Correlation of Endothelial Cell Shape and Wall Shear Stress in a Stenosed Dog Aorta

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The pattern of endothelial geometry at various locations along stenosed dog aortas was examined. This was done to test the hypotheses that the shape of an endothelial cell is related to the local wall shear stress associated with the flowing blood and that alterations in hemodynamics, produced by vascular geometrical changes, influence endothelial cell geometry. Aortic stenosis with a reduction of 71% of the cross-sectional area was produced. The animals were sacrificed 12 weeks later, and the endothelial cell geometry and orientation were studied using the vascular casting technique and a computerized analysis to determine cell area and shape index. The regions of the stenosis examined were those known to experience different hemodynamic conditions. The value of the shape index was found to fall rapidly in the convergent region of the stenosis and to increase suddenly in the divergent region, eventually returning to the prestenotic value at a more distal site. Using a model of a stenosis made from a vascular cast, laser Doppler anemometry was applied to measure velocity profiles and to estimate the local wall shear stress in a stenosed aorta. It is shown that the shape index distribution along these stenosed vessels may be correlated with the level of wall shear stress, with more elongated cells occurring in regions of higher shear stress. (Arteriosclerosis 6:220–229, March/April 1986)

The evidence for the involvement of fluid dynamics in the atherosclerotic process centers primarily on the pattern of the disease.1–3 It is often regions of arterial branching and sharp curvature that have the greatest predilection for the development of atherosclerosis. These are also regions where the flow will assume unusual characteristics or at least deviate from what otherwise might be considered a well-behaved arterial flow. The indictment provided by this indirect evidence, particularly as it relates to the bifurcations and geometrical contortions of the arterial vasculature, presently motivates much of the interest in arterial fluid dynamics.

It has been suggested that vascular geometry may affect the atherogenic process through its influence on the hemodynamic environment to which the intima is exposed.4,5 Under such a hypothesis, whatever affects vascular geometry would alter the local detailed flow characteristics and correspondingly influence endothelial morphology and function. Our interest in hemodynamic forces, in particular arterial wall shear stress, stems from the belief that it is through this hemodynamically imposed frictional force that a fluid mechanic effect on the endothelium becomes manifest. In this context, the topic of interest is the influence of hemodynamic forces on endothelial morphology, cell function, cell turnover rate, and transendothelial transport, and it is the first of these, endothelial morphology, more specifically, en face cell shape, which is the subject of this investigation.

There is a body of accumulating data that indicates that endothelial cell geometry and orientation are determined by hemodynamic forces. In vivo, Flaherty et al.6 demonstrated that the orientation of endothelial cell nuclei (and thus by implication the orientation of the endothelial cells themselves) is determined by the hemodynamic stress associated with the flow of blood. Silkworth and Stehbens7 studied qualitatively the shape of endothelial cells using the en face Hautchen technique. They found that endothelial cells tended to align themselves with the flow field, and had an elongated tear-drop configuration, with the cell nucleus and the bulk of the cell cytoplasm distal to the midpoint of the longitudinal axis of the cell. In addition, endothelial cells about orifices of branches were often polygonal in outline. These investigators thus concluded that the shape and orientation of endothelial cells is influenced by the flowing blood and that changes from a true spindle shape could be the consequence of shear stresses.

In our own work, we have conducted quantitative studies8 on the morphology of aortic endothelium using the new technique of vascular casting that was developed by Reidy and Levesque.9 Using this vascular casting technique,10 we have found that in uniform segments of rabbit...
vessels (i.e., away from branch points) the endothelial cells are elongated and aligned with the axis of the vessel, which is presumed to be the direction of blood flow. In regions of branching, however, the endothelial cell pattern not only is altered but also appears to be indicative of a time-averaged flow pattern in the immediate vicinity of the endothelium which would be consistent with that anticipated on the basis of fluid mechanic considerations. Not only do the cells appear to align themselves with the flow direction, but the endothelial cells also appear to be more elongated in regions presumably characterized as high shear.

