**Endothelial Shear Stress**

**A Critical Determinant of Arterial Remodeling and Arterial Stiffness in Humans—A Carotid 3.0-T MRI Study**

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**Background**—Low endothelial shear stress (ESS) elicits endothelial dysfunction. However, the relationship between ESS and arterial remodeling and arterial stiffness is unknown in humans. We developed a 3.0-T MRI protocol to evaluate the contribution of ESS to arterial remodeling and stiffness.

**Methods and Results**—Fifteen young (aged 26±3 years) and 15 older (aged 57±3 years) healthy volunteers as well as 15 patients with cardiovascular disease (aged 63±10 years) were enrolled. Phase-contrast MRI of the common carotid arteries was used to derive ESS data from the spatial velocity gradients close to the arterial wall. ESS measurements were performed on 3 occasions and showed excellent reproducibility (intraclass correlation coefficient, 0.79). Multiple linear regression analysis accounting for age and blood pressure revealed that ESS was an independent predictor of the following response variables: carotid wall thickness (regression coefficient [b], −0.19 mm² per N/m²; P=0.02), lumen area (b, −15.5 mm² per N/m²; P<0.001), and vessel size (b, −24.0 mm² per N/m²; P<0.001). Segments of the artery wall exposed to lower ESS were significantly thicker than segments exposed to higher ESS within the same artery (P=0.009). Furthermore, ESS was associated with arterial compliance, accounting for age, blood pressure, and wall thickness (b, −0.003 mm²/mm Hg per N/m²; P=0.04).

**Conclusions**—Our carotid MRI data show that ESS is an important determinant of arterial remodeling and arterial stiffness in humans. The data warrant further studies to evaluate use of carotid ESS as a noninvasive tool to improve the understanding of individual cardiovascular disease risk and to assess novel drug therapies in cardiovascular disease prevention. (Circ Cardiovasc Imaging. 2010;3:578-585.)

Key Words: endothelium ▪ remodeling ▪ atherosclerosis pathology ▪ magnetic resonance imaging

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**Clinical Perspective on p 585**

The interaction between blood flow and the endothelium has been proposed to play a role in the atherosclerotic disease process. Two ultrasound studies in humans reported a relationship between intima-media thickness and endothelial shear stress (ESS) in healthy subjects. In fact, prolonged decreases in ESS force endothelial cells to switch to an atherogenic phenotype. Endothelial cell turnover, endothelium-derived inflammatory mediators, and extracellular matrix degradation are tightly regulated by ESS. In line, low ESS promotes increased permeability and enhanced low-density lipoprotein cholesterol uptake into the artery wall. These processes are known to facilitate arterial remodeling. Furthermore, ESS regulates endothelium-derived NO,
which plays a central role in the regulation of large-artery stiffness in vivo.\textsuperscript{15,16}

Despite these data from in vitro and animal studies, the relationship between ESS and arterial remodeling and arterial stiffness has not been investigated in vivo in humans. The scarcity of data on this topic is predominantly because accurate quantification methods to estimate ESS in vivo are challenging to create. Most existing approaches either use highly complicated methods such as computed fluid dynamics, which are unmanageable in trials investigating larger populations, or use oversimplified methods that assume Poiseuille flow.\textsuperscript{17} Similarly, assessment of arterial stiffness as well as arterial structure is technically difficult. We therefore developed a noninvasive 3.0-T MRI protocol that enables quantification of all these dimensional and functional aspects in a single MRI scanning session. We based our ESS assessment on velocity gradient modeling comparable to methods previously used by Oyre et al.\textsuperscript{18} Additionally, we performed repeat MRI scans to assess the reproducibility of our ESS method. Subsequently, we investigated the relationship between local shear stress and arterial wall remodeling and arterial wall stiffness in the carotid arteries of young and old healthy subjects and patients with cardiovascular disease (CVD). The hypothesis that ESS is a determinant of arterial remodeling and arterial stiffening was then tested.

