Effect of endovascular stent strut geometry on vascular injury, myointimal hyperplasia, and restenosis

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Purpose: Early restenosis and the development of myointimal hyperplasia in stented blood vessels have been attributed to deep vascular injury with fracture of the internal elastic lamina (IEL). The purpose of this study was the evaluation of the vascular wall response to superficial injury (without IEL rupture) after balloon angioplasty and intravascular stent placement in porcine arteries and the determination of the effect of stent strut geometry on the degree of vessel injury and early restenosis.

Methods: Balloon-expandable stainless-steel stents were placed into the iliac arteries of 10 Sinclair miniature swine that had been fed an atherogenic diet. A Palmaz stent, with rectangular struts and smooth corners, was randomly assigned to one iliac artery (group 1), and a novel stent, which was designed and manufactured in the laboratory with thicker struts and sharper corners specifically to induce large wall stress concentrations, was placed in the contralateral iliac artery (group 2). Intravascular ultrasound scan was used in all deployments to ensure accurate balloon sizing and to avoid stent overexpansion and deep vascular injury. At 90 days after implantation, the animals were killed, the stented vessels harvested, and histomorphometric analysis performed.

Results: Deployment of novel stents in group 2 resulted in a statistically higher incidence rate of deep vascular injury (fracture of the IEL) compared with group 1, despite identical balloon size used for deployment (with Student t test, P < .05). Vessels with deep injury showed a 10-fold increase in myointimal thickening compared with those vessels in which the IEL remained intact. A statistically higher restenosis rate was observed for group 2 (33.5% ± 19.90%) compared with group 1 (20.39% ± 14.70%). For both stent designs, there was a trend toward lower degrees of restenosis within the mid-portion of the stent. For superficially injured arteries in both groups, no correlation was observed between the amount of vessel wall/medial layer compression and the development of restenosis from myointimal hyperplasia.

Conclusion: Maintenance of an intact IEL is an important factor in the prevention of myointimal hyperplasia and restenosis in stented porcine iliac arteries. The alteration of stent strut height and geometry does not significantly affect restenosis and the development of myointimal hyperplasia in vessels with superficial injury. Superficial injury elicits a response that is independent of stent strut geometry and vessel wall compression. Stent strut profile may, however, increase local vessel wall stress concentrations, leading to IEL rupture and an exaggerated response to injury. (J Vasc Surg 2002;36:143-9.)

Increasingly, repair of atherosclerotic arteries involves the use of balloon angioplasty (percutaneous transluminal angioplasty [PTA]) and intravascular stents. Although animal studies have shown that stented arteries rapidly gain an endothelial lining, thus preventing an exaggerated intimal hyperplastic response, clinical studies document a 20% to 30% rate of restenosis in stented peripheral and coronary arteries, largely the result of myointimal hyperplasia. Myointimal hyperplasia may be caused by a number of hemo-dynamic factors that are believed to cause vascular injury, including recirculation, flow separation, and wall shear stress gradients. In addition, vessel wall injury can be caused by penetration of stent struts into the arterial wall.1,2

Smooth muscle proliferation is proportional to the degree of arterial injury caused by a balloon or stent. Schwartz et al3 embedded coiled stents into porcine coronary arteries. Most of the stent struts actually fractured the internal elastic lamina (IEL), causing deep arterial wall injury, and a minority of struts simply compressed the underlying medial layer without breaking the IEL (superficial injury). These investigators concluded that it is the injury caused by the stent strut rather than the material itself that is responsible for cell proliferation and restenosis. Techniques designed to increase initial luminal diameter during stent implantation, including oversizing, aggressive balloon dilatation before stent implantation, and high-pressure angioplasty, may in fact cause substantial vessel wall injury, leading to early restenosis from intimal hyperplasia.4,5

Although the link between vessel wall injury and smooth muscle cell proliferation is well known, little is
known about the minimization of stresses on the tunica media and the IEL during deployment and expansion of an intravascular stent. We hypothesize that stresses and injury on the arterial wall, and subsequently the amount of restenosis caused by intimal hyperplasia after the deployment of an intravascular stent, are affected through the geometric design of the stent or, more specifically, the design of the stent struts. The purpose of this study was the evaluation of the impact of stent strut geometry on restenosis caused by intimal hyperplasia with a miniature swine model. Specifically, the effect of the outer profile geometry of an endovascular stent on the amount and distribution of superficial and deep vessel injury and its relationship with neointima formation will be examined.

