postulated that this association may explain why recurrent transient ischaemia predicts a poor outcome in unstable angina patients who appear to be well treated with antiischaemic agents.

Both sets of authors urge that intensive therapeutic approaches be considered in the more ischaemic patients. Specifically, Akkerhuis et al. [6] suggest that continuous on-line ST segment monitoring can influence the triage and risk stratification of patients with unstable angina. Enhanced antithrombotic treatment and revascularization can then be used in those patients with persistent episodes of transient ischaemia who were initially thought to be at low risk for future cardiac events. Patel et al. [5] also favour using revascularization procedures in their ‘refractory’ patients. The continuing instability of the vascular endothelium is a source of ongoing concern and probably warrants other approaches as well. I am thinking specifically of the decrease in transient ischaemia (and subsequent cardiac events) reported with statin therapy in patients with stable angina [8, 9].

This class of drugs makes the endothelium less vulnerable to the kinds of lesions associated with increased cardiovascular morbidity and mortality and may be especially valuable when a full regimen of ‘traditional’ antiischaemic agents (nitrates, calcium blockers, antiplatelet drugs) are already being employed. There is preliminary data that ACE inhibitors may also be helpful. In the final analysis, however, it may be that coronary revascularization—and especially bypass surgery—offers the best prognosis for patients with ongoing ischaemia, whether stable or unstable, silent or symptomatic [10].

References


All stents are not alike or is the difference in the eye of the observer only?

See pages 2007 and 2015 for the articles to which this Editorial refers

Coronary artery stents have emerged as the preferred tool for percutaneous coronary interventions during the past decade [11]. Their ubiquitous acceptance results from the ease and speed of applicability in an ever-broader array of anatomical lesions, the improved safety by elimination of abrupt closure and need for urgent coronary artery bypass grafting (CABG) [2], and the angiographically pleasing result. The basic principle underlying the acute therapeutic value is common to all coronary artery stents and consists of (1) increasing the arterial lumen by scaffolding...
the arterial vessel wall, (2) tagging of intimal flaps between the stent surface and vessel wall, and (3) sealing of dissections[9]. As stents eliminate constrictive arterial remodelling, late lumen loss following stenting in human coronary arteries has been attributed exclusively to neointimal hyperplasia[4]. The neointimal proliferation typically exceeds that seen after balloon angioplasty and produces clinical in-stent restenosis in 10–30% of cases, representing a new, difficult to treat entity[5].

The pathobiology of vascular repair mechanisms following stent implantation is increasingly understood[6,7]. Stent struts elicit vascular injury by endothelial denudation, intima laceration, and media penetration. This results in platelet and fibrin deposition on subendothelial connective tissue within the first 1–3 days, and the extent of vascular injury determines the local thrombotic response. Activated platelets release cytokines and adhesion molecules which perpetuate inflammatory cell recruitment and migration across the endothelium into the arterial wall during the second phase on days 3–7 after stent implantation. The third phase is characterized by intimal proliferation mediated by migration and proliferation of monocytes and medial smooth muscle cells with extracellular matrix formation. Neutrophils and monocytes contribute to neointimal thickening by elaborating oxygen radicals with release of growth and chemotactic factors attracting smooth muscle cells, production of metalloproteinases degrading extracellular matrix and thereby facilitating cell migration. The vasculoproliferative cascade following stent implantation observed in experimental restenosis models has been confirmed in human atherosclerotic lesions[8,9]. Thus, early after stenting platelets, fibrin and acute inflammatory cells are omnipresent surrounding stent struts. Beginning 2 weeks after stent implantation a neointima composed of macrophages and α-actin-negative spindle cells is formed. This is followed by staged smooth muscle cell redifferentiation and extracellular matrix formation. The healing process is completed by reendothelialization occurring weeks to months after stent implantation.