Methods

Subject Population
We selected 15 young (age range, 18 to 30 years) healthy subjects, 15 older (age range, 50 to 70 years) healthy subjects, and 15 subjects with CVD. CVD was defined as a history of myocardial infarction, transient ischemic attack, or stroke. Healthy subjects did not show any signs or symptoms of CVD and had no known traditional risk factors for CVD. In all subjects, repeat MRI scans were acquired on 3 separate occasions 1 to 3 weeks apart. All image analyses were done offline. Before the studies, approval was obtained from the institutional review board of the Academic Medical Center (Amsterdam, The Netherlands). All subjects gave written informed consent.

Image Acquisition
MRI scans were obtained on a 3.0-T MRI scanner using a single-element microcoil with a diameter of 5 cm. In all subjects, common carotid MRI scans were done bilaterally. To localize the left and right common carotid artery and carotid bifurcation, axial magnetic resonance angiography images were acquired using a time-of-flight sequence. These images together with projection images were used for positioning the scan planes perpendicular to the vessel at a predefined distance proximal to the flow divider. For hemodynamic assessments, axial gradient echo phase-contrast images were acquired with a temporal resolution of 17 milliseconds (ms), and temporal interpolation was performed by the scanner software to 60 phases per heartbeat (retrospective ECG gating). The scan plane was positioned 27 mm proximal to the carotid flow divider (sequence parameters: slice thickness, 3 mm; noninterpolated pixel size, 0.65×0.65 mm; field of view, 60×60 mm; velocity encoding, 150 cm/s [unidirectional]; repetition time, 8.1 ms; echo time, 5 ms; flip angle, 10°; number of signal averages, 2; total scan time, 3 to 4 minutes). Both magnitude images and velocity-encoded phase images were reconstructed. To assess arterial wall dimensions, axial T1-weighted Turbo Spin Echo image stacks were acquired at end diastole using double-inversion recovery black blood preparation (sequence parameters: slice thickness, 5 mm; imaging matrix size, 240; field of view, 60×60 mm; noninterpolated pixel size, 0.25×0.25 mm; echo time, 9 ms; repetition time according to subject heart rate [approximately 900 ms], echo train length, 7; echo train duration, 63 ms). Active fat suppression (spectral attenuated inversion recovery technique) was applied to improve the definition of the outer wall boundary and avoid chemical shift artifacts. All imaging was performed with cardiac gating.\textsuperscript{19} Total scan time for hemodynamic and artery wall imaging was approximately 45 minutes. All images were stored in the Digital Imaging and Communications in Medicine format. Standardized equipment and protocols were used for image storage and data management.

Image Analysis
For ESS quantification, offline semiautomated qualitative and quantitative image analysis was performed using software written in Matlab and developed at the Academic Medical Center. Inter- and intraobserver variability of scan analyses were assessed. For those purposes, 2 image analysts independently analyzed all scans (interobserver variability), and 1 of the image analysts analyzed all scans twice on separate occasions (intraobserver variability). To assess the lumen area (LA, mm$^2$) of all 60 phases per cardiac cycle, the software performed automated tracing of the lumen-wall boundaries on the gradient echo images. For LA delineation, the software used an algorithm developed by Li et al.\textsuperscript{20} This algorithm is a region-based active contour model in a variational level set formulation. An energy function is defined with a local intensity fitting term and an auxiliary global intensity fitting term that provide smooth and closed contours to recover object boundaries with subpixel accuracy, which typically is not possible in classical methods, such as edge detection and thresholding. After the lumen was delineated, the shortest distance to the artery wall was calculated for each pixel. Subsequently, the lumen-wall boundaries were projected on the velocity-encoded images. The velocity of each pixel in the artery lumen was measured (Figure 1). Endothelial shear rate (ESR, seconds$^{-1}$) was assessed by determining the spatial gradient of the velocities close to the artery wall using second-order curve fitting of the velocity profile. The second-order fit was applied independently per quadrant of the vessel, and the resulting gradients were averaged for each artery. The center (radius of 1.3 pixels from the center) was excluded from the analysis. The border (0.5 pixel from the border) also was excluded because those pixels were partially located in the lumen and partially in the vessel wall. The fit was forced to include the position of the artery wall with a velocity of 0 to conform to the zero-slip condition. ESR was calculated for all 60 time frames (Figure 2). ESS was calculated by multiplying the mean ESR of all 60 phases per cardiac cycle, with blood viscosity taken as 3.2 Pa s.\textsuperscript{21} Furthermore, we compared our peak systolic ESR to those previously reported to assess whether our improved temporal resolution resulted in higher values compared to prior work.

