New trends in the interventional treatment of ischaemic heart disease

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Direct revascularization of an ischaemic vascular bed represents an attractive treatment option for patients with coronary artery disease. Coronary artery bypass surgery has been demonstrated to provide both symptomatic improvement and, in certain circumstances, to improve prognosis, while catheter-based techniques offer substantial improvement in symptomatology, with reduced morbidity compared with bypass surgery. Although balloon angioplasty has been associated with lesion success rates approximating to 89%, a number of anatomical substrates have proved refractory to this approach and restenosis remains a significant problem. Newer interventional modalities, such as directional atherectomy, rotablation, transluminal extraction catheterization, laser coronary angioplasty and coronary stenting, all have the potential to offer improved rates of restenosis under specific circumstances. With the exception of stents, most have not been shown to provide an overall improvement in rates of restenosis. Numerous pharmacological agents have also been investigated in an attempt to reduce levels of restenosis. Calcium channel blockers have been assessed in five trials, none of which has demonstrated a conclusive benefit, although meta-analysis of the data generated in these trials has shown a 30% reduction in the likelihood of restenosis associated with their use. More recently, monoclonal antibodies to glycoprotein IIb/IIIa have been linked to a reduction in restenosis.

Introduction

Direct revascularization of an ischaemic coronary bed represents an attractive treatment option for the patient with coronary artery disease. Coronary artery bypass surgery has been shown to improve the symptoms of ischaemic heart disease and, in select anatomical circumstances, to prolong survival. Although not documented to alter survival, catheter-based techniques offer substantial improvement in clinical symptomatology, with reduced morbidity compared with bypass surgery. Newer interventional techniques and newer modalities of adjuvant medical therapy have been explored for the purpose of (1) improving the success of initial coronary angioplasty; (2) reducing morbidity and complication rates associated with the procedure; (3) reducing the rate of coronary restenosis.

Advances in technology associated with balloon catheters, guide wires and guiding catheters in the early to mid 1980s elevated lesion rates for balloon angioplasty to approximately 89%. Recognition of the importance of adequate anti-coagulation, directed against both platelets and the humoral clotting cascade, contributed substantially to this success. However, a number of anatomical substrates have proven refractory to high rates of success and safety with conventional balloon approaches. These include ostial lesions, heavily calcified lesions, stenoses in vein grafts, long lesions, chronic total occlusions and distal disease. Some conditions, including unstable angina and complex lesions, are associated with a higher rate of early reclosure. Importantly, the overall risk of restenosis following balloon angioplasty has remained between 30 and >50%. Thus, newer devices and medical modalities have primarily been directed towards improvement in initial success rate and rates of acute reclosure and restenosis.

Newer devices

Enormous efforts have gone into identifying a mechanical alternative to balloon angioplasty that will yield improved initial success, reduced complication, including fewer acute reclosures, or reduced rate of restenosis. Much of the rationale for this investigation has come from the presumption that improvement may be made in acute or long-term results by employing an alternative approach to enlargement of the vessel lumen, instead of displacing the diseased segment by balloon inflation. It
has been suggested that restenosis rates may be reduced by eliminating the ‘baro-trauma’ associated with balloon inflation\(^9\),\(^10\) (although this hypothesis remains unproven). Table 1 contains a list of the possible advantages of newer devices, based on published clinical experiences. Compared with the enormous body of literature on the subject, relatively few of the reports have yielded a clear message based on randomized, controlled data.

