

Vascular Stents and Atherosclerosis

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The fantastic voyage into interventional cardiovascular medicine launched by Andreas Gruentzig 11 years ago has generated enormous excitement among cardiologists. It is understandably exciting to be able to “work safely inside the coronary arteries,” as Gruentzig expressed it. Excitement translates into dreams, and these may lead to even further advances in the battle against

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atherosclerotic vascular disease. This excitement, however, sometimes produces expectations for the future that leap beyond the necessary tedium of scientific investigation. One of my European colleagues recently quipped that investigators from the United States, in describing their latest endeavors, often use the words, “I’m excited.”

Well, we *are* excited about the possibility of expanding the capabilities of cardiologists to work safely and effectively inside the coronary and other arteries. After all, Gruentzig envisioned balloon angioplasty as only the beginning of interventional cardiovascular medicine.

The editorial by Schatz in this issue, “A View of Vascular Stents,”¹ expresses sufficient excitement to cause me to ask several questions. Is there a problem? Can the proposed approach address the problem (potential efficacy)? Is the treatment worse than the disease (safety)? If the weapons devised work in the ideal (experimental) setting, can they be made sufficiently foolproof to be used in the clinical setting (value)?

First, is there a problem? Acute closure of the coronary artery being dilated results in the need for emergency bypass surgery in 3–5% of patients and myocardial infarction in approximately half that number. Acute closure results largely from plaque disruption and dissection, with spasm and thrombosis being secondary events. As more patients with multivessel and diffuse disease are undergoing angioplasty, the problem of acute closure increases. A solution to acute closure would make percutaneous transluminal coronary angioplasty (PTCA) safer for those who have it and would significantly expand

the pool of patients who could be safely approached with the technique.

Restenosis is present in about 30% of lesions dilated and has been refractory to all attempts to control it over the past 11 years. Systemic approaches, including anticoagulation, antiplatelet therapy, antispasm therapy, lipid alterations, and anti-inflammatory therapy, have failed to reduce the restenosis rate from this 30% value that was seen by Gruentzig in the first patients dilated. Any solution leading to a real reduction in restenosis would dramatically reduce the cost of repeat PTCA and subsequent surgery for lesions that cannot otherwise be controlled.

Efficacy

Second, can the proposed approach address the problem? The answer concerning acute closure is frequently “yes,” and concerning restenosis, possibly “no.” Recent reports from the European investigators with the Medinvent stent² and the Emory group with the coil (Gianturco) stent³ document that abrupt closure occurring after angioplasty can be reversed and normal flow can be restored, facilitating elective bypass surgery or continued medical management. Certainly in emergency use, the stents seem to work. Starting from the position of a totally occluded artery after abrupt closure, any therapy that results promptly in an effectively open one has a great deal to be said for it. Almost all the patients treated with the stent as a “bail-out” device have gone to surgery without ischemia and have emerged without myocardial infarction. The long-term results in these patients treated without surgery is not sufficient, but the early restudies of some of these patients have shown wide patency within the first few weeks of implantation.

Will the stents reduce restenosis? The answer is possibly “no.” There was a great deal of enthusiasm regarding the early reports of the Medinvent stent and the apparent low restenosis rate observed. Further observation of these patients has shown that of the patients having repeat angiography, restenosis within the stent has been significant and differs little from what would be expected from PTCA without a stent.⁴ The lesson is clear from many previous trials that before definitive statements can be made regarding restenosis, a large percentage of patients who have undergone the procedure must have repeat angiography 4–6 months

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after the procedure. This has simply not yet been done with any of the stent models described.

Schatz mentioned several theoretical and experimental advantages of the Palmaz stent. The thickness of the metal struts of the stent will influence the degree of neointimal proliferation. It is necessary, of course, that the proliferation cover the stent wires, and therefore, the thickness of the wire will somewhat determine that. It is not clear, however, that this difference in thickness is of clinical importance because the lumen diameter may not be affected by the increased thickening, depending on the amount of dilatation accomplished in the artery. Indeed, the Palmaz stent inserted in the iliac arteries resulted in an 800- μm neointimal thickness as measured angiographically.⁵

