GEOMETRIC RISK FACTORS FOR ARTERIOSCLEROSIS

Some of the unexplained variability in the distribution and rate of development of cardiovascular disease among individuals may result from corresponding variations in the detailed geometry of susceptible arterial segments. Geometric features that promote the disease can be regarded as "geometric risk factors." Initial results suggest that two geometric risk factors at the aortic bifurcation are a sharply angulating daughter vessel, particularly in combination with branch angle asymmetry, and a flow divider tip that is offset from the aortic axis.

INTRODUCTION

Cardiovascular disease, leading to heart attack and stroke, is the largest killer in the United States today. Almost half the people in this country who died in 1982 were its victims. In 1983 alone, over 600,000 people will die from heart attacks, and strokes will claim another 175,000 or more.¹

It has been known for some time that the rate of development of cardiovascular disease varies among individuals. Epidemiological studies of this variability have led to the identification of so-called "risk factors," whose possession by an individual is associated with an increased likelihood of that person’s developing earlier or more serious disease. The more commonly accepted cardiovascular risk factors include elevated levels of blood cholesterol, high blood pressure, and cigarette smoking. Notwithstanding the extensive studies of risk factors that have been carried out in the last few decades, fully half of the variability in the occurrence of cardiovascular disease remains unexplained. One conclusion is that additional risk factors remain to be found.

It is proposed that some of this unexplained variability is due to corresponding variations in the detailed geometry of susceptible arterial segments. The vascular geometry indirectly affects the disease process through its influence on the fluid mechanical environment of the inner lining of the artery where the disease begins. Geometric features that promote harmful stresses on the wall can be regarded as "geometric risk factors." This paper describes the results of two protocols that have been implemented to identify such risk factors: the first examines the response of the vessel wall to its fluid dynamic environment, and the second addresses the sensitivity of fluid mechanical stress to normal variations in arterial geometry.

It is appropriate to begin with a description of the disease that has motivated our research, starting with the anatomy of the healthy artery.

THE ARTERY, ARTERIOSCLEROSIS, AND ATHEROSCLEROSIS

The schematic in Fig. 1 shows how the major arteries of the body are organized as a series of concentric layers. The blood travels through the opening in the center of the artery, called the lumen. The lumen is lined with a layer of endothelial cells, whose functions include keeping the blood from clotting at the wall. The endothelia lie on a basement membrane surrounded by a layer of muscle cells and fibrils of the protein, collagen. This fibromuscular layer, which is usually very thin when one is young, lies on another membrane known as the internal elastic membrane. The portion of the artery from the endothelial lining to the internal elastic membrane is referred to as the intima of the vessel; for reasons that will shortly become apparent, it is the intima that is of greatest interest in our research.

Around the intima is another layer, called the media. The media, which is generally thicker than the intima, consists of fibrous and elastic tissue that gives the artery its strength and allows the vessel to support the blood pressure. Outside the media is a final layer, known as the adventitia, through which small blood vessels (vasa vasorum) pass to nourish the outermost layers of the artery itself.

Unfortunately, as we grow older, the vessel departs increasingly from the pristine state shown in Fig. 1. With the passage of time, fatty materials (lipids) that are in the blood pass through the endothelial layer and accumulate underneath the endothelial cells. The endothelium continues to maintain a continuous lining around the lumen, but as increasing amounts of fat accumulate inside the intimal lining of the artery, the passage for blood to go through becomes smaller. Indeed, the area of the lumen can be reduced to the point that the blood supply to the organ or tissue that is being fed by the artery becomes compromised. This can lead in some cases to overt symptoms. For instance, if the artery is a coronary artery and the
blood flow becomes too small to satisfy the demands of the heart muscle, a person may experience angina pectoris when exercising. With time, the smooth endothelial lining of the vessel can become interrupted and ulcerated, and a clot (thrombus) may form in the lumen. If this happens in a coronary artery, coronary thrombosis, or a heart attack, can occur. If it develops in a vessel feeding the brain, a stroke can ensue.

