Extension of Increased Atherosclerotic Wall Thickness Into High Shear Stress Regions Is Associated With Loss of Compensatory Remodeling

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Background—Atherosclerosis preferentially develops at average low shear stress (SS) locations. SS-related signaling maintains lumen dimensions by inducing outward arterial remodeling. Prolonged plaque accumulation at low SS predilection locations explains an inverse relation between wall thickness (WT) and SS. No data exist on WT-SS relations when lumen narrowing and loss of compensatory remodeling commence.

Methods and Results—In 14 patients, an angiographically normal artery (stenosis <50%) was investigated with ANGiography and ivUS (ANGUS) to provide 3D lumen and wall geometry. Selection of segments ≥5 mm in length, in between side branches, yielded 25 segments in 12 patients. SS at the wall was calculated by computational fluid dynamics. WT smaller than 0.2*lumen diameter was defined as normal. Largest arc of normal WT defined reference cross sections. Lumen area relative to the reference cross sections defined area stenosis (AS). Average segmental AS smaller or greater than 10% defined preserved or narrowed lumen, respectively. Total vessel area relative to the reference defined vascular remodeling (VR). For the preserved lumens (n=11, AS=1.7±5.6%, P<0.05), axially averaged WT and SS were inversely related (slope, -0.46±0.55 mm/Pa, P<0.05) and VR was positive (7±9%, P<0.05). Narrowed segments (n=13, 1 excluded, AS=18±6%, P<0.05) showed no relation between WT and SS or vascular remodeling.

Conclusions—In patient coronary arteries, the often-reported inverse WT-SS relationship appears restricted to lumen preservation and positive vascular remodeling. Its disappearance with lumen narrowing suggests a growing importance of non-SS–related plaque progression. (Circulation. 2003;108:17-23.)

Key Words: atherosclerosis • coronary disease • stress • remodeling

Atherosclerotic plaques are preferentially located near side branches, in inner curves of arteries, and in the bulb of the carotid arteries. Therefore, in the presence of systemic risk factors, additional localizing factors are involved in the atherosclerotic process. One such factor is the local shear stress (SS) induced by blood flow on the vessel wall. Indeed, several investigators showed that the deposition of atherosclerotic plaque is increased at natural average low SS locations, implying an inverse relation between wall thickness (WT) and SS.

The main purpose of the endothelium in sensing SS is the control of lumen dimensions. During early atherosclerosis, this control mechanism is still operable. Hence, Glagov et al suggested that SS control might explain his observations on lumen preservation by compensatory enlargement of arteries during early plaque accumulation. Only if the plaque area exceeded 40% of the intima-bounded area was lumen narrowing observed. A consequence of lumen preservation by compensatory enlargement is that plaque buildup remains clinically and angiographically unnoticed until this compensation gradually fails or acute coronary syndromes occur. Presently, the opinion exists that non-SS–related plaque fissuring and healing play an important role in plaque progression. In addition, acute events occur more frequently in compensatory enlarged arteries. This might be a consequence of the prolonged development of unfavorable types of plaques at low SS predilection locations because of SS control, which preserves normal lumen and normal SS distribution, thereby maintaining locations with less-favorable flow conditions.

Studies determining SS control and its relation with vessel remodeling and plaque accumulation in human coronary
arteries in vivo have not been performed. In vitro studies determined WT and SS relations in casts derived from autopsy specimens. To study SS, WT, and remodeling and their mutual relations in individual patients we applied a newly developed 3D arterial reconstruction technique using angiography and IVUS combined with computational fluid dynamics (CFDs). Previously, we confirmed that atherosclerotic plaques were located at the low SS locations for a single patient. In this study, we determine SS, plaque amount, and plaque dynamics (CFDs). Previously, we confirmed that atherosclerotic plaques were located at the low SS locations for a single patient.10 In this study, we determine SS, plaque amount, and plaque location in relation to lumen preservation and the state of remodeling in coronary arteries in a patient population. We hypothesize that at the transition from lumen preservation to lumen narrowing, loss of the often-observed inverse relation between WT and SS may signify a growing importance of non-SS–related plaque growth.

Methods

Patients

Angiographically normal coronary arteries of 14 patients were studied with angiography and intravascular ultrasound (IVUS) at intake of a substudy (Perspective) of the EUROPE study, aimed at studying the influence of ACE inhibition on atherosclerosis. The institutional medical ethical committee approved the study, and every patient gave written informed consent to participate in this study.