The experimental evidence that an inflexible stent design may have some advantage regarding restenosis is interesting, but as mentioned by Schatz, flexibility is essential if stents are to be implanted in other than the literally most straightforward circumstances. The Medinvent stent and the wire coil stent both have flexibility as a current design feature. The Palmaz stent is undergoing a modification whereby it will also be flexible in an articulated configuration. Does Schatz imply that this flexibility will lead to a higher incidence of restenosis? Schatz also mentions the radial noncompliance of the Palmaz stent as being an important feature. Although the Medinvent stent continues to expand for the first few hours, it is unlikely that there is any real radial compliance in the three stent designs after they are fully deployed. This is not to minimize the difference in design features between the stents, as there may be features that will be important. It should be pointed out, however, that there have not been controlled trials testing whether these different stent designs do indeed lead to different restenosis rates. The follow-up studies of the iliac stents⁴ are probably not translatable to the expected coronary experience because iliac restenosis is unusual with balloon angioplasty alone. The restenosis data on the Palmaz coronary stents is not available at the time of this writing. Again, it should be emphasized that restenosis data should be judged angiographically in a large percentage of the patients who underwent stenting. It is hoped that the outcome of these repeat angiographic studies will be encouraging, but one must not forget the early enthusiasm for the ability of the Medinvent stent to prevent restenosis. This has not proved true with actual angiographic follow-up.

Safety

Third, is the treatment worse than the disease? Use of vascular stents involves placement of a metallic foreign body into the small arterial system. As Dr. Schatz pointed out, there has been a problem of abrupt vessel closure documented in the European experience.^{6,7} Certainly if the stents are used as a bail-out device in the setting of abrupt

closure, then little is to be lost. If, on the other hand, stents are placed in the setting of an uncomplicated angioplasty procedure in order to prevent the restenosis phenomenon, then one must realize that the consequences of gradual restenosis without a stent do not equate with sudden thrombosis of the stent before full endothelial regrowth.

Acute problems with the Palmaz stent have also been noted, particularly dislodgement of the stent from the delivery catheter with embolization into the arterial system before placing in the coronary arteries and some acute closure adjacent to the stent because of technical problems of placing the very short stent precisely on the point of interest. These stents measure 15 mm in length before deployment and are slightly shorter once expanded. There may be some underestimation of abrupt closure or restenosis with the use of the Palmaz stent based on the patient selection. The clinical protocol calls for patients who have good collateral vessels serving the artery to be stented. This implies that the patient either has total occlusion or a very high grade stenosis and that a portion of the distal perfusion is already coming from collateral circulation. In this setting, progression to a total occlusion could be silent; therefore, once again confirmation of the patent artery can only be made angiographically. It is encouraging that in-laboratory episodes of abrupt closure have not occurred, even with this selection criteria.

Value

Fourth, can stents be made satisfactorily fool-proof to be used in the general clinical setting? Lessons learned from the three stent designs described may be helpful. In the Medinvent stent experience, there has been a wide variance in results. Placement of this stent requires a good deal of precision, and misplacement has been shown to result in problems. In the Palmaz protocol, the lesson has been taken to heart, and virtually all stents have been placed under the supervision of one senior investigator (R.A.S.). The coil stent has thus far been used only by three investigators in a single center. Several problems still exist with all these stents. Visibility is poor with each one, making the documentation of placement difficult. The Medinvent stent and the Palmaz stent, both of which shorten somewhat in deployment, require more precision than the coil stent, which is placed with a technique very similar to routine angioplasty. Both the Palmaz and the coil stent need to be improved so that they will slide easily through the proximal coronary segments without points of resistance or friction. Pliability and the absence of snag points is more important than low profile because the lesions to be crossed will have already been dilated with balloon catheters.

Finally, the ultimate use of stents may not be only to provide mechanical buttressing of the arterial wall. This mechanical feature may be exactly what

is needed to overcome arterial dissection and abrupt closure but in the long run may not alter the neointimal proliferative response, which leads to restenosis. Most believe a pharmacologic approach will be necessary to achieve victory over the restenosis problem. It is purely speculation of course, but effective therapy, which prevents platelet deposition, thrombosis, and replication of smooth muscle cells and uncontrolled growth of neointimum, may prove too toxic if given systemically. In that case, local application of compounds by a stent delivered polymer may provide effective local therapy by replacing some of the normal endothelial function. It may be speculated that compounds that retard platelet aggregation and thrombosis, release endothelium-derived relaxing factor, and block platelet-derived growth factor and other mitogens might be delivered by such a biodegradable polymer located on the stent until functional endothelial regrowth has occurred. Existing polymers can perform some of these functions, and if more ideal drug delivery systems can be developed, then pharmacology and mechanics may be able to join hands to effectively inhibit the restenosis process.

As Schatz has pointed out, significant experimental work has been devoted to stent development; however, a great deal more remains to be done. The difference between established clinical practice and experimental investigation needs to be kept in mind. Certainly, there are exciting possibilities for stents,

but before they are reality, there are many areas of tedious but necessary research that remain.

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