Increasing arterial wall injury after long-term implantation of two types of stent in a porcine coronary model

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Aims There is increased late loss in luminal diameter following long-term coronary stenting, compared with balloon angioplasty. We evaluated short- and long-term vessel wall injury after experimental implantation of two stent designs as well as balloon angioplasty and their relationship to neointimal hyperplasia.

Methods and Results Wiktor stents and Palmaz-Schatz stents were implanted in normal coronary arteries of pigs (balloon/artery ratio: 0.9–1.1). In control coronary arteries, balloon angioplasty was performed. At 1, 4 and 12 weeks, the vessel injury score, neointimal thickness and inflammatory response were assessed by histology. The vessel injury score increased over time in both Wiktor and Palmaz-Schatz stents: 0.9 ± 0.1, 1.5 ± 0.5 and 1.7 ± 0.6 (mean ± SD) for Wiktor stents and 0.7 ± 0.2, 1.0 ± 0.1 and 1.2 ± 0.3 for Palmaz-Schatz stents at 1, 4 and 12 weeks follow-up, respectively. No increase in injury was seen in balloon angioplasty controls. Inflammation was seen in both stented groups but was absent 12 weeks after balloon angioplasty. No strong correlation between injury and neointimal thickness was apparent.

Conclusion Stents induce chronic injury in contrast to balloon angioplasty. Stent design (coil vs slotted tube) as well as inflammation may influence vessel response.

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Key Words: Stent, coronary arteries, vascular injury, pigs, angioplasty, histology.

Introduction

A greater acute gain in luminal diameter is the mechanism for favourable late restenosis rates in stenting compared to balloon angioplasty[1,2], despite increased late luminal loss[3]. With minimal stent recoil, and remodelling, this late loss is exclusively due to neo-intimal thickening[4–6], while elastic recoil and remodelling are both major components of restenosis after balloon angioplasty[7–13]. A correlation between neo-intimal thickening and arterial damage after balloon angioplasty and stenting has been reported[14–18].

Schwartz et al.[14] have developed a vessel injury score for stents enabling analysis of arterial damage and neointimal thickening. This score has been validated in porcine coronary arteries 4 weeks after implantation of tantalum coil stents, which were over-sized to create arterial injury. A high correlation was reported between vessel injury score and neointimal thickening. However, creating deep arterial injury by over-sizing will cause a non-specific tissue response which might blur more subtle changes in tissue reaction, making the comparison of different stents difficult. Whether vessel injury score at 4 weeks represents acute damage at implant or includes additional chronic damage by the presence of the stent in the vessel wall cannot be evaluated.

The importance of stent design in arterial injury and neointimal thickening was recently demonstrated by Rogers et al. in rabbit iliac arteries[19]. The goal of the present study was therefore to investigate the relationship between coronary arterial wall damage and neointimal hyperplasia in two different stent designs without over-sizing. Furthermore, several time points were studied, from 1 up to 12 weeks. We also evaluated the inflammatory response in each stented segment. To find out whether the observed arterial injury, neointimal thickening and inflammatory reaction are specific features after stenting, or a general healing response.

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to the acute implantation trauma, additional animals underwent balloon angioplasty only.

**Methods**

**Animal preparation**

Domestic pigs (n=53, weight: 26–46 kg, HVC, Hedel, The Netherlands) underwent the experimental procedures according to the Guide for the Care and Use of Laboratory Animals[20], and after approval by the Committee on Experimental Animals of Erasmus University Rotterdam. Experiments were performed as previously described[21]. Briefly, after an overnight fast animals were sedated with ketamine hydrochloride (20 mg kg\(^{-1}\)). Following endotracheal intubation, pigs were mechanically ventilated with 30% oxygen in nitrous oxide. Anaesthesia was maintained with 1–4 vol% enflurane. An intramuscular injection of procaine penicillin G (200 000 I.E./ml) and dihydrostreptomycin sulphate (200 mg per 10 kg body weight) was administered as antibiotic prophylaxis. Arteriotomy of the left carotid artery was performed under sterile conditions and a 9F introduction sheath was inserted. Heart rate and arterial blood pressure were monitored and arterial blood was sampled to control blood gases and acid-base balance. After administration of 200 IU . kg\(^{-1}\) of heparin sodium and 250 mg acetyl salicylic acid, a 9F guiding catheter was advanced into the ascending aorta. Left coronary angiography was performed using iopamidol (Iopamiro 370, Dagra, Diemen, the Netherlands) as contrast agent after injection of 1 mg of isosorbide dinitrate.

