Relationship Between Neointimal Thickness and Shear Stress After Wallstent Implantation in Human Coronary Arteries

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Background—In-stent restenosis by excessive intimal hyperplasia reduces the long-term clinical efficacy of coronary stents. Because shear stress (SS) is related to plaque growth in atherosclerosis, we investigated whether variations in SS distribution are related to variations in neointima formation.

Methods and Results—In 14 patients, at 6-month follow-up after coronary Wallstent implantation, 3D stent and vessel reconstruction was performed with a combined angiographic and intravascular ultrasound technique (ANGUS). The bare stent reconstruction was used to calculate in-stent SS at implantation, applying computational fluid dynamics. The flow was selected to deliver an average SS of 1.5 N/m². SS and neointimal thickness (Th) values were obtained with a resolution of 90° in the circumferential and 2.5 mm in the longitudinal direction. For each vessel, the relationship between Th and SS was obtained by linear regression analysis. Averaging the individual slopes and intercepts of the regression lines summarized the overall relationship. Average Th was 0.44 ± 0.20 mm. Th was inversely related to SS:

\[ \text{Th} = (0.59 \pm 0.24) - (0.08 \pm 0.10) \times \text{SS (mm)} \ (P<0.05). \]

Conclusions—These data show for the first time in vivo that the Th variations in Wallstents at 6-month follow-up are inversely related to the relative SS distribution. These findings support a hemodynamic mechanism underlying in-stent neointimal hyperplasia formation. (Circulation. 2001;103:1740-1745.)

Key Words: stents • restenosis • coronary disease • stress

Stents have been shown to reduce restenosis by preventing the artery from arterial shrinkage (negative remodeling). However, excessive neointima formation may still be observed, causing renarrowing of the treated arteries.1,2 Neointima formation is often observed at specific locations in the stented segment.3 A number of risk factors, such as thrombus formation4 and endothelial dysfunction,5 are related to restenosis, but their relationship with a specific intima hyperplasia distribution is unknown. Localizing factors that have been studied include plaque burden6,7 and wall stress.8 In the present study, we focus on the role of shear stress (SS). SS plays an important role in growth-related processes.9,10 For instance, low SS regions in vascular bypass grafts show increased neointimal growth.11 To study localization patterns of SS and neointimal thickness (Th), we applied a recently developed technique that combines a 3D reconstruction technique (ANGUS12) with computational fluid dynamics. Our aim was to investigate the relationship between local variations in SS and Th after stent placement to evaluate the hypothesis that low SS locations show more neointimal growth than locations with high SS.

Methods

Patients

Fourteen patients were studied 6 months after implantation of a coronary Wallstent (Schneider AG). Only patients with <3 major side branches in the stented segment were included in the present study. Table 1 reports the demographic parameters and risk factors of the patient population. Written informed consent was obtained from every patient to participate in this study, which was approved by the institutional medical ethics committee.

3D Reconstruction

3D reconstruction of the coronary arteries was performed by applying a combination of ANGiography and intravascular UltraSound (ANGUS).13 A detailed description of the 3D reconstruction method has been presented elsewhere.12 Briefly, a sheath-based intravascular ultrasound (IVUS) catheter (CVIS 2.9F) was positioned distally from the stented vessel segment and was filmed with a biplane angiographic system (Siemens, Bicor) just after the start of pullback. To eliminate respiratory and cardiac motion artifacts, a single plane view at end diastole of the catheter position was selected and digitized. From the biplane views, the transducer path was reconstructed in 3D space. In addition, (IVUS) images were collected at end diastole with an ECG-triggered, motorized pullback operating
with a step size of 0.5 mm (TomTec). Subsequently, the frames were
digitized and analyzed with a semiautomatic contour-detection
program. Output of the program consisted of lumen contours,
signifying the blood-vessel interface, and stent contours, represent-
ing the stent-neointima interface. Figure 1A displays these respective
borders.