Directional atherectomy provides the ability to remove atheromatous material from the site of a coronary lesion\(^11\). The atherectomy device is positioned at the lesion over a guide wire and the atheroma is forced into the eccentric cutting chamber by inflation (at a low inflation pressure) of a stabilizing balloon located on the opposite side of the catheter. A rotating cutter is then advanced within the cutting chamber. The resected atheroma is held within the chamber and removed. Multiple cuts are made following rotation of the device and efforts may be particularly directed towards the position of eccentric disease. Use of this device has yielded an enormous amount of information regarding the pathology of primary and restenotic lesions\(^12\). In two recent randomized trials of directional atherectomy vs balloon angioplasty, one\(^13\) showed a marginal reduction in the restenosis rate at 6 months in lesions within the proximal LAD coronary artery. This slight benefit was probably the result of a better initial anatomical result. It came at the cost of a higher rate of early complications and increased cost and was not associated with apparent clinical benefit. The second study\(^9\), which enrolled patients with lesions within the proximal LAD coronary artery, showed no benefit in terms of angiographic restenosis or clinical outcome. Despite these negative findings, it remains likely that this technique offers advantages in selected cases, particularly in ostial lesions, eccentric lesions and vein grafts.

Several other types of cutting devices for angioplasty are currently employed, particularly the Rotablator\(^13\)-\(^16\) and the transluminal extraction catheter\(^17\). The Rotablator contains a diamond-tipped burr, which rotates at 180 000 rpm and tends to cut differentially, relatively sparing soft pliable tissues\(^13\)-\(^16\). It grinds tissue into particles that are mostly <5 microns in diameter. It appears to be particularly useful for ostial lesions, heavily calcified lesions and tight bends. For optimal results, cutting must proceed slowly to assure dissipation of the lesions, rather than displacement, and to minimize the rate at which particulate matter is presented to the distal vessel. Although the sizes of particles produced are predominantly less than the capillary diameter, ‘sludge’ results from a large particle burden and may severely impair distal flow, particularly with treatment of long lesions. In a registry of 709 patients\(^13\), primary success (without balloon use) is reported at 81% and success in combination with balloon angioplasty at almost 95%. These are possibly the highest initial success rates reported with any device.

The transluminal extraction catheter employs a hollow, cone-shaped cutting edge, which rotates relatively slowly (<1000 rpm) and extracts material into a vacuum bottle\(^17\). Its application is currently relatively limited but it may be particularly useful in vein grafts, where distal embolization of atheromatous material is a particular problem, and in the presence of substantial thrombus that is best managed with extraction.

Although these cutting devices offer the potential advantage of minimizing ‘baro-trauma’, in practice they are often employed in conjunction with balloon angioplasty and no randomized data have substantiated the hope for reduced rates of restenosis. Thus, their present value remains their application in selected cases in which balloon angioplasty does not offer a satisfactory initial result. Limitation of these procedures to such an indication is further supported by the increased cost compared with balloon angioplasty.

Extensive experience has been gathered with the use of laser coronary angioplasty, particularly with the excimer laser, a pulsed laser in the ultraviolet range, in which thermal injury is minimized and there is disruption of atheromatous tissue along a relatively fine edge\(^18\). There is evidence of a narrow layer of injury within surrounding tissue, which has been described histologically as of a ‘smudged’ or ‘ground glass’ appearance\(^18\).

A registry of 3592 lesions in 3000 cases of excimer laser coronary angioplasty\(^19\) contained a substantial number of chronic total occlusions (10%) and lesions >20 mm in length (20%). The initial technical success rate (>20% improvement) was 84% and the primary procedural success rate (≤50% residual stenosis without inhospital Q wave infarction, coronary bypass surgery or death) with adjunctive balloon angioplasty was 90%. Rate of early reclosure was 3-4%, urgent bypass surgery 3-8%, perforation 1-2%, Q wave MI 2-1% and mortality 0-5%. There is no clear evidence that rates of restenosis were reduced compared with balloon angioplasty. Thus, laser angioplasty may have a role in increasing the primary success rate in selected cases, such as heavily calcified lesions, chronic total occlusions and long or distal lesions.