**Stents**

The Wiktor stent (Medtronic Inc., M inneapolis, M inn., U.S.A.) and the Palmaz-Schatz Coronary Stent (PS 153, Johnson & Johnson Interventional Systems Co., Warren, NJ, U.S.A.), were studied. The Wiktor stent consists of a single tantalum wire (0·127 mm diameter) formed into a sinusoidal wave and wrapped into a helical coil structure[21]. The Palmaz-Schatz Coronary Stent is composed of two segments (7 mm each) of slotted tubes (strut thickness: 0·064 mm), connected by a short (1 mm) coupler[22].

**Stent implantation**

Coronary angiograms were measured on-line, with a quantitative analysis system using the edge-detection method (CMS, Medis Inc., Nuenen, The Netherlands)[23]. A segment with a mean diameter of approximately 2–5 mm (for 3·0 mm balloon) or 3·0 mm (for 3·5 mm balloon) was selected from the left anterior descending or left circumflex coronary artery. The stent-mounted catheter was advanced to this pre-selected segment over a steerable guide-wire. A single 30 s inflation was performed at 6–8 atmospheres and the maximally inflated contrast-filled balloon was measured to determine the balloon/artery ratio. Angiography was repeated immediately after implantation for assessment of patency and acute result. Finally, the introduction sheath was removed, the carotid artery ligated, the skin closed and the animals were allowed to recover from anaesthesia.

**Balloon angioplasty**

In two groups of five animals, only balloon angioplasty was performed with a balloon inflation of 30 s at 6–8 atmospheres. The sites of balloon injury were chosen at anatomical landmarks (side branches) which could easily be identified at follow-up.

**Follow-up procedure**

At 1, 2, 4 or 12 weeks post-implant, animals were anaesthetised as described above. The thorax was opened by a mid-sternal split, and the ascending aorta was cross-clamped after injection of a lethal dose of sodium pentobarbital and fibrillation of the heart with a 9 V battery. Saline (300 ml) was infused, followed by 400 ml of buffered (pH 7·3) formaldehyde under a pressure of 120 mmHg just above the coronary ostia. Finally, the heart was excised, the coronary arteries dissected free from the epicardial surface and the stented or ballooned segments placed in 4% formaldehyde for at least 24 h in preparation for microscopy. After removal of the stent struts, the tissue was processed for parallax embedding. Haematoxylin-eosin was used as a routine stain while resorcin-fuchsin was used as an elastin stain.

**Morphometry and injury score**

From each stented or ballooned coronary artery segment, three transverse sections from the proximal, middle and distal part were used for histological analysis. Neointimal thickness was measured on top of the stent struts using a calibrated microscope reticle, as used for standard microscopic measurements. Individual thickness at each stent strut from all three sections was averaged to obtain the mean neointimal thickening per stent. In the ballooned vessels, neointimal thickening was measured at areas of fragmentation of the internal elastic lamina or medial proliferation. The mean for all three sections was taken as mean neointimal thickening.

To evaluate the vessel wall damage caused by the stent, the same elastin stained transverse sections used for morphometry were used for analysis of injury. At each stent strut, damage was quantified by the vessel injury score, according to Schwartz et al.[14]. This score
A Kruskal–Wallis one-way analysis of variance was used. Within the same groups at different points in time, a value <0.05 (two-tailed) was considered statistically significant. To evaluate differences in vessel injury score within the same groups at different points in time, Krukal–Wallis one way analysis of variance was used.

