Arterial Remodeling of the Common Carotid Artery After Aortic Valve Replacement in Patients With Aortic Stenosis

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Background and Purpose—Aortic stenosis, causing flow abnormalities, disturbs the normal hemodynamics in the common carotid arteries. The aim of the present study was to investigate the remodeling process of the common carotid arteries after surgical correction of aortic stenosis.

Methods—Eleven subjects with aortic stenosis were studied before and 1 and 6 months after aortic valve replacement. Arterial diameter, intima-media thickness (IMT), and flow velocity were measured by echo-Doppler examination. Shear stress, blood flow, and pulsatility index were calculated. Blood viscosity and hematocrit were measured by standard methods. A control group was also enrolled.

Results—Before surgery, compared with controls, patients had lower systolic peak velocity but higher mean and end-diastolic velocity. Arterial diameter, IMT, and blood flow were comparable in the 2 groups. Blood viscosity, hematocrit, wall shear stress, and pulsatility index were markedly lower in patients. After surgery, IMT was reduced (0.741 ± 0.152 versus 0.627 ± 0.108 mm before and 6 months after surgery, respectively; P<0.0001), and hematocrit and blood viscosity increased, leading to increased wall shear stress (mean wall shear stress, 7.83 ± 1.97 versus 9.65 ± 3.12 dyne/cm² before and 6 months after surgery, respectively; P<0.02).

Conclusions—The present results demonstrate that aortic valve replacement, in subjects with aortic stenosis, leads to reduction of the common carotid artery IMT. Wall shear stress is increased after the intervention and probably mediates the remodeling process. (Stroke. 2002;33:2446-2450.)

Key Words: carotid arteries • remodeling • stenosis, aortic • stress

Endothelial cells are subject to mechanical forces, such as blood pressure, cyclic strain, and wall shear stress, that are able to influence vascular tone and geometry. The location at the interface between flowing blood and vessel wall is optimal to allow them to sense these forces and respond to their variation by synthesizing and releasing substances that acutely regulate smooth muscle cell tone and chronically lead to remodeling of the vessel.1-5

Thickening of the vessel wall is considered an early marker of atherosclerosis and a key element of the remodeling process.6 It is known that intima-media thickness (IMT) of the arteries is strongly associated with systemic cardiovascular risk factors such as aging, hyperlipidemia, hypertension, and diabetes mellitus and with local hemodynamic forces, especially wall shear stress.7-9 In animal and in vitro experimental models, it has been demonstrated that changes in vascular tone and structure occur as a consequence of increased or decreased blood flow velocity. It is not known whether human common carotid arteries undergo a similar remodeling process in response to sustained hemodynamic variations.

The present study was designed to evaluate, in vivo, the possible arterial remodeling of common carotid arteries after changes in hemodynamic conditions. Aortic stenosis is usually associated with common carotid artery flow abnormalities, detected by Doppler examination, such as decreased peak velocity and rounded waveform. These abnormalities are reversible after surgical correction of the valvular defect. Therefore, subjects with severe aortic stenosis were enrolled and investigated before and after aortic valve replacement.

Subjects and Methods

Subjects
Fifteen consecutive patients referred for isolated critical aortic stenosis to the Institute of Cardiovascular Surgery of the Monaldi Hospital in Naples, Italy, were enrolled. Exclusion criteria were the presence of valvular defects other than aortic stenosis and coronary artery disease requiring coronary artery bypass surgery. The effective orifice area was 0.55±0.11 cm², and peak pressure drop was 117±22 mm Hg. Patients were informed about the aim of the study and all technical procedures and gave informed consent. The vascular examination was performed before and 1 and 6 months after
surgery. Three patients were excluded from the analyses for missing data and 1 because of a perioperative complication. Blood pressure, height, and weight were measured by routine methods. Body mass index was computed as weight (kg) divided by height (m²). Blood was withdrawn in the morning, after the subjects had fasted overnight, for blood glucose, lipids, packed cell volume, and blood viscosity.

A control group of 11 subjects, matched for sex and age, was enrolled among relatives of the hospital staff. After any aortic valve defect was excluded by echocardiography, these subjects underwent the same clinical and biochemical examinations and carotid echo-Doppler procedure as the patients.

