Effect of Endothelial Shear Stress on the Progression of Coronary Artery Disease, Vascular Remodeling, and In-Stent Restenosis in Humans

In Vivo 6-Month Follow-Up Study

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Background—Native atherosclerosis and in-stent restenosis are focal and evolve independently. The endothelium controls local arterial responses by transduction of shear stress. Characterization of endothelial shear stress (ESS) may allow for prediction of progression of atherosclerosis and in-stent restenosis.

Methods and Results—By using intracoronary ultrasound, biplane coronary angiography, and measurement of coronary blood flow, we represented the artery in accurate 3D space and determined detailed characteristics of ESS and arterial wall/plaque morphology. Patients who underwent stent implantation and who had another artery with luminal obstruction <50% underwent intravascular profiling initially and after 6-month follow-up. Twelve arteries in 8 patients were studied: 6 native and 6 stented arteries. In native arteries, regions of abnormally low baseline ESS exhibited a significant increase in plaque thickness and enlargement of the outer vessel wall, such that lumen radius remained unchanged (outward remodeling). Regions of physiological ESS showed little change. Regions with increased ESS exhibited outward remodeling with normalization of ESS. In stented arteries, there was an increase in intima- medial thickness, a decrease in lumen radius, and an increase in ESS at all levels of baseline ESS.

Conclusions—The present study represents the first experience in humans relating ESS to subsequent outcomes in native and stented arteries. Regions of low ESS develop progressive atherosclerosis and outward remodeling, areas of physiological ESS remain quiescent, and areas of increased ESS exhibit outward remodeling. ESS may have a limited role in in-stent restenosis. This technology can predict areas of minor plaque likely to exhibit progression of atherosclerosis. (Circulation. 2003;108:438-444.)

Key Words: endothelium ■ atherosclerosis ■ coronary disease ■ shear stress

Coronary atherosclerosis is focal and eccentric,1,2 and each coronary obstruction progresses or regresses in an independent manner, including areas after percutaneous revascularization.3 Local hemodynamic factors are crucial to determine the evolution of coronary obstructions.1,4 The vascular endothelium is in a pivotal position to respond to the dynamic forces acting on the vessel wall owing to the complex 3D geometry of the artery.5 Fluid shear stresses elicit a large number of responses in endothelial cells.4,5 The response of genes sensitive to local hemodynamic forces likely leads to creation of a raised plaque; subsequent hemodynamic forces created by the plaque may lead to a cycle of cellular recruitment and proliferation, lipid accumulation, and inflammation.4,6

The pathobiology of restenosis after percutaneous coronary interventions may be due to 2 independent processes: geometric remodeling and neointimal hyperplasia. In segments undergoing angioplasty alone, late lumen loss is largely due to geometric remodeling, whereas in stented arteries, late lumen loss correlates primarily with intimal hyperplasia.7 The effect of endothelial shear stress (ESS) within the stent or at the stent edges has not been fully explored as a mechanism contributing to in-stent restenosis.8

Current methodologies cannot provide adequate information about the microenvironment of the coronary arteries. We developed a unique system by using coronary intravascular ultrasound (IVUS), biplane coronary angiography, and measurements of coronary blood flow to represent the artery in
accurate 3D space and to produce detailed characteristics of ESS and arterial wall/plaque morphology.\textsuperscript{9–12} The purpose of the present study was to determine whether in vivo characterization of ESS in humans would permit prediction of the sites and rate of progression of coronary artery disease (CAD) in arteries with minor obstruction, as well as the development of in-stent restenosis.

Methods

The present study was part of a larger study looking at the effects of candesartan versus felodipine on progression of atherosclerosis and in-stent restenosis. It also served as a pilot study to determine the feasibility of serial intracoronary investigations. Patients were eligible if they underwent stent deployment, had another coronary artery with a 25% to 50% luminal obstruction, and had a history of arterial hypertension. Exclusion criteria included ejection fraction <40%, serum creatinine >1.5 mg/dL, 3-vessel coronary disease, or valvular disease. Intracoronary profiling was performed on the stented arterial segment and the arterial segment with <50% luminal obstruction, after administration of parenteral nitroglycerin or verapamil. One patient had low blood pressure at the baseline study and could not receive nitroglycerin. After completion of intracoronary profiling, patients were randomized to receive candesartan or felodipine titrated to maintain blood pressure \( \leq 140/90 \) mm Hg. Patients were readmitted 6 months after randomization for repeat intracoronary profiling. The study was approved by the investigative review board of Brigham and Women’s Hospital. Each patient provided written informed consent.