Experimental studies of neointimal thickening have convincingly shown that increased vascular injury causes greater thrombus formation and more inflammation, both of which result in stronger neointimal growth[10,11]. This finding begs the question whether changes in stent design and implantation technique translate into different clinical outcome. Evidence from experimental models strongly support the notion of stent-design dependent vascular injury and subsequent neointimal proliferation. Comparing two different stent configurations with identical diameter, length, strut thickness and metal surface, a corrugated-ring stent was found superior to a slotted tube design with respect to injury score, inflammatory cell recruitment, thrombus formation and subsequent neointimal thickness[12]. The corrugated ring configuration featured a third fewer strut–strut intersections with less radial force application, reducing neointimal hyperplasia by half. Not only the deep vascular injury imposed by the stent struts penetrating the internal elastic lamina and media, but also balloon-artery interactions between stent struts resulting in endothelial denudation[6,7]. Stent struts elicit vascular injury by endothelial denudation, intima laceration, and media penetration. This results in platelet and fibrin deposition on subendothelial connective tissue within the first 1–3 days, and the extent of vascular injury determines the local thrombotic response. Activated platelets release cytokines and adhesion molecules which perpetuate inflammatory cell recruitment and migration across the endothelium into the arterial wall during the second phase on days 3–7 after stent implantation. The third phase is characterized by intimal proliferation mediated by migration and proliferation of monocytes and medial smooth muscle cells with extracellular matrix formation. Neutrophils and monocytes contribute to neointimal thickening by elaborating oxygen radicals with release of growth and chemotactic factors attracting smooth muscle cells, production of metalloproteinases degrading extracellular matrix and thereby facilitating cell migration. The vasculoproliferative cascade following stent implantation has been found to be an important predictor of intimal thickening independent of arterial injury. Thus, stent configurations featuring an increased strut number and regularity achieve a more circular luminal geometry and demonstrate significantly less neointimal hyperplasia[14].

Several stent-vs-stent equivalency trials have been performed comparing second generation devices against the benchmark Palmaz–Schatz slotted tube stent[15–18] in patients. Except for the Gianturco-Roubin II stent with its less recoil-resistant configuration (coil design)[15], the other trials revealed no significant differences in minimal luminal diameter, late loss and binary restenosis rates at follow-up. The ACS MultiLink Stent Clinical Equivalence in De Novo Lesions Trial (ASCENT) randomized 1040 patients with single de novo native coronary artery lesions to treatment with the Multilink or Palmaz–Schatz stent[15]. The primary end-point of target vessel failure was observed in 15.1% of Multilink compared with 16.7% of Palmaz–Schatz patients (P=NS). Angiographic restenosis showed a non-significant trend in favour of the Multilink stent (16.0% vs 22.1%, P=NS), but this potential beneficial effect was largely due to the better acute result, with late loss being nearly identical between the two groups.

Against this background information favouring a corrugated-ring design in experimental studies and lack of benefit in clinical investigations, the study by Hoffmann et al. reported in this issue[18] investigated the amount of neointimal hyperplasia, using intravascular ultrasound in human coronary arteries in response to two slotted tube and one corrugated-ring stent. The analysis consisted of angiographic
and intravascular ultrasound measurements of 41 Palmaz–Schatz, an articulated slotted tube stent, 50 ACS RX Multilink HP, a corrugated-ring design stent, and 40 Inflow, a slotted tube stent with interconnected sinusoidal waves. Again, angiographic follow-up revealed no significant differences between the three stent types with respect to minimal lumen diameter, percent diameter stenosis, late loss and binary restenosis, except for a trend towards higher restenosis for the Inflow (35%) compared with the Palmaz–Schatz (17%) and Multilink stent (20%). In contrast, intravascular ultrasound assessment of mean intimal cross-sectional area was lowest for the Multilink, intermediate for the Palmaz–Schatz and highest for the Inflow stent, which was maintained after correction for lumen size (intimal thickness and mean intimal hyperplasia cross-sectional area/stent cross-sectional area). The relative reduction in neointimal thickness amounted to 59% for the Multilink and to 33% for the Palmaz–Schatz compared with the Inflow stent. The authors have to be complemented on transferring the experimentally established evidence of reduced neointimal proliferation with a corrugated-ring stent to the clinical setting in patients with atherosclerotic coronary arteries. In addition, this study nicely demonstrates the advantages of intravascular ultrasound, including higher sensitivity of measurements and imaging of the entire vessel rather than lumen, compared with angiography with intravascular ultrasound derived parameters more closely mirroring histological findings of experimental restenosis models.

However, the results should be interpreted cautiously in the light of some important shortcomings. First, patients were initially part of three separate studies, and only patients implanted with stents of 14–15 mm in length were included in the analysis. Although no significant differences were found with respect to clinical and baseline angiographic data, the small sample size and non-randomized, retrospective analysis may have obscured selection bias. In addition, subtle differences in lesion characteristics such as complex and unstable plaques underlying the treated segment may alter vascular repair processes. Thus, stent implantation in atherosclerotic human arteries provokes different degrees of inflammation and neointimal proliferation, depending on the vicinity to damaged media and exposed lipid cores.

