Relation of Vessel Wall Shear Stress to Atherosclerosis Progression in Human Coronary Arteries


The purpose of this study was to determine the relation between vessel wall shear stress and the rate of atherosclerosis progression. Quantitative angiography was used to calculate the change in coronary arterial diameter over 3.0 years in patients enrolled in the Harvard Atherosclerosis Reversibility Project pilot study (n=20 arterial segments). Vessel wall shear stress was calculated by means of a validated finite-difference model of the Navier-Stokes' equation that assumes a coronary flow rate of 8 ml/sec. The correlation between vessel wall shear stress and the change in arterial diameter at multiple points (mean, 70) along the length of the artery was then calculated for each of the 20 segments with a focal stenosis. In 15 of the 20 arterial segments there was a significant correlation (p<0.05) between low shear stress and an increased rate of atherosclerosis progression. A Fisher's z transformation was then used to combine the correlation coefficients from all 20 segments. Low shear stress was significantly correlated (z=0.37 ± 0.00074, p<0.0001) with an increased rate of atherosclerosis progression. This serial quantitative evaluation of human coronary arteries is consistent with previous data that have suggested that low shear stress promotes atherosclerosis progression. Variations in local vessel wall shear stress may explain the previously reported near-independent rate of atherosclerosis progression in multiple lesions within the same patient despite exposure to the same circulating lipoprotein values and systemic hemodynamics. (Arteriosclerosis and Thrombosis 1993;13:310-315)

KEY WORDS • atherosclerosis progression • vessel wall shear stress • hemodynamics • quantitative angiography

There is a large body of evidence, provided largely by serial angiographic techniques, to support the role of lipoproteins in promoting coronary atherosclerosis progression. However, we have previously reported that despite being exposed to the same concentrations of serum lipoproteins and systemic hemodynamics, coronary arterial obstructions within the same patient progress at near-independent rates. Similarly, right coronary artery lesions seem to progress at a more rapid rate than those of the left anterior descending coronary artery, and coronary segments proximal to the insertion of a saphenous vein graft progress at a more rapid rate than those distal to graft insertion. These recent findings support the hypothesis that in addition to systemic risk factors, local mechanical forces may also play a role in determining the rate of atherosclerosis progression. The role of mechanical forces in human coronary atherosclerosis progression has been previously investigated by the use of casts of vascular structures such as the aorta or carotid circulations. The purpose of this study was to determine by means of quantitative angiography if shear stress at multiple points along the length of the human coronary artery could be related to the rate of atherosclerosis progression over time in vivo.

Methods

Patient Selection

The Harvard Atherosclerosis Reversibility Project (HARP) pilot study was undertaken to assess the rate of change in coronary artery diameter in patients treated by means of either diet or medication over 3.0 years to develop quantitative angiographic techniques and statistical methods for the analysis of atherosclerosis regression data. Angiographic data from all 26 patients (total of 74 lesions) randomly assigned to one of two dietary therapies or a third stepped-drug therapy were available for analysis. A group of eight patients followed standard American Heart Association dietary guidelines and consumed less than 300 mg/day of dietary cholesterol. Dietary fat was restricted to less than 35% of daily caloric intake and saturated fats to less than...
10%. A second group of nine patients were counseled to consume less than 80 mg/day of dietary cholesterol, and saturated fats were restricted to less than 3% of daily calories. The second group of patients did not reach the dietary goals: 6.9% of their daily calories actually contained saturated fats. A third group of nine patients were treated with 1.5–3.0 g niacin daily with a target total cholesterol of 150 mg/dl. Two of the nine patients also required the addition of cholestyramine in an attempt to reach this target.

**Cardiac Catheterization Methods**

The initial cardiac catheterization conditions were reproduced at the time of repeat coronary angiography to minimize potential variability in vasomotor tone and hemodynamic parameters; they included the dosing of vasoactive and cardioactive medications (β-blockers, nitrates, and Ca^2+ channel blockers), the type of contrast agent, and the sequence of angiographic views. The angle and skew of the gantry were also reproduced to minimize changes in the magnitude of out-of-plane magnification and ensure that eccentric lesions would be filmed at the same angulation.