Our methods of intracoronary profiling have been previously described.\textsuperscript{9–12} In brief, the 3D anatomy of the artery was reconstructed from IVUS images and biplane coronary angiography. IVUS (Boston Scientific) was performed with controlled pullback at 0.5 mm/s. The ECG was recorded on the IVUS images. The arterial lumen and outer vessel wall were reconstructed from digitized and segmented end-diastolic IVUS frames,\textsuperscript{11} using a previously validated semiautomated segmentation approach to identify lumen and external elastic membrane (EEM) borders.\textsuperscript{9} The physical 3D path of the IVUS transducer during pullback was determined by using the corresponding biplane angiographic projections. The 3D reconstructed catheter core served as the stem on which to rebuild the 3D geometry. The 3D position of each ECG-gated IVUS frame was determined from the reconstructed trajectory of catheter pullback and pullback speed.\textsuperscript{13} The rotation of the frame was determined by using computational geometry.\textsuperscript{11} Each frame was aligned perpendicular to the catheter core.

The boundary points of each frame were connected by spline curves to rebuild the luminal geometry in 3D space. A structured grid that used a body-fitted coordinate system was employed to represent the lumen volume. The lumen was divided into computational control volumes comprising 0.3-mm-thick slices along the segment, 40 equal intervals around the circumference (lumen interface), and 16 intervals in the radial direction from the center of the reconstructed lumen.

Coronary blood flow for the arterial section being studied, a section chosen free of significant side branches that may significantly alter the flow, was calculated directly from the time required for the volume of blood contained within the section to be displaced by radio-opaque material during a contrast injection. The true 3D volume of the segment was first calculated from the lumen borders, as described above. The number of cine frames required for the opacified material to pass from the inlet of the section to the outlet was counted. The flow rate (mL/s) was calculated as 15 frames per second \( \times \) volume (mL)/frame count.

The detailed intravascular flow characteristics were obtained by solving the transport equations governing the conservation of mass and momentum.\textsuperscript{10} We assumed that the arterial wall was stiff and that blood was incompressible, homogeneous, and newtonian.\textsuperscript{14} For simplicity, we assumed steady flow. The governing equations were integrated over the computational control volumes, and the resulting algebraic equations were solved by using a fully implicit, guess-and-correct algorithm embodied in the PHOENICS computer code. The computations were considered converged when the maximum change in the velocity field between iterations was <0.1%. The shear stress at the luminal surface of the artery was calculated as the product of viscosity (calculated from the measured hematocrit) and the gradient of blood velocity at the wall.

The 3D geometry of the outer vessel wall (area within the EEM) was recreated in a manner similar to that described for the lumen geometry. The 3D geometry of the plaque (plaque plus media thickness) was taken as the difference between the outer vessel wall and the lumen.\textsuperscript{15} Figure 1 illustrates an example of the coronary angiogram and the 3D reconstructed coronary artery.

The processes of data acquisition and data analysis are highly reproducible.\textsuperscript{16} The \( r \) values for reproducibility for measurements of lumen radius, outer vessel wall radius, plaque thickness, and ESS were 0.96, 0.96, 0.94, and 0.91, respectively (each, \( P<0.0001 \)). The SD of repeated coronary blood flow measurements was 3% between measurements, with a maximum of 5%.

Statistical Analysis

Each arterial segment was mapped and divided on its lumen surface into \( \approx 2560 \) to 10 640 independent rectangular patches (average of 5900 zones [250×300 mm]/arterial segment). Each lumen surface patch had an ESS and a corresponding lumen radius, outer vessel wall radius, and plaque thickness (ie, an “icepick” view of the arterial wall) (Figure 2). Adjacent surface patches of similar ESS values were grouped into regions, and these regions were classified into 6 endothelial “categories,” based on the cumulative percentiles of ESS values, to obtain adequate representation of all values of baseline ESS: category 1, 10th percentile of ESS values (<9.1 dyne/cm\(^2\)); category 2, 25th percentile of ESS (9.1 to 12.6 dyne/cm\(^2\)); category 3, 50th percentile of ESS (12.6 to 19.1 dyne/cm\(^2\)); category 4, 75th percentile of ESS (19.1 to 26.9 dyne/cm\(^2\)); category 5, 90th percentile of ESS (26.9 to 38.3 dyne/cm\(^2\)); and category 6, 97th percentile...
of ESS (38.3 to 55 dyne/cm²). The measurements made at baseline were compared with those made at 6-month follow-up, by matching the regions with the use of IVUS-derived and angiography-derived anatomical landmarks.

