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Correlation of Human Arterial Morphology With Hemodynamic Measurements in Arterial Casts

A realistic pulsatile flow was passed through a cast of the aortic bifurcation of a 63-yr-old male with mild atherosclerosis, and a laser Doppler anemometer was used to measure fluid velocities in the cast at 15 selected sites near the lateral and medial walls. Intimal, medial and adventitial thicknesses were measured and sudanophilia was scored at corresponding sites in the vessel from which the cast had been made. A negative correlation was found between intimal thickness (IT) and wall shear rate. The strongest negative correlation ($p<0.005$) was between IT and "pulse shear rate" (PSR), defined by analogy with pulse pressure. Sudanophilia also correlated negatively with PSR ($p<0.01$). Medial thickness correlated positively with shear rate, and most strongly with the mean (i.e., time-average) rate ($p<0.005$). From an analysis of the fluid mechanical data, it appears possible to separate the effects of bifurcation geometry and the shape of the arterial cross section on interfacial shear.

Introduction

The distribution of atherosclerotic lesions in the large arteries suggests that the hemodynamics adjacent to the vessel wall plays a role in the development of the disease. Our approach to identifying those aspects of the blood flow which are most important in this regard has been to make hemodynamic measurements near the walls of casts of human arteries, and to compare the hemodynamics with the histology of the corresponding sites in the arterial segment from which the cast was made. This approach offers the following advantages:

1 The geometry of the cast is that of a real, rather than an idealized, arterial segment.

2 In-vitro experimentation permits the use of measurement techniques which either cannot be used or do not provide adequate resolution in vivo.

3 Sites at which hemodynamic measurements are made can be precisely identified with sites in the original vessel; this is not the case when idealized experimental or computational models are used. Also, confounding of results by variability among individuals is avoided.

4 Material from humans, the species of ultimate interest, is used.

The first set of experimental studies, one of which will be reported here, employ minimally diseased aortic bifurcations. The purpose is to identify the normal vascular responses to a variety of hemodynamic environments; hemodynamic factors which evoke possibly preatherosclerotic responses are especially sought for the insight they may lend into the pathophysiology of the disease.

Studies carried out using steady flow have been reported elsewhere (e.g.,[1, 2]); in this paper, pulsatile flow results are presented which show (*i*) a negative correlation between the intimal thickness and sudanophilia of the vessel, and the time-varying shear rate measured in the cast; (*ii*) an equally strong positive correlation between medial thickness and shear rate; and (*iii*) that the effects on wall shear of bifurcation geometry and local variations in luminal cross section may be separable.

Methods

Arterial segments are obtained at autopsy and fixed at mean physiological pressure. A silicone rubber compound, Silastic E RTV, is injected into the arterial segment and allowed to cure. The mold of the vessel lumen is then removed by splitting the arterial segment longitudinally. The cross-sectional area at various locations in the aorta and iliacs is estimated by assuming the cross section to be elliptical and using calipers to measure the axes of the ellipse from the mold, as in an earlier study [2].

A short length of Teflon rod is butted against and faired into the promixal end of the mold to provide smooth cylindrical inlet to the cast, and an optically clear Bio-Plastic (Wards Natural Science, Rochester, N.Y.) cast is then made by pouring the liquid polyester monomer around the rubber mole in a casting box. When polymerization is complete, the cast is removed from the casting box and the rubberlike characteristics of the mold allow it to be pulled from the plastic cast, leaving a rigid reproduction of the lumen of the arterial segment.

A laser Doppler anemometer (LDA) [3] is used to make velocity measurements fractions of a millimeter from the wall, without disturbing the flow; the spatial resolution of the measurements is approximately 0.2 mm. A rotating dif-

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fraction grating, whose axis can be revolved about the optical axis of the LDA [4], is used to allow the measurement of the time-varying direction and magnitude of any velocity component in the plane of the bifurcation. The working fluid is eugenol, which was chosen to match the index of refraction of the plastic cast.

A lifelike pulsatile flow is generated in the cast by a cam-driven piston system in parallel with a constant-rate metering pump which provides the mean flow. The experimental flow wave is computed from measurements of the centerline velocity in the cylindrical inlet; the velocity is Fourier decomposed, and the flux is synthesized by inverse FFT.

The time-varying signal from the LDA is averaged over 200 cycles by a Honeywell SAI-43A correlator which is triggered by a pulse from the flow system. The correlator samples the signal frequency at about 300 equally spaced (2ms) intervals during the unsteady flow cycle.