MATERIALS AND METHODS

A novel balloon-expandable stent (Clemson stent) was designed and manufactured (by Dr Ainsworth) specifically for the purpose of this study, on the basis of the following requirements: (1) expandability with standard balloon angioplasty devices and techniques; (2) ability to be manufactured with currently available techniques; (3) ability to expand uniformly so as to contact the vessel wall throughout its length and circumference; and (4) resistance to elastic recoil once expanded. Computational analysis was used to determine the stent strut configuration that would concentrate stresses in the arterial wall at the point of contact. The Clemson stent design was based on that of commercially available balloon-expandable stents and was constructed from annealed 316L stainless steel bar stock. With die-sinking electron discharge machining techniques, a stainless steel tube was constructed. The outer configuration of the stent was machined with a wire electron discharge machining process. The resulting 1-in tubes then were slotted with a laser technique and electropolished. The profile of the novel (Clemson) stent struts is compared with that of the Palmaz stent struts in Fig 1. The study protocol for live vertebrates was approved by the Clemson University Animal Research Committee. Housing and care were provided by the Godley-Snell Research Facility, an American Association for Accreditation of Laboratory Animal Care–accredited research facility at Clemson University, Clemson, SC.

Twelve 20-lb to 30-lb Sinclair Mini-Swine (Harlan Sprague Dawley, Inc, Columbia, Mo) were acclimated for 2 months before surgery. The animals were fed a special atherogenic diet, which has proven to result in atherosclerotic lesion formation in pigs. With general anesthesia, the right common carotid artery was exposed and an 8F introducer sheath was placed for arterial access. Heparin (5000 U) was administered as an arterial bolus injection immediately after sheath placement. A diagnostic catheter was advanced with fluoroscopic guidance into the distal abdominal aorta, and aortoiliac arteriography was performed. An intravascular ultrasound scan (IVUS) catheter was advanced into the external iliac arteries for accurate vessel sizing, in an effort to avoid oversizing and deep injury of the vessel wall. Either a Palmaz (P204 biliary stent) or a Clemson stent was selected and randomly deployed in the right external iliac artery with a coaxial balloon catheter. The second stent then was deployed in the contralateral iliac artery. IVUS was used to ensure adequate apposition of the stent to the arterial wall. If either stent was not fully deployed, a slightly larger balloon was used for postdilatation and the deployment was reevaluated with IVUS. A sham operation was performed in two pigs. These pigs went through the exact same procedures listed previously, including balloon angioplasty, but did not have stents placed. These sham procedures were used to create a baseline for any reaction as the result of balloon angioplasty alone and not specifically related to stent placement. The animals were continued on the atherogenic diet and were closely observed for 90 days.

At the end of the follow-up period (90 ± 1 days), the pigs were brought to a plane of anesthesia and IVUS measurements of lumen and stent diameter in vivo were performed. Immediately after measurement, the pigs were killed with 120 mg/kg pentobarbital sodium with American Veterinary Medicine Associates standards. The iliac
arteries were excised, with placement of a stitch to mark the proximal end of each stented vessel, and placed in labeled specimen jars containing 10% buffered neutral formalin for fixation.