In addition, we assessed compliance as a measure of arterial stiffness. The maximal LA and the end-diastolic LA were measured on the magnitude images (Figure 1). The areas together with the brachial artery systolic blood pressure (SBP) and diastolic blood pressure (measured with an Omron blood pressure monitor before MRI scanning) were used to calculate the carotid artery compliance as follows: compliance=$\frac{\text{systolic area}−\text{diastolic area}}{\text{SBP}−\text{diastolic blood pressure}}$. For further insight in the carotid artery hemodynamics, we assessed peak systolic velocity and blood flow by MRI. Furthermore, the heart rate was determined with ECG during MRI scanning.

For the carotid arterial wall thickness quantification, using the T1-weighted images, semiautomated image analysis was performed using VesselMass software. VesselMass performs automated tracing of the lumen-wall boundaries and the outer wall boundaries (Figure 1). The software algorithm for boundary detection is described elsewhere.\textsuperscript{22} Mean wall thickness (MWT, mm), maximum wall thickness (maxWT, mm), LA, and outer wall area (OWA, mm$^2$) were calculated for each carotid artery as mean values of the 8 images per artery. We defined outward remodeling as increased OWA and MWT with preservation or increase of lumen diameter.
We defined inward remodeling as decreased lumen diameter with increased MWT.

Statistical Analysis
Continuous variables are expressed as mean±SD. The agreement between successive MRI scans, successive MRI analyses, and the 2 image analysts was assessed using intraclass correlation coefficients, SD of paired differences, and the coefficients of variation. The coefficients of variation were calculated by dividing the SD of paired differences by the mean value of the population for each parameter. To evaluate differences in all ESS and other parameters, we performed a 1-way ANOVA for between-group differences and a least squares difference analysis to compare the younger healthy subjects with the older healthy subjects and subjects with CVD. We used multiple linear regression analysis to assess the association between MWT and ESS, with MWT as the response variable and ESS as the explanatory variable. We adjusted for potential confounders (ie, age, SBP, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, C-reactive protein, body mass index, and body surface area) using backward elimination. The same procedure was performed for each response variable (maxWT, OWA, LA, and compliance) separately. Within carotid anatomic locations, we also investigated the association of ESS and carotid artery wall thickness at those locations. For this purpose, we divided the carotid artery lumen and wall into quartiles. For each carotid quartile, the MWT values were measured and expressed as a z score relative to the mean thickness of the quartiles. We calculated z scores to prevent bias due to the differences in vessel wall eccentricity in the 3 groups. Subsequently, for each carotid quartile, the ESS was expressed as a rank, with 1 being the lowest ESS quartile and 4 being the highest. The MWT z scores at the different ESS ranks were compared by analyses of repeated measures using a linear mixed model, which provided good insight into the local effects of ESS on arterial remodeling because the systemic factors for all quartiles are identical. All statistical analyses were performed using SPSS version 16.0 for Windows.

Results
Patient Characteristics
Three MRI scans were performed in all 45 subjects (20 women, 25 men). The mean Prospective Cardiovascular Munster Study risk score, which estimates the 10-year risk of developing a coronary event, for the younger and older healthy subjects was 1.9±3.4. Patient characteristics are shown in Table 1.