The pattern of change in the outcome variables in the 6 categories of similar baseline ESS values was compared against baseline ESS. The changes in these regions were assessed by repeated-measure linear regression, adjusted for within-patient correlation. All analyses were performed by using SAS (version 8.0, SAS).

Results
Ten patients were enrolled. Nine of the patients were male; mean age was 60.8 years (range, 37 to 83 years). All patients were treated with β-blockers, statins, and aspirin. The mean fasting lipids were total cholesterol 156 mg/dL, LDL 95 mg/dL, HDL 36 mg/dL, and triglycerides 150 mg/dL. Mean blood pressure at enrollment was 156/89 mm Hg and at end of the study 137/78 mm Hg. One patient refused recatheterization, and 1 patient developed an acute coronary syndrome and required urgent repeat coronary stenting before the time of the follow-up catheterization. A total of 8 patients underwent serial intracoronary profiling and are included in this report. Twelve coronary arteries were serially studied and were suitable for analysis: 6 native and 6 stented arteries. The native artery studied in these patients included the left anterior descending in 2 patients, the circumflex in 1 patient, and the right coronary in 3 patients. The stented arteries were the left anterior descending in 3 patients, the circumflex in 2 patients, and the right coronary in 1 patient. The hemodynamic parameters for each arterial segment at baseline and follow-up are shown in Table 1. The stent designs used were Scimed Nir Sox stent in 4 patients, Cordis BX Velocity stent in 2 patients, ACS Tetra stent in 1 patient, and AVE stent in 1 patient. Of the 8 patients, 5 were randomized to receive felodipine and 3 to receive candesartan. The study was not powered to compare the effects of the 2 medications and no differences in outcomes were observed on the basis of drug assignment; consequently, all patients were analyzed together.

An example of an artery with a region of abnormally low baseline ESS and a region of increased baseline ESS is displayed in Figure 3.

In the native arterial segments, there were 82 regions of similar baseline ESS (mean region size, 24 mm²; range, 1 to 129 mm²) (Figure 4). The number of regions and the endothelial surface area in each ESS category contributed by each patient are presented in Table 2. Regions of low baseline ESS (categories 1 and 2) showed progression of atherosclerosis, evidenced by an increase in plaque thickness and enlargement of the EEM radius (outward or positive remodeling). The lumen radius did not change, but ESS increased at follow-up. Regions of physiological baseline ESS (categories 3 and 4) showed little change in any vascular variable. Regions of increased baseline ESS (categories 5 and 6)

TABLE 1. Hemodynamic Parameters for Each Arterial Segment at the Index and Follow-Up Catheterization Procedures

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Segment</th>
<th>Heart Rate, bpm</th>
<th>Blood Flow Rate, mL/s</th>
<th>Blood Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Entry</td>
<td>Follow-Up</td>
<td>Entry</td>
</tr>
<tr>
<td>Native segments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>LAD</td>
<td>75</td>
<td>65</td>
<td>0.84</td>
</tr>
<tr>
<td>2</td>
<td>LCX</td>
<td>60</td>
<td>68</td>
<td>1.13</td>
</tr>
<tr>
<td>3</td>
<td>LAD</td>
<td>55</td>
<td>59</td>
<td>0.79</td>
</tr>
<tr>
<td>4</td>
<td>RCA</td>
<td>58</td>
<td>65</td>
<td>1.38</td>
</tr>
<tr>
<td>5</td>
<td>RCA</td>
<td>69</td>
<td>62</td>
<td>1.63</td>
</tr>
<tr>
<td>6</td>
<td>RCA</td>
<td>63</td>
<td>53</td>
<td>1.46</td>
</tr>
<tr>
<td>Stented segments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>LCX</td>
<td>70</td>
<td>68</td>
<td>0.89</td>
</tr>
<tr>
<td>2</td>
<td>LAD</td>
<td>57</td>
<td>69</td>
<td>0.64</td>
</tr>
<tr>
<td>3</td>
<td>RCA</td>
<td>53</td>
<td>59</td>
<td>0.68</td>
</tr>
<tr>
<td>4</td>
<td>LAD</td>
<td>58</td>
<td>70</td>
<td>0.73</td>
</tr>
<tr>
<td>7</td>
<td>LCX</td>
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<td>63</td>
<td>0.84</td>
</tr>
<tr>
<td>8</td>
<td>LAD</td>
<td>52</td>
<td>49</td>
<td>0.99</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending; LCX, circumflex; and RCA, right coronary artery.
Figure 3. Example of an arterial segment with a region of abnormally low baseline ESS (<9.1 dyne/cm²) outlined (A) and a region of increased baseline ESS (>27 dyne/cm²) outlined (B). Data are presented as a “topographical map,” with the artery opened longitudinally and laid flat as a pathologist would view it. A color-coded scale of absolute values is provided. Adjacent endothelial patches of similar ESS form a region, and the regions are classified on the basis of baseline ESS.