**Quantitative Angiographic Analysis**

Initial and repeat cinefilms were simultaneously viewed on two cineprojectors so that five consecutive frames from the same phase of the cardiac cycle (preferably end-diastolic frames) could be chosen by two angiographers for quantitative angiographic analysis. A previously described and validated automated edge-detection algorithm was used. The cineframes were optically magnified by a factor of 2.3 with a Nikon AF Micro Nikor 55-mm 1:2.8 lens. The cinefilm images were digitized as 512x512x8 bits by means of a Vidicon camera/digitizer interfaced with a MicroVax 2 computer, which provided a spatial resolution in the image field that was 6–8 pixels/mm. An approximation of the centerline of the arterial segment was provided by the operator; then a preliminary estimate of the arterial border was made. A series of 256 gray-scale densitometric profiles that characterized the intensity of pixels aligned orthogonally to this centerline were generated at each pixel (approximately 0.12–0.16-mm intervals) along the length of the artery in a second iteration. A fifth-degree polynomial was fit to the left and right sides of each densitometric profile, and the edge of the vessel was defined as the inflection point or the zero value of the second derivative of this expression. A second determination of the centerline was recalculated based on this estimate of the refined vessel edge. Then a third iteration of the vessel border calculation was performed based on this refined centerline. The pincushion distortion generated by each image intensifier was independently characterized with an orthogonal grid and corrected for by means of bilinear interpolation.

At every pixel (approximately 0.12–0.16 mm, depending on the optical magnification) along the length of the vessel, the arterial diameter was calculated as described above. The minimum arterial diameter was defined as the minimum value of a polynomial fit to the five consecutive diameters adjacent to the smallest single-diameter estimate in a region of interest. The “normal” reference arterial segment diameter was defined as the average arterial diameter of an operator-selected portion of the vessel that appeared normal by angiography. Percent stenosis was defined as

\[
(1 - \frac{\text{minimum diameter}}{\text{normal" reference arterial segment diameter}}) \times 100
\]

**Hemodynamic Evaluation of Arterial Stenoses by Computer Simulation**

To ensure that the same portion of the segment was analyzed at the time of the initial and repeat studies, fixed anatomic landmarks such as branch points were used. The segments were aligned according to these fixed landmarks, and only those identical portions of the segment that were present at both cardiac catheterizations were compared to estimate the change in diameter. Coronary arterial segments were deemed suitable for analysis subject to the following conditions: they contained a narrowing of greater than 20% stenosis by visual inspection, and the length of the segment at the time of repeat cardiac catheterization was within 10% of that at initial catheterization. The latter condition was intended to eliminate those segments in which there was a significant change in the degree of foreshortening at the time of the follow-up (repeat) study.

A previously described and validated finite-difference model of the Navier-Stokes’ equation (FLUENT Inc.) was used to assess vessel wall shear stress at numerous points along the vessel length. The geometry of the vessel at the time of the baseline (initial) study was used to calculate shear stress. This model assumes that blood density is constant (i.e., it is not compressible) and its rheological behavior is newtonian (i.e., shear stress equals viscosity times velocity gradient across the plane of stress). The single-plane dimensions of the coronary arteries were assumed to be axially symmetrical and rigid, with a constant coronary flow rate. The model simulates two-dimensional flow characteristics, including the potential for flow separation.

The diameter of the artery was calculated by means of quantitative angiography at 0.12–0.16-mm intervals, depending on the optical magnification used in the digitization process. These vessel diameters and their coordinates along the length of the vessel were then downloaded to the hemodynamics program, which in turn identified the discrete “wall elements” necessary for the analysis. The entrance velocity profile was assumed to be fully developed and parabolic.

**Statistical Methods**

All results are expressed as mean±SEM. The correlation coefficient between the change in arterial diameter and vessel wall shear stress at each point (every 0.12–0.16 mm) along the length of the artery was calculated for each segment. The number of data points analyzed along the length of the vessel numbered 36–93, with a mean of 70.3. The 20 correlation coefficients from the different arterial segments were then combined by Fisher’s z transformation: Let \( r_i \) denote the correlation coefficient for the \( i \)th vessel. Then

\[
z_i = \frac{1}{2} \ln \left[ 1 + r_i \right] - \ln \left[ 1 - r_i \right]
\]
The mean $z$ value for all $i$ segments, $z_{\text{mean}}$, is then calculated as

$$z_{\text{mean}} = \frac{\sum_{i=1}^{20} z_i w_i}{\sum_{i=1}^{20} w_i}$$

where $w_i = n_i - 3$ and $n_i$ equals the number of diameter estimates along the length of the vessel used to calculate $r_i$ in the $i$th vessel. The variance of $z_{\text{mean}}$ or $\sigma_{z_{\text{mean}}}^2$ can be calculated as

$$\sigma_{z_{\text{mean}}}^2 = \frac{1}{\sum_{i=1}^{20} w_i} \sum_{i=1}^{20} w_i z_i^2 - \left( z_{\text{mean}} \right)^2$$

The $z_{\text{mean}}$ was divided by the standard error of $z_{\text{mean}}$ to arrive at the value used to test significance by use of the cumulative normal-frequency distribution (i.e., a $z$ test). Other statistical values are presented as mean±SEM.