Subsequently, the lumen contours were filtered and positioned
perpendicularly onto the reconstructed 3D catheter path, which
served as a backbone for the reconstruction. The same procedure
was performed for the stent contours only. The angular position of the
ultrasound transducer, and thus of the ultrasound images, was
determined from a comparison between simulated silhouette images
derived from the 3D stent reconstruction with the actual coronary
angiogram. Finally, two 3D reconstructions were obtained from
(1) the coronary vessel lumen and (2) the stent contours only. The
3D reconstruction of the stent was used as the approximate
lumen after stenting to calculate SS at the stent surface.

Computational Fluid Dynamics
For SS calculations, the nonlinear, incompressible 3D Navier Stokes
equations need to be solved. For this purpose, a well-validated
finite-element software package (Sepra) was used, which
was implemented on a workstation (Hewlett Packard 715/80). For
application of such a finite-element method, it is necessary to
subdivide the 3D space into bricks (“mesh generation”) and to define
appropriate boundary conditions.

Mesh Generation
To generate a mesh of the 3D reconstructed lumen, the vessel was
axially divided into ~100 cross sections (axial resolution 0.2 to 0.9
mm). Each cross section contained 32 bricklike elements, each
covering a cross-sectional surface ranging from 0.05 to 0.83 mm²,
with the highest resolution near the wall. Each element contained 27
nodes. The same procedure was applied to the 3D reconstruction of
the stent. The axial resolution of the mesh in the stent was equal to
the resolution of the mesh in the lumen.

Boundary Conditions and Numerical Solution
The Navier Stokes equations were implemented in each node of the
mesh. The nonlinear convective terms in these equations were
linearized by a Newton-Raphson method. To obtain the pressure
unknowns, a penalty-function approach was used. In combination
with the boundary conditions, the differential equations were solved
with a numerical accuracy of 0.1 mm/s by applying a direct-profile
method. We used the following assumptions and boundary
conditions.

We assumed that blood behaves as a Newtonian fluid with a
viscosity of 3×10⁻³ Pas and a density of 1050 kg/m³. Because our
aim was to investigate the distribution of SS variations, this assump-
tion would not affect our results. At the wall, no-slip conditions
were applied, and at the outflow, zero-stress conditions were applied.
Because the diameter of the stented vessel segment will generally be
restored to normal dimensions, it was assumed that a normal value
for SS, ie, 1.5 N/m², would be obtained. Therefore, the selected
entrance flow to induce this average SS in each stent reconstruction
was calculated from the Poiseuille formula and the average stent
diameter. As a first numerical calculation, this entrance flow was
applied to the proximal lumen of the artery, with a parabolic profile,
to obtain the velocity profiles in the lumen of the artery. Second,
from the obtained 3D velocity profiles in the lumen at the entrance
of the stent, the entrance velocity profile to be used for the bare stent
reconstruction was derived (Figure 1B). For this purpose, the profile
was magnified in area and shape to fit the stent entrance, while
maintaining the previously determined flow. Only the latter entrance
condition determined the SS at the surface of the stent used in the
present study.

Analysis of Th and SS
Only the stented vessel segments were analyzed. The locations of
side branches were selected with the help of the IVUS data, and cross
sections containing the side branch, as well as adjacent segments
with a length equal to the diameter of the side branch, were removed
from our data set. Furthermore, a part of the entrance and exit of the
stent, covering a length of 1 stent diameter, was excluded from the
data set. This minimized the influence of the inflow velocity profile,
as well as of the outflow conditions, on our results. The following
parameters, based on either the 3D vessel geometry or 3D velocity
calculations, were calculated with in-house developed software
implemented in Matlab (Mathworks Inc).

The location of the inner and outer curve of the 3D reconstructions
was calculated with a plane fitted through all points of the geometric
centers of the lumen. In each cross-sectional IVUS plane, the vector
passing through the center of mass and parallel to the fitted plane
indicated the inner and outer vessel wall, respectively.

For each cross section, the distance between lumen and stent
contours determined Th at 16 locations over the vessel circumfer-
ce. The Th was filtered in the axial and circumferential direction
by a 5×5-point moving average filter. For each cross section, the
minimal and maximal Th was determined, and their location was
compared with the location of the outer and inner curve.

