Does stent design influence restenosis?

J. Gunn and D. Cumberland

Section of Interventional Cardiology, University of Sheffield, Sheffield, U.K.

Introduction

Stents are now used in 40–80% of percutaneous coronary interventional procedures[1]. This popularity is based upon extrapolation from available data, which discloses a better immediate angiographic appearance than after PTCA, an ability to ‘bail out’ poor PTCA results[2] and superior late clinical and angiographic results compared with PTCA in certain lesion subsets[3,4]. The enthusiasm for stents has translated into an outpouring of stent designs, each with competing claims for superiority. Meanwhile in-stent restenosis, although occurring in a smaller proportion of patients than restenosis after PTCA (in highly selected subsets), is the most important limiting factor of stenting. There are a number of reasons for this. First, it is frequent; though we are, as yet, not experiencing the epidemic that was first feared. The steadily increasing number of percutaneous procedures brings with it a concomitant number of stenting procedures. About half of these patients will experience a cardiac event in the 3 years after stenting[5]. Second, more challenging lesions are being treated, so that the majority are ‘non-Benestent’, and may be expected to have a higher rate of in-stent restenosis than seen in the early trials[6]. Third, in-stent restenosis is technically challenging to treat, especially when diffuse, in the setting of long stented segments and in bifurcations. Fourth, in-stent restenosis is preventing the use of stent implantation in a large number of patients and lesions, notably in small vessels and in the setting of diffuse disease. And yet there is very limited clinical evidence that one stent design is associated with a lower rate of in-stent restenosis than any other.

In-stent restenosis

What is in-stent restenosis? Unlike restenosis after PTCA, it consists predominantly of neointimal growth, rather than the combination of neointima, recoil and downsize remodelling seen after PTCA[7,8]. In-stent restenosis occurs principally, but by no means exclusively, at the site of the primary lesion[9] and, as predicted by the ‘response to injury’ hypothesis, the degree of in-stent restenosis is related to the extent of damage done at the time of implantation[10]. The composition of the neointima of in-stent restenosis is similar to that seen after PTCA, and includes vascular smooth muscle cells and inter-cellular matrix[11–13]. Any subtle differences in the composition of the neointima of the in-stent restenosis and post-balloon injury, for example a suggestion of more matrix relative to cells in the former, may be explained by the different nature and time-course of the two injuries: stent struts produce local deep trauma, and the stent as a whole produces chronic stretch; whereas balloon injury, which may also be deep, is transient and tends to be focal, with unilateral dissection rather than circumferential stretch[14]. In the first days after implantation, thrombus adheres to the region around the struts, with endothelialization by the 14th day and vascular smooth muscle cells proliferation continuing up to 6 months[15]. There have been suggestions that in-stent restenosis is a prolonged phenomenon, but such good evidence as there is suggests that it is essentially complete, like restenosis after PTCA, by 6 months, with little worsening thereafter[16–19].

Clinical predictors

Important clinical predictors of in-stent restenosis have now been established. These include post-implantation minimum lumen diameter by quantitative angiography[4,20,21,22], small vessel calibre[23], lesion length[21,24], the number of stents used[22,25], stent overlap and residual dissection[6]. A lesion in the saphenous vein graft[26], in a restenotic lesion[27] and, like restenosis after balloon dilatation, diabetes[20,22,28] and prior chronic total occlusion[20,21,22,24] are also important. Intravascular ultrasound measurements (generally more accurate than angiographic ones), notably in-stent luminal cross-sectional area, accurately predict the occurrence of target vessel revascularization[29]. These predictors may help assess the risk of stenting a specific lesion in a
particular patient. Stent designs which perform well in these adverse settings may produce better results generally. It is not yet established, however, how significant any additive risk of design-related restenosis is compared with known clinical risk factors. Nor is it known which variables of stent design and deployment might translate into improved results. It makes sense, though, to minimize such risks wherever possible, however great or small the lesion- or patient-related risks might be, without sacrificing good stent performance.