Because of multiple testing, the Bonferroni correction was applied to correct for increasing type I error and significance was stated at the 0.025 level. After curve fitting, regression analysis was used to investigate progression over time of injury response and differences between stent types. Regression analysis was also performed to describe the correlation between vessel injury score and neointimal thickening. (Statistical package: SPSS, release 6.0, SPSS Inc. Chicago, Illinois, U.S.A.).

**Table 1** Values for vessel injury score according to Schwartz et al.[14] (with permission)

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

Grades wall damage from 0 when the internal elastic lamina is intact to 3 when even the external elastic lamina is disrupted (Table 1). Individual scores of the stent struts of the three sections of one stent were averaged to obtain the mean vessel injury score per stented segment. For the balloon angioplasty groups, the vessel injury score cannot be applied because the grading of injury is directly coupled to the presence of a stent strut. Therefore, we graded the injury in the balloon angioplasty groups in analogy to the fracture length method[24], but for a non-over-sized model. Fragmentation of the internal elastic lamina, often accompanied with some degree of medial hypertrophy occurred in one or more areas; it was rare to see one area with a totally ruptured and disintegrated internal elastic lamina. The circumferential lesion length \( L_{\text{lesion}} \) divided by the total circumferential internal elastic lamina length \( L_{\text{tot}} \) was used as a measure of magnitude of damage \( \frac{L_{\text{lesion}}}{L_{\text{tot}}} \).

### Inflammatory response

Inflammation was assessed in the HE-stained sections corresponding to those used for analysis of vessel injury score and neointimal thickening measurements, according to the following semi-quantitative score: 0: non-existent inflammatory response; 1: inflammatory infiltrates in the adventitia; 2: diffuse, clearly recognizable inflammatory infiltrates in the adventitia; 3: severe, often granulomatous, inflammatory response in the adventitia, sometimes extending to the intima.

### Statistical analysis

All data were expressed as mean ± SD. Differences in the balloon/artery ratio, vessel injury score and neointimal thickening between the different stent and balloon groups at the same point in time were evaluated with the non-parametric Wilcoxon Rank Sum Test. A P value <0.05 (two-tailed) was considered statistically significant. To evaluate differences in vessel injury score within the same groups at different points in time, Krukal–Wallis one way analysis of variance was used.

### Results

#### Systemic haemodynamics and blood gases during intervention

During interventions, heart rate (94 ± 14 beats. min⁻¹, 99 ± 14 beats. min⁻¹ and 97 ± 14 beats. min⁻¹) and mean arterial blood pressures (82 ± 17 mmHg, 74 ± 14 mmHg and 73 ± 8 mmHg) were similar for the Wiktor stent, Palmaz-Schatz stent and balloon groups, respectively, while arterial blood gases remained within the normal range (pH: 7.35–7.45; PO₂: 120–160 mmHg; PCO₂: 35–45 mmHg).

#### Stent implantation

Twenty-one Wiktor stents were placed (one stent per artery) in 16 pigs. Three stented arteries were excluded from final analysis: one stent migrated during implant, a second was erroneously oversized in a small marginal branch, while a third stented animal died suddenly after 23 days without macroscopic evidence of stent occlusion. In total, 18 Wiktor stents were analysed.

Twenty-eight Palmaz-Schatz stents were implanted in 27 animals. Nine stents were excluded from analysis following the death of three animals from arrhythmia during the implantation procedure and six (six stents) from stent thrombosis within 48 h post-implantation. Thrombosis, confirmed by light microscopy, was not accompanied by vascular damage, and was therefore excluded from analysis. In total 19 Palmaz-Schatz stents were analysed.

Angiography during the implantation procedure showed that stents were properly sized, as demonstrated by balloon-artery ratios of 0.9–1.1 (Table 2(a)).