Clinical trials to date support a role for stenting of coronary stenosis for: (1) salvaging lesions with

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**Table 1 Possible advantages of newer catheter devices for coronary revascularization**

<table>
<thead>
<tr>
<th>Device</th>
<th>Possible role/advantage</th>
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<tbody>
<tr>
<td>Excimer laser</td>
<td>Ostial, calcified, long, distal lesions; chronic total occlusion</td>
</tr>
<tr>
<td>Directional atherectomy</td>
<td>Ostial, eccentric lesions; vein grafts</td>
</tr>
<tr>
<td>Rotablator</td>
<td>Ostial, calcified lesions; sharp bends</td>
</tr>
<tr>
<td>Extraction catheter</td>
<td>Vein grafts; lesions with extensive thrombus</td>
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<tr>
<td>Stents</td>
<td>Dissection; acute reclusion; reduced restenosis</td>
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Figure 1 Comparisons of lesion minimal luminal coronary arterial diameter at baseline, immediately following the procedure and at 6 months (follow-up) in patients randomized to conventional balloon angioplasty or placement of a Palmaz-Schatz stent. —— diameters following angioplasty and —— shows diameters following stent. Stenting was associated with a substantial benefit in the initial lesion gain and a modest improvement in lesion diameter at time of follow-up. (Reproduced from Fischman et al[26], with permission.)

Figure 2 Comparison of the rates of major clinical events following randomization to conventional balloon angioplasty or placement of a Palmaz-Schatz stent. ■—■—■ shows event rate with angioplasty and —— the event rate with stent. Stenting was associated with a significantly reduced event rate (P=0.017).

Pharmacological treatment

Numerous classes of drugs have been investigated in an attempt to reduce the rate of coronary restenosis. These efforts have yielded only limited success.

Platelet activation contributes substantially to early reclosure and, through cytokine release, may play an important role in vascular proliferative responses and restenosis[28]. Success at reduction in acute reclosure has been achieved with aspirin and ticlopidine use, with less certain benefits on restenosis[29-31].

Recent efforts have been directed towards further inhibition of platelet activity and particularly towards blockade of glycoprotein IIb/IIIa, a platelet-binding site for adhesive macromolecules, including von Willebrand factor and fibrinogen. Investigation of the potential value of glycoprotein IIb/IIIa inhibitors has been encouraging. One study in patients thought to be at high risk for abrupt closure, because of complex anatomy or clinical instability, showed reduction of early closure rates by infusion of an inhibitory monoclonal antibody (c7E3 Fab)[32]. In addition, follow-up at 6 months showed evidence of reduced rates of major cardiovascular events (Fig. 3)[33]. Thus, platelet inhibition appears to be a ripe area for addition to conventional medical management in conjunction with coronary angioplasty.

Medical therapy beyond anti-platelet agents has met with limited success. Fish oil may reduce the rate of restenosis, although results have been mixed[34-36].

A number of trials have examined the effect of calcium channel blockers in preventing stenosis. Although to date no single study has conclusively shown benefit, a recent meta-analysis of five randomized, controlled trials for preventing angiographic restenosis with calcium channel blockers[37] showed a 30% reduction in the likelihood (odds ratio 0.68; 95% confidence interval 0.49-0.94) of restenosis for patients randomized to active drug vs placebo.
Molecular approaches

The restenotic lesion is a result of a fibro-proliferative response that appears to be initiated by growth factor stimulation of smooth muscle cell migration, proliferation and collagen secretion. This response may have a common molecular pathway that may be specifically inhibited. Recent exciting work has shown the delivery of functional oligonucleotides into a vascular lesion and the potential for inhibiting the proliferative response that appears to be initiated by growth factor stimulation directed against platelet glycoprotein IIb/IIIa, bolus alone or bolus plus infusion, at the time of balloon coronary angioplasty. Active treatment was associated with significant reduction in the number of clinical events (P<0.001). (Reproduced from Topol et al, with permission.)

References


Figure 3 Comparisons of combined rates of major ischaemic events and revascularization procedures during 6 months of follow-up in patients randomized to placebo (-----) or to treatment with monoclonal Fab (c7E3) fragment directed against platelet glycoprotein IIb/IIIa, bolus alone (-----) or bolus plus infusion (-----), at the time of balloon coronary angioplasty. Active treatment was associated with significant reduction in the number of clinical events (P<0.001). (Reproduced from Topol et al, with permission.)

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