3D Reconstruction

3D reconstruction of the coronary arteries was performed by fusing information from ANGiography and ivUS (ANGUS), as has been presented previously. Briefly, a sheath-based IVUS catheter (CVIS 2.9F) was positioned in the studied vessel. The catheter in most distal position was filmed (25 frames/s) by a biplane angiographic system (Bicor, Siemens), and IVUS images were collected at successive end diastoles (EDs) using an ECG-triggered, motorized stepped pullback (0.5-mm steps, TomTec).

For analysis, a single biplane set of images of the IVUS catheter at ED was used to reconstruct in 3D space the path of the transducer to be followed at successive ED moments. The IVUS frames were analyzed with a semiautomatic contour detection program to provide lumen contours, signifying the blood vessel interface and media contours at the lamina elastica externa. Subsequently, the lumen contours were positioned onto the reconstructed lumen wall. The angular rotation of the contours was determined from the best quantitative correspondence between the actual angiograms and simulated silhouette images derived from the 3D lumen reconstructions. Finally, adding the media contours completed the 3D lumen reconstruction with the vessel wall.

Analysis of Morphological Parameters

Segments were defined in between 2 branches. Data from cross sections up to a distance of 1 lumen diameter from the branch were excluded from analysis. Only segments of sufficient length (>5 mm) were included.

From the lumen and media contours at each cross section, lumen area (LA), media bounded (total vessel) area (VA), plaque area (PA = VA–LA), and the ratio PA/VA were calculated. At each cross section, WT was determined at 16 equidistant circumferential locations. WT was considered normal if smaller than 0.2*lumen diameter [calculated as \(\sqrt{4LA/\pi}\)]. Plaque free vessel wall (PFVW) was defined as the arc showing normal WT.

Per segment, the cross section with maximal PFVW served as reference (ref) for the remodeling analysis. Vascular remodeling (VR) was determined as \((VA–VA_{\text{ref}})/VA_{\text{ref}}\*100\%\). Lumen area stenosis (AS) was defined as \((LA_{\text{ref}}–LA)/LA_{\text{ref}}\*100\%\). The ratio PA/PA_{\text{ref}} expressed PA relative to the reference cross section. Table 1 summarizes the introduced abbreviations and definitions.

Computational Fluid Dynamics

SS was determined at the same locations as WT, applying a well-validated finite element software package (Sepran, Sepra). This software solved the nonlinear incompressible fluid flow Navier-Stokes equations in a multitude of nodes contained in brick-like elements (axial resolution, 1 mm), which filled the luminal space of the full 3D reconstruction. Each slice contained 32 finite elements, each covering a cross-sectional area ranging from 0.05 to 0.83 mm², with the highest resolution near the wall. Each element contained 27 calculation nodes. Blood was modeled as a non-Newtonian fluid described by the Casson equation with a density of 1050 kg/m³. Entrance flow was determined to induce a normal Poiseuille-derived average SS of 0.68 Pa over all normal cross sections, showing a PFVW >180 degrees. Velocity profile of the entrance flow was parabolic. At the wall, no slip was assumed, and at the outflow, zero stress conditions were applied. Convergence was reached when differences in velocity between iterations fell below 0.1 mm/s. Subsequently, the obtained SS data were scaled, being appropriate as evaluated before, to achieve per segment an average SS of 0.68 Pa over the normal cross sections.

Statistics

Segments showing lumen preservation, defined to have an average AS (AS_{\text{avg}}) < 10%, were compared, with narrowed segments showing...
TABLE 2. Characteristics of Segments With and Without Lumen Preservation

<table>
<thead>
<tr>
<th></th>
<th>AS &lt;10%</th>
<th>AS &gt;10%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>11</td>
<td>14</td>
<td>...</td>
</tr>
<tr>
<td>Reference lumen area, mm²</td>
<td>9.0±3.9</td>
<td>11.9±2.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Reference vessel area, mm²</td>
<td>14.1±5.9</td>
<td>19.3±4.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Reference plaque area, mm²</td>
<td>5.1±2.4</td>
<td>7.4±1.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Reference PA/VA</td>
<td>0.37±0.08</td>
<td>0.38±0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>8.8±3.7</td>
<td>9.8±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Vessel area, mm²</td>
<td>15.0±6.1</td>
<td>18.8±4.4</td>
<td>NS</td>
</tr>
<tr>
<td>Plaque area, mm²</td>
<td>6.2±2.9</td>
<td>9.0±2.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Axial location in vascular tree*</td>
<td>0.73±0.42</td>
<td>0.29±0.38</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Linear interpolation from proximal (0) to distal (1).