This process of progressive arterial occlusion is called atherosclerosis, the most significant of the arteriosclerotic diseases. Arteriosclerosis is a more general term that refers to the diseases that are characterized by thickening or stiffening of vessels in the arterial side of the vasculature. Atherosclerosis is the particular condition described above, which is accompanied by the entry of lipids into the arterial wall and their accumulation in the wall. Its name is derived from the Greek ἄθερος, meaning gruel, because of the mushiness of the lipid material in the wall, at least in the early stages of the disease.

RISK FACTORS

We are all subject to the atherosclerotic process. However, the rate of progression of the disease, and thus the likelihood that it will kill us, varies. It varies among individuals and it varies among populations. Starting in about 1950, epidemiological studies have been carried out to see if one could predict which persons might be more or less likely to develop early or complicated atherosclerosis. It was found that certain features in an individual’s lifestyle, his medical history, or his blood chemistry seemed to favor the disease. Those features were referred to as risk factors: factors that predicted a person’s increased risk of suffering from atherosclerosis.
Some risk factors, such as abnormalities in an electrocardiogram, are actually signs of the disease itself in its more advanced stages. Other risk factors, such as xanthomas, which are accumulations of fat under the skin, are a consequence of high lipid levels in the blood, which also promote atherosclerosis. But some risk factors, it was felt, could actually be causes of accelerated atherosclerosis, or be related very closely to such causes; these are particularly interesting because their identification may suggest ways to control the atherosclerotic process. Indeed, the term “risk factor” is often limited to factors that are related to the actual causes of the disease; among these, the best established are an elevated level of cholesterol in the blood (hypercholesterolemia), high blood pressure (hypertension), and cigarette smoking. The identification of these three factors, and others of lesser significance, has been given much of the credit for the continuing decline in mortality from cardiovascular disease that began in the 1960’s.

It is unhealthy to possess any one of these risk factors; it is worse to possess more than one. Figure 2 compares the incidence of coronary heart disease in normal individuals, in people with high blood pressure, in those with elevated blood cholesterol, and in those who have both hypertension and hypercholesterolemia. It is easily seen—and is not too unexpected—that those who possess multiple risk factors have a higher probability of developing coronary disease than those who possess only a single risk factor.

Interestingly, perhaps half the people who die of premature atherosclerosis have none of the commonly accepted risk factors. This suggests that there are other risk factors, perhaps not so easily detected, that are also predictors of cardiovascular disease. It would be very exciting to identify some of them because they would surely further our understanding of the atherosclerotic process and might suggest ways to prevent the disease or retard its progress. Our research described in this article has as its objective the identification of such risk factors. It has led us to propose a new set of risk factors based on individual variations in arterial geometry.

**Figure 2** — Incidence of coronary heart disease in normal individuals and in possessors of one or more risk factors (from Ref. 5).

To develop the rationale for this work, we begin by observing that atherosclerosis does not occur uniformly in the arterial tree. Figure 3a shows where it tends to predominate in man. It is immediately apparent that an above-average occurrence of atherosclerotic disease is found at almost every branch of the major vessels. The disease tends to form at bends as well. Figure 3b shows sketches of bends in the carotid arteries of the head, indicating where lesions were found. In this collection of specimens, they formed exclusively on the inside curvatures of the bends. The figure is very reminiscent of aerial views of silting in a meandering river, a fact not lost on students of atherosclerosis who travel by air.

The inevitable inference from this predisposition of the disease for bends and branches is that blood fluid mechanics, or hemodynamics as it is called, is very likely to be involved in atherogenesis (the beginning of atherosclerotic disease) and in atherosclerotic development. Many hypotheses along these lines have been suggested. By now, almost every conceivable—and some inconceivable—fluid mechanical mechanism has been proposed to explain the localization of atherosclerotic disease, including turbulence, separation, vortices and eddies, both high shear stress and low shear stress, and high pressures and low pressures. But in spite of all this speculation, the most important hemodynamic factor or factors have not, in fact, been confirmed.