Materials and surfaces

Stent materials and the nature of the stent surface or coating are relevant to in-stent restenosis. Copper, for example, is associated with more frequent subacute thrombosis than steel\(^{30}\), whilst electrochemical polishing or coating with the semi-conductor silicon carbide has shown, however, that the pattern of in-stent restenosis is fairly uniform\(^9\). Intravascular ultrasound (IVUS) study in this stent is associated with more frequent subacute thrombosis than steel\(^{30}\), whilst electrochemical polishing or coating with the semi-conductor silicon carbide can decrease the acute vascular response\(^{31,32}\).

Early work with biodegradable polymers, such as with a braided mesh stent made entirely from polyethylene terephthalate, demonstrated a severe inflammatory reaction\(^{33}\). This, together with poor radial strength, led to a trend towards polymer coating of metal frameworks. Fibrin coating reduces the incidence of thrombosis and neointimal hyperplasia\(^{34}\). A synthetic polymer containing phosphorylcholine, mimicking the phospholipid of the cell membrane, has recently been applied to stents and does not lead to an excessive tissue reaction compared to bare steel, unlike other polymers\(^{35,36}\). There is a conundrum, through, with coatings. Whilst emerging evidence shows that some of these coatings may dramatically reduce protein deposition and platelet adhesion, a commensurate decrease in in-stent restenosis does not seem to follow. Similarly, the modern generation of stent designs, even in the uncoated state, shows very little tendency to subacute thrombosis. Coatings, therefore, currently confront a sceptical attitude. In response to this, the attention of the coating manufacturers has shifted somewhat towards considering coatings as vehicles for local drug delivery. In this role, coatings may provide a valuable function in combating in-stent restenosis. This topic will be dealt with in a later paper.

Stent vs Stent

Is there any clinical evidence that stent geometry influences in-stent restenosis? One widespread perception is that tissue prolapses at the central articulation of the Palmaz-Schatz stent, increasing in-stent restenosis at that site\(^{37,38}\). A serial intravascular ultrasound study has shown, however, that the pattern of in-stent restenosis in this stent is fairly uniform\(^9\). Intravascular ultrasound has also revealed that in-stent restenosis within coil-stents is related to recoil, whereas in-stent restenosis within slotted tubes is related to sub-expansion\(^{39}\). In a retrospective study of matched lesions, the flexible Microstent was associated with a higher restenosis rate than the more rigid Palmaz-Schatz stent\(^{40}\). Similarly, a coil-stent has been shown to be associated with increased in-stent restenosis compared with a slotted tube stent in chronic total occlusions, a situation where radial strength is probably paramount\(^{41}\). There a number of other small, comparative studies which demonstrate, despite similar implantation parameters, superiority in the performance of the latest generation of stent designs compared with the old\(^{42,43}\).

Study design

There are major problems with using the standard ‘Benestent’-type lesion in randomized ‘stent vs stent’ trials. The necessarily restrictive inclusion criteria result in selection of patients with favourable anatomy, lesions and clinical characteristics, so that, with ever improving event rates, the randomization of thousands of patients becomes necessary. ‘Matched’ retrospective trials are one way round this problem, but are flawed by inevitable differences in imponderables such as proximal anatomy, implantation technique and other factors. Detailed morphometric analysis of the vascular reaction to the implantation of different stent designs under identical conditions in undiseased porcine coronary arteries is, however, starting to identify subtle differences which may, in the long run, prove important, particularly where implantation conditions are stringent; for example in smaller vessels\(^{44}\). This is probably a more sensitive, and certainly far quicker and cheaper, way of testing the effect of variations in stent geometry than large, clinical ‘stent vs stent’ trials.