Formalin-fixed tissues were placed in solutions of polymethylmethacrylate and allowed to polymerize overnight. Two 0.5-mm slices of stented artery were taken at each of three locations (distal, middle, and proximal stent), which then were ground and polished. Stented specimens were stained with basic fuchsin/methylene blue to observe cellular components and Verhoff’s elastic stain to visualize the internal and external elastic laminae. Histomorphometric analysis was performed to determine percent restenosis (as a percent of cross-sectional area), the thickness of neointima on top of each strut, medial layer thickness below each strut, and the thickness of uncompressed media between struts. For a given cross section, the degree of superficial injury (as determined by the magnitude of medial layer compression beneath a stent strut as compared with the thickness of a stretched, nonremodeled tunica medium after stent placement and acute harvest) was calculated by the average of the values for all stent struts. The same was done for neointimal thickness measurements. Results also were grouped according to the geometry of the strut (Clemson versus Palmaz). Fig 2 shows the locations at which these measurements were taken.

Struts that did not break the IEL were given a vessel injury score of zero. These also were subjected to further breakdown as described previously for the determination of vessel response to degree of superficial injury. All other struts were scored according to the scale created by Schwartz et al (Table I). Statistical analysis was performed with Student $t$ test (95% CI).

### RESULTS

Ten animals underwent successful stent implantation, for a total of 20 implants. One animal died 2 hours after implantation because of inadvertent rupture of an iliac artery. Two other pigs underwent successful balloon angioplasty without stent placement. On the basis of IVUS measurement, mean vessel diameter before stent implantation was 5.73 ± 1.04 mm. After stent implantation, mean vessel diameter was 5.8 ± 0.92 mm, yielding a 1.01:1 stent-to-vessel ratio. At the time of death, mean luminal diameter (with IVUS) was 5.61 ± 0.53 mm.

The neointimal areas calculated with the cross sections are compiled in Table II. There was a statistically significant difference between the Clemson stent and the Palmaz stent in comparison of restenosis for both groups (Clemson > Palmaz). There was also a significant difference between

### Table I. Vessel injury score\(^{21}\)

<table>
<thead>
<tr>
<th>Injury score</th>
<th>Description of injury</th>
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<tbody>
<tr>
<td>0</td>
<td>Internal elastic lamina intact; endothelium typically denuded; media compressed but not lacerated</td>
</tr>
<tr>
<td>1</td>
<td>Internal elastic lamina lacerated; media typically compressed but not lacerated</td>
</tr>
<tr>
<td>2</td>
<td>Internal elastic lamina lacerated; media visibly lacerated; external elastic lamina intact but not compressed</td>
</tr>
<tr>
<td>3</td>
<td>External elastic lamina lacerated; typically large lacerations of media extending through external elastic lamina; coil wires sometimes residing in adventitia</td>
</tr>
</tbody>
</table>

### Table II. Neointimal area calculations for Palmaz and Clemson stented arteries and for balloon-only controls

<table>
<thead>
<tr>
<th>Stent/location</th>
<th>Mean restenosis</th>
<th>SD</th>
<th>No.</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmaz</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>25.42</td>
<td>11.03</td>
<td>7</td>
<td>8.17</td>
</tr>
<tr>
<td>Middle</td>
<td>14.49</td>
<td>8.49</td>
<td>10</td>
<td>5.26</td>
</tr>
<tr>
<td>Proximal</td>
<td>23.37</td>
<td>12.09</td>
<td>8</td>
<td>8.58</td>
</tr>
<tr>
<td>Total</td>
<td>20.39</td>
<td>14.70</td>
<td>25</td>
<td>5.76</td>
</tr>
<tr>
<td>Clemson</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>35.97</td>
<td>10.34</td>
<td>7</td>
<td>7.66</td>
</tr>
<tr>
<td>Middle</td>
<td>27.04</td>
<td>8.45</td>
<td>10</td>
<td>5.24</td>
</tr>
<tr>
<td>Proximal</td>
<td>37.18</td>
<td>9.77</td>
<td>9</td>
<td>6.38</td>
</tr>
<tr>
<td>Total</td>
<td>33.50</td>
<td>19.90</td>
<td>26</td>
<td>7.65</td>
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<tr>
<td>Balloon</td>
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<td></td>
</tr>
<tr>
<td>Distal</td>
<td>15.33</td>
<td>11.54</td>
<td>6</td>
<td>9.23</td>
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<td>Middle</td>
<td>11.28</td>
<td>9.42</td>
<td>3</td>
<td>10.66</td>
</tr>
<tr>
<td>Total</td>
<td>13.98</td>
<td>13.60</td>
<td>9</td>
<td>8.88</td>
</tr>
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</table>