Echocardiographic Evaluation
A complete echocardiographic study was conducted on each patient preoperatively and 1 and 6 months after surgery. All collected data about cardiac parameters and cardiac function were in accordance with British Society of Echocardiography and US Food and Drug Administration guidelines.1011 The evaluation of aortic stenosis was performed with continuous-wave Doppler recordings from right intercostal, suprasternal, and apical views in the left lateral decubitus. The Doppler waveform with maximal shift frequency was used to evaluate peak (∆P peak) and mean (∆P mean) pressure drop across the stenotic aortic valve. The use of the modified Bernoulli equation, these values were calculated as follows

\[
\Delta P_{\text{peak}} (\text{mm Hg}) = 4 \cdot (V_{\text{max}})^2
\]

\[
\Delta P_{\text{mean}} (\text{mm Hg}) = 4 \cdot (V_{\text{mean}})^2
\]

where \(V_{\text{max}}\) represents the maximal peak flow velocity distal to the obstruction, and \(V_{\text{mean}}\) represents the mean flow velocity throughout the velocity complex.

Doppler measurements were averaged over 3 cycles in sinus rhythm. The accuracy and validity of the ultrasonographic approach, in aortic stenosis quantification, have been confirmed in numerous laboratories.1213 The effective orifice area (EOA) on the aortic valve was calculated as follows

\[
\text{EOA} (\text{cm}^2) = \text{CSA} \cdot \left(\frac{\text{VTI}_{\text{LVOT}}}{\text{VTI}_{\text{jet}}}\right)
\]

where CSA is the cross-sectional area of the left ventricular outflow tract, \(\text{VTI}_{\text{LVOT}}\) is the velocity time integral from the left ventricular outflow tract, and \(\text{VTI}_{\text{jet}}\) is the velocity time integral from the transaortic waveform.14

Carotid Artery B-Mode Ultrasound
Carotid artery examination was performed with an ECG-triggered echo-Doppler Acuson AU4-Idea (Esaote Biomedica) equipped with a 7.5-mm probe, by the same sonographer during the whole study. Common, internal, and external carotid arteries and carotid bulb were studied in longitudinal and transverse planes with anterior, lateral, and posterior approaches. Data collected on the left common carotid artery were used for statistical analyses.

A preliminary scan verified the presence of plaques and/or stenosis in the carotid tree. Afterward each examination was recorded on videotape for an offline measurement of IMT and diameter in the common carotid artery, which was performed by a different investigator who was, however, the same during the whole study. IMT was defined as the distance between the lumen-intima interface and the media-adventitia interface of the far wall. Internal diameter (ID) was defined as the distance between the leading edge of the lumen-intima interface of the near wall and the leading edge of the lumen-intima interface of the far wall. Frames from video recording were displayed on a computer screen and analyzed by software that allows quantitative evaluation of IMT and diameter.9 The reader was blinded to the patient and time to which the images belonged. IMT was measured on 3 systolic frames (taken at the T wave of the ECG) in anterior, lateral, and posterior scans, 1 cm proximal to the bulb. Intraobserver coefficient of variation for IMT measurement was 3.3±1.64. ID was measured at the R wave (ID R) and T wave (ID T) of the cardiac cycle in the same scan. The former represents the narrowest luminal diameter and the latter the largest. Flow velocities were automatically detected by the instrument using the smallest size of the sample volume placed in the center of the vessel and keeping the angle between ultrasound beam and the longitudinal vessel axis between 45° and 56°. After 1 minute for stabilization, systolic peak velocity (V sp) and mean centerline velocity (V cl) were recorded as the mean of 3 cardiac cycles. The coefficient of variation was 3.14±2.05 for V sp measurement and was 5.39±1.41 for V cl.

Blood Viscosity and Shear Stress Evaluation
On the same day as the echo-Doppler examination, a blood sample was withdrawn from an antecubital vein after the subject had fasted overnight. Hematocrit was measured by a standard method. Blood viscosity (η) was measured at the shear rate of 225/s, in vitro at 37°C, with the use of a cone/plate viscometer (Wells-Brookfield DV III; Brookfield Engineering Laboratories).

Peak (τ p) and mean (τ m) wall shear stress were calculated according to the following formulas

\[
\tau_p (\text{dyne/cm}^2) = 4 \cdot \eta \cdot V_{\text{sp}} / ID_R
\]

\[
\tau_m (\text{dyne/cm}^2) = 4 \cdot \eta \cdot V_{\text{cl}} / ID_R
\]

where V is expressed in centimeters per second, ID in centimeters, and η in poise.

Reproducibility data and coefficients of variation for wall thickness, diameter, and wall shear stress calculation have been previously reported.9

Blood flow (BF) was calculated as the product of mean cross-sectional velocity, assumed to be half the V cl, and area, according to the following formula

\[
\text{BF} (\text{mL/s}) = V_{\text{cl}} \cdot 2 \cdot \pi \cdot (ID_R/2)^2
\]

Pulsatility index (PI) was calculated as an estimate of vasomotor tone in the circulation downstream in the common carotid.1516 PI was obtained from velocities in the common carotid artery with the use of the following formula

\[
\text{PI} = (V_{\text{sp}} - V_{\text{Ed}}) / V_M
\]

where V ed is end-diastolic velocity.