Image Data
Of all 270 MRI scan sets, 252 (93%) were adequate for ESS image analysis. Images inadequate for analysis had either a low signal-to-noise ratio or image artifacts due to subject movements during scanning. Mean values of ESS parameters and hemodynamic parameters and the differences of all parameters among the 3 groups are shown in Table 1. The mean peak systolic ESR was 0.74±0.21 seconds. The interscan, interobserver, and intraobserver variability are shown in Table 2. Multiple linear regression analyses adjusted for SBP and age revealed that ESS was an independent predictor of MWT, maxWT, OWA, LA, and compliance (Table 3). ESS remained an independent predictor for compliance if we adjusted not only for SBP and age, but also for MWT (regression coefficient [β], −0.003 mm²/mm Hg per N/m²; 95% CI, −0.006 to −0.0002; P=0.04). The R² of the combined model (age, SBP, ESS) was 0.67 for MWT, 0.31 for LA, 0.46 for OWA, and 0.66 for compliance. The marginal relationship between ESS and response variables MWT, compliance, and LA, adjusted for age and SBP, is shown by means of partial regression plots in Figure 3.
Table 1. Patient Characteristics, Hemodynamic Parameters, Carotid Wall Parameters and ESS Parameters Measured by 3.0-T MRI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Control Subjects</th>
<th>Patients With CVD (n=15)</th>
<th>P</th>
<th>ANOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>25.9±2.6</td>
<td>57.4±3.2</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>67</td>
<td>47</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.2±0.7</td>
<td>5.6±1.0</td>
<td>&lt;0.001</td>
<td>4.4±0.8</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>2.3±0.6</td>
<td>3.5±1.0</td>
<td>&lt;0.001</td>
<td>2.5±0.8</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.6±0.3</td>
<td>1.7±0.4</td>
<td>0.87</td>
<td>1.3±0.4</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.6±0.3</td>
<td>1.0±0.5</td>
<td>0.11</td>
<td>1.4±0.9</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.8±0.3</td>
<td>5.3±0.8</td>
<td>0.07</td>
<td>5.7±0.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23±3</td>
<td>25±2</td>
<td>0.15</td>
<td>25±3</td>
</tr>
</tbody>
</table>

Hemodynamic parameters

- Heart rate, s⁻¹: 61±9, 63±11, 0.53, 68±10, 0.18, 0.13
- SBP, mm Hg: 118±10, 127±11, 0.06, 137±16, 0.03, 0.001
- DBP, mm Hg: 68±5, 77±8, <0.001, 72±5, 0.04, 0.001
- Carotid flow, cm³/s: 5.1±1.0, 4.5±1.0, 0.20, 4.1±1.7, 0.44, 0.12
- Carotid peak systolic velocity, m/s: 88.8±13.8, 68.1±7.7, <0.001, 64.2±12.4, 0.37, <0.001

Carotid wall and lumen

- MWT, mm: 0.51±0.05, 0.72±0.16, 0.001, 0.95±0.22, <0.001, <0.001
- MaxWT, mm: 0.60±0.08, 0.86±0.19, 0.002, 1.10±0.33, 0.007, <0.001
- OWA, mm²: 41.8±6.9, 46.3±7.8, 0.28, 56.1±16.1, 0.02, 0.004
- LA, mm²: 30.9±5.3, 30.4±4.2, 0.87, 34.1±11.2, 0.19, 0.36
- Compliance, mm²/mm Hg: 0.18±0.04, 0.09±0.03, <0.001, 0.11±0.06, 0.24, <0.001
- ESS, N/m²: 0.83±0.16, 0.92±0.27, 0.43, 0.70±0.33, 0.04, 0.12

Subsequently, we investigated whether carotid MWT varied among quartiles of ESS within a carotid artery. There was a significant difference in MWT between the highest and the lowest ESS rank (P=0.009) and a significant difference among all ranks (P=0.05), indicating that in the highest ESS quartile, the carotid wall was thinnest, and in the lowest ESS quartile, the carotid wall was thickest (Figure 4).

Discussion

To our knowledge, the present study shows for the first time that low ESS, estimated using a reproducible MRI method, is correlated with carotid wall thickening, lumen expansion, and increased vessel size in humans. Because local ESS has a strong inverse relationship with local arterial wall thickness throughout the carotid wall, low ESS is implicated in a causal relationship with local vessel wall thickening. In addition, we observed a relationship between ESS and arterial stiffness, accounting for the thickness of the artery wall. These findings lend further support to the concept that ESS is a critical determinant of arterial remodeling and arterial stiffness in humans. The present data imply that ESS may be an attractive noninvasive surrogate marker to assess CVD risk and risk modification.