Significantly increased neointimal areas (stenosis) were identified for Clemson versus Palmaz and for Clemson versus balloon but not for Palmaz versus balloon. Note trend for increased restenosis at ends of stents. SD, Standard deviation.
the Clemson stent and the balloon injury group (Clemson > balloon). There was no significant difference between the Palmaz stent and the balloon injury group (with Student t test, P < .05). There was a tendency for more restenosis at the ends of the stent compared with the middle. Although not statistically significant, this phenomenon is clearly visible.

The results seen in the previous plots show how random restenosis seems to be. Each cross section was further analyzed to look beyond the overall restenosis figures and to better understand what happened at each individual strut. Three different measurements were made at each strut in a given cross section. These included assignment of an injury score (0 to 3), measurement of the thickness of the neointima on top of the strut, and measurement of the thickness of the media beneath each strut. Assembling these quantities creates a clearer picture of what occurs within the stented region than does overall percent restenosis.

Fig 3 is a scatter plot of each vessel’s injury score (an average of the injury score for each strut in the section) compared with the neointimal thickness of each vessel. Linear regression was performed with standard methods to derive slope, an intercept, and a correlation coefficient for this plot. A direct correlation between average neointimal thickness and vessel injury score was identified for vessels with an injury score greater than zero. These data then were separated into design groups. The Clemson stent injury rating-to-neointimal thickness plot and the Palmaz stent injury rating-to-neointimal thickness plot are both shown in Fig 4. Linear regression was performed on each design group separately. For a given injury score, there is no significant difference in neointimal thickness in comparison of the two stent types. As seen from the plot, however, a greater number of Clemson stents (n = 6) had injury scores greater than zero, compared with three Palmaz stents with injury scores greater than zero.

Nine implants received injury scores of zero (ie, the IEL remained intact). Of these nine, six were Palmaz stents and three were Clemson stents. To illustrate the difference in neointimal thickness between an intact IEL and a fractured IEL, vessels were separated into two groups: IEL intact versus IEL fractured. For further comparison, each group was separated again according to design: Clemson versus Palmaz (Fig 5). Vessels with an intact IEL (injury score = 0) had significantly less restenosis than those vessels in which the IEL was fractured (injury score > 0), regardless of stent type.

The neointimal thickness among the group of implants that only inflicted superficial vessel injury (injury score = zero) also varied. To quantify the extent of superficial injury, the amount of tunica media compression beneath each stent strut was measured as described in the Materials and Methods section. These values then were normalized with the thickness of a stretched nonremodeled tunica medium (0.0802 mm), with the specimen from the pig that died acutely, because no vascular remodeling had taken place. With the division of the measured values by the normalized value, a superficial vessel injury ratio was determined. Linear regression was used to determine whether there was a relationship between superficial vessel injury and neointimal thickness. No such relationship was identified.

DISCUSSION

Since the inception of PTA, investigators and clinicians have sought ways to improve the technique; most of those efforts have focused on improvement of initial lumen diameter to improve the immediate cosmetic and hemodynamic result. To this end, intravascular stents have been designed...
and used to act as a “scaffold” within the artery, preventing elastic recoil and tacking down flow-limiting dissection. In certain vascular territories, especially the coronary and infragastric beds, early restenosis limits the usefulness of angioplasty and stenting; these restenotic lesions are typically caused by myointimal hyperplasia.1,2,8 Some of the techniques currently used to improve the initial results of angioplasty and stenting, including high-pressure balloon inflation and oversizing balloons with respect to the native vessel, may induce substantial arterial wall injury and lead to myointimal hyperplasia.5,9

Atherogenic swine models have been successfully used to simulate restenotic lesions similar to those in human arteries.1,10-13 Most published research regarding intimal hyperplasia after PTA and stenting with these models suggests that most smooth muscle proliferation occurs within the first month after intervention. Although most authors cite a connection between the degree of arterial wall injury and the magnitude of the hyperplastic response, stent design and method of deployment have not been substantially influenced by these findings. The cause of restenosis is likely multifactorial, including stent material and size, stent strut geometry, technique of implantation, rheologic factors, and location of disease within the arterial system. From a purely mechanical perspective, the stent strut imposes a contact stress on the arterial wall that may influence the magnitude of vessel injury and hyperplasia.