AS <10% applying Student’s t test. One sample t test was applied, where appropriate.

Per segment, SS and WT data were averaged in the circumferential direction to deliver SSₘ and WTₘ at every 1-mm distance along the axial (longitudinal) direction (Figure 1). This method is most sensitive to local effects by axial variations of lumen size affecting SS (and WT). Similarly, averaging along the axial direction delivered SSₘ and WTₘ at 16 circumferential locations (Figure 1). This method is most sensitive to detect global effects of a long-time persisting SS pattern in a curved segment.

Linear regression analysis between WT and SS delivered the slopes ΔWT/ΔSS_k and ΔWT/ΔSS_k. The slopes were tested for a relation with the previously defined morphological parameters VA, LA, PA, PA/VA, PFVW, VR, AS, PA/PA ref, and age by linear regression analysis. P<0.05 was considered significant. All values were expressed as mean±SD unless stated otherwise. SPSS 9.0 (SPSS Inc) was used for all statistical calculations.

Results

Patient Population

From the 14 patients (10 male, 4 female, age 59±10 years), 12 arteries (5 right coronary artery, 4 left anterior descending artery, and 3 left circumflex coronary artery) could be successfully analyzed, providing 25 segments. One artery did not contain segments >5 mm in length, and another artery had a too irregular lumen shape precluding the CFD solver to converge.

General Shear Stress and Morphological Parameters

The flow applied in the 25 segments was 65±33 mL/min, resulting in an average SS of 1.41±0.32 Pa. Averaged over all segments, LA was 9.3±3.1 mm²; VA, 17.1±5.5 mm²; PA, 7.8±3.0 mm²; WT, 0.62±0.18 mm; PA/VA, 0.45±0.08; and PFVW, 209±66 degrees. Average plaque area was larger than at the reference cross section (PA/PA ref, 1.23±0.2; P<0.05), and because no vascular remodeling was observed (1±9%, P=NS), the lumen appeared slightly stenosed (ASₘ=11±10%, P<0.05).

Lumen Preservation Versus Lumen Narrowing, Morphological Data

Comparing the segments with lumen preservation (n=11) versus narrowing (n=14), ASₘ was 1.7±5.6% (P=NS) versus 18.4±5% (P<0.01), VR was positive versus absent (7±9% versus −3±6%, P<0.01), PFVW was larger (241±65 versus 183±57 degrees, P<0.05), PA was smaller (6.2±2.9 versus 9.0±2.6 mm², P<0.05), age was younger (52±8 versus 62±8 years, P<0.01), and PA/VA tended to be lower (0.42±0.08 versus 0.48±0.08, P=0.06). Both groups showed the same greater (P<0.05) average PA relative to the reference; ie, PA/PAₘₐₙ was 1.22±0.18 versus 1.25±0.25. Table 2 summarizes additional absolute morphological characteristics of both groups. Interestingly, segments with lumen preservation were located more distally in the arterial tree and therefore showed smaller values for LAₘₐₙ, VAₘₐₙ, and PAₘₐₙ.

Wall Thickness Related to Shear Stress, Local Data

The locally obtained WTₘ and SSₘ showed for all segments, except for 1 (NS), a positive linear relationship, being significant for 18 segments. The average slope ΔWT/ΔSSₙₐₙ was 0.13±0.09 mm/Pa (n=25, P<0.05). There was no difference between the predefined groups. Relating the slope to the morphological parameters and age, only age showed a significant relationship, as follows: ΔWT/ΔSSₙₐₙ=0.0038×age−0.087 mm/Pa, r²=0.16, P<0.05.

Wall Thickness Related to Shear Stress, Global Data

The slope for the axially averaged data, ie, ΔWTₘ/ΔSSₘₐₙ showed wide variation. One outlier (slope, −3 mm/Pa, P<0.05) deviated 5 SDs from the slope (−0.11±0.61 mm/Pa, n=24) of all other segments. Classification of the other segments showed a significant inverse relationship between WTₘ and SSₘₐₙ for 9 segments (slope, −0.70±0.46 mm/Pa). Another 9 segments showed no relationship, and 6 showed a significant positive relationship (slope, 0.51±0.4 mm/Pa).