The opened vessel, which had been split longitudinally to permit the removal of the latex mold, is stained with Sudan IV. The intensity of staining is evaluated at all points of interest using a semiquantitative (0–4+) estimate of the proportion of intimal tissue showing sudanophilia. Histologic sections are prepared from blocks of tissue removed from the margins of the opened vessel corresponding to the regions studied by anemometry. Taking shrinkage into account, the appropriate points on the sections are located with an ocular micrometer. Thickness of the intima, media, and adventitia at each point is measured using an ocular graticule calibrated with a stage micrometer.

The experimental technique is described in greater detail in reference [5].

Results

The measurements to be reported here were made in a cast of the aortic bifurcation of a 63-yr-old male with mild atherosclerotic involvement. A pulsatile flow was passed through the cast; the inlet centerline velocity and calculated flow wave are shown in Fig. 1. The mean Reynolds number (based on inlet diameter) was 370 and the unsteadiness number (defined as $[\omega D^2/(4\nu)]^{1/2}$, where ω is the frequency of the piston pump in radians/s, D is inlet diameter, and ν is the kinematic viscosity of the working fluid) was 8.65. Using fluid mechanical scaling to correct for the difference between the viscosities of blood and eugenol, the flow through the cast was equivalent to a mean blood flow rate of 15 cc/s, a maximum flow rate of 92 cc/s, and a pulse rate of 65. These parameters, and the flow waveform, are physiologically realistic. The flow in the cast partitioned essentially equally between the two iliacs; the in-vivo flow probably partitioned similarly, since the subject's vasculature showed no significant occlusion.

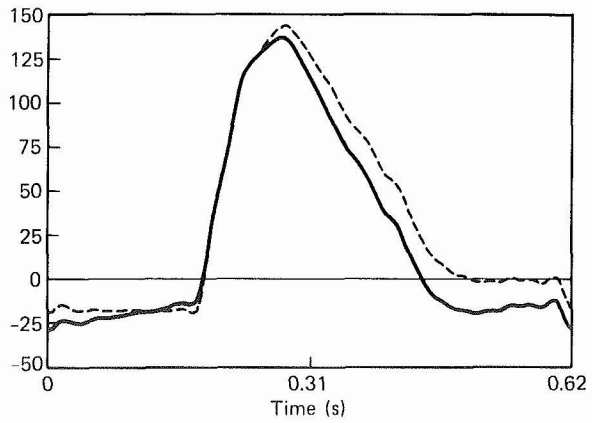

Fig. 1 Centerline velocity at inlet (— — —) and calculated flow wave (—). Units are cm/s and cc/s, respectively.

Unsteady velocities were measured in the cast at 15 sites along the flow divider and lateral walls; the intimal, medial, and adventitial thicknesses were measured at the

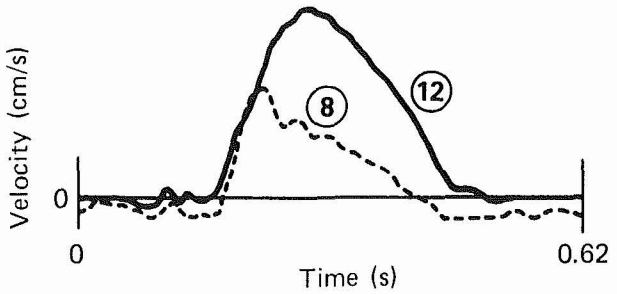

Fig. 2(a) Velocity profiles at Sites 8 and 12. At each site, the velocity measurements were made at a perpendicular distance of 0.058 cm from the wall. The maximum and minimum velocities at Site 8 were 74 and −15 cm/s, and at Site 12 they were 137 and −4 cm/s. The mean velocities were 6 and 35 cm/s, respectively.