Our original objective in this research program was to understand the role of hemodynamics in atherogenesis and to identify which hemodynamic variables, if any, were important in the localization of the disease. One way to do that would be to examine the flowfield in a minimally diseased artery and look for correlations between various aspects of the fluid mechanics near the wall of the vessel and the level of beginning disease at that site. A minimally diseased artery would be used so that the flow would not yet have been altered by the lesions themselves. Such correlations should reflect the response of a relatively normal vessel to its local hemodynamic environment. Then one would simply identify those fluid mechanical variables that appeared to be eliciting an atherosclerotic response. This information would be a starting point for developing models of the atherogenic process.

Such a procedure, though simple in concept, is essentially impossible to carry out in practice. The fluid mechanical measurements cannot be made in the living system with the needed resolution. Furthermore, our interest is in the response of human tissue, and there is no way to examine an individual’s arterial wall without removing the vessel. Accordingly, we have done one of the next best things. We make flow-through casts of minimally diseased human arteries obtained at autopsy, pass a realistic pulsatile flow through the cast, and measure time-varying velocities at a number of sites near the cast wall using laser
Doppler anemometry. Then we compare these fluid mechanical results with histological observations and morphological measurements at corresponding sites in the original vessel from which the cast had been made.\(^6\)

Figure 4a shows the front (ventral) half of an aortic bifurcation (the arterial segment circled in Fig. 3a), where the terminal aorta divides to feed the legs. Almost all of our work has been limited to this particular branching segment because the aortic bifurcation, being both large and relatively symmetric, is the easiest to work with among those that can satisfy our experimental objectives. A latex mold of the lumen of the vessel (Fig. 4b) is used to make a polyester flow-through cast for fluid mechanical experimentation using laser Doppler anemometry (see box).

The use of an optical technique such as laser Doppler anemometry to probe the flowfield introduces a problem. The flow channel is a replica of the lumen of a real artery, which has an irregular internal contour. Refraction at the fluid-wall interface makes it difficult to know where the incident beams will cross and can cause the beams to miss one another entirely. We deal with this problem by using a working fluid, clove oil, which has nearly the same refractive index as the plastic cast, so there is negligible refraction at the interface. Figure 5 shows a cast filled with clove oil and one filled with air. When filled with oil, the lumen of the cast would be invisible were it not for the fact that the clove oil is slightly colored; the word “CLOVE” can be read through the bifurcation. The cast is then put in our flow tunnel (see cover) and a cam-driven piston system is used to generate a lifelike flow through it.

RELATIONSHIPS BETWEEN HEMODYNAMICS AND MORPHOLOGY

The kinds of data that we get and how we treat them are the subject of this section and the one that follows. Figure 6 shows the flow wave passed through a cast of the aortic bifurcation of a 63-year-old man. Since the original vessel was only mildly atherosclerotic, the flow channel had not been altered substantially by lipid accumulation in the wall. A real in vivo flow wave\(^9\) is shown in the inset at the upper right of the figure. The piston system reproduces the most important features of the flow, namely, the very sharp rise that occurs when the heart ejects blood and the relatively protracted period during which there is rather little flow through the vessel. The flow of fluid through the cast is dynamically scaled to mimic the in vivo situation; that is, the non-dimensional groups that characterize the in vivo flow are reproduced in the cast. This is done so that phenomena such as separation and turbulence, should they have occurred in vivo, will also be seen in the cast. The working fluid lacks the cellular elements that are present in blood, and its rheology is more Newtonian. Fortunately, neither blood cells nor non-Newtonian behavior have much effect on hemodynamics in the large arteries.
Using the laser Doppler anemometer, we measured the longitudinal component of velocity parallel to the wall at 15 sites along the lateral (outer) walls of the cast and along the flow divider. The measurements were made as close to the wall as possible because that is where the atherosclerotic process takes place. We also measured the thicknesses of the intima and the media at corresponding sites in the vessel from which the cast was made. The vessel was stained with Sudan IV, which has an affinity for lipids; the intensity of staining at each site was graded (scored) on a scale of 0 to 4.