Features of stent geometry

What are the features of stent geometry which make one stent superior to another? In one systematic study, changing the stent configuration to reduce strut-strut intersections reduced the vascular injury score by 42%, thrombosis by 69% and neointimal hyperplasia by 38%. Coating with an inert polymer did not alter vascular injury or neointimal hyperplasia, although thrombosis was eliminated\(^{45}\). Uniform (modest oversize) deployment of multiple examples of one design of stent in a normal porcine coronary artery, with many sections analysed at a consistent timepoint, allows precise mathematical analysis of the relationship between as many parameters of stent geometry as are thought useful in in-stent restenosis. Using this technique, extreme strut protrusion, large inter-strut distance, fracture of the internal elastic lamina, medial compression and location near the distal ends of the stent have been identified as of particular importance. There was no direct relationship between the number of struts and in-stent restenosis unless the stent was over-deployed, in
which case more struts were advantageous, presumably distributing the forces of stretch more evenly and preventing isolated strut protrusion. In the same study there was greater lumen loss and neointimal growth at the distal end compared with the middle of the stents, possibly reflecting the taper seen in a porcine artery. There was also a suggestion that eccentricity of stent deployment (oblateness of the cross-section) adversely affected in-stent restenosis. There is clinical intravascular ultrasound-based evidence for this, too; deviation from the circular in a stented vessel is associated with a trend towards increased target vessel revascularization at long-term follow-up in one study.

**Optimal metal coverage**

There is, of course, a fundamental doubt relating to the single feature common to all stents: the presence of metal on the artery wall. The doubt concerns the optimum percent metal coverage. Very little data exist to guide us in this matter. In one study, a more compact wave design in a coil stent, conferring 15% more struts per unit length than the standard (Wiktor) design, produced a 27% smaller neointimal area at 28 days in the minipig coronary artery. Is greater coverage a good or bad thing? In contrast to the early days of stenting, when the fear of a ‘foreign body’ reaction was still present, results such as this now point away from a minimalist approach towards generous coverage of the wounded vessel wall, with a high metal/artery ratio. The concept of maximizing the metal barrier is, of course, limited by poor ‘crimpability’, unacceptable profile, inflexibility and compromise of side-branches. The answer here may lie in the development of hybrid ‘covered’ stents, with a conventional metal frame and an inert, expansile inter-strut membrane. Such designs (for example, the Jomed covered stent) are already marketed, but have not yet reached wide acceptance.

Perhaps the main reason for in-stent restenosis being reduced in one design of stent rather than another, at least in experimental models, is the impact of the stent’s physical properties upon vascular injury. There are some astonishing differences in these properties. There is a 21-fold range, for example, in the elastic moduli of the Wallstent, Palmaz and Streeker Stents. Similarly, there is a continuing increase in the stent expansion ratio as late as 8 weeks after deployment in self-expanding, as opposed to balloon-expandable stents. Non-uniformity of expansion increases vascular injury and experimental in-stent restenosis. Similarly, several small studies demonstrate that, with standard deployment characteristics, different stents produce different injury scores and subsequent levels of in-stent restenosis.

**Deployment strategies**

Deployment strategies are also likely to affect the long-term results of stenting. Very high balloon pressures, for example, predispose to in-stent restenosis. Moderately high pressure deployment, however, may be advantageous, by increasing acute gain without increasing late loss, thereby increasing net gain at 6 months compared with low pressure stenting. The restenotic lesions so produced are less eccentric and have a greater minimum lumen diameter. Finite element analysis has revealed that low balloon compliance and the lowest possible balloon pressure to achieve adequate deployment are important variables. Balloon- (and stent)- artery ratio (BAR) are also contributory. In his early studies, Schwartz used a BAR of 1.5:1, and produced dramatic injury with a high experimental animal mortality rate. Thomas, however, using a BAR of 1.1:1, experienced 100% patency and minimal rupture of the IEL and minimal neointima. Our own work at modest BAR (1.25:1) showed that simple compression of the vessel wall without rupture of its components was sufficient to trigger moderate neointimal growth without dramatic loss of luminal cross-sectional area. Squire et al. demonstrated that the ends of a slotted tube deploy first, scraping inwards until the centre expands, giving 71% greater injury scores and 61% greater intimal hyperplasia than for a corrugated ring stent.