For the cross sections near the stent edges, the Th was calculated
and filtered as described previously. Average Th at the edges was
compared with thickness in the remaining part of the stent.

SS at the stent surface was calculated from the product of the local
velocity gradient at the wall and viscosity. The SS values were also
filtered by application of a 5×5-point moving average filter. For
each cross section, the minimal and maximal SSs were determined.

### TABLE 1. Demographic Parameters and Risk Factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of vessels</td>
<td>14</td>
</tr>
<tr>
<td>Age, y</td>
<td>63±11</td>
</tr>
<tr>
<td>Sex</td>
<td>8M, 6F</td>
</tr>
<tr>
<td>Hypercholesterolemia (previous &gt;6.5 mmol/L)</td>
<td>5</td>
</tr>
<tr>
<td>Smoking (previous/current)</td>
<td>8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Hematocrit, U</td>
<td>0.38±0.04</td>
</tr>
<tr>
<td>RCA</td>
<td>5</td>
</tr>
<tr>
<td>LAD</td>
<td>7</td>
</tr>
<tr>
<td>LCx</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
</tr>
</tbody>
</table>

RCA indicates right coronary artery; LAD, left anterior descending coronary artery; and LCx, left circumflex coronary artery.
and their location was compared with the location of the inner and outer curve. The ratio of the maximal to the minimal value of the Th and SS at each cross section was used as an asymmetry index. For each artery, the average of the local asymmetry indexes was calculated.

Statistics
A paired \( t \) test was used to compare average Th at the stent edges with the average thickness of the central part. The relationship between SS and Th, for each vessel separately, was studied by linear regression analysis. Averaging the obtained individual slopes and intercepts summarized the relationship between Th and SS. Student’s \( t \) test or univariate regression analysis was used to test the influence of the demographic parameters and risk factors on the slope of the relationship between Th and SS, average Th, and the asymmetry index for Th. A \( P \) value of \( <0.05 \) was considered significant. All values were expressed as mean \( \pm \) SD. SPSS version 8.0 was used for all statistical calculations.

Results
For all patients, 3D reconstruction of the coronary arteries and stents was performed successfully. Figure 2 shows a 3D reconstruction of a right coronary artery 6 months after Wallstent implantation, showing vessel lumen and vessel wall. Table 2 shows angiographic data of the patients before and after stent implantation and at follow-up. During the follow-up period, the stent length decreased by 2.7% (paired \( t \) test, \( P<0.05 \)).

Neointimal Thickness
The Th for the entire group of patients was \( 0.44 \pm 0.13 \) mm. Figure 3 shows an example of a 2D map of Th from which the asymmetrical pattern can be clearly observed. The average of the minimal and maximal Th for the entire group of vessels was \( 0.30 \pm 0.10 \) and \( 0.58 \pm 0.16 \) mm (\( P<0.05 \)), respectively.

Th Related to SS
For 9 of 14 vessels, an inverse relation (\( r=0.04 \) to 0.65) between Th and SS was observed (Figure 5). Intimal thickness at the low SS locations was higher than at the high SS locations (\( P<0.05 \)). The average relationship between Th and SS

The average of all asymmetry indexes was \( 2.04 \pm 0.36 \), being different from 1 (\( P<0.05 \)). The average Th at the stent entrance (\( 0.43 \pm 0.20 \) mm) was not different from that at the mid part (\( 0.44 \pm 0.12 \) mm) or at the exit of the stent (\( 0.45 \pm 0.13 \) mm) (paired \( t \) test, \( P=\text{NS} \)). Male patients tended to have greater Th (\( 0.50 \pm 0.12 \) mm) than female patients (\( 0.37 \pm 0.11 \) mm, \( P=0.055 \)), whereas Th was inversely related to the age of the patient [Th=(0.84±0.19)−(6.4×10^{-3}±2.9×10^{-3})×\text{age mm}; \( P=0.049 \)].