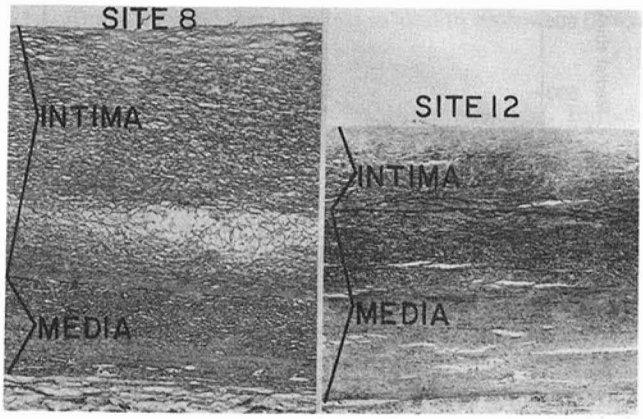

Fig. 2(b) Histology at Sites 8 and 12. The lumen is at the top and the adventitia is at the bottom. The junction of intima and media is at the internal elastic lamina seen as a slightly wavy or interrupted darkly stained line. The intima consists of mesenchymal cells and extracellular connective tissue fibers, chiefly collagen; elastic fibers are rare. The loose pale stained area deep in the intima of Site 8 contained lipid which dissolved out in the preparation of the slide. The media consists of smooth muscle cells, collagen fibers, and incomplete elastic laminae. The intima of Site 8 is 970 microns thick and the intimal thickness at Site 12 is 260 microns; the corresponding medial thicknesses are 330 and 700 microns. (Both Verhoeff-van Gieson elastic stain, × 80.)

Table 1 Correlations of intimal and medial thickness versus shear rate ($n = 15$)

	Intimal thickness	Medial thickness
Correlation against:		
Mean shear rate	$r = -0.63$ ($p < 0.02$)	$r = 0.722$ ($p < 0.005$)
Maximum shear rate	$r = -0.67$ ($p < 0.01$)	$r = 0.70$ ($p < 0.005$)
Pulse shear rate	$r = -0.685$ ($p < 0.005$)	$r = 0.68$ ($p < 0.01$)

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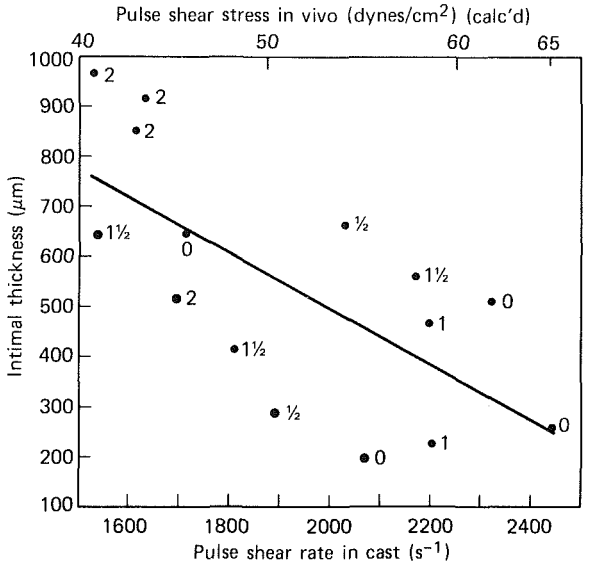

Fig. 3(*a*) Intimal thickness versus pulse shear rate. Sudanophilia scores are given at each site. Upper abscissa is the estimated in-vivo pulse shear stress.

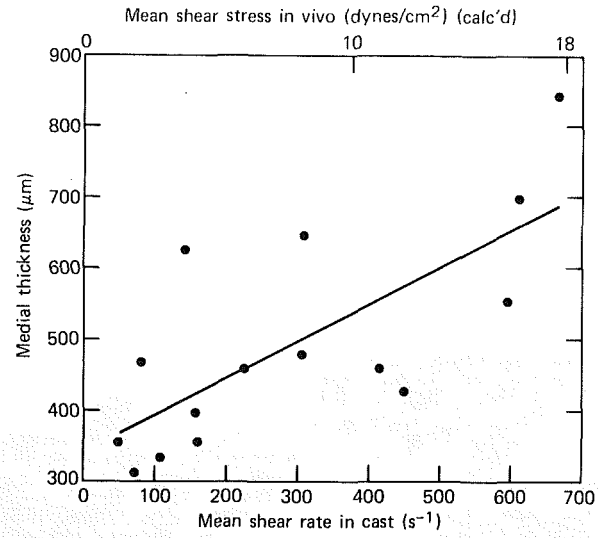

Fig. 3(*b*) Medial thickness versus mean shear rate. Upper abscissa is the estimated in-vivo mean shear stress.

corresponding sites in the vessel itself. The velocities were divided by the perpendicular distance from the measurement site to the wall, to give approximate longitudinal shear rates at each site. Correlations were sought between intimal and medial thickness and three shear measures: mean shear rate, maximum instantaneous shear rate, and the difference between the maximum and minimum shear rates (which will be termed pulse shear rate, analogous to pulse pressure). The results of linear fits of thickness to shear rate are summarized in Table 1. It can be seen from the signs of the correlation coefficients that sites exposed to relatively higher shears have relatively thinner intima and thicker media.