showed outward remodeling with an increase in lumen radius and EEM radius and consequent decrease in ESS. The atheroma thickness in regions of increased baseline ESS appeared to decrease as the vessel enlarged, most likely representing redistribution of the plaque volume.

In the stented arteries, there were 29 regions of similar baseline ESS values (mean region size, 24 mm²; range, 2 to 96 mm²) (Figure 5). Within the stented portions of the arteries, there was an increase in intima-medial thickness, a decrease in lumen radius, and, consequently, an increase in ESS at virtually all levels of baseline ESS.

Discussion
The present study represents the first experience in humans relating baseline ESS to subsequent arterial behavior 6 months later. We observed highly focal and independent responses within an artery. In native portions of the artery, regions of pathologically low ESS developed progressive atherosclerosis with outward or positive remodeling, regions of physiological ESS demonstrated little change in vascular morphology, and regions of increased ESS exhibited outward remodeling without progressive atherosclerosis. The dynamic and highly interrelated processes of atherogenesis and vascular responses as a function of ESS are evident. In stented portions of the artery, there was evidence of neointimal hyperplasia, with a decrease in lumen radius and increase in ESS at all levels of baseline ESS.

The different responses observed in atherosclerotic progression and outward remodeling are due to different phenotypic responses in the cellular constituents of the arterial wall. It is likely that the endothelial cells transduce ESS forces that, in turn, trigger many of the responses of the other cellular constituents, including myofibroblasts, smooth muscle cells, and macrophages. Regions with low ESS correlate with sites of atherosclerotic lesions and demonstrate molecular and cellular characteristics of atherosclerosis progression.

We observed that as the plaque thickness enlarged in arterial regions with low ESS initially, the outer vessel wall also significantly enlarged, such that the lumen radius remained unchanged (Figure 4). These in vivo observations provide the first serial studies confirming the predictions made by Glagov et al from autopsy studies. In addition to local ESS, outward remodeling may also be owing to local factors related to the plaque itself or to heterogeneities in circumferential wall stress. The ability to identify where plaque will progress with outward remodeling may be particularly important because recent studies have suggested that plaques responsible for acute coronary syndromes are those that occur in areas of outward remodeling.

Vascular areas in which the ESS was initially in the “physiological” range are known to be protected from atherosclerosis and remain quiescent. Endothelial responses to ESS in this range include tight alignment and elongation of endothelial cells, as well as an enhanced balance favoring cell stability.

We observed outward remodeling in regions of low baseline ESS where the plaque progressed, as well as in regions of increased baseline ESS where there was no plaque progression. There are likely multiple stimuli and mechanistic pathways responsible for outward remodeling as the vessel attempts to restore or maintain the endothelial milieu to the normal hemodynamic range.

Evidence of in-stent restenosis appeared to occur to some degree in each category of baseline ESS in our patients. In the porcine model of in-stent restenosis, as in humans, neointimal thickness is correlated with local factors relating to vessel injury, such as the anatomic depth to which the stent strut penetrates the vessel wall and the local inflammatory response to the stent struts. The effect of ESS on the process of in-stent restenosis, however, is less clear. In a small 6-month study of patients receiving a Wallstent, neointimal thickness was inversely related to ESS, suggesting that a hemodynamic mechanism may contribute to neointimal hyperplasia.

Interestingly, we observed that there were increases in both intimal-medial thickness and outer vessel radius in the stented segments, and these increases were more substantial in areas of baseline increased ESS (Figure 5). Nakamura et al also observed from serial volumetric IVUS analyses that vascular proliferation outside the stent (positive remodeling) was common, and there was a highly significant inverse correlation between change in proliferation outside the stent and the percentage of change of neointima proliferation within the stent.
Limitations

Our study is limited by the small numbers of patients studied. All patients were treated with either candesartan or felodipine. The study was not powered to detect a difference between the 2 agents, and no consistent effect in any variable was observed between them. Although animal data suggested that agents that interfere with the angiotensin system protect against atherosclerosis or in-stent restenosis, clinical trials in humans have not demonstrated such an effect. Similarly, calcium-channel blocking agents have not influenced atherogenesis or restenosis.