Second, the stent implantation protocol was different for Palmaz–Schatz patients, which required intravascular ultrasound guidance and was more aggressive, as evidenced by the larger acute gain, larger balloon diameter and higher maximal implantation pressure. Third, stent implantation required pre-dilation with an undersized balloon in the majority of cases. However, the pre-dilation protocol was not standardized, and two of the stents (Palmaz–Schatz, Inflow) were self-crimped. Important differences in vascular injury due to balloon–artery interactions, edge effects, and different degrees of endothelial denudation may have confounded the observed neointimal proliferation. Fourth, the study fails to provide an explanation for the observed difference between the Palmaz–Schatz and Inflow stent, which share a similar design. Fifth, the data are derived from patients with discrete lesions of <15 mm length in vessels with a mean diameter of approximately 3.0 mm and may not apply to more complex or diffuse disease. Notwithstanding, the study provides clinical evidence of the superiority of a corrugated-ring design over slotted-tube stents in human coronary arteries.

While vascular injury emerged as a strong determinant of neointimal proliferation in experimental studies, clinical investigations consistently supported a somewhat contradictory hypothesis, where restenosis is inversely related to final luminal diameter, suggesting ‘Bigger Is Better’. The second study reported by Hoffmann et al. in this issue addresses these conflicting hypotheses by investigating the effect of high vs low pressure stent deployment on intimal hyperplasia using intravascular ultrasound. A total of 120 patients were randomly assigned to undergo either high (16–20 atm) or low pressure (8–10 atm) stent implantation using the ACS RX Multi-Link HP stent. High pressure stent deployment resulted in greater acute stent expansion and lumen diameter, which was maintained at follow-up due to similar late loss. There was no difference in the amount of neointimal thickness between stents deployed with high vs low pressure, and the mechanism of greater stent expansion was related to the larger effective balloon diameter when balloon compliance was accounted for. These findings confirm that high pressure stent implantation does not result in exaggerated neointimal proliferation, does not eliminate the net benefit of greater initial stent expansion, and therefore supports the ‘Bigger Is Better’ approach.

How then can we reconcile the conflicting theories of vascular injury on the one side and luminal diameter on the other? An important consideration is, that the present study was conducted in human atherosclerotic arteries, which differ from non-diseased arteries of other species when exposed to vascular injury. Thus, pathological specimens from coronary artery stents in humans revealed a markedly lesser degree of vascular injury and media penetration than typically observed in experimental studies. This observation suggests that differences in vascular...
injury in response to high vs low pressure stent implantation may be less pronounced in human than experimental coronary arteries, and therefore fail to provoke exaggerated neointimal hyperplasia. Furthermore, stent implantation in the present study was preceded by balloon dilatation in all cases resulting in circumferential endothelial denudation. Experimental studies have shown that partial retension of endothelium in the case of primary stent implantation is associated with reduced mural thrombosis, inflammation and subsequent neointimal hyperplasia."\cite{19}. Therefore, endothelial injury imposed by balloon pre-dilatation in the present study may have obscured subsequent pressure-mediated differences during stent induced vascular injury.

Can high pressure stent implantation now be embraced for universal stent delivery? Certainly not, based on the available evidence and the following shortcomings. First, the pressure used for high pressure stent implantation in the present study exceeded the rated burst pressure of most commercially available delivery systems and imposes the risk of balloon rupture with subsequent arterial damage and air or particulate embolization. Second, high pressure stent delivery certainly inflicts a higher degree of vascular injury (unless the balloon size is sized conservatively), which could become clinically noticeable when other forms of stent delivery, such as primary stent implantation without balloon predilation are chosen. Finally, differences in stent expansion were only detected by intravascular ultrasound, whereas angiographic and clinical end-points were similar. This is in concert with a previously reported study by Dirschinger et al.\cite{24}, who observed no differences in clinical and angiographic outcome up to 1 year after the procedure in a much larger study population comparing high vs low pressure stent delivery. Thus, differences in implantation pressures act predominantly via the balloon-to-artery ratio and may be too subtle to become clinically relevant.

Taking the two studies together, differences in stent design such as surface material, strut configuration and geometry appear to impact to a greater degree on vascular repair and neointima formation than pressure mediated injury during stent delivery. Modifications in stent design such as surface material, drug elution, and stent delivery (primary stenting) are currently under investigation to further attenuate neointimal hyperplasia in response to stent implantation in human coronary arteries.

**S. WINDECKER**  
**B. MEIER**  
**Swiss Cardiovascular Center, Bern, Switzerland**

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