Comparing groups, segments with a preserved lumen (n=11) had a negative slope (−0.46±0.55 mm/Pa, P<0.05), whereas the narrowed segments (n=14) showed no relationship between WTₘ and SSₘₐₙ (−0.07±1.1 mm/Pa, NS). Exclusion of the outlier from additional analysis showed the slope of the narrowed group (0.19±0.5 mm/Pa, NS) to be different (P<0.05) from the preserved group. Applying the exclusion to the previous analysis did not change the differences between groups. Results are presented in Figure 2.

Because flow was a selected variable for the calculations, this might affect the difference in slope. Therefore, a subsequent analysis tested whether just the sign of ΔWTₘ/ΔSSₘₐₙ was different between the groups. This analysis showed that
9 of the 11 segments with lumen preservation (82%) had a negative slope, which was different ($P<0.05$, Fisher’s exact test for 2×2 table) from the narrowed segments that had a positive slope for 10 of 13.

Relating the slope to the morphological parameters and age, again age showed to be predictive as follows: $\Delta \text{WT}_{ax}/\Delta \text{SS}_{ax}=0.036^*\text{age}−2.19\ \text{mm/Pa}$ ($r^2=0.32$, $P<0.01$, $n=24$). The regression equation indicates a transition from negative to positive slope at 61 years. As was likely from the group-wise analysis, $\Delta \text{AS}_{av}$ was highly predictive, as follows: $\Delta \text{WT}_{ax}/\Delta \text{SS}_{ax}=0.037^*\text{AS}_{av}−0.5\ \text{mm/Pa}$, $r^2=0.36$, $n=24$, $P<0.05$; in addition, for VA, $\Delta \text{WT}_{ax}/\Delta \text{SS}_{ax}=0.046^*\text{VA}−0.88\ \text{mm/Pa}$, $r^2=0.17$, $P<0.05$.

A subsequent multivariate stepwise analysis on the slope as independent variable, with age, VA and $\text{AS}_{av}$ as independent predictors, showed that age contributed with borderline significance ($P=0.06$), whereas $\text{AS}_{av}$ was significant, as follows: $\Delta \text{WT}_{ax}/\Delta \text{SS}_{ax}=−1.72+0.026^*\text{AS}_{av}+0.023^*\text{age}\ \text{mm/Pa}$, $r^2=0.46$, $P<0.05$ (Figure 3).

Apparantly in these patients being treated for coronary artery stenosis, the studied segments with angiographically normal lumens were at the brink of narrowing. This may explain the high sensitivity of our measurements, which is probably also achieved by using all cross-sectional data rather than a single minimal lumen area cross section. Consequently, data like AS, VR, and PA/PA_ref showed smaller values than usually reported. From all tested parameters, age and lumen area stenosis (related to remodeling) were the only predictors for the slope of the WT-SS relationship.

Shear Stress
The average SS found in our study is above the aimed 0.68 Pa for the reference segments. Averaging of SS at the reference
segments with the much higher SS values (third power relation with diameter) at the most narrowed cross sections explains this finding.

**Reference Segments**

Maximal arc of PFVW defined reference cross sections, arguing that at those locations, the control by SS would be least affected by atherosclerotic disease. Previous studies showed that PFVW was inversely related to disease parameters as PA/VA \(^{15}\) and AS. \(^{16}\) We obtained similar observations (data not shown). For both groups, at the reference, PA/VA showed the same degree of normality. Furthermore, at the reference, lumen, plaque, and vessel area were largest in the narrowed segments. This can be explained by the observation that the narrowed segments were proximally located in the arterial tree (Table 2). This agrees with previously reported increased atherosclerotic wall thickening in the proximal part of right coronary arteries. \(^{17}\)

**Area Stenosis**

Average area stenosis \(<10\%\) and \(>10\%\) differentiated states of lumen control. It turned out to be a crucial factor in identifying different segment groups regarding morphological properties, thereby confirming earlier studies on VR. \(^{6}\) Moreover, it clearly revealed important differences in our SS-related parameters. Obviously, AS is dependent on lumen control in a continuous fashion, and indeed the axial WT-SS slope parameter appeared linearly related to AS.