Recently, in vitro studies of endothelial cellular dynamics have been initiated using cultured populations of vascular cells. Dewey et al.12 have reported the use of a rotating cone-plate viscometer to study cultured bovine aortic endothelial cells under conditions of a uniform fluid shear stress. These studies suggest a shear stress effect on cell orientation, and more recent studies23 indicate that there are cytoskeletal changes and that the uptake of horseradish peroxidase by endothelial cells is dependent on a change in the level of shear stress. In our own laboratory we are using a parallel plate, channel flow device for similar studies. Our initial studies have also used cultured bovine aortic endothelial cells (fifth through tenth passage) on a plastic or glass substrate; those cells are exposed to a constant shear stress in the range of 8 to 85 dynes/cm² for a time period of 1 to 24 hours. These results14 clearly indicate a shear stress effect on both orientation and cell shape, but one which is dependent on substrate attachment.

Thus there is clear indication that hemodynamic wall shear stress does influence endothelial morphology and orientation. There is, furthermore, a suggestion of a direct correlation between the level of wall shear stress and the shape of the cell, with more elongated cells occurring in regions of higher wall shear stress. The present study was initiated to test this hypothesis further using an in vivo experimental model where the hemodynamics or fluid mechanics is altered in a predictable way through a change in vessel geometry. The model chosen for this study was that of dog aortic stenosis. The local endothelial geometry was analyzed with a Videoplan image analyzer (Carl Zeiss, Incorporated). The following parameters were obtained: area, perimeter, length, width, and the shape index (4πarea/ perimeter²). These parameters have been defined elsewhere.

From all these studies, we know that in a weak stenosis there is very little influence on the velocity field; however, in a severe stenosis, there will be elevated shear stresses in the "throat," i.e., the most constricted part of the stenosis, and immediately distal a jet will form which separates from the wall only to reattach further downstream. The region between the separated jet and the wall will contain a recirculation zone in which the flow will be slowly moving in a vortical pattern and the level of wall shear stress will be on the low side. We also know from the above noted studies, however, that the exact details of flow through a stenosis (e.g., the coherent structure, turbulence, and the recirculation zone) are dependent on the Reynolds number, the Womersley parameter, \( \alpha \), and the degree and exact geometry of the stenosis. It was for this reason that we decided to conduct our own fluid dynamic studies in a model stenosis made from one of our vascular casts.

### Methods

#### In Vivo Studies

Ten mongrel dogs weighing 10 to 12 kg were used in this study. Six served as controls and four underwent surgical procedures to introduce an aortic stenosis. Animals were maintained in quarters approved by the American Association for Laboratory Animal Care, and the procedures followed were in accordance with institutional and National Heart, Lung, and Blood Institute guidelines. The animals were fully anesthetized with Nembutal (30 mg/kg body weight intravenously) and Xylazine (5 mg/kg intramuscularly). During the surgical procedure, isotonic Ringer was infused (2 ml/min), and respiration was maintained by a Harvard respirator (VT = 200 cc; 16 strokes/minute). The surgery was performed under sterile conditions in the surgical area in the animal care facilities specifically assigned for chronic experimentation. The thorax was opened at the level of the first set of intercostal vessels through a 5 cm long incision between the ribs. Through this opening, a cotton band (0.3 mm wide) was placed around the aorta. The band was tightened until the presence of a thrill or a bruit was felt distal to the band. This indicated that the stenosis created flow disturbances. In this way, the aortic cross-sectional area was decreased by 71% ± 3%, and a small poststenotic dilation was also present. The animal was fully awake 4 to 6 hours after the procedure and was maintained free of pain with Xylazine (2 mg/kg intramuscularly) until the animal recovered its full level of activities. For 5 days, the animal received penstrep (0.05 ml/kg intramuscularly). The care for these animals was provided by the investigator and included outdoor walks twice daily (7 days/week, morning and evening). Upon returning from their walk, the animals were rewarded with a treat (8 oz of high protein meat product). Dry dog chow and water were provided at all times, and the animals were kept under sanitary conditions in the animal care housing facilities.