The relationship among the thicknesses of the arterial layers and their hemodynamic environment is illustrated in Fig. 2. Site 8, along the lateral wall of the right iliac, experienced the lowest maximum velocity during the pulsatile cycle, while Site 12, the site closest to the flow divider tip, exhibited the highest maximum velocity.

It can be seen from Table 1 that intimal thickness correlated best against pulse shear rate, and medial thickness against mean shear rate. These correlations are presented in Fig. 3.

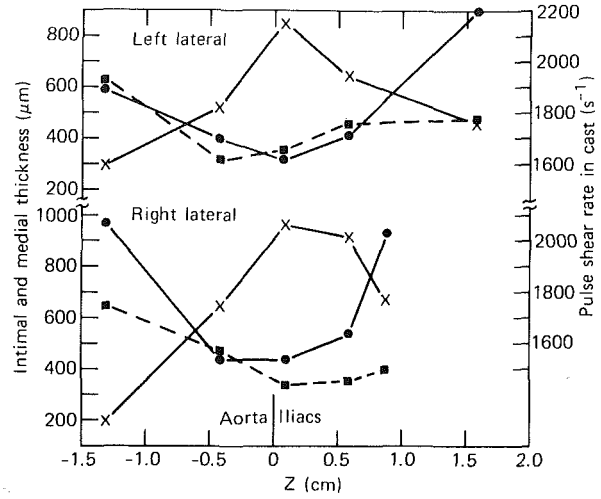

Fig. 4 Profiles of pulse shear rate in the cast (•), and intimal (x) and medial (■) thicknesses, along the lateral walls of the bifurcation.

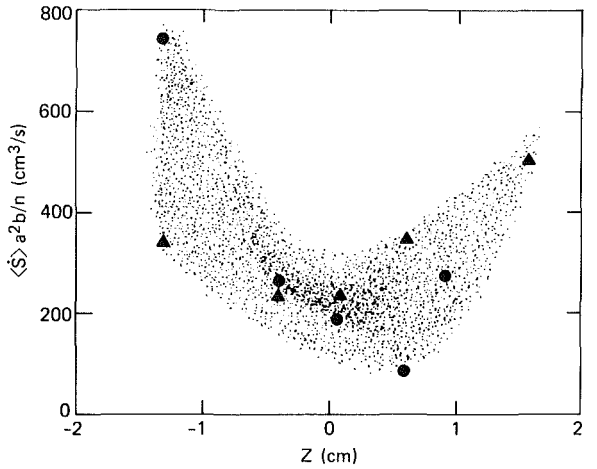

Fig. 5 Variation of the quantity $\langle \dot{S} \rangle a^2 b/n$ (see text for definition) along the right (•) and left (▲) lateral walls of the bifurcation. Stippling is used to suggest the general trend of the data.

The level of sudanophilia generally follows intimal thickness (Fig. 3(*a*)); the correlation coefficient between the lipid scores and pulse shear rate was -0.65 ($p < 0.01$).

The shear rates in the cast can be converted into equivalent in-vivo values by multiplying the former quantities by the ratio of the kinematic viscosity of blood (assumed to be 4 cs) to that of the working fluid (6 cs). The in-vivo shear stress is obtained by multiplying the shear rate by the viscosity of blood, and values of these stresses are also shown in Fig. 3. The values of up to 65 dynes/cm^2 in Fig. 3(*a*) are estimates of the peak-to-peak excursions of longitudinal shear stress experienced by the vascular intima; as can be seen from Fig. 3(*b*), the mean stresses are considerably less. The largest instantaneous in-vivo shear stress is calculated to be 64 dynes/cm^2, at Site 12.

There was no evidence of turbulence or a region of separated flow in the cast; however, transient flow reversal was observed at almost every site.

Discussion

Correlation of Hemodynamics and Morphology. The results obtained here show a correlation among high shear stresses, thin intimas, and thicker media under realistic conditions of flow in a rather healthy aortic bifurcation. This correlation would appear to be inconsistent with the known

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traumatic effect of sufficiently large shear stresses on the arterial endothelium; however, it is not unreasonable to suppose that the damage thresholds in man, which are unknown, may not have been exceeded in vivo. The most frequently cited "critical shear stress" is ca. 380 dynes/cm^2[6]; this stress is that above which the fraction of cells with normal architecture falls rapidly, as measured acutely in dogs. The mean stresses in near-normal human bifurcations predicted from the present study are more than an order of magnitude below this figure. The exposure to hemodynamic stress is of course chronic in a living subject, and the extent to which Fry's figure should be reduced for chronic exposure is uncertain. In any event, the suggestion from the present work that large excursions of interfacial shear, at levels too low to cause damage, may actually inhibit intimal thickening is not inconsistent with the acute data. The mechanism of this inhibition (or that of intimal thicknening in regions exposed to more gentle stress) is not known, but would be of considerable interest if the correlation presented here is confirmed in additional vessels.