Previous work by Schwartz et al5 in porcine coronary arteries has shown that the degree of arterial wall injury (as measured by fracture of the layers of the arterial wall) is proportional to the subsequent hyperplastic response. This study was designed to investigate the impact of stent strut geometry on arterial wall injury and specifically to observe what impact the degree of superficial wall injury (ie, compression of the tunica media without fracture of the IEL) has on intimal hyperplasia and early restenosis. This was

Fig 4. Injury score compared with neointimal thickness separated by geometry design (Clemson versus Palmaz).

Fig 5. Neointimal thickness versus injury with respect to IEL. Those vessels with intact IEL have significantly less intimal hyperplasia than those with fractured IEL, irrespective of stent design.
accomplished with a novel stent specifically designed to induce maximal stress concentrations on the adjacent arterial wall and comparison of this stent with a commercially available stent and with balloon angioplasty alone.

IVUS is an important clinical tool in PTA and stenting in humans. A number of studies with IVUS in the peripheral and coronary beds have shown that IVUS helps to eliminate oversized or undersizing of intravascular stents, allowing for complete apposition of the stent to the target artery and avoiding overdistention of the vessel.14,15 IVUS was an important part of this study in that we were able to obtain arterial diameters before intervention, use an appropriate-sized balloon catheter for stent implantation, confirm stent apposition to the vessel wall after deployment, and minimize (although not completely eliminate) rupture of the IEL. The sole iatrogenic arterial rupture, which led to exsanguination of the study animal, was caused by inadvertent misplacement of the stent into a branch of the iliac artery and was not the result of inaccurate IVUS measurement of the target vessel.

One of the key factors in neointimal thickening is the height of the stent strut. The Clemson stent, because its strut height is greater than that of the Palmaz stent, creates a 10% to 20% greater degree of intimal thickening within the same degree of vessel wall injury. Similar results have been reported by Barth et al16 in comparison of Palmaz stents, Wallstents, and Strecker stents. Stent profile or stent strut height was found to significantly influence neointimal thickness in their study. These authors state that the neo-intimal response attempts to smooth the arterial surface by “leveling the valleys between the hills caused by the stent strut rising over the luminal surface.”16 In an attempt to normalize our data for stent struts of differing height, intimal thickness (as a response to vessel wall injury) was measured from the “top” of the stent strut toward the lumen of the vessel. Two distinct geometric variables therefore were measured: stent strut height, which affects overall neointimal thickness, and stent strut outer profile, which impacts the degree of medial layer compression.

Previous studies in human coronary arteries have described patterns of restenosis caused by intimal hyperplasia after angioplasty and stenting. Weissman et al17 examined 140 coronary stents with IVUS. In their nonradiated stent population, 29% of the stent volume (on average) was filled with intimal hyperplasia at 6 months; they found wide variation in its distribution and no prediction for any specific location within the stent. Stent edge restenosis has been described after brachytherapy. Why we found an increased propensity for restenosis at the stent ends in this study is unclear.

Most Palmaz stents (seven of 10) were deployed without causing deep vessel wall injury (ie, the IEL remained intact, injury score was 0), as opposed to the Clemson stent, in which six of 10 caused deep injury. The stents were deployed in the same fashion, on the basis of IVUS measurements. The Clemson stent struts are, however, twice as thick as the Palmaz controls; a Palmaz stent deployed on a 6-mm balloon achieves an outer diameter of 6.34 mm, and that for the Clemson stent is 6.60 mm. This extra 5% diameter, along with the more “aggressive” profile of the Clemson strut (causing increased stress concentration at the point of contact with the arterial wall), may have been the difference between maintaining or rupturing the IEL. This difference may have been even more pronounced in smaller arteries (eg, the coronaries).