**Relationship Between Wall Thickness and Shear Stress**

**Local Effects**

In this study, the observed positive relationship between WT\(_{cir}\) and SS\(_{cir}\) seems to contradict previous reports stating that atherosclerotic plaques preferentially develop at average low SS locations. \(^{1-4,10}\) Several factors may explain this finding. First, in contrast with our global type of analysis, the circumferentially averaged data do not account for long-lasting natural variations in SS over the circumference. Because of curvature, such variations certainly exist. Second, the endothelium in controlling lumen size regulates SS in a negative feedback control loop. \(^{18}\) Therefore, cross-sectional SS increments (induced by wall thickening, Figure 4C) will induce positive vascular remodeling, \(^{6}\) causing SS to decrease. However, almost any control loop will leave some residue of the initial disturbance. In our case, this may lead to some lumen narrowing and SS increase at cross sections with increased WT, explaining the positive relationships also for segments with a preserved lumen. Third, for the narrowed segments, a gradual loss of SS control by loss of PFVW allows additional encroachment of a lesion into the lumen, thereby increasing both the SS\(_{cir}\) and WT\(_{cir}\). This may explain the similarity in WT-SS slopes of the narrowed versus the preserved lumens. The minor increase in slope with age may be related to the fact that \(\Delta \text{WT}_{cir}\) rose more with age than \(\Delta \text{SS}_{cir}\) (data not shown). Therefore, the observed positive WT\(_{cir}\)-SS\(_{cir}\) relations do not contradict the generally accepted theory of atherogenesis at average low SS locations. In summary, circumferential data averaging, as may be also performed when estimating SS from Doppler measurements combined with diameter measurements from angiograms, needs careful interpretation.

**Global Effects**

For geometrical reasons, the SS control loop cannot create constant SS values everywhere in the arterial system. For example, at the inner curve of a bend, SS will be always lower...
Global effects

than at the outer curve. This also holds when lesions at the inner curve induce an average rise of SS over the cross section (Figure 5C). Therefore, either different target values for the SS control loop exist or other additional mechanisms regulate vascular size. Presently this issue has not been resolved.

We aimed to extract the natural variations in SS. Because relatively short segments were studied, the coronary arteries can be considered to be curved in mainly 1 plane, and thus averaging in the axial vessel direction, as done before, delivers the long-term persisting relative differences in shear stress. Figures 5B and 5C illustrate SS variations with their global summation in a curved artery. The observed (Figure 2) inverse WTax -SSax relations accompanied with positive VR and a larger PFVW (implying a smaller circumferential lesion extent) make it most likely that indeed the local plaque build up is prolonged by SS control. Recently, in human coronary arteries, an association was found between expansive arterial remodeling and macrophage-rich atherosclerotic plaques, being associated with increased vulnerability. Indeed, patients with these plaques may be at higher risk, because major cardiovascular events were reported in the presence of positive VR.

The rise in slope of ∆WTax/∆SSax from negative to zero or positive with AS (loss of lumen preservation) indicates that plaque location is no longer restricted to the average low SS locations. A reason for this is lateral plaque extension (indicated by PFVW decrease) possibly induced by repetitive small ruptures of the plaque and healing at its shoulders.

In addition to AS, the slope ∆WTax/∆SSax also tended to increase with age. It has been found that younger age is predictive for positive VR, which according to the current study predicts an inverse relationship. Moreover, it is well known that VR is regulated by the SS-dependent production of NO. At higher age, a loss of endothelial NO synthase has recently been reported. Therefore, the loss of the inverse WTax-SSax relationship at increasing age with loss of positive VR might also point to a diminished protection of relatively high SS locations by NO.

Extrapolating the findings of Glagov et al, who observed lumen preservation until PA exceeded 0.4*intimal area, we expected a relationship between PA/VA and global slope ∆WTax/∆SSax, because both parameters change with degree of disease and are related to the existence of lumen control. Indeed, PA/VA tended to be lower and compensatory enlargement was observed for segments with lumen preservation as described by Glagov et al. That we did not find a continuous relationship may be explained from differences between the studied vessels, diseased area determination (we also included the media), and population in both studies. For example, the range of PA/VA in our population was very small because cross sections showing PA/VA >0.4 were scarce, as also exemplified by the average PA/VA of 0.37 to 0.38 at the reference location (Table 2).

Limitations

We selected flow boundary conditions to obtain a reported normal SS in least-diseased cross sections. Although this selection may influence the magnitude of the slope of the WT-SS relationship, it does not influence its sign. We showed that negative slopes are associated with lumen preservation and positive slopes with lumen narrowing, strengthening our observation. Because we could not yet study patients over time, interpreting our observations as a course of events demands a cautious attitude.
Conclusion
In coronary arteries of patients, the presence of the often-observed inverse relationship between WT and SS appears restricted to lumen preservation and compensatory vascular remodeling. The association of disturbance of this relation with lumen narrowing may signify the growing contribution of non-SS-related plaque progression.

Acknowledgments
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References
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