#### Balloon angioplasty

Ten coronary artery segments in 10 pigs underwent balloon angioplasty with a balloon/artery ratio of 1.0 ± 0.1 (Table 2(b)). Further augmentation of injury up to 12 weeks could not be demonstrated.

At 1 week, the vessel injury score was lower in the Palmaz-Schatz stent group despite a slightly higher mean balloon/artery ratio compared to the Wiktor.
Table 2(a) Morphological parameters and balloon/artery ratios of the Wiktor and Palmaz-Schatz stent groups at 1, 4 and 12 weeks follow-up

<table>
<thead>
<tr>
<th>Follow-up (weeks)</th>
<th>Wiktor Stent</th>
<th>Palmaaz-Schatz stent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>VIS</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>0 9 ± 0 1*</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>1 5 ± 0 5</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>1 7 ± 0 6†</td>
</tr>
</tbody>
</table>

Data are mean ± SD; # = number of animals; VIS = vessel injury score; NT = mean neointimal thickness; B/A = balloon/artery ratio. * = P < 0 05 W vs PS for same time-point; † = P < 0 025 vs other time-points of same stent design. ‡ = P < 0 025 vs 1 week of same stent design.

Table 2(b) Morphological parameters and balloon/artery ratios of the balloon angioplasty groups at 2 and 12 weeks follow-up

<table>
<thead>
<tr>
<th>Follow-up (weeks)</th>
<th>(#)</th>
<th>Balloon angioplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>L_lesion/L_tot</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>0 29 ± 0 29</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>0 26 ± 0 23</td>
</tr>
</tbody>
</table>

Data are mean ± SD; # = number of animals; L_lesion/L_tot = length of fragmented IEL (L_lesion) divided by total circumferential IEL length; NT = mean neointimal thickness at L_lesion; B/A = balloon/artery ratio.

Figure 1 Progression of vessel wall injury between 1 and 12 weeks for both stent designs. * P < 0 025 vs 4 and 12 weeks Wiktor; † P < 0 05 vs 1 week Wiktor; ** P < 0 01 vs 12 weeks Palmaz-Schatz. Linear regression showed a significant progression of vessel injury score between 1 and 12 weeks (P = 0 0004) as well as a difference in vessel injury score between both stent designs (P = 0 0013). □ = Wiktor; ▲ = Palmaz-Schatz.

stents. Although the increase in the vessel injury score between 1 and 4 weeks in the Palmaz-Schatz stents showed only a trend, the progress of the vessel injury score between 1 and 12 weeks was significant in this analysis (P = 0 0004) (Fig. 1). In both stent designs linear regression analysis revealed a continued difference in vessel wall injury at follow-up (P = 0 0013) (Fig. 1). The slope of increase in the vessel injury score over time was not significantly different (P = 0 62) between the stent types.

After balloon angioplasty, vessel wall damage was very mild, expressing itself at follow-up as
fragmentation of the internal elastic lamina accompanied by an increase in medial thickness. There was no increase in injury from 2 to 12 weeks (Table 2(b)).

**Inflammatory response**

Table 2(a) shows the inflammation score for both stent groups. Extensive inflammation was not observed in either group, with most scores being <1. The balloon angioplasty vessels showed a very mild inflammatory reaction at 2 weeks, but at 12 weeks the inflammatory response was absent in all vessels studied.

**Morphometry**

Mean neointimal thickening at the stent wires in the Wiktor stent groups increased from $61 \pm 10 \mu m$ at 1 week to $151 \pm 50 \mu m$ at 4 weeks and $305 \pm 155 \mu m$ at 12 weeks ($P < 0.025$). In Palmaz-Schatz stented coronary arteries, the neointimal thickening also increased significantly from $61 \pm 35 \mu m$ at 1 week to $103 \pm 3 \mu m$ at 4 and $198 \pm 54 \mu m$ at 12 weeks respectively (Table 2(a)).

Table 2(b) shows that neointimal thickening at 2 weeks after balloon angioplasty was limited ($23 \pm 24 \mu m$) and significantly less than after stent implantation. There was no progression of neointimal thickening between 2 and 12 weeks.