The Reynolds number (R) was calculated according to the following formula

\[
R = \rho (V_{\text{sp}}/2) (ID_R/2) / \eta
\]

where ρ is the blood density (assumed to be 1060 · 10³ kg/m³). A Reynolds number value <1000 is usually considered characteristic of laminar flow.

Aortic Surgery
After median sternotomy, all patients underwent aortic valve replacement with mechanical bileaflet prostheses under mild hypothermic cardiopulmonary bypass. Myocardial protection was achieved both with topical hypothermia and with intermittent infusion of cold crystalloid solution (St Thomas) directly in the coronary ostia. The same group of surgeons performed all the procedures. Aortic prostheses were implanted in intra-annular position with simple interrupted sutures (without pledgets) (Tevdek 2/0). The hinge area was positioned at 90° with the intraventricular septum. Mechanical bileaflet prosthesis was implanted in all cases.

Statistical Analysis
All analyses were performed with Statview 4.5/Macintosh statistical software. ANOVA for repeated measures and Bonferroni post hoc test were used to compare vascular parameters and shear stress at baseline and at different times after surgery. The Pearson correlation coefficient was used to test the association between wall shear stress and IMT.
TABLE 1. Clinical and Biochemical Characteristics of Studied Subjects

<table>
<thead>
<tr>
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<th>Patients</th>
<th>Controls</th>
<th>P</th>
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<tbody>
<tr>
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<td>11</td>
<td></td>
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<tr>
<td>Age, y</td>
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<td>63.5±6.8</td>
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<tr>
<td>Sex, M/F</td>
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<td>4/7</td>
<td>NS</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<td>27.3±4.6</td>
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<tr>
<td>SBP, mm Hg</td>
<td>128.6±20.5</td>
<td>134.0±12.9</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>80.9±15.3</td>
<td>81.1±6.9</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.18±1.43</td>
<td>6.05±1.38</td>
<td>≤0.04</td>
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<tr>
<td>Triglycerides, mmol/L</td>
<td>1.35±0.35</td>
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<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.31±0.38</td>
<td>1.25±0.41</td>
<td>NS</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>5.49±1.03</td>
<td>5.73±0.67</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Values are mean±SD.

### Results

Clinical, biochemical, and anthropometric data of studied subjects are reported in Table 1. Two patients had body mass index >30 kg/m², 1 had diabetes mellitus treated by diet and oral hypoglycemic drugs, 2 had mild hypercholesterolemia treated by diet, and 2 were current smokers. Moreover, 2 patients had a positive history for vascular acute accident (stroke and myocardial infarction). Controls had slightly but significantly higher levels of triglycerides.

Baseline hemodynamic, hemorheologic, and echographic parameters recorded in the left common carotid artery of patients and controls are reported in Table 2. Systolic peak velocity was significantly higher in healthy subjects, whereas end-diastolic and mean velocity were significantly higher in patients. Internal diameter and IMT of the common carotid were similar in both groups. Patients had lower hematocrit, blood viscosity, and peak and mean wall shear stress. Blood flow was slightly higher in patients, but the difference was not statistically significant. Pulsatility index was markedly lower in patients with aortic stenosis than in control subjects. Echo-Doppler examination of carotid arteries showed the presence of plaques in 7 patients: in 3 the plaques were located in the internal carotid artery, and in 4 they were located in the bulb. Five control subjects had plaques in extracranial carotid arteries.

Aortic valve replacement, as expected, led to marked reduction in peak pressure drop (117±22 versus 24±13 mm Hg before versus 1 month after, respectively; P=0.0001) and mean pressure drop (73±14 versus 13±8 mm Hg; P<0.0001), while effective orifice area significantly increased (0.55 versus 1.78 cm²; P<0.0002).

Table 3 shows hemodynamic and echographic characteristics of patients before and at different times after surgery. Systolic peak velocity increased by 12% 1 month after surgery but returned to basal levels 6 months later. End-diastolic velocity, mean velocity, and internal diameter were unchanged throughout the study. Hematocrit and blood viscosity, almost unchanged 1 month after surgery, significantly increased at 6 months. Peak and mean wall shear stress increased during the study. IMT decreased by 17% 1 month after aortic valve replacement and remained constant at the 6-month follow-up (Figure 1). No variations were observed in blood flow, Reynolds number, and pulsatility index.

IMT was strongly and inversely associated with peak (r=0.451; P=0.008) and mean wall shear stress (r=0.467, P=0.006), as shown in Figure 2.