**Geometry vs lesion**

Are the subtleties of stent design discussed here anywhere near as important as lesion morphology in deciding long-term outcome? Some would argue that, apart from the difference between copper and steel, and between coil and slotted tube, between-stent differences are of theoretical rather than practical importance. The data suggest otherwise. In a study of 588 successfully stented lesions, the restenosis rate in AHA/ACC Type A lesions was 23% and in Type C 32%. This is a small difference indeed, and may be compared with the magnitude of difference seen between different stent designs in similar lesions. Clearly, this sort of analysis may be biased by patient selection and the well-known limitations of the A/B/C classification, but this difference might be further reduced or eliminated if the results of improvements in stent design discussed here were translated into the clinical setting.

**Testbeds**

The present profusion of stent designs with subtle differences in geometry, materials, expansion characteristics and coatings, therefore, demands a simple, reproducible and sensitive system for comparative testing, and more information about the parameters which are likely to impact upon both acute thrombosis and chronic neointima formation. Systematic animal testing, with agreement as to implantation protocols, will be vital. For sure, the ideal animal model has yet to be found. Disease models are expensive, time-consuming and...
introduce an element of lesion variability which makes interpretation of results of intervention more difficult, though more realistic. As hinted at above, in some ways a normal artery wall, with no variability whatsoever, may reveal the biological effects of subtleties of stent design, and elucidate the mechanisms of in-stent neointima formation, most effectively. Lesion-specific stenting may then become elevated from empiric speculation to scientific discipline, hopefully without resorting to enormous ‘head to head’ clinical trials.

There is, then, a disparity between experimental models, which currently reveal small but significant differences between different stent designs, and clinical trials which tend to blur the differences between them. Such clinical data may be confounded by the constraints imposed by tight inclusion criteria in rather non-stringent lesions, not really reflecting the ‘real world’ of stenting. For once, animal models may be important in revealing the implications of refinements in stent design where clinical trials, so far, have not. The investigation of stent performance in long lesions and small vessels may redress this balance, and justify investment in design and engineering innovation and excellence.

The ideal stent

Is it possible to draw any conclusions from the data available about the ‘ideal’ stent? A pattern is starting to emerge. Whilst preserving the desirable characteristics of low profile, trackability, conformability and visibility, it should have many, closely spaced struts giving good, well-distributed radial strength. The inter-strut connections, whilst allowing for even balloon expansion and access to side-branches, should form a close meshwork which prevents large spaces from opening up between the struts, or from one strut protruding beyond its neighbours. As the struts separate, there should be a tendency to increasing resistance to further expansion compared with struts that are still closely spaced, rather than the reverse. The forces of expansion should be distributed evenly so that the stent expands symmetrically, without eccentricity. Attention should be paid to the design of the ends of the stent, so that a smooth transition to normal vessel is created, and distal oversizing avoided. The design should preclude the development of large defects in metal coverage. Sizing of the stent relative to the normal ‘reference’ segment should not be over-zealous, especially where a long stent is used. Self-evidently, some of these ideal characteristics are mutually incompatible (side-branches and close mesh for example), but development of a logical ‘family’ of stents for every occasion should circumvent this problem.

References


[40] Caixeta A, Brito FS, Rati M et al. Acute angiographic benefits of high pressure balloon inflation during MultiLink stent implantation are maintained at 6 months follow-up (Abstr). Am J Cardiol 1997; TCT (Suppl): 3S.

[41] Brito FS, Caixeta AM, Rati M et al. Does high pressure balloon inflation have any influence on quantitative angiographic characteristics of restenotic lesions within stented segments? (Abstr) Am J Cardiol 1997; TCT (Suppl): 3S.