**Correlation between injury and neointimal response**

The correlation between vessel injury score and the neointimal thickening was poor in each of the stent groups (Fig. 2). The correlations for all Wiktor stents together ($y = 155x - 29$, $r = 0.69$, $P = 0.001$) and all Palmaz-Schatz stents together ($y = 96x + 47$, $r = 0.36$, $P = 0.14$) were not significantly different from each other. To increase the power of the analysis, all data were pooled. Even then correlation between vessel injury score and neointimal thickening remained weak (Fig. 3; $y = 107x + 17$, $r = 0.49$, $P = 0.002$).

**Discussion**

**Background and purpose of study**

The use of stents is increasing exponentially worldwide. However, concerns remain as regards thrombogenicity and vessel wall tissue response to the stent. Tissue response and thrombosis have been strongly related to acute vessel wall damage during the procedure. Stent injury in the porcine model has therefore been used to study restenosis. Schwartz et al. by oversizing the stent (Wiktor at 4 weeks) and thereby creating deep arterial injury, showed a strong correlation between vessel injury score and neointimal thickening.

Rogers et al. were able to reduce vessel wall injury and neointimal thickening after stenting by modifying the geometric configuration of the stent. However, their data derive from peripheral rabbit arteries and are also limited to one time point at 14 days. Colombo et al. have emphasized the importance of correct sizing of the stent using high-pressure inflation guided by intravascular ultrasound. Applying these rules of stent deployment, Serruys et al. observed no subacute thrombosis and a restenosis rate of only 6% at 6 months after implantation of a heparin coated Palmaz-Schatz stent in 50 patients of the Benestent II pilot trial.

We investigated the vessel injury score concept in two different stent designs, at various time points and without deliberately creating deep arterial damage (mean balloon/artery ratio: 0.9-1.1). The data were compared with a control group that underwent balloon angioplasty alone.

**Main findings**

The major finding of the present study is that in properly sized stents, but not after balloon angioplasty alone, vessel wall injury increases over time. Although neointimal thickening increases concurrently, no strong correlation could be found between vessel injury score and neointimal thickening. In all stent groups the inflammatory response was very mild. However, in contrast to the balloon angioplasty group, inflammation was still visible after 12 weeks and may have influenced the progression of vessel injury score over time.

**Acute vs chronic injury**

A cute vessel wall damage is caused during the interventional procedure. If this damage is predominantly caused by stretching of the vessel wall, then this damage is comparable in balloon angioplasty and stenting (with a balloon-expandable stent), except for the profile of the stent on the outer surface of the balloon. For the Palmaz-Schatz stent this implies an extra profile of 2 times 64 $\mu m$ (128 $\mu m$), and for the Wiktor stent 2 times 127 $\mu m$ (254 $\mu m$). In stenting a 3-0 mm coronary artery with a 3.0 mm stent-mounted balloon, this would mean at 4 or 8% increase in diameter, respectively. However, in our data this increase in profile was not accompanied by a proportional increase in damage within the given ranges of balloon/artery ratios of 0.9 to 1.1 (+ 8%). Stent strut geometry (round vs rectangular) is an additional factor which may modify vessel wall injury caused during stretching. We found a significant lower mean vessel injury score in the Palmaz-Schatz stent compared to the Wiktor stent at 1 week follow-up, which might represent lower acute damage at...
Further studies assessing damage directly after implantation might elucidate this further.

Chronic damage was defined as vessel wall damage occurring during follow-up. The present data show a significant increase in damage, as assessed by the vessel injury score, between 1 and 12 weeks post-stenting ($P = 0.0097$). This was probably caused by the continued presence of the stents, as chronic damage was not observed after balloon angioplasty alone. Unfortunately, it was not possible to use the same injury scoring system in stented and ballooned arteries. However, we feel that the large difference in outcome in this study allows for the above conclusion.