**Results**

The mean initial percent stenosis was 43.9±3.1% (the "normal" proximal reference arterial segment [if present] was used to gauge percent stenosis and the "normal" distal one if it was not) and the mean initial minimum diameter 1.74±0.15 mm. Along the length of the 20 coronary arteries, a total of 1,406 calculations of coronary blood flow velocity at the vessel wall were made. Among these calculations there were 20 instances of coronary blood flow reversal. By visual assessment 17 of the lesions were concentric and 10 of the segments analyzed were straight and three were curved. Ten of the lesions were concentric and 10 eccentric (the ratio of atherosclerotic plaque thickness in the most diseased portion of the wall to the less diseased opposite wall was greater than 2) by visual assessment. None of the lesions was extremely eccentric, in which case there was outward bulging of the less diseased side of the vessel wall to accommodate the large amount of plaque on the opposite wall. Over the course of 3 years in these 20 arterial segments, there was a significant ($p<0.05$) decrease ($-0.19±0.09$ mm) in the minimum diameter and a worsening (i.e., an increase in percent stenosis) of 2.9±2.4% ($p=NS$). Analysis of those segments with both a proximal and distal "normal" reference arterial segment present ($n=8$) showed that the proximal one decreased in diameter by $-0.01±0.11$ mm ($p=NS$) and the distal one by $-0.19±0.13$ mm ($p=NS$). Although the distal segment decreased in diameter at a slightly more rapid rate than the proximal one, this 0.18-mm difference was not significant by paired $t$ test.

The correlation between local wall shear stress and the change in arterial diameter is displayed in Table 1, and an example is illustrated in Figure 1. In 15 of the 20 arterial segments, lower shear stress at each point along the length of the vessel at the time of initial coronary angiography was significantly ($p<0.05$) correlated with a larger reduction in arterial diameter at the time of follow-up coronary angiography. The significant correlation coefficients ($r$ values) ranged from $-0.26$ to $-0.66$. As shown by one of the lesions illustrated in Figure 1, the relation between shear stress and the change in diameter was continuous. When all 20 of the correlation coefficients from each arterial segment were combined by Fisher's $z$ transformation, the $z_{\text{mean}}$ value was 0.37±0.00074 and was highly significant ($p<0.0001$).

**Discussion**

There is considerable evidence to support the role of lipoproteins in atherosclerosis progression. The role of mechanical forces in the progression of human coronary artery disease has been previously investigated. This study demonstrates that there is a significant correlation between low vessel wall shear stress and an increased rate of atherosclerosis progression in human coronary arteries in vivo. Variations in local coronary artery hemodynamics may explain the previously observed independent rate of atherosclerosis progression among multiple vessels within the same patient despite exposure to the same lipoprotein concentrations.

It has previously been observed that human atherosclerotic lesions form more frequently at the outer walls of vessel branch points and along the inner walls of curved arterial segments. Both sites show low shear stress, in which flow separation, flow reversal, turbulence, and eddying occur. Friedman et al., Zarins et al., and Ku et al. have estimated shear stress with laser-Doppler anemometry and found that low shear stress correlates with increased intimal thickening. In the analysis of human coronary arteries, Asakura and Karino have recently used high-speed cinemicrography to analyze flow in Plexiglas coronary arterial casts.
They observed complex secondary flow patterns and standing recirculation zones. These regions of low shear stress seemed to be the preferred sites of atherogenesis. No lesions were observed at the flow divider of branch points, which are sites of high shear stress.

This study extends the results of these previous studies by examining the relation between shear stress and the change in luminal diameter over time instead of the relation between shear stress and the presence of lesions at a signal point in time in a cast of a vessel. This study also provides quantitative data regarding both the change in coronary arterial diameter and shear stress. Our findings are consistent with the hypothesis that low shear stress promotes an increased rate of luminal narrowing in moderately diseased human coronary arteries.

While previous studies have focused largely on the relation between flow separation or flow reversal and the presence of atherosclerotic lesions, this study involved lesions of moderate severity (mean percent stenosis, 43.9%), and there were few instances of frank flow reversal (1.4% of velocity values). However, despite the infrequency of frank flow reversal, low velocity near the wall (not necessarily reversed flow) was correlated with an increased rate of luminal narrowing. Asakura and Karino have also observed the presence of lesions in regions of slow flow (not exclusively in regions of reversed flow) and low shear stress. Furthermore, we have found that there is a continuous relation between low shear stress and an increased rate of luminal narrowing, and there were no discrete subpopulations of shear stresses at which luminal narrowing occurred. This observation is consistent with previous ones that atherosclerotic lesions arise and taper gradually, which has been postulated to be the result of a smooth, continuous rise and fall in shear stress along the length of the vessel.