Shear Stress
The average SS for the entire group of vessels was \( 1.99 \pm 0.24 \) N/m². Figure 4 shows a 2D map of the SS corresponding to the example shown in Figure 3. For the entire group of patients, the averages of minimal and maximal SS values were, respectively, \( 1.39 \pm 0.27 \) and \( 2.57 \pm 0.55 \) N/m² (\( P<0.05 \)). The average of the asymmetry indexes was equal to \( 2.12 \pm 0.96 \), being different from 1 (\( P<0.05 \)).

![Figure 2. A, Angiogram of stented right coronary artery. B, 3D ANGUS reconstruction of right coronary artery showing vessel lumen and wall.](image)

![Figure 3. 2D map of Th of human coronary artery shown in Figure 2. Left to right: vessel circumference. Bottom to top: proximal to distal axial vessel location.](image)

![Figure 4. 2D map of SS of human coronary artery shown in Figures 2 and 3. Left to right: vessel circumference. Bottom to top: proximal to distal axial vessel location.](image)
SS was Th=(0.59±0.24)−(0.08±0.10)× SS mm (P<0.05; 95% CI slope −0.14 and −0.02; intercept 0.45 and 0.72). Of all the tested parameters and risk factors, only a history of hypercholesterolemia affected this relationship. For patients without such history (n=9), the relationship was Th=(0.69±0.19)−(0.12±0.10)× SS mm (P<0.05; 95% CI slope −0.18 and −0.05; intercept 0.57 and 0.81) and for patients with a history of hypercholesterolemia (n=5), it was Th=(0.40±0.23)−(0.007±0.06)× SS mm (P=NS; 95% CI slope −0.05 and 0.06; intercept 0.2 and 0.6).

The geometric relationship between Th and SS can be appreciated from a presentation of the location of the lesions and of the location of low or high SS in relation to vessel geometry. Figure 6A shows the distribution of the difference in angle between the location of the inner curve and the location of the maximal Th in the cross-sectional plane. In Figure 6B, a similar graph is displayed for the minimal SS location related to the location of the inner curve. A combined 3D view of these data (Figure 6E) revealed that the maximal Th was preferentially located near the inner curve of the coronary artery, where the minimal SS was also observed. Similarly, the minimal Th was more frequently detected in the outer curve (Figure 6C), which is primarily where the maximal SS was also located (Figure 6D). The latter correspondence in location was less pronounced than the former, as can also be appreciated from Figure 6F.

**Discussion**

Although neointimal hyperplasia was moderate in the present study, a significant asymmetry in its cross-sectional distribution was observed. Neither the average neointimal hyperplasia nor its asymmetrical distribution could be explained by well-accepted risk factors. However, neointimal hyperplasia distribution was related to SS distribution, such that compared with average values, low SS regions were accompanied by maximal intimal thickness and high SS regions by minimal Th.

**Neointimal Thickness**

The observed average Th of 0.44 mm implies a diameter loss of 0.88 mm, which is comparable to our observed 1.09 mm angiographic change in minimal luminal diameter. Other...
studies of Wallstent implantation in native human coronaries reported a late loss of 0.78±0.61 mm. 18, 19

The similarity in Th at the edges and the mid part of the stent is in contrast to observations in the Palmaz Schatz stent, where more neointima formation was observed at the edges and in the middle near the articulation. 20 These differences may be caused by the differences in stent design, such as the existence of an articulation in the Palmaz Schatz stent. 20

Shear Stress
The average SS in the bare stents derived from the fluid dynamic finite-element calculations was 1.99 N/m2. This is above the aimed level of 1.5 N/m2. Variations in the actual diameters, together with the third-order power relation between SS and diameter, explain the above finding. In the present study, the relationship between Th and SS is investigated in a relative sense, ie, high SS regions are compared with low SS regions. In previous work, 21 we showed that for a wide variety of flow entrance conditions, the same distribution pattern of low and high SS regions was found. Therefore, we do not expect that the choice for the entrance flow conditions, based on the average SS values to be expected, will affect the inverse relation of neointimal variation versus SS distribution.

Relation Between SS and Th
Factors thought to be responsible for neointima formation are mostly systemic in nature and are not likely to be responsible for the observed asymmetrical pattern in neointima formation. Indeed, in the present study, no relationship between the demographic factors and the asymmetry index for neointima was observed, and thus, local factors must be involved in this process. In the present study, SS is proposed as such a local factor.

