at a site of initial plaque dissection with laceration of the media. This finding unequivocally demonstrates that atheromatous plaque rupture had occurred and that cholesterol embolisation is a potential complication of the procedure. Peripheral cholesterol embolisation in man
has been reported, but seems to be rare. A search for such emboli is tedious, however, and small emboli may be easily overlooked, as shown by experimental animal studies.

Despite the histological complexity of the lesions, we identified attentuation of smooth muscle cells with separation and disruption of the media in three arteries. The remaining specimens showed partial medial rupture. The interpretation of changes in the smooth muscle cells of the media of coronary arteries is not easy. Advanced arterial atherosclerosis usually produces thinning of the media with attentuation of smooth muscle cells. But we also found changes that were highly suggestive of overstretching in segments of media without substantial intimal changes and when there was only a slightly elevated atheromatous lesion. This impression was supported by the observation of fragmented and often curly elastin fibres within the segments, which was commonly accompanied by an increase in fibrous tissue. These changes are distinct from the obvious thinning that occurs in association with atherosclerosis that was described by Isner and For- tin.

It is tempting to view the observed changes in the media as being caused by overstretching of the wall by the radial pressure of the balloon. Attentuation and disruption of smooth muscle cells have also been
fibrocellular tissue reaction depends upon the presence of viable cells activated by the procedure. In patients who have repeated percutaneous transluminal coronary angioplasty and restenosis there is evidence of a potent growth factor and the aggregation of platelets at sites of laceration may be vital to this process. In theory the more advanced the maturation of the fibrocellular response, that is when there is more collagen and fewer cells, the less likely is a second injury to cause further tissue response because the injury inflicted by the balloon affects only the acellular fibrous tissue. Because older (that is more mature) repair tissue contains fewer cells and more connective elements than reported by Düber et al. They described necrosis of smooth muscle cells as a feature that occurs after vessel wall dilatation.

Dissection is another hazard of repeated percutaneous transluminal coronary angioplasty. This occurred in patient 4. The initial procedure had resulted in a dissection, which became partially filled with thrombus and partially coated by fibrous tissue. The repeat percutaneous transluminal coronary angioplasty procedure produced further dissection and the catheter was guided through the false channel from the left circumflex artery into the obtuse marginal branch. Inflation of the balloon then caused a massive dissection that extended into the myocardium and immediately caused death.

The results indicate that restenosis after repeated percutaneous transluminal coronary angioplasty is caused by a fibrocellular tissue response that resembles the major event causing restenosis after the first attempt. This is not surprising as the fibrocellular tissue reaction depends upon the presence of viable cells activated by the procedure. In patients who have repeated percutaneous transluminal coronary angioplasty and restenosis there is evidence of a potent growth factor and the aggregation of platelets at sites of laceration may be vital to this process. In theory the more advanced the maturation of the fibrocellular response, that is when there is more collagen and fewer cells, the less likely is a second injury to cause further tissue response because the injury inflicted by the balloon affects only the acellular fibrous tissue. Because older (that is more mature) repair tissue contains fewer cells and more connective elements than reported by Düber et al. They described necrosis of smooth muscle cells as a feature that occurs after vessel wall dilatation.

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younger repair tissue (that is the loosely arranged connective tissue found soon after angioplasty), when it is disrupted by a further angioplasty procedure it is less capable of producing tissue that will obstruct the lumen. This maturation of the initial tissue response may explain why a repeat percutaneous transluminal coronary angioplasty is successful in most patients with restenosis. The composition of the atherosclerotic plaque will determine whether or not the procedure will achieve lasting success. In plaques that are mainly composed of dense fibrous tissue and almost acellular, the tissue response leading to restenosis may be minimal or even absent. On the other hand, plaque injury to cellular tissues may lead to an early response and restenosis. These theoretical considerations fit nicely with the practical approach presently advocated in patients in whom a repeat angiogram reveals restenosis. Redilatation, under such circumstances, should primarily be based on the severity of the angina pectoris, rather than on the results of the various testing procedures.15

We also found that plaque haemorrhages, which are almost certainly the result of the dilatation procedure, may become organised and incorporated into the pre-existing atherosclerotic lesion. Occasionally this may be the sole reason for early restenosis in cases where this particular mechanism probably accelerates “normal” atherosclerosis. These observations could explain why Waller et al reported that three out of four cases of late restenosis were caused by “classic” atherosclerotic lesions

Fig 5 Photomicrograph showing medial dissection extending from the epicardial artery into intramyocardial branches. (a) Cross section through the obtuse marginal artery and a side branch, both showing medial dissection. (b) Extension of the dissection into an intramyocardial branch. Elastic tissue stains (a) original magnification, × 21; (b) original magnification, × 55).
Fig 6  Photomicrograph showing cross section through a coronary artery with severely obstructive atherosclerotic lesions after percutaneous transluminal coronary angioplasty. (a) Overall view showing several sites of laceration. The area indicated by the asterisk is shown in detail in (b). It shows a organizing plaque haemorrhage. (a) Elastic tissue stain (original magnification x 14); (b) haematoxylin and eosin stain (original magnification x 90).

without any signs attributable to a previous percutaneous transluminal coronary angioplasty. Similarly, Giraldo et al described a successful percutaneous transluminal coronary angioplasty of the posterior descending coronary artery, while necropsy 69 day later showed a 75% luminal obstruction by a "common atherosclerotic plaque".

The present study indicates that fibrocellular tissue proliferation is the most common mechanism underlying restenosis, and that healing of an injured atherosclerotic plaque may occasionally be an alternative mechanism.

During the course of this study Dr Ueda was on a leave of absence from the Department of Pathology, Osaka City University Medical School, Osaka, Japan.

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Pathological changes induced by repeated percutaneous transluminal coronary angioplasty


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