An example of the kind of data we get is shown in Fig. 7. Figure 7a shows the mold from which the cast was made. Two experimental sites are identified: site 8 on the outer wall of the vessel and site 12 on the flow divider. Figure 7b shows velocity profiles obtained at those two sites at a distance of 0.58 millimeter from the wall. Figure 7c presents the histolog-
Laser Doppler Anemometry

In this technique for measuring point velocities in a fluid without disturbing the flow, two laser beams (usually from the same source) are brought to an intersection at the point in the flow where the velocity is sought. The fluid is seeded with submicrometer particles that presumably travel with the same velocity as the fluid. When it passes through the beam intersection, a particle scatters light from both beams. Because the particle is moving, the scattered light has a Doppler-shifted frequency different from that of the incident beams. The frequency shift depends in part on the angle between the velocity vector of the particle and the direction of the beam. Since that angle is different for each incident beam, the frequencies of the light scattered from each beam are different; the difference between the two frequencies is proportional to the velocity of the particle. The two scattered beams are mixed on a photomultiplier tube; the photomultiplier signal is processed to yield the difference frequency, from which the particle velocity (and, by inference, the fluid velocity) at the beam intersection is calculated.

This is done by constructing linear regressions between the thicknesses of the intima and media and wall shear rates ($\tilde{S}$) derived from the velocity measurements. The shear rate is the normal gradient of velocity at the wall (Fig. 8, inset), and we approximate it by dividing the measured velocity by the perpendicular distance from the measurement site to the wall of the cast.

Three different measures of shear rate are used in the correlations (Fig. 8). They are: the maximum shear rate to which the site was exposed during the pulsatile cycle, $S_{\text{max}}$; the time-average shear rate,
Figure 7 — (top) Latex mold with two measurement sites marked. (center) Measured velocities in the cast at the two sites. The maximum velocity at site 12 was about 140 centimeters per second. (bottom) Light-microscopic sections at corresponding sites in the original vessel. The lumen is at the top and the adventitia is at the bottom. The junction of intima and media is at the internal elastic membrane, seen as a slightly wavy or interrupted darkly stained line. The intima consists of connective tissue cells and extracellular fibers, chiefly collagen; elastic fibers are rare. The loose, pale stained area deep in the intima of site 8 contained lipid that dissolved out in the preparation of the slide. The media consists of smooth muscle cells, collagen fibers, and incomplete elastic laminae. The intimal thickness at site 8 is 970 micrometers and that at site 12 is 260 micrometers. Verhoeff-van Gieson elastic stain was used.

Figure 8 — Shear rate measures.

\[ \dot{S} = \frac{1}{r} \int_0^T \dot{S} \, dt \]

\( \dot{S}_{\text{max}} \)

Period, \( r \)

\[ \frac{\Delta \nu}{\Delta t} \]

Pulse shear rate, which is the algebraic difference between the maximum and minimum shear rates experienced by the wall in each pulse.

Although correlations against both intimal and medial thicknesses are made, we have stressed the relationship between shear and intimal thickness because the intima is the layer that is most involved in the early stages of atherosclerosis. As might be suspected from Fig. 7, we found a negative correlation between intimal thickness and shear for this vessel; that is, we found that the intima was generally thinner where the shear was higher. We also found that intimal thickness correlated better with pulse shear rate than with either of the other two measures.

Figure 9 is a plot of intimal thickness at the 15 experimental sites versus the corresponding pulse shear rates measured in the cast. The correlation between the two sets of data is quite good; the probability that it is due to chance is less than 0.05. The numbers next to each data point in the figure are the scores for lipid staining; the larger numbers correspond to more intense staining. Lipid staining also correