The impact of high pressure vs low pressure stent implantation on intimal hyperplasia and follow-up lumen dimensions

Results of a randomized trial

R. Hoffmann\(^1\), P. Haager\(^1\), G. S. Mintz\(^2\), G. Kerckhoff\(^1\), R. Schwarz\(^1\), A. Franke\(^1\), J. vom Dahl\(^1\) and P. Hanrath\(^1\)

\(^1\)Medical Clinic I, University RWTH Aachen, Aachen, Germany; \(^2\)Washington Hospital Center, Washington, DC, U.S.A.

Aims
Histology and retrospective clinical studies have indicated that the amount of neointimal hyperplasia is dependent on the arterial injury induced during stent implantation. This study analysed, prospectively, the impact of high vs low pressure stent implantation techniques using a second generation stent on intimal hyperplasia and follow-up lumen dimensions.

Methods and Results
Post-intervention and follow-up (mean \(\pm\) SD 5.5 \(\pm\) 1.3 months) angiographic and intravascular ultrasound studies were performed on 120 Multi-Link HP stents randomized to implantation at either low (8–10 atm) or high (16–20 atm) pressure. Intravascular ultrasound measurements of the external elastic membrane, stent, and lumen cross-sectional area were performed at 1 mm axial increments. Peri-stent plaque+media cross-sectional area (external elastic membrane–stent cross-sectional area, intimal hyperplasia cross-sectional area (stent–lumen cross-sectional area at follow-up), intimal hyperplasia thickness and peri-stent tissue proliferation cross-sectional area were calculated. Intravascular ultrasound demonstrated a larger minimal lumen cross-sectional area post-intervention in the high pressure group (7.3 \(\pm\) 2.0 vs 6.2 \(\pm\) 1.8 mm\(^2\), \(P<0.001\), high vs low pressure group, respectively). At follow-up, the mean intimal hyperplasia cross-sectional area (1.7 \(\pm\) 0.9 vs 1.5 \(\pm\) 0.8 mm\(^2\), \(P=0.708\)), the mean intimal hyperplasia thickness (0.16 \(\pm\) 0.12 vs 0.16 \(\pm\) 0.12 mm, \(P=0.818\)) and peri-stent tissue proliferation cross-sectional area were not greater in the high pressure group. Thus, the minimal lumen cross-sectional area at follow-up continued to be greater (5.5 \(\pm\) 2.0 vs 4.7 \(\pm\) 1.7 mm\(^2\), \(P=0.038\)) in the high pressure group.

Conclusions
High pressure stent implantation results in greater stent expansion even with the less rigid second generation Multi-Link stent. Larger lumen dimensions persist at follow-up, while intimal hyperplasia is not significantly greater after high pressure implantation compared to the low pressure technique.


© 2001 The European Society of Cardiology

Key Words: Angioplasty, restenosis, stents, ultrasonics.

See page 1973, doi:10.1053/euhj.2001.2847 for the Editorial comment on this article

Introduction

High pressure implantation techniques have been recommended for the Palmaz–Schatz stent, to optimize stent expansion and reduce the rate of subacute stent thrombosis\(^{[1,2]}\). These recommendations were the consequences of intravascular ultrasound studies, which demonstrated inadequate stent expansion in a considerable number of cases using low implantation pressures\(^{[3]}\). Meanwhile, there is doubt about the need for high pressure stent implantation and concern about its negative impact. Subacute stent thrombosis is rare after conversion to an antiplatelet regimen\(^{[3]}\). Stent restenosis is known to be almost exclusively the result of intimal hyperplasia\(^{[4,5]}\).
Animal studies and retrospective analysis in man indicated that aggressive stent implantation techniques, including the use of high implantation pressures, might result in increased neointimal growth and even an increased risk of restenosis[6-9]. Subsequently, lower stent implantation pressures have again become more common in clinical practice. However, it is unknown to what extent histology results, with intentionally severe vessel injury, can be translated to normal interventional settings, and whether retrospective human studies are potentially biased by different lesion characteristics resulting in different stent implantation techniques. Even the results of a large randomized angiographic study[10], which showed no advantage of high pressure stent implantation for clinical and angiographic follow-up parameters, could not finally resolve the debate on the impact of high pressure stent implantation.

While high pressure stent implantation is known to result in greater stent cross-sectional area, as tracked by intravascular ultrasound[1,2,11,12], several large scale studies have shown that a large minimal stent cross-sectional area is an important predictor of a low restenosis and a target vessel revascularization rate[13-15]. Most previous studies have been angiographic reports, with the known limitations of angiography to accurately determine the luminal dimensions in stented lesions and its inability to assess intimal hyperplasia[2,11,10]. Intravascular ultrasound is known to provide accurate measurements of lumen dimensions and intimal hyperplasia within stents[16].

The objective of this randomized intravascular ultrasound based study was to assess the impact of high vs low pressure implantation on intimal hyperplasia proliferation and follow-up lumen dimensions using a second generation coronary stent.

## Methods

### Patients and lesions

Serial intravascular ultrasound studies after stent implantation and at follow-up at a mean interval of 5.5 ± 1.3 months were performed on 120 lesions in 120 consecutive patients undergoing single lesion stent placement. Patients with symptomatic one- vessel coronary artery disease treated with angioplasty were eligible for this study. There were 98 men and 22 women in the study (mean age 59.6 ± 10.4 years). Coronary lesions had to be located in a native artery of 2.5 to 4.0 mm diameter, to be less than 15 mm long, not to be a restenotic lesion and not to be in an ostial location. All 120 lesions were treated with an ACS RX Multi-Link HP stent (Guidant, Santa Clara, CA, U.S.A.). Lesion location was in the left anterior descending in 45, in the left circumflex in 27 and in the right coronary artery in 48 cases. The study was approved by the ethics committee of the University Hospital Aachen. All patients were studied after giving written, informed consent.

### Stent implantation

Multi-Link HP stents were implanted according to standard protocols, including pre-dilatation of the coronary lesion with an undersized balloon of 2.0 to 2.5 mm before stent implantation. The size of the pre-mounted stent was defined by the reference vessel diameter, assessed by on-line quantitative coronary angiography measurements. The ACS RX Multi-Link HP stent is pre-mounted on a high pressure balloon with a nominal pressure of 9 atm for the 3.0 mm diameter balloon and 10 atm for 3.5 and 4.0 mm diameter balloons. All stents were 15 mm long. Sixty-five stents were implanted with a 3.0 mm delivery balloon, 46 stents with a 3.5 mm delivery balloon and 9 stents with a 4.0 mm delivery balloon. After the operator had decided which stent size should be used, each of the 120 patients was randomized to low or high stent implantation pressure by means of a sealed envelope.

Stents were implanted at either 8–10 atm (low pressure group) or 16–20 atm (high pressure group) using the stent delivery balloon. An inflation time of 20 s was requested, to secure equalization of pressures between the deflator and the delivery balloon. The intention was not to apply additional balloon angioplasty. Intravascular ultrasound was performed after stent implantation. Insufficient stent apposition or expansion was considered if the angiographic result was deemed insufficient (>30% residual diameter stenosis), intravascular ultrasound demonstrated in any cross-section non-apposition of the stent in more than 30% of the circumference, or the minimal lumen diameter within the stent was less than 2.0 mm.

In cases of inadequate stent apposition or expansion, the study protocol requested additional balloon angioplasty within the stent. As a first step this would require additional balloon angioplasty with a prolonged inflation time (60 s) using a non-compliant balloon with a diameter and inflation pressure of the initial balloon. In cases of prolonged inadequate stent apposition or expansion, an inflation pressure 4 atm higher than the assigned pressure was allowed. Patients were treated with aspirin 100 mg . day⁻¹ for the whole follow-up period and with clopidogrel 75 mg . day⁻¹ for 4 weeks.

### In-hospital and 6-month follow-up clinical outcomes

Procedural success (per patient) was defined as a <50% final diameter stenosis in the treated lesions and the absence of a major clinical complication (in-hospital death, Q wave myocardial infarction, or emergency coronary bypass surgery). Creatine kinase was measured once daily until discharge if the patients were asymptomatic, and every 6 h where symptoms persisted after the procedure. Patients were followed-up for 6 months after the procedure. When patients did not return for the routine 6-month angiographic follow-up, clinical
outcome was evaluated by telephone contact. The occurrence of death, myocardial infarctions and late target vessel revascularization were recorded and verified by source documentation.

Quantitative angiographic analysis

Standard quantitative morphological criteria were used to assess lesion length (‘shoulder to shoulder’), eccentricity, calcification and angulation >45 degrees. The development of post-procedural complications such as dissections, abrupt closure, distal embolization, and post-procedural thrombus was recorded. Antegrade flow was evaluated using the Thrombolysis in Myocardial Infarction (TIMI) flow classification. Off-line quantitative coronary angiography analysis was performed, by operators unaware of the pressure strategy to which the patient was assigned, using an automated edge-detection algorithm (CAAS II System, PieMedical, Maastricht, The Netherlands). Determined parameters were reference diameter, minimal lumen diameter) and diameter stenosis. Acute lumen gain was determined as the improvement in minimal lumen diameter (post-intervention minus pre-intervention minimal lumen diameter). Late lumen loss was calculated as post-intervention minus follow-up minimal lumen diameter. Net gain was calculated as acute gain minus late loss. Angiographic restenosis was defined as a diameter stenosis of ≥50%.

Intravascular ultrasound imaging protocol

Studies were performed using a single-element 30-MHz transducer within a 3·2 Fr short monorail imaging sheath (Cardiovascular Imaging Systems) and an automated pullback with a speed of 0·5 mm·s⁻¹ to obtain a complete and homogeneous image sequence. Intravascular ultrasound imaging was started after intracoronary administration of 0·2 mg nitroglycerin. The intravascular ultrasound catheter was advanced approximately 10 mm beyond the distal edge of the stent and an imaging run was performed to the aortoostial junction. During imaging, care was taken to set the overall gain and the time-gain-compensation curve to avoid suppressing the echoluent neointimal tissue present in the near field. Studies were recorded onto 0·5 inch, high resolution s-VHS videotape for off-line analysis.

Quantitative intravascular ultrasound measurements

Intravascular ultrasound analysis was performed using computer planimetry. Motorized transducer pullback permitted cross-sectional area measurements at 1 mm axial increments throughout the length of the stent. In stented segments, the stent, lumen and external elastic membrane cross-sectional area were measured. Measurements of external elastic membrane, lumen, plaque plus media, and stent cross-sectional areas by intravascular ultrasound have been validated. We have previously reported on the reproducibility of stent, lumen and external elastic membrane measurements. The term ‘external elastic membrane’ corresponds to the media–adventitia border, which is a reproducible measurement of the total arterial cross-sectional area. Each border was routinely traced three times, and the results averaged. If the neointimal tissue appeared to encompass the imaging catheter, the lumen cross-sectional area was assumed to be the size of the imaging catheter (0·9 mm²). If the stent was completely occluded at follow-up, neointimal tissue accumulation was assumed to equal the stent size immediately after stent implantation. The following calculations were then performed within the stent length:

(1) Peri-stent plaque plus media cross-sectional area = (external elastic membrane cross-sectional area − stent cross-sectional area)

(2) Intimal hyperplasia cross-sectional area = (stent cross-sectional area − lumen cross-sectional area) at follow-up

(3) Peri-stent tissue growth cross-sectional area = Δ(post-intervention to follow-up) peri-stent plaque plus media cross-sectional area

(4) Mean stent diameter = 2√(stent cross-sectional area/π)

(5) Mean lumen diameter = 2√(lumen cross-sectional area/π)

(6) Mean intimal hyperplasia thickness = (mean stent diameter − mean lumen diameter at follow-up)/2.