Table 2. Measurement Variability of ESS Measurements and Analyses

<table>
<thead>
<tr>
<th>Measurement</th>
<th>ESS, N/m²</th>
</tr>
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<tbody>
<tr>
<td>Interscan Variability</td>
<td>0.79 (0.67–0.88)</td>
</tr>
<tr>
<td>Interobserver variability</td>
<td>0.99 (0.99–1.00)</td>
</tr>
<tr>
<td>Intraobserver variability</td>
<td>0.96 (0.94–0.97)</td>
</tr>
<tr>
<td>SDpd, N/m²</td>
<td>0.22</td>
</tr>
<tr>
<td>COV, %</td>
<td>26</td>
</tr>
</tbody>
</table>

Data are presented as intraclass correlation coefficient (95% CI), unless otherwise indicated. COV indicates coefficient of variation for all subjects; SDpd, SD of the paired differences between scans for all subjects.

Table 3. Multiple Linear Regression Analyses To Assess the Association Between Carotid Artery ESS and MWT, MaxWT, OWA, LA, and Compliance

<table>
<thead>
<tr>
<th></th>
<th>ESS, N/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>MWT, mm</td>
<td>−0.19</td>
</tr>
<tr>
<td>MaxWT, mm</td>
<td>−0.25</td>
</tr>
<tr>
<td>OWA, mm²</td>
<td>−24.0</td>
</tr>
<tr>
<td>LA, mm²</td>
<td>−15.5</td>
</tr>
<tr>
<td>Compliance, mm²/mm Hg</td>
<td>−0.07</td>
</tr>
</tbody>
</table>

All analyses are adjusted for age and SBP.
Methodology of ESS Quantification

In vivo ESS quantification is challenging, and various methods are used to quantify it. Computational fluid dynamics is a method that seeks the Navier-Stokes solutions of fluid flow. For a given artery geometry, 3D velocity patterns are calculated at a high resolution based on observed or assumed velocity profiles or pressures in inlet and outlet vessels. Yet, critical choices have to be made for, among others, quantification of the geometry and incorporation of boundary conditions, making the method intensive in terms of both human and computer resources and thereby less applicable for clinical trials.

Other studies on more-straightforward geometries assumed Poiseuille flow, which itself assumes a parabolic velocity profile. However, it has been demonstrated that a parabolic velocity profile does not develop in vivo in human carotid arteries, posing a severe limitation to this method.

In the present study, we assessed ESS based on velocity gradient modeling comparable to methods previously used by Oyre et al and others. We further optimized the protocol by using high temporal resolution, which should be more sensitive in detecting the true peak ESR value. Previous studies using 16 to 32 phases per heartbeat found peak systolic ESR values of 0.24, 0.27, and 0.59 seconds whereas we found in the present study peak systolic ESR values of 0.74 seconds. Furthermore, we abandoned the assumption of circularity of the carotid artery, and our protocol enabled per-segment ESS quantification. Using this protocol, we observed an interscan intraclass correlation coefficient of 0.79, whereas inter- and intraobserver reproducibility for offline image analysis found intraclass correlations coefficients exceeding 0.95. The excellent reproducibility of ESS quantification by MRI allows for its use in longitudinal follow-up studies.

ESS in Younger and Older Healthy Subjects and Patients With CVD

Decreased ESS has been shown to profoundly alter endothelial gene expression, causing the endothelium to switch to an atherosclerotic phenotype in experimental models. In agreement, a relationship between arterial wall thickness and ESS has been reported in healthy subjects. However, these ultrasound studies used suboptimal methods that assume Poiseuille flow to quantify ESS. In the present study, the older healthy subjects presented with modest arterial wall thickening compared to the younger healthy subjects without outward remodeling. ESS was comparable between groups.

In contrast, we observed marked carotid wall thickening with concomitant outward remodeling as well as decreased ESS in patients with CVD compared with the older healthy subjects. The fact that outward remodeling and decrease in ESS coincided in patients with CVD and not in the older healthy subjects implies that there is a potential relationship among ESS, arterial remodeling, and CVD. The pathophysiological mechanism to explain this finding might be found in the interaction between the hemodynamic shear forces and the endothelium. The endothelium is a key regulator of vascular homeostasis that acts as an active signal transducer for circulating influences that modify the vessel wall phenotype. Because prolonged decreased ESS is known to initiate endothelial dysfunction, decreased ESS might precede the development of morphological atherosclerotic changes and can

Figure 3. Partial regression lines with 95% CI, adjusted for age and SBP. A, Association between ESS (N/m²) and MWT (mm). B, Association between ESS and compliance (mm²/mm Hg). C, Association between ESS and LA (mm²).