Medial thickness is greater where shear stress is higher. We can only speculate about the mechanisms underlying this correlation. The shear stress developed by the flowing blood at the luminal interface is transmitted through the intima, to or through the medial layer of the arterial wall. Owing to the intervening intima, the time-varying longitudinal shear at the internal elastic lamina will differ from that at the intimal surface; however, it is reasonable to expect that this medial shear will be highest subjacent to sites experiencing the highest fluid mechanical shear. Thus the thickened media below sites of relatively high fluid shear could be a response to the associated higher longitudinal shear in the tissue, possibly interrelated with other hemodynamic factors such as pulse pressure. The mechanism could be similar to that of medial thickening caused by hypertension [7]. Alternatively, the observed variations in medial thickness may be secondary to changes in intimal thickness and not dependent on fluid shear in any direct fashion. The nutrition of the inner media relies on transport of metabolites from the blood, and medial thinning is observed in more advanced atherosclerosis [8]; under such conditions, the intima may have thickened to the point that such transport is compromised.

The complementary variations in pulse shear rate, intimal thickness, and medial thickness along the left and right lateral walls of the branch are presented in Fig. 4. The mean shear rate, against which medial thickness correlated best, is omitted for clarity; it is, of course, highly correlated with pulse shear rate ($r = 0.82$, $p < 0.001$).

Geometric Effects on Wall Shear. In earlier steady flow experiments [2] in aortic bifurcation casts, there appeared to be a close correlation between fluid velocities measured close to the outer wall of the cast and the velocities calculated from the equations for fully developed parallel flow in pipes having circular or elliptical cross sections. These results suggested that longitudinal variations in cross section were a principal determinant of velocity and shear profiles along the outer walls of branches, and that the effects of topology, and wall curvature in the plane of the bifurcation, were less important.

This relationship was explored further in the present work. Since shear rate has proven to be more convenient than velocity for correlation purposes [5], the equations of reference [2] were replaced by the following expression for shear rate in steady fully developed laminar flow through a straight elliptical pipe:

$$\dot{S} = \frac{32q}{\pi a^2 b}$$

Here, q is the flow rate through the vessel whose axes are a and b, and $\dot{S}$ is the shear rate at the end of the axis a.

Equation (1) applies not only to steady flow, but to unsteady flow as well, provided that $\dot{S}$ and q are replaced by their mean values. Thus, equation (1) can be used with the present data to examine the relation between lateral wall shear stress and the shape of the luminal cross section in pulsatile flow. The degree to which luminal cross section determines mean shear stress is measured by the constancy of the product $\langle \dot{S} \rangle a^2 b / \langle q \rangle$, where the braces on $\dot{S}$ and q denote mean values. Multiplying this product by the mean aortic flow $\langle q_a \rangle$, we obtain the quantity $\langle \dot{S} \rangle a^2 b \langle q_a \rangle / \langle q \rangle \equiv \langle \dot{S} \rangle a^2 b/n$, where $n = 1$ in the aorta and 1/2 in the iliacs.

The quantity $\langle \dot{S} \rangle a^2 b/n$ was evaluated at ten sites along both lateral walls; its standard deviation was 59 percent of its mean, reflecting considerable variability within the branch. However, as can be seen from Fig. 5, $\langle \dot{S} \rangle a^2 b/n$ does show a smooth variation with longitudinal distance, passing through a minimum at about the level of the flow divider tip. Since the effect of cross section is already included in the ordinate, the variation in Fig. 5 can be regarded as reflecting the effect of the branching geometry per se. Then, the shear rate at the lateral wall is the resultant of two effects: a large-scale, broad minimum caused by the bifurcating geometry, upon which is superimposed a more local effect of longitudinal variations in luminal cross section. It should be stressed that this simplified decomposition of the shear profile is restricted to the lateral walls of the vessel, which are approximately in the plane of the bifurcation, and therefore less subject to secondary flows.

Acknowledgments

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