The minimal lumen cross-sectional area within each stent was compared with the reference segment. The reference segment was defined as the most normal-looking cross-section within 5 mm proximal and distal to the stent lesion, but before any major side branch. The results for each stent were averaged over the stent length to obtain mean values.

Statistics

Statistical analysis was performed using SPSS 7.0. The primary end-point was the minimal lumen cross-sectional area at follow-up. The target sample size of 120 was based on the assumption that a 20% greater lumen cross-sectional area observed post-intervention after high pressure compared to low pressure stent placement would persist at follow-up. Estimating an intravascular ultrasound follow-up rate of 80%, a sample size of 60 lesions for each group was necessary to give the study a statistical power of 0·90 and an alpha level of 0·05.

Continuous data are presented as mean ± SD. Qualitative data are presented as frequencies. Comparisons between groups were performed using chi-square
Lesion length (mm) 10

Eur Heart J, Vol. 22, issue 21, November 2001

Table 2 Pre-intervention, post-intervention, follow-up and serial quantitative coronary angiographic results

<table>
<thead>
<tr>
<th></th>
<th>Low pressure (n=60)</th>
<th>High pressure (n=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length (mm)</td>
<td>10.0 ± 2.9</td>
<td>9.7 ± 2.7</td>
<td>0.428</td>
</tr>
<tr>
<td>Pre-intervention reference diameter (mm)</td>
<td>2.85 ± 0.65</td>
<td>2.94 ± 0.63</td>
<td>0.342</td>
</tr>
<tr>
<td>Pre-intervention MLD (mm)</td>
<td>0.96 ± 0.63</td>
<td>0.91 ± 0.50</td>
<td>0.281</td>
</tr>
<tr>
<td>Post-intervention reference diameter (mm)</td>
<td>2.91 ± 0.63</td>
<td>3.02 ± 0.41</td>
<td>0.105</td>
</tr>
<tr>
<td>Post-intervention MLD (mm)</td>
<td>2.52 ± 0.63</td>
<td>2.67 ± 0.49</td>
<td>0.152</td>
</tr>
<tr>
<td>Follow-up MLD (mm)</td>
<td>1.62 ± 0.74</td>
<td>1.72 ± 0.69</td>
<td>0.399</td>
</tr>
<tr>
<td>Acute diameter gain (mm)</td>
<td>1.55 ± 0.72</td>
<td>1.77 ± 0.69</td>
<td>0.067</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>0.90 ± 0.91</td>
<td>0.93 ± 0.75</td>
<td>0.879</td>
</tr>
<tr>
<td>Net gain (mm)</td>
<td>0.64 ± 0.87</td>
<td>0.85 ± 0.83</td>
<td>0.089</td>
</tr>
<tr>
<td>Loss index</td>
<td>0.60 ± 0.74</td>
<td>0.54 ± 0.57</td>
<td>0.218</td>
</tr>
<tr>
<td>Follow-up diameter stenosis (%)</td>
<td>37.8 ± 22.5</td>
<td>34.0 ± 20.2</td>
<td>0.381</td>
</tr>
<tr>
<td>Restenosis rate (%)</td>
<td>26.7</td>
<td>21.7</td>
<td>0.673</td>
</tr>
<tr>
<td>Target vessel revascularization rate (%)</td>
<td>18.3</td>
<td>15.0</td>
<td>0.809</td>
</tr>
</tbody>
</table>

MLD=minimal lumen diameter.

In-hospital and 6-month follow-up clinical outcomes

The procedural success rate was 100% in the high pressure group and 98% in the low pressure group. There was one myocardial infarction due to vessel dissection in the low pressure group. Additionally, three patients in the low pressure group and four in the high pressure group demonstrated a non-Q wave myocardial infarction (creatine kinase elevation >3 times normal with simultaneous creatine kinase-MB elevation). At the 6-month follow-up, the rate of Q wave myocardial infarction and target lesion revascularization was 12% in the high pressure group and 15% in the low pressure group (P=0.791).

Angiographic results

Table 2 shows that there were no differences in baseline quantitative angiographic characteristics between either lesion group. Similarly, there were no differences in morphological lesion characteristics. In particular, 17% and 15% of the lesions in the high and low pressure groups, respectively, demonstrated signs of calcification. Angiography demonstrated a trend towards greater acute lumen gain and larger post-intervention minimal lumen diameter in the high pressure group.

Results

Patients and lesions

Sixty lesions were randomized to low pressure and 60 to high pressure dilatation. Table 1 shows the baseline clinical characteristics of the patients, which were similar for the two groups.

Final balloon pressure was 17.0 ± 1.1 atm in the high pressure and 9.9 ± 1.0 atm in the low pressure group (P<0.001). Nominal balloon diameter was similar, with 3.29 ± 0.33 mm in the high pressure and 3.27 ± 0.40 mm in the low pressure group (P=0.671). The expected balloon diameter, taking into account balloon compliance, was 3.60 ± 0.31 mm in the high pressure and 3.22 ± 0.33 mm in the low pressure group (P<0.001). In three lesions (5.0% of the low pressure group, the operator considered it appropriate to use additional balloon angioplasty with a pressure of 14 atm because of insufficient stent expansion determined by intravascular ultrasound. All lesions in the high pressure group were treated as initially assigned. A significant margin dissection required additional stent placement in one patient of the low pressure group.
Table 3  Post-intervention intravascular ultrasound results

<table>
<thead>
<tr>
<th></th>
<th>Low pressure (n=55)</th>
<th>High pressure (n=57)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-intervention reference vessel CSA (mm²)</td>
<td>9·0 ± 2·3</td>
<td>9·4 ± 2·5</td>
<td>0·343</td>
</tr>
<tr>
<td>Post-intervention minimal stent CSA (mm²)</td>
<td>6·2 ± 1·8</td>
<td>7·3 ± 2·0</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Post-intervention mean stent CSA (mm²)</td>
<td>7·2 ± 1·8</td>
<td>8·5 ± 2·0</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Post-intervention MLD (mm)</td>
<td>2·40 ± 0·41</td>
<td>2·72 ± 0·42</td>
<td>0·028</td>
</tr>
<tr>
<td>Post-intervention EEM CSA (mm²)</td>
<td>16·3 ± 4·1</td>
<td>18·0 ± 3·7</td>
<td>0·014</td>
</tr>
<tr>
<td>Post-intervention mean persistent P+M CSA (mm²)</td>
<td>9·3 ± 3·0</td>
<td>9·4 ± 2·5</td>
<td>0·991</td>
</tr>
<tr>
<td>Post-intervention minimal stent CSA/reference CSA</td>
<td>0·70 ± 0·21</td>
<td>0·87 ± 0·26</td>
<td>&lt;0·001</td>
</tr>
</tbody>
</table>

CSA=cross-sectional area; MLD=minimal lumen diameter; EEM=external elastic membrane; P+M=plaque plus media.

Table 4  Follow-up and serial intravascular ultrasound results

<table>
<thead>
<tr>
<th></th>
<th>Low pressure (n=50)</th>
<th>High pressure (n=49)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up minimal stent CSA (mm²)</td>
<td>6·2 ± 1·6</td>
<td>7·3 ± 2·1</td>
<td>0·002</td>
</tr>
<tr>
<td>Follow-up mean stent CSA (mm²)</td>
<td>7·2 ± 1·7</td>
<td>8·6 ± 2·6</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Follow-up minimal lumen CSA (mm²)</td>
<td>4·7 ± 1·7</td>
<td>5·5 ± 2·0</td>
<td>0·038</td>
</tr>
<tr>
<td>Follow-up mean lumen CSA (mm²)</td>
<td>5·7 ± 1·8</td>
<td>6·9 ± 2·5</td>
<td>0·009</td>
</tr>
<tr>
<td>Follow-up mean EEM CSA (mm²)</td>
<td>17·6 ± 3·7</td>
<td>19·3 ± 3·7</td>
<td>0·098</td>
</tr>
<tr>
<td>Follow-up mean persistent P+M CSA (mm²)</td>
<td>10·3 ± 2·6</td>
<td>10·6 ± 2·5</td>
<td>0·832</td>
</tr>
<tr>
<td>Mean intimal hyperplasia CSA (mm²)</td>
<td>1·5 ± 0·8</td>
<td>1·7 ± 0·9</td>
<td>0·708</td>
</tr>
<tr>
<td>Mean intimal hyperplasia thickness (mm)</td>
<td>0·16 ± 0·12</td>
<td>0·16 ± 0·10</td>
<td>0·818</td>
</tr>
<tr>
<td>Mean persistent tissue proliferation CSA (mm²)</td>
<td>1·0 ± 2·7</td>
<td>1·3 ± 2·1</td>
<td>0·312</td>
</tr>
</tbody>
</table>