The animals were sacrificed 12 weeks later with an overdose of Nembutal, and their aortas were prepared by the vascular casting procedure.8 From these vascular casts the cross-sectional area was calculated from diameters measured with a caliper in two planes, perpendicular to one another, at locations proximal, distal and in the stenosed portion. The average hydraulic diameter was used to calculate the cross-sectional area at selected sites. Micrographs of endothelial cells were obtained from the ventral aspect of the cast at various locations by using light microscopy (Olympus BH). Endothelial cells were analyzed with a Videoplan image analyzer (Carl Zeiss, Incorporated). The following parameters were obtained: area, perimeter, length, width, and the shape index (4πarea/ perimeter²). These parameters have been defined elsewhere.
velocity profiles under steady flow conditions were plotted was ±50 Mm. Under the pulsatile flow conditions de-

The mean Reynolds number, however, was 450 and should be a reasonable representation of the flow through such a stenosis.

Figure 1 illustrates the experimental set-up. The fluid was pumped from a receiver into a reservoir. To maintain a constant fluid pressure in the complete system during the measurements, any fluid surplus was piped back to the receiver via an overflow pipe. The mean volume flow rate was adjusted by positioning a small regulator tank. The entrance tube was 100 diameters in length, and the flow was thus fully developed. The pulsatile flow was generated by a piston pump. A continuous adjustable motor produced the superimposed sinusoidal oscillation had an amplitude of ± 20 mm Hg. For these studies, the frequency used was 1.23 Hz; the Womersley frequency parameter \( \alpha = R \pi f \) had a value of 6.5; the mean Reynolds number was approximately 450; and the maximum Reynolds number, 910. The radial positions of the measuring points were always selected so that there would be seven points across the tube diameter including one at the centerline. For example, for a tube diameter of 10 mm (at the measuring point 30 mm proximal to the stenosis), the measuring points across the diameter were at distances of -4.3, -3.3, -1.6, 0, 1.6, 3.3, 4.3 mm relative to the centerline; while at a position with a tube diameter of 6 mm, the distances were -2.6, -2, -1, 0, 1, 2, and 2.6 mm.

Flow studies were also carried out with a non-Newtonian fluid that was a mixture of AP 30 (0.05%) and AP 45 (0.04%) with MgCl₂ (0.01%) and 4% isopropanol. The MgCl₂ was added to provide a refractive index that would be nearly equal to that of the silicon rubber model, and both the MgCl₂ and the isopropanol are agents which chemically stabilize the mixture. The complex viscosity was determined with a Haake rotating viscosimeter of the Couette type. This mixture has nearly the same viscosity as human blood with a hematocrit of 45%. The viscous component for this fluid corresponds to that for blood, whereas the visco-

elastic component shows some differences. Although the viscosity of the Newtonian and non-Newtonian fluids were different, the Reynolds number was virtually the same (\( Re = 450 \)). The velocity pattern results obtained were quite similar and qualitatively showed little difference. This is in contrast to previous studies by one of the authors²⁴ and is believed to be due to the relative simplicity of a stenosis geometry as compared to the branch geometry used in earlier studies. Thus, the non-Newtonian fluid results provided little, if any, different for the geometry used and are not discussed any further or used in later analyses here.

From the velocity measurements for steady flow, the velocity gradients near the wall were determined and the shear stress, \( \tau_w \), was calculated. This was done by using the velocity measurement at the closest point, which was 100 \( \mu \)m from the wall for steady flow. The determination of shear stress from the model experiments then must be scaled to the in vivo conditions corresponding to the endothelial cell shape data. If \( Re_{in\,vivo} = Re_{model} \), then:

\[
\left( \frac{\tau_w}{\mu \cdot \frac{D}{2} \cdot \frac{2}{2}} \right)_{in\,vivo} = \left( \frac{\tau_w}{\mu \cdot \frac{D}{2} \cdot \frac{2}{2}} \right)_{model}
\]
Equation (1) indicates that it is the ratio of shear stress to dynamic pressure, $\frac{1}{2} \rho u^2$, that is constant in going from the model system to in vivo conditions. Since $Re = \frac{pUD}{\mu}$ (where $U$ represents the mean velocity and $D$ is the diameter) and the diameter of the model is identical to that in vivo, then equation (1) can be rewritten as:

$$\left( \frac{f_w}{f_w} \right)_{model} = \frac{H_{model}}{H_{vivo}} \left( \frac{\rho_{model}}{\rho_{vivo}} \right)^2$$

where $\mu$ is the fluid viscosity and $\rho$ is the fluid density. Although such a determination of the shear rate and the shear stress at the wall based on the velocity measurement at the closest point to the wall is only approximate, it does give a quantitative indication of the shear stress environment to which the endothelial cells were exposed.