From a global observation of our geometrical data (Figure 6), it became apparent that SS and neointimal asymmetry were interrelated. However, in contrast to earlier work, 21 in the present study we also wanted to investigate the relation between SS and intimal thickness variations in the axial vessel direction. Indeed, this extension appeared to be crucial to reach statistically significant results. Therefore, the study of only the cross-sectional data will underestimate the importance of SS in relation to Th, particularly in this population of stented patients. This probably has to do with axial SS variations within the stent, as has been presented previously. 22

The observed relation between relative SS distribution and Th distribution shows similarity with results of animal studies of neointima formation in bypass grafts. 11, 23 In these studies, SS was measured in a global way. Low SS was related to neointimal growth, 11 and high SS inhibited neointima formation. 11, 23

Wall stress is another local factor that may influence Th. It is sensed by the arterial wall, and in normal arteries, the wall thickness adapts to the local radius to control wall stress. Whether variations in wall stress exerted by the stent can influence wall asymmetrical thickening is not clear. Vorwerk et al 18 showed that differences in radial force of a Wallstent did not influence neointimal hyperplasia formation. We reasoned that for stability, average force exerted by a stent on the wall of the inner curve must equal average force exerted on the outer wall. The outer surface wall area slightly exceeds the inner wall area, and therefore we expect the wall stress difference between the outer and inner walls to differ by the ratio of these areas. In our range of curvatures and vessel diameters, we estimate this difference as <10%, which is far less than the observed difference in SS between inner and outer curves (by a factor of 2). In addition, because the observed relation between vessel wall thickness and wall stress 24 is linear, we do not expect that a 10% wall stress variation will produce a 100% variation in neoimal hyperplasia.

Another often-described local risk factor for local promotion of neointimal hyperplasia is the persistent plaque burden covered by the stent. 6, 7 However, previous studies only report on the relationship between cross-sectional area of the plaque burden and cross-sectional area of the neointima formation. 6, 7 No data exist as to whether the asymmetries in neointimal formation may be explained by the eccentricity of the persistent plaque burden. This subject warrants further study because in eccentric lesions, a confounding factor, such as progression of atherosclerosis at the low SS 24 side, may be present. In contrast with this, the balloon-induced damage and healing response may be located opposite of the plaque at the remaining free wall.

Of the investigated parameters and risk factors, only a history of hypercholesterolemia was found to abolish the slope of the relationship between Th and SS, whereas mean Th was not different. Although we did not intend to investigate this subject when we designed the present study, we thought the reporting of this post hoc finding to be relevant for future research in this area. From animal and patient studies, it is known that SS-dependent endothelial functions involved in neointima formation, such as nitric oxide and endothelin production, 25, 26 are influenced by hypercholesterolemia. However, because the majority of the patients received cholesterol-lowering drugs to normalize cholesterol levels after enrollment in this study, this does not explain the observed difference. Whether the history of hypercholesterolemia may be related to long-term persistent changes in endothelial cell phenotype is unknown, and further studies are warranted in this area.

Limitations of the Study
In this study, only patients with intermediate neointima formation and no restenosis could be studied, because the stepped IVUS pullback device could only be applied for those patients. Therefore, our results could be biased and only concern mildly neointimal hyperplasia.

In this study, no flow measurements were performed. Therefore, it was not possible to evaluate the effects of absolute differences in SS levels between patients.

For the 3D reconstruction of the stents and subsequent computational fluid dynamics, only vessel geometries at 6 months were available. Therefore, changes in geometry over the follow-up period might have influenced our results. However, the observed 3% change in stent length is relatively
small. Furthermore, it is not likely that this minor change is responsible for the observed asymmetrical pattern in Th.

Conclusions
The variations in Th in Wallstents evaluated at 6-month follow-up after implantation are inversely related to the relative SS distribution. These findings support a hemodynamic mechanism contributing to the process of in-stent neointimal hyperplasia formation.

Acknowledgment
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References
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