For abbreviations, see Table 3.

Patients without adverse events within the first 30 days after the procedure were considered eligible for a 6-month invasive follow-up. It was carried out in 53 patients (88·3%) in the high pressure group and in 54 patients (90·0%) in the low pressure group eligible for angiographic follow-up. The results of the quantitative assessment of the follow-up angiogram are presented in Table 2. The minimal lumen diameter at follow-up was not different between the groups.

**Serial intravascular ultrasound results**

Intravascular ultrasound could be performed on 112 lesions (93%) after stent implantation; 57 lesions in the high pressure group and 55 lesions in the low pressure group. Data on the intravascular ultrasound measurements after stent placement are given in Table 3. Mean stent cross-sectional area was 18% larger in the high pressure group immediately after stent implantation. Similarly, the minimal stent cross-sectional area and the minimal lumen diameter measured by intravascular ultrasound were significantly larger in the high pressure group. In the three patients of the low-pressure group, who obtained additional balloon angioplasty to improve stent expansion, the minimal stent cross-sectional area increased from 2·9 mm² to 3·6 mm².

At follow-up, intravascular ultrasound could be performed in 99 lesions (83%); 49 lesions (82%) in the high pressure group and 50 lesions (83%) in the low pressure group. Intravascular ultrasound measurements at follow-up are given in Table 4. Mean stent cross-sectional area at follow-up was unchanged (7·8 ± 2·1 mm² vs 7·9 ± 2·4 mm² for all lesions). Mean and minimal lumen cross-sectional area at follow-up remained larger in the high pressure group. There was a weak non-statistically significant trend for intimal hyperplasia cross-sectional area to be 13% greater in the high pressure group (P=0·708). Thus, the 18% greater stent cross-sectional area in the high pressure group was accompanied by a similar increase in intimal hyperplasia cross-sectional area at follow-up. Mean intimal hyperplasia thickness was identical for both groups. The neointimal tissue accumulation and the lumen cross-sectional area were uniform over the length of the stent in both treatment groups (Figs 1 and 2). Exclusion of the three lesions in the low pressure group who obtained higher pressures does not significantly alter the data.

Figures 3 and 4 demonstrate the cumulative frequency distribution curves of the mean and minimal lumen cross-sectional area post-intervention and at follow-up for the low and high pressure groups. In a multivariate analysis which included diabetes, stent implantation pressure as being high or low, lesion location, minimal lumen diameter before intervention and reference vessel diameter, the stent implantation pressure as being high or low was the only predictor of minimal lumen cross-sectional area at follow-up (P=0·015). In a multivariate
analysis which included diabetes, stent implantation pressure, lesion location, reference vessel diameter and post-intervention minimal stent cross-sectional area, post-intervention minimal stent cross-sectional area was the only predictor of intimal hyperplasia cross-sectional area ($R^2=0.125$, $P=0.035$), while the stent implantation

---

**Figure 1** Plot of the mean ± SD of the follow-up intravascular ultrasound intimal hyperplasia cross-sectional areas over the entire stent length in 1 mm axial increments for stents implanted at low (●) and high (■) pressure.

**Figure 2** Plot of the mean ± SD of the follow-up intravascular ultrasound lumen cross-sectional areas over the entire stent length in 1 mm axial increments for stents implanted at low (●) and high (■) pressure.
pressure was no independent predictor. The peri-stent plaque plus media cross-sectional area increased by 15% at follow-up.

**Discussion**

This randomized study with serial intravascular ultrasound analysis (post-intervention and follow-up) demonstrated that (1) acute lumen dimensions are larger with high pressure implantation techniques, even using the less rigid second generation Multi-Link stent, (2) follow-up lumen dimensions remain larger with high pressure stent implantation, (3) intimal hyperplasia and peri-stent tissue proliferation are not significantly greater with high pressure stent implantation compared with low pressure techniques, and (4) angiography fails to demonstrate differences in lumen dimensions acutely and at follow-up.

**Impact of high pressure implantation on stent expansion**

Intravascular ultrasound showed a 18% larger mean lumen cross-sectional area immediately after high pressure stent implantation, while angiography demonstrated no significant difference between the low and high pressures.
pressure group. This is in the range of previous intravascular ultrasound studies on the Palmaz–Schatz and Multi-Link stents, which have already shown a significantly larger lumen cross-sectional area immediately after higher stent implantation pressures, while angiography was too insensitive to prove a difference between low and high pressure implantation\[^{1,2,11,13}\].

**Impact of high pressure implantation on tissue proliferation and follow-up lumen dimensions**

The impact of high stent implantation pressure on the long-term results has been debated controversially. Histology studies have indicated that intimal hyperplasia thickness after stent placement increases with the extent of vessel trauma induced during stent placement\[^{6,7,23}\]. However, in these animal studies severe vessel trauma was intentionally induced with laceration of media or external elastic membrane. A recent histology study by Farb et al.\[^{7}\] on 55 stents implanted for >30 days in human coronary arteries indicated that significant vessel injury due to stent placement also occurs in clinical practice. Neointimal thickness was significantly greater when medial damage was present at the strut site compared to struts in contact with an intact media. However, these histology studies could not relate the induced vessel injury to the impact of stent implantation techniques used in clinical practice, in particular the implantation pressure and the balloon-to-artery ratio. On an individual basis, a high degree of interventional aggressiveness might not necessarily translate into a high histological injury score as different lesion configurations encountered in clinical practice may result in different histological injury scores for a given interventional aggressiveness. Thus, a translation of histology results into routine interventional practice might not be possible and it remained unclear whether high pressure stent implantation causes frequently significant vessel trauma.

Conflicting results have been presented from angiographic studies in humans. Several retrospective follow-up studies in humans suggested that high pressure stent implantation may be associated with a 30–58% increased lumen loss as compared to a low pressure implantation technique\[^{8,9,24}\]. However, these reports were retrospective with a significant potential for bias. Different levels of stent implantation aggressiveness might have been used due to different lesion characteristics. Thus, differences in tissue proliferation and late loss may reflect different lesion characteristics instead of modifications in stent implantation pressures. This impression is supported by the known importance of lesion plaque burden as a predictor for subsequent tissue proliferation\[^{13,25}\] with greater lesion plaque burden requiring greater stent implantation forces. Two other angiographic studies indicated that high pressure stent implantation has at least no adverse effect on follow-up outcome\[^{10,26}\]. In a retrospective angiographic study, Goldberg et al.\[^{26}\] found that greater lumen dimensions are obtained immediately after intervention and at follow-up in stents implanted with greater interventional aggressiveness. Greater interventional aggressiveness was a combination of higher pressure and oversized balloons. Thus, the mere effect of implantation pressure could not be determined. There is one prospective, randomized study on 934 patients by Dirschinger et al.\[^{10}\] which compared the impact of high vs low balloon pressure during stent placement on clinical and angiographic outcome. This study did not show a difference in follow-up clinical event rate, minimal lumen diameter, diameter stenosis or restenosis rate between high and low pressure implantation techniques. The disparity between the present trial and the study by Dirschinger et al. may be for several reasons. Differences between the two stent implantation techniques were smaller in the study by Dirschinger and the cross-over rate considerably higher. The most important reason is that the study by Dirschinger used angiography to determine differences between the two implantation techniques. As angiography is insensitive for the detection of differences in acute lumen dimensions\[^{1,2,11}\], it is likely to be too insensitive to detect slight differences in follow-up lumen dimensions. Nevertheless, it is of note that the binary angiographic restenosis rate, even though an insensitive marker, tended to be lower for the high pressure group in this as well as the study by Dirschinger et al.\[^{10}\]. Similar to angiographic parameters, clinical end-points require significantly larger numbers than intravascular ultrasound end-points to determine a significant difference between the two implantation techniques. The authors of a previous validation study, which showed intravascular ultrasound to be a very precise means to evaluate in vivo intimal hyperplasia growth and lumen dimensions within stents\[^{17}\], concluded that studies using intravascular ultrasound end-points will require much smaller sample sizes than angiographic studies to show differences in treatment strategies.

This study does not support concerns that high pressure as compared to low pressure stent implantation stimulates excessive neointimal hyperplasia. It is supportive of recent reports which demonstrated minimal stent cross-sectional area post-intervention, as tracked by intravascular ultrasound, to be an important predictor of restenosis and target vessel revascularization\[^{13–15}\]. Of note, stent implantation pressure being high or low was the only predictor of minimal lumen cross-sectional area at follow-up in a multivariate analysis. Such a result can be explained by the strong impact of stent implantation pressure on the minimal stent cross-sectional area post-intervention, while neointimal hyperplasia is not significantly increased after high pressure stent implantation.

**Study limitations**

This study was not deemed to determine the optimal stent implantation pressure for greatest lumen
dimensions at follow-up. However, as the increase in tissue proliferation at follow-up was only minor in the high pressure group in comparison with the additional lumen gain after stent placement it should not be expected that a stent implantation pressure below the high pressure level used in this study will result in a better follow-up outcome. This study did not evaluate whether changes in the balloon-to-artery ratio have an important impact on subsequent neointimal hyperplasia, as this variable was kept constant between the two groups. The residual diameter stenosis after stent placement was greater than in most of the more recent stent trials. Knowing the results of this study, it might have contributed to a restenosis rate that was higher than anticipated after optimal stent placement. The study design requested stent placement with the delivery balloon at the assigned pressure and no additional balloon angioplasty, unless the result after stent placement urgently required additional stent expansion. This protocol was used not to blur the results of both stent deployment techniques. The consequences might have been a less than optimal stent expansion in some cases. In this study, only the Multi-Link stent has been used. We intentionally confined the study to one stent type as the stent type itself is known to have an impact on the amount of intimal hyperplasia[27] and different stent types in the two study groups might have diluted the analysis of the impact of stent implantation pressure on intimal hyperplasia. This study did not show a significant difference between the two groups in terms of angiographic and clinical results. However, the study was not intended and powered to show a difference in these parameters. It was intended as an intravascular ultrasound study with the contention that intravascular ultrasound is the only in-vivo imaging modality to evaluate intimal hyperplasia. The effective balloon diameter under consideration was larger in the high pressure group. This difference is likely to be part of the mechanism of high pressure stent implantation, leading to greater stent expansion. It should be noted that the applied pressure in the high pressure group was above the rated burst pressure recommended by the manufacturer for the Multi-Link HP stent delivery system. It cannot therefore be recommended for routine use with this delivery system. However, to keep the impact of other factors apart from the stent implantation pressure as low as possible we preferred not to use an additional high pressure post-dilation balloon in the high pressure group.

Conclusions

To obtain optimal stent expansion, a low pressure stent implantation technique is inadequate even with the new less rigid Multi-Link stent. High pressure stent implantation does not cause significantly more neointimal tissue proliferation compared to a low pressure technique. Thus, greater lumen dimensions persist during follow-up after high pressure stent implantation.

We acknowledge the expert statistical analysis of Ralph Minckenberg.

References