### Discussion

The results of the present study demonstrate that carotid artery remodeling occurs after aortic valve replacement in subjects with aortic stenosis. IMT of the common carotid artery decreases, along with a marked increase in wall shear stress. Arterial diameter is almost unchanged after surgical
Aortic stenosis is usually not associated with carotid atherosclerosis; instead, it has been previously reported to have a protective effect on the wall thickness of carotid arteries. The aortic valve narrowing probably avoids blood pressure increases, thus protecting the arterial wall. We selected subjects with severe aortic stenosis for 2 reasons. First, they have a disturbed blood flow, caused by narrowing of the aortic valve, which can be promptly reversed by surgical therapy. This provides advantages over other experimental models, eg, chronic heart failure. Indeed, in patients with chronic heart failure the blood flow is probably disturbed, and the condition can be reversed by appropriate medical therapy, but the improvement is gradual and not of the same extent in all the subjects. The second reason deals with the relative protection of the arterial tree of these subjects. In the present study none of the patients had flow-disturbing lesions of the carotid tree, although 7 had plaques either in the internal carotid or in the bulb. This allows avoidance of the disturbing influence of severe atherosclerotic lesions on flow parameter measurement.

Three main findings arise from the present study. First, patients with aortic valve stenosis have lower levels of wall shear stress compared with age-matched control subjects. The difference, at least in the present population, is accounted for by lower blood viscosity and lower flow velocity, whereas vessel diameter is comparable in patients and controls. The low blood viscosity is mainly due to the reduced hematocrit level. In subjects with aortic stenosis, a reduced survival time of red blood cells, which is dependent on pressure gradient, has been described. Although frank hemolysis was excluded in all participants by routine laboratory tests, it cannot be excluded that reduction of red blood cell survival is responsible for the low hematocrit level of these subjects. The reduced peak flow velocity is directly dependent on aortic stenosis and has been previously described by others. In the present study peak velocity, before valve replacement, was directly associated with the effective orifice area of the aortic valve (data not shown). It must be emphasized that, despite peak flow velocity reduction, the blood flow was similar or even slightly higher in subjects with aortic stenosis. In our opinion, this might be the consequence of a marked reduction in vascular resistance, as demonstrated by extremely low values of pulsatility index in subjects with aortic stenosis. The increased blood flow probably warrants appropriate oxygen delivery, otherwise impaired by the low hematocrit.

Second, aortic valve replacement is able to modify wall shear stress in the common carotid artery. Indeed, after valve replacement the effective orifice area significantly increased in all subjects, and as well the flow velocity increased 1 month after the intervention, approaching values observed in control subjects. Other authors have reported similar findings. In the study by Cardon et al, all of 30 patients scheduled for aortic valve replacement for aortic stenosis showed higher systolic peak velocity postoperatively. In the present study, 4 weeks after surgical treatment, no changes of hematocrit and blood viscosity were recorded. Mean velocity and internal diameter were also constant, and therefore blood flow was substantially unaltered. The increase in peak flow velocity yielded higher wall shear stress levels. In the long term, on the other hand, peak flow velocity returned to basal levels, but a substantial increase in hematocrit and blood viscosity occurred, resulting in a further rise in wall shear stress. At this time, blood flow dropped to levels observed in control subjects. It can be hypothesized that the hematocrit level plays a central role in regulating blood flow to precisely meet oxygen demand.

Third, IMT of the common carotid artery promptly decreases after surgical intervention. It is known that common carotid wall shear stress and IMT are inversely related. However, it was not known whether, in vivo in humans, variations in wall shear stress were followed by similar variations in IMT. Indeed, in the present study IMT was inversely related to wall shear stress measured before and after aortic valve replacement. This is probably the first in vivo demonstration that wall shear stress changes are related to correspondent IMT variations. This supports the hypothesis that improved hemodynamic condition, in terms of increased shear stress, is able to influence a profound arterial remodeling. It is known that shear stress modulates the transcription of genes for nitric oxide synthase, platelet-derived growth factor, transforming growth factor-β1, and other factors, all involved in vascular remodeling. Our present data suggest that the modulation of these genes leads to arterial remodeling, detectable by echography in terms of IMT modification, in a short time (4 weeks). This observation has important potential implications for studies that seek to verify IMT variations after lifestyle and/or therapeutic inter-
vention. Stable hemodynamic conditions are mandatory throughout these studies to avoid marked IMT variation independent of the intervention.

In conclusion, the results of the present study, although obtained in a relatively small number of patients, clearly demonstrate that arterial remodeling occurs in the common carotid artery after surgical intervention for aortic stenosis. The remodeling process is extremely rapid and is probably sustained by variation in wall shear stress.

References
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