We acknowledge the limitations and assumptions used in our calculations. The methodology determines morphology of the arterial segment at end-diastole, a time during which most of the coronary blood flow occurs and the heart is relatively stable. The assumption of steady-state coronary blood flow obscures all phasic phenomena, including the effects of wall compliance. However, we have previously demonstrated that using the average flow in steady-flow calculations yields essentially the same values of ESS (and related parameters) as does calculating the average shear stress from the phasic solution. The errors caused by the assumption of Newtonian viscosity and rigid arterial walls are insignificant in the flow ranges of interest here. We calculated coronary blood flow in the arterial segment by dividing the known volume of the reconstructed segment by the time required for the opacified wave front of blood to travel from the inlet to the outlet of the lumen. Minor errors in determination of flow may result from this technique because some portion of blood flows to very small side branches. However, the arterial segments we studied were free of significant side branches. Other techniques that estimate coronary flow from Doppler velocity measurements yield similar results. The vascular changes observed in the native segments may suggest regression-to-the-mean phenomena. Because the vascular changes observed in the native segments and the stented segments are so different using the same methodology, regression-to-the-mean is likely exerting little, if any, effect. The fact that the observed outcomes from using our methodology are entirely consistent with predictions based on previous in vitro and animal experiments supports the adequacy of the methodology. Focal changes in lumen radius may actually be underestimated by our method because there may be multiple ESS regions at a cross section and any changes in one region may be blunted by changes in neighboring regions.

Conclusions

The methodology used in the present study allows, for the first time in humans, the serial in vivo investigation of the natural history of native and stented coronary disease. Our studies underscore the rapidly changing behaviors of different areas within a coronary artery in response to different environments. Detailed ESS evaluation may give further insight to understand the initial development and growth of arterial plaque.

Figure 4. Artery outcomes in the native arteries as a function of baseline ESS. The x-axis displays the baseline ESS categorized into 6 categories on the basis of cumulative percentiles of ESS values, as described in the text. Within each category of baseline ESS, the regions of the artery at baseline with those ESS values are presented. Within each ESS category, the total area of the respective regions on each bar and the number of regions in the category in parentheses are displayed. The y-axis displays the change in the vascular variable after 6 months. There were significant changes in plaque thickness and ESS (P < 0.001) and lumen radius (P = 0.03) as a function of baseline ESS. EEM radius appeared to increase most within regions of low baseline ESS, but it increased to some degree in most categories of baseline ESS.
progression of atherosclerosis, the subsequent vascular responses to the abnormal environment created by the atherosclerosis, and the vascular responses to stent implantation.

### Acknowledgments

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**TABLE 2. Regions and the Endothelial Surface Area Contributed by Each Patient in Each ESS Category of Native Arterial Segments at Baseline**

<table>
<thead>
<tr>
<th>ESS Category</th>
<th>1</th>
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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Total</th>
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<tbody>
<tr>
<td>No. of regions</td>
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<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>...</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>2</td>
<td>1</td>
<td>...</td>
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<td>4</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>...</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>12</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>9</td>
<td>82</td>
</tr>
</tbody>
</table>

| Total area, mm² | 1 | 7.3 | 35.7 | 97.3 | 23.2 | 19.6 | 14.5 | 198 |
| 2 | 2.8 | 16.8 | 106 | 116 | 10.6 | ... | ... | 252 |
| 3 | ... | 30.6 | 42.8 | 20 | ... | ... | 93.4 |
| 4 | 8.4 | 11.1 | 36.8 | 189 | 160 | 76.9 | 482 |
| 5 | 136 | 91.1 | 138 | 75.3 | 72.6 | 22.1 | 535 |
| 6 | 86 | 161 | 82.7 | 55 | 3.05 | ... | 367 |
| Total | 240 | 346 | 504 | 478 | 266 | 114 | 1948 |

**Figure 5.** Artery outcomes after 6 months in the stented portions of the stented arteries as a function of baseline ESS. Structure as in Figure 4. Intima-medial thickness increased, lumen radius decreased, and ESS increased in each category of baseline ESS. The magnitude of changes in lumen radius ($P=0.02$), ESS ($P=0.003$), and EEM ($P=0.003$) were associated with the category of baseline ESS.
References


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