Figure 4. Carotid MWT (mm) at high and low ESS (N/m²) levels in the common carotid artery. MWT is expressed as z scores relative to the mean±SEM per carotid artery. ESS is expressed as ranks per carotid artery, with 1 being the lowest ESS quartile and 4 the highest ESS quartile. We found a significant difference in MWT between the highest and the lowest ESS rank (P=0.009) and significant between-rank differences of all ranks (P=0.03).
contribute to lesion development and later clinical complications.

ESS and Lumen Expansion
To further probe the relationship between ESS and outward remodeling, we evaluated the correlations between ESS and LA. Adjusting for age and SBP, ESS was inversely correlated with carotid LA. Considering that LA is a major constituent in the quantification of ESS, a close relation between LA and ESS is not surprising. In this respect, it is interesting to note that arterial lumen diameter, as a surrogate measure for ESS, is an independent predictor of CVD. Thus, common carotid artery diameter was associated with cardiovascular events in 3393 subjects included in the Impact of Managed Pharmaceutical Care on Resource Utilization and Outcomes in Veterans Affairs Medical Centers (IMPROVE) study (hazard ratio, 3.01; 95% CI, 1.69 to 5.38; \( P = 0.0002 \) for diameters above the median).\textsuperscript{31} Similar results for brachial artery diameter in 2792 adults were found in the Cardiovascular Health Study, where arterial diameter was associated with cardiovascular events (hazard ratio, 1.15; 95% CI, 1.03 to 1.29; \( P = 0.01 \) per 1-mm increase in diameter).\textsuperscript{32}

ESS and Artery Size and Thickness
ESS was also inversely correlated with carotid MWT, maxWVT, and OWA, accounting for age and SBP. This finding implies that low ESS is associated with both atherogenesis and outward remodeling. This relationship, however, does not prove causality yet because independent systemic factors may affect both parameters simultaneously.\textsuperscript{33–35} To further unravel potential causality, we evaluated the relationship between ESS and MWT in various areas within the same artery. This evaluation revealed that regions within a carotid cross-section exposed to low ESS were characterized by significant wall thickening with an inverse linear trend between carotid wall thickness and ESS rank. Systemic risk factors, such as lipid levels and hemodynamic factors,\textsuperscript{36} such as blood pressure, per definition are identical for all quartiles simultaneously.\textsuperscript{33–35} To further unravel potential causality, we evaluated the relationship between ESS and outward remodeling in 24 swine. In line with our findings in humans, the authors showed that the level of ESS predicted the development of outward remodeling, whereas ESS also was correlated with the development of vulnerable plaques.\textsuperscript{36}

ESS and Arterial Stiffness
We found ESS to be correlated with arterial stiffness, accounting for age and blood pressure. Theoretically, ESS can contribute to arterial wall stiffness in 2 ways. First, the structural changes in the arterial wall associated with low ESS directly increase arterial stiffness. Second, low ESS decreases endothelial function and diminishes NO bioavailability. Low ESS has been associated with low expression of endothelial NO synthase in animal studies and has been associated with decreased flow-mediated vasodilation in vivo in humans.\textsuperscript{37,38} Endothelial function is an important regulator of arterial stiffness. In animal models, removal of the endothelium increased arterial stiffness.\textsuperscript{39} Moreover, blocking NO synthesis in humans increases arterial stiffness.\textsuperscript{40} Arterial stiffness also is inversely correlated with endothelial function in healthy subjects as assessed by flow-mediated vasodilation.\textsuperscript{41} Interestingly, our data show a correlation between ESS and arterial stiffness, accounting not only for age and SBP, but also for wall thickness. This correlation indicates that the relationship between ESS and arterial stiffness can be partly explained by the effect of ESS on endothelial function and NO bioavailability. A direct effect of ESS on arterial stiffness further adds to the relevance of ESS assessment as a potential therapeutic target because arterial stiffness has been shown to independently predict cardiovascular outcome in a large number of patient populations.\textsuperscript{2,3}