This study analyzed the progression of disease not only in the narrowest portion of the vessel but also in the "normal" reference arterial segment adjacent to the minimum diameter. Inclusion of portions of the vessel adjacent to the focal stenosis is necessary because it ensures that the length of the artery analyzed will extend from branch point to branch point. Only through the use of these fixed landmarks can the segments be precisely aligned for comparison of the initial and repeat studies. Inclusion in the analysis of changes in the ostensibly "normal" adjacent reference arterial segment is appropriate because there is abundant autopsy data that demonstrate that these regions are diffusely diseased despite an angiographically "normal" appearance. For example, in the study by Arnett et al., none of the 467 arterial segments was free of atherosclerotic disease in these asymptomatic patients, and 90% of the segments were narrowed by greater than 25% in cross-sectional area. More recently, Leung et al. used quantitative angiography to show that angiographically "normal" reference arterial segments adjacent to focal stenoses are smaller than those without focal lesions in control subjects. Therefore, in the present analysis, the inclusion of a portion of the vessel adjacent to the minimum diameter seems justified because of the diffuse nature of coronary atherosclerosis.

Several hypotheses have been advanced to explain the mechanism by which low vessel wall shear stress might promote the development of atherosclerotic lesions. It has been shown that endothelial cells undergo morphological alterations in response to changes in the degree and orientation of shear stress, with elongated endothelial cells that are located in regions of high shear stress having their long axes aligned parallel to the direction of flow and polygonal endothelial cells in low shear stress regions being aligned in haphazard directions. It has been postulated by Asakura and Karino that these alterations may be responsible for the changes in endothelial cell permeability to atherogenic lipoprotein particles. Yoshizumi et al. have recently shown that low shear stress stimulates the expression of endothelin mRNA and the release of endothelin into the culture medium from cultured porcine endothelial cells. Increased synthesis of endothelin may in turn promote local smooth muscle cell and fibroblast proliferation.

It has also been hypothesized that a reduction or stagnation in the velocity of blood flow permits increased uptake of atherogenic particles as a result of "increased residence time" or prolonged contact with the endothelium, which allows "concentration-induced endocytosis." Once lipoprotein particles are incorporated into the intima, they may then drift because of regional pressure differences to areas of low shear stress, which may act as low pressure "sinks" for atherogenic particles and allow for their permanent deposition. In regions of reduced coronary blood flow velocity and reduced local shear stress, there is also increased...
time for platelets (which may release platelet-derived growth factor and stimulate smooth muscle cell proliferation) and monocytes (which may initiate immunologic injury) to adhere to and interact with the vessel wall.\textsuperscript{24,49} Caro et al\textsuperscript{25} earlier proposed a shear-dependent mass transfer mechanism by which high shear stress increases the gradient favoring efflux of atherogenic particles from the diseased wall. In this hypothesis, further efflux of lipoproteins from the vessel wall is facilitated by the fact that particles that have recently migrated into the bloodstream are washed away.

The present study has several limitations. The mean percent diameter narrowing in this study was only 43.9%, and the hypothesis that low shear stress favors atherosclerosis progression should be restricted to mild to moderately diseased vessels. This hypothesis also does not explain the rapid progression of some lesions that sometimes results from plaque rupture (which may be mediated by high shear stress), with subsequent endothelialization. The contribution of vessel curvature is not addressed in the present study because 17 of the 20 vessels analyzed were straight. However, the finite-difference model used in this study can accommodate curved vessels, and future studies will be able to address the contribution of vessel curvature to atherosclerosis progression. In addition, the present analysis used two-dimensional images, and future studies may be able to address these issues with the use of biplane images, three-dimensional reconstruction techniques, and three-dimensional flow modeling. The present analysis also assumed that flow was nonpulsatile and the vessels are inelastic. However, Ku et al\textsuperscript{30} have shown that pulsatile flow may result in even greater degrees of flow separation and flow reversal than steady-state flow; consequently, the incidence of flow reversal in the present study may have been underestimated. Additionally, in this study the blood flow was assumed to be fully developed and parabolic, which may not be the case with some lesions that are located very proximally near the origin of the vessel from the aorta. Finally, the portions of arterial segments analyzed did not contain branches, and subsequent inclusion of branches in the analysis will also require more sophisticated modeling.

One unresolved issue is the interplay between changes in plasma lipoprotein concentrations and mechanical forces in determining the rate of atherosclerosis progression. Changes in the cholesterol values in these control patients, who were treated with conventional therapy, were probably too small to affect the relation between shear stress and atherosclerosis progression, but more potent lipid-lowering agents may permit the detection of such a phenomenon. To date Zarins et al\textsuperscript{25} have found that serum lipids do not modulate the adaptive diameter changes in experimentally induced arteriovenous fistulas in hyperlipidemic monkeys. Furthermore, the atherogenic role of tensile stress, another mechanical distending force perpendicular to a longitudinal section of the wall, remains undetermined. Finally, future techniques such as intraluminal ultrasound, which can evaluate not just intraluminal diameters but also vessel wall composition and its compliance, may provide further insight into the role of the vessel wall, not just luminal forces, in atherosclerosis progression.

References


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