Most studies that examined vessel injury after intervention have followed the practice of oversizing, with a 1.15:1 stent:vessel diameter ratio. Clinically, this practice ensures stent apposition to the vessel wall and creates a large luminal diameter, which is believed to be important in obtaining immediate success and preventing acute thrombosis and restenosis in the coronary circulation.18 This study used a ratio that approached 1:1 to avoid stent overexpansion and IEL fracture. Superficial injury was defined as medial thickness beneath the stent strut compared with medial thickness at the time of stent implantation. Because the medial layer remodels (expands between stent struts) after implantation, we believed that this value was not appropriate for comparison; instead, the value for the animal that died acutely was used as a standard thickness, with the realization that it is somewhat arbitrary and may not be identical for all animals.

The results of our examination of superficial injury show that there is no correlation between amount of medial compression (short of IEL rupture) and degree of restenosis and neointimal hyperplasia. This observation holds for both the Palmaz and Clemson stents. These observations may not hold true for the more muscular coronary arteries in swine because previous studies have shown differences in the response in coronary and iliac arteries in pigs.6,19,20

The most impressive finding in this study was the difference in intimal response between those arteries with intact and ruptured IEL. Vessels with a ruptured IEL showed a dramatic increase in neointimal hyperplasia (independent of strut thickness) when compared with IEL-intact arteries, regardless of the degree of medial compression. Even stent struts that had a minimum of media beneath them showed little intimal response if the IEL remained intact. This has been recognized in the literature but has not been substantiated with data.1,7 Apparently, superficial vessel injury elicits a low-level response that is not a function of stent strut geometry or degree of medial compression. Once the IEL is fractured, however, there is a 10-fold increase in the neointimal response. Stent strut geometry may, however, be a significant factor in causing IEL fracture. Six of 10 Clemson stents caused fracture, and only 30% of Palmaz stents did so. This may be a function of overall strut thickness, strut geometry, or both.

These findings may have important clinical implications. Although other investigators have noted that restenosis is proportional to degree of injury, most vessels were subjected to significant deep injury (IEL fracture and beyond). This finding does not give the practicing interventionalist any indication as to what degree of injury is “tolerable.”1,4,21 This study may help define that threshold the interventionalist may not cross to avoid early restenosis; a
balance between maximum lumen diameter and avoidance of IEL rupture must be achieved. How one avoids IEL rupture in the clinical setting is unclear. Perhaps with advances in IVUS, real-time imaging of the IEL can be performed during PTA and stent deployment. It is important to note, however, that these data may not extrapolate to the human circulation, arteries with substantial plaque burden, or, for that matter, even to other circulatory beds (eg, coronary) in the swine.

On the basis of this work, several practices may necessitate reexamination. Should the standard practice of 10% oversizing during coronary angioplasty and stenting be revisited? Perhaps an “exact fit” or minimal (<5%) oversizing is more appropriate to minimize the hyperplastic response. Although the problem is apparent in healthy vessels, it is further magnified in arteries with a heavy plaque burden because of the presence of largely incompressible tissue between the stent and the arterial wall. In addition, stent struts should be as thin as is feasible, with a geometry that minimizes wall shear stress concentrations.

CONCLUSION

Maintenance of an intact IEL is an important factor in the prevention of myointimal hyperplasia and restenosis in stented porcine iliac arteries. Alteration of stent strut height and geometry does not significantly affect restenosis and the development of myointimal hyperplasia in vessels with superficial injury. Superficial injury elicits a response that is independent of stent strut geometry and vessel wall compression. Stent strut profile may, however, increase local vessel wall stress concentrations, leading to IEL rupture and an exaggerated response to injury. Novel stent designs should focus on low-profile struts with geometries that reduce local stress concentrations. These findings may have important clinical implications, especially in small arteries with heavy plaque burden.

REFERENCES


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