Study Limitations
Our study has several limitations. First, in our ESS calculations, we used blood viscosity as a constant. Measuring blood viscosity with a viscometer or estimating it by measuring hematocrit would have been more accurate. Second, patients were not fasted, and follow-up scans were not necessarily made at the same time of day as the initial scan. Potentially, ESS might be influenced by diet and circadian rhythm, which may have decreased the interscan reproducibility. Third, the in-plane resolution was 0.65 mm. Although the resolution was adequate, improving it would have increased the accuracy of the method. Additionally, we measured primary flow but not secondary flow. Secondary flow contributes to ESS; therefore, we may have underestimated the ESS. Fourth, we performed blood pressure measurements before MRI scanning but not during. Finally, we did not perform longitudinal follow-up scans to assess whether subjects with low ESS had more outward remodeling and more arterial stiffening than those with higher ESS. Cross-sectional data do not allow one to establish a causal relationship between ESS and atherosclerosis. Moreover, plaque development in the arterial wall itself may alter shear stress. It remains unknown what the temporal relationship is between low shear stress in a plaque-free vessel and development of any atherosclerosis.

Conclusion
In the present study, we show for the first time that ESS is an independent and critical determinant of carotid artery remodeling and arterial stiffness. These findings bear clinical relevance because outward remodeling and arterial stiffness are associated with increased risk of cardiovascular events. The quantification of ESS therefore provides us with a direct measure that is known to affect endothelial function, which can contribute to our understanding of individual CVD risk. The fact that noninvasive carotid ESS quantification has excellent reproducibility and can be combined with imaging
and quantification of carotid atherosclerosis and stiffness in a single scan session offers a promising and valuable tool to investigate atherosclerosis progression and regression in mechanistic studies and evaluation of innovative antiatherosclerotic compounds in controlled clinical trials.

Acknowledgments
We thank A.M. van den Berg and H. Afzali for assisting in data acquisition and analysis and A.H. Zwinderman, PhD, for assisting with statistical analysis.

Disclosures
None.

References
In vitro and animal studies have shown a strong interaction between blood flow and the endothelium and have proposed that endothelial shear stress (ESS) plays a key role in the atherosclerotic disease process. However, data to verify the relationship between ESS and atherogenesis in vivo in humans are scarce mostly because accurate quantification of ESS is challenging. We developed a 3-T MRI protocol that enables noninvasive in vivo ESS quantification in humans. In this study, we performed repeat MRI scans and showed that ESS is a reproducible measure. Subsequently, we investigated the relationship between local shear stress and arterial wall remodeling and arterial wall stiffness in healthy subjects and patients with cardiovascular disease. We observed that patients with cardiovascular disease had decreased ESS. Furthermore, we showed that low ESS was associated with arterial stiffness, carotid wall thickening, lumen area increase, and vessel size increase. In fact, segments of the artery wall exposed to lower ESS were significantly thicker than segments exposed to higher ESS within the same artery. To our knowledge, these data show for the first time in vivo in humans that there is a significant interplay among ESS, arterial remodeling, and arterial stiffness. Longitudinal studies using MRI-based ESS measurement should help to define the role of ESS in atherosclerosis development.
Endothelial Shear Stress: A Critical Determinant of Arterial Remodeling and Arterial Stiffness in Humans—A Carotid 3.0-T MRI Study

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/content/4/2/e3.full.pdf

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In the article by Duivenvoorden et al, “Endothelial Shear Stress: A Critical Determinant of Arterial Remodeling and Arterial Stiffness in Humans—A Carotid 3.0-T MRI Study,” which published ahead of print on June 24, 2010, and appeared in the September 2010 issue of the journal (Circ Cardiovasc Imaging, 2010;3:578–585), several corrections are needed with regard to the reported flow values and peak systolic velocity values in Table 1.

This error was made due to a mistake in the analysis software. The shear stress values were not affected by this mistake. The right carotid flow values are: for the young subjects 6.5±1.1 cm³/s, the older healthy subjects 6.2±0.9 cm³/s and subjects with CVD 5.9±1.4 cm³/s. The right peak systolic velocity values are: for the young subjects 90.3±12.0 m/s, the older healthy subjects 70.3±8.8 m/s, and subjects with CVD 67.3±12.7 m/s.

These corrections have been made to the current online version of the article, which is available at: http://circimaging.ahajournals.org/content/3/5/578.abstract. The authors regret the error.

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