**Results**

**In Vivo Studies**

Endothelial cells from various locations along aortic stenoses with cross-sectional area reductions of 71% ± 3% (range, 69 to 74) were analyzed and the results are shown qualitatively in Figure 2 (A to D) and quantitatively in Figures 3 and 4. In these, endothelial cells located far proximal to the stenosed area may be seen to have the same size and shape as the endothelial cells from unstenosed aortas. However, in more immediate proximity to the "throat" of the stenosis, the size and the shape of the cells have changed dramatically. In the convergent area of the stenosis, just proximal to the throat, the shape index decreased, and the cells were very elongated (Figure 3). The appearance of a cell (i.e., the degree of elongation or roundness) was reflected by the value of its shape index. By definition, a circle has a shape index of 1.0 and a straight line has a shape index of 0.0. Therefore, the smaller the shape index, the more elongated a cell is. In this region immediately proximal to the throat, the cells were also much smaller in area as is evident in Figures 2 B and 4.

In contrast, in the divergent area, i.e., just distal to the throat of the stenosis, the cells were rounder with no specific orientation, and their boundaries had a higher affinity for silver staining (Figure 2 C). The values for the shape index increase suddenly and then subsequently decrease as seen in Figure 3. The largest cells were located 2 radii distal to the throat (Figure 4); however, at a more distal site (i.e., 8 radii) the cell morphology was not significantly different from control or prestenotic values. In the region where a thrill and a bruit were felt (approximately 5 radii distally), endothelial cell patterns resembling vortex-like...
Figure 2. Light micrographs of endothelial cell patterns obtained from stenosed aortas at selected locations. 
A. 3 diameters proximal to stenosis.  
B. Throat of the stenosis.  
C. Immediately distal to stenosis.  
D. 2 diameters distal to stenosis. Arrow indicates direction of flow; Bar = 100 μm.
structures were observed (Figure 2 D). In this area, a mixture of cells with different morphology (i.e., area and shape index) was found. These are responsible for the hump shown in Figure 3.

**Laser Doppler Anemometer Studies**

Figure 5 presents the velocity profiles obtained for steady flow in the model stenosis where the Reynolds number proximal to the stenosis in the region corresponding to the normal aorta of the dog is approximately 450. Proximal to the stenosis, we obtained the normal Hagen-Poiseuille profile. However, as the tube narrowed and the tube diameter decreased, the velocity increased, and the peak velocities in the stenosis region of the model were on the order of 150 cm/s. Near the vessel wall, high fluctuations in velocity were observed. The separation point, as determined by the onset of flow reversal at the wall, lay about 3 mm (0.3 diameter or 0.6 radii) distal to the throat, i.e., the point of the smallest diameter or the center of the stenosis. Because the stenosis and thus the cast were not exactly symmetric, there are velocity differences between the upper and lower wall as can be seen in Figure 5. The reverse flow zone initially grew, and its maximum thickness lay about 4 to 6 radii downstream or distal to the stenosis. The reattachment point, on the other hand, did not occur until approximately 6 diameters or 12 radii downstream. The growth of the separation region and the location of the reattachment point depended on the form of the
stenosis and the Reynolds number, and thus cannot be compared directly with measurements found in the literature. However, the tendency is similar.

The pulsatile flow results are illustrated in Figure 6 for four different locations, two on the proximal side (-30 and -4 mm upstream of the throat of the stenosis) and two on the distal side (4 and 6 mm downstream of the throat). As may be seen, on the upstream side of the most proximal position, the profile, though pulsatile, at any instant of time approximated that of Poiseuille flow. As the flow entered the stenosis, the velocity increased and there was no flow separation from the wall in this proximal region at any time during the entire cycle. Distal to the stenosis at locations of 4 and 6 mm downstream, reverse flows were found throughout the entire cycle as may be seen in Figure 6. At these locations, flow separation was also found in the steady flow studies. In general, with the obvious exception being the time-varying magnitude of the velocities, the flow patterns as measured for steady flow and pulsatile flow were qualitatively the same. As was mentioned earlier, this was also true of results obtained with a non-Newtonian fluid. Furthermore, cell culture studies indicated that the time needed to orient the direction of a cell is on the order of hours, not fractions of a second. This, coupled with the similarity in results between steady vs pulsatile flow studies, and between Newtonian vs non-Newtonian fluid studies, has led us to only use the Newtonian steady flow results for further analysis. It should be noted, however, that, in a more complicated geometry, non-Newtonian effects may be important. Also, although flow pulsatility is not believed to be an important determinant of cell shape and orientation, transient fluid dynamic phenomena may have an important influence on cell function.13