Possible implications of chronic injury

In this study, the progressive damage caused by the stent in the first weeks after stenting may act as a direct stimulus for smooth muscle cell proliferation through the release of several growth factors and chemotactic agents from the damaged cells$^{[34-37]}$. However, the

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Figure 2  (a) Correlation between mean vessel injury score and mean neointimal thickness per individual Wiktor stent at 1, 4 and 12 weeks follow-up. No significant correlation can be found in either group. (b) Correlation between mean vessel injury and mean neointimal thickness per individual Palmaz-Schatz (PS) stent at 1, 4 and 12 weeks. No significant correlation can be found in either group.
resultant neointimal thickening is probably not influenced by damage alone as no strong correlation was evident between vessel injury score and neointimal thickening in the present study. Our data indicate that the largest increase in vessel injury score occurs between 1 and 4 weeks, while the largest increase in neointimal thickening occurs between 4 and 12 weeks.

The weak correlation between vessel injury score and neointimal thickening may also be due to the very low mean neointimal thickenings (151 μm for Wiktor and 103 μm for Palmaz-Schatz, both at 4 weeks). These values, however, are comparable to other studies by our group[21,38]. It is unlikely that an increase in the number of experiments in this study will result in a better correlation, as pooling all the data did not show a better correlation (Fig. 3). Therefore, in the present study, damage is probably only one of the contributing factors to the resultant neointimal thickening. The study by Schwartz et al. indicated that damage played a more important role than in ours, but this does not contradict our results. Their model was characterized by immense acute damage, resulting in neointimal thicknesses of up to 1400 μm.

Rogers et al.[19] have shown that the difference in geometry or surface characteristics between stents may be important in relation to the injury inflicted to the vessel wall. Our results show that this effect is most pronounced during the first weeks after stenting.

The role of inflammation

In all groups, mild inflammation was seen in the first weeks. Although a correlation between inflammation score and vessel injury score or neointimal thickening could not be observed, the persisting mild inflammatory response in the stent groups at 12 weeks may have contributed to the progression of vessel wall injury, as this was not observed in the group who received balloon angioplasty alone. Theoretically, persistent inflammation may have facilitated the increased morphological injury by allowing deeper stent strut penetration into the vessel wall, resulting in a higher vessel injury score. Furthermore, by releasing growth factors and cytokines, inflammatory cells may also influence neointimal thickening and chronic endothelial dysfunction[39].

Study limitations

Our first time point of follow-up was chosen at one week. We are aware that this does not represent true acute damage at implant. However, histological assessment of acute injury requires removal of stent struts from ‘freshly’ injured vessel wall tissue, which may induce more handling damage than removal after several days to weeks. After one week, a measurable neointima is present, which data could be included in this analysis.

In the Wiktor stent group, no early stent thrombosis was seen while six Palmaz-Schatz stents thrombozed in the first 48 h post implantation, causing the death of the animals. These six Palmaz-Schatz stents were not included in the analysis, because increased vessel wall damage could not be found in either of these cases and therefore bias was not likely to be introduced.

In this study, nonatherosclerotic coronary arteries of juvenile pigs were stented. Vessel wall injury and tissue response may be different when stenting atherosclerotic lesions. However, in the pig model, hypercholesterolaemic diets or endothelial abrasion before stenting do not significantly change the tissue.
response. Moreover, our model has extensively been used in pre-clinical stent testing, and it seems valid to assess vessel wall injury, tissue response, thrombotic response and restenosis in the same model.

Conclusions
This study shows progression of vessel wall injury up to 12 weeks after stenting, but not after balloon angioplasty alone. Different stent designs cause different degrees of acute injury and this difference persists at longer follow-up.

As (mild) inflammatory response was persistent in the stent groups in contrast to balloon angioplasty, this may be important in influencing progression of vessel wall injury subsequent to mechanical injury caused by stenting. In this study, no strong correlation between injury score and neointimal hyperplasia could be demonstrated.

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References