Figure 6. Velocity profiles as a function of position in cycle for pulsatile flow of a Newtonian fluid through model stenosis and for selected positions both proximal and distal to stenosis; upper left shows the time-dependence of pressure gradient. Re = Reynolds number; α = Wormersley parameter; and f = frequency.

Discussion

Our technique has enabled us to produce a short axisymmetric stenosis of moderate severity with a 71% cross-sectional area reduction in the dog upper thoracic aorta. The stenosis was created 12 weeks prior to sacrifice to ensure that any injury and physical trauma caused by the surgical procedure would be repaired. In fact, we believe that the endothelium was traumatized by the surgery and that the measurements made 12 weeks later were on a new, regenerated endothelium. The animals remained healthy and active during the course of the experiment. At the time of sacrifice, endothelial integrity was maintained all along the stenosed aortas. The vascular casting technique was chosen mostly because of its small amount of shrinkage as well as the maintenance of the three-dimensional geometry of the specimen. It is preferable to other traditional methods of studying the endothelium when quantitative information is required.6,9 From our previous study, we have shown that morphometric changes occur near branching vessels.11 Therefore, to avoid morphometric bias that would be introduced by the presence of intercostal branches, the analysis was limited to the ventral aspect of the vascular casts.

The presence of a stenosis in an artery alters the flow field in the artery both locally and distally. Flow instability and turbulence can occur in the neighborhood of arterial stenosis, giving rise to a vascular murmur. In general, the blood velocity in the stenosed area increases and the pressure decreases.10,23 Distal to the stenosis, the flow separates from the wall and a negative velocity is seen as part of the annular recirculation zone. Further downstream, the flow recovers and eventually becomes like a Poiseuille flow. This representation is based on the assumption that the flow is laminar and steady. The pulsatile nature of the arterial flow during a cardiac cycle will change this picture. For example, it should be noted that for pulsatile flow, flow reversal during the cycle will occur and the location of flow separation and reattachment points will move forward and backward. Nevertheless, the results described in the last section suggest little qualitative difference between the basic character of steady versus pulsatile flow through a stenosis. Also, cell culture studies suggest that the orientation of a cell is not responsive to transient hemodynamic conditions with a time-scale characteristic of a normal cardiac cycle. We thus believe that, if the endothelial cell pattern is to be indicative of the flow pattern in the immediate vicinity of the arterial wall, it then is the mean flow suitably averaged over some length of time that is reflective. Therefore, our results are discussed here in the light of hemodynamic conditions expected for steady flow through a rigid stenosis. Furthermore, based on the similarity between studies with a Newtonian vs a non-Newtonian fluid, as noted previously, it is the results for the steady flow of a Newtonian fluid through a model stenosis that are used for further analysis.

The results from this study show that endothelial cells are smaller and more elongated (i.e., have a smaller shape index) in the throat of a stenosis. It is the throat of a stenosis where the velocity would be high and the wall shear stress the highest. In the region immediately distal to the stenosis, the endothelial cells are larger and have a more rounded appearance which is reflected by a larger value for their shape index. Two radii downstream from the stenosis point (i.e., the throat) the endothelial cell shape index values are close to control values, although their surface area is still greater than that for control cells. It is believed
that the region located distal to the stenosis point corresponds to the recirculation zone where reversed flow is likely to occur. Further downstream (4 to 6 radii) in the region where a thrill and a bruit were felt, endothelial cell patterns resembling vortex-like structures were observed (Figure 2D). These patterns have centers made up of rounder cells with elongated cells surrounding them. We believe that these patterns reflect unusual flow patterns which could include the possibility of flow recirculation and severe fluctuations.

The rounder cells have a larger surface area and their boundaries have a higher affinity for silver staining. In comparison with other studies, rounder endothelial cells are found in regions suspected of low shear stress.\(^{11,14,36-39}\) It is possible that rounder cells may indicate some form of cellular damage in spite of the fact that an intact endothelial integrity is maintained. These cells may have a higher level of metabolism and permeability. Furthermore, rounder cells (regardless of their location) are multinucleated and occur in areas of repeated injury or high turnover.\(^{38-37}\)

The most striking feature of the results shown in Figure 3 are the extremely elongated cells in the "throat" of the stenosis, followed almost immediately downstream by very round cells. In a region of just a few millimeters, the shape index goes from a value of 0.1 to 0.74. In all the studies that we have conducted using the vascular casting technique to determine arterial endothelial cell shape, we have never seen as low or as high a value as represented by these two extremes. Yet these results are entirely consistent with the fluid mechanics in the context of the hypothesis. In the throat the wall shear stress should be the highest; however, downstream, when the jet separates, there should be a very low level of shear stress associated with the recirculation zone.

The relationship between endothelial cell elongation and wall shear stress can be examined further by comparing the data in Figure 3 with wall shear stress values calculated from the steady flow velocity profiles in Figure 5. The latter is shown in Figure 7 where the wall shear stress is presented as a function of X/D through the stenosis. Figure 7 suggests that there is a strong correlation between the elongation of an endothelial cell and the local wall shear stress. This is certainly true in the range of shear stress between 5 and 50 dynes/cm\(^2\). Below 5 dynes/cm\(^2\), where all of the data are from the recirculation zone, the data are too scattered to support any conclusion, particularly considering the interpolation necessary to produce this figure.

There is one cautionary note. The wall shear stress values have been obtained in a model stenosis where the mean Reynolds number in the unstenosed portion of the aorta is 450. Although such a value for the Reynolds number is representative of the dog aorta, it is an assumed
value. If in a given animal, the flow rate and thus the Reynolds number were higher, then the shear stress would also be higher. In this case, the data points in Figure 8 would have to be shifted to the left. Another assumption used in the conduct of the model stenosis flow study was that far upstream the flow was fully developed with the classical Poiseuille parabolic velocity profile. If the actual in vivo profile were blunter, this would probably have little effect on the flow in the region of the throat or further downstream. However, upstream or proximal to the throat, there could be an effect and shear stress values would be higher. This would tend to steepen the appearance of the proximal to stenosis data in Figure 8, i.e., lower shear stress points would be moved more to the right than the higher shear stress points. Qualitatively, however, the trend would be the same.

It should also be pointed out that there is a variation in circumferential wall tension and strain along the aorta. LaPlace’s law for a cylinder states that the wall tension (force/unit length) is equal to the product of pressure multiplied by vessel radius. This indicates that there would be a smaller wall strain in the stenosed than in the unstenosed region of the aorta. In fact, the banding of the aorta produces a rather rigid stenosis region, whereas away from the stenosis the aorta is free to distend and will have normal values for circumferential strain. Although one cannot preclude this exerting some effect on the geometry of the vascular endothelial cells, there are no data available and this has not been taken into account in the analysis of the present data.

In spite of these limitations, the study shows that aortic endothelial cell morphology can be altered in vivo by a vascular geometric change that is known to influence local hemodynamics. It may be seen that the shape index distribution along these stenosed vessels can be correlated to the level of wall shear stress theoretically expected, i.e., the endothelial cells are more elongated in regions of high shear and more rounded in regions of low shear. There is substantial evidence based on other studies that shows that high flow rates (high shear stresses) tend to protect against atherosclerotic lesion formation, and that atherosclerotic lesions tend to be accentuated in regions of low flow velocity. Furthermore, there is also a suggestion that lesions preferentially occur in regions of more rounded endothelial cells and also that cell turnover is enhanced in areas of rounder endothelial cells. It is in this context that we believe that vascular geometry — through its influence on hemodynamics, including wall shear stress, and flow velocity. Furthermore, there is also a suggestion that against atherosclerotic lesion formation, that high flow rates (high shear stresses) tend to protect substantial evidence based on other studies that shows shear and more rounded in regions of low shear. There is the level of wall shear stress theoretically expected, i.e., vascular geometric change that is known to influence local vascular endothelial cells, there are no data available and this has not been taken into account in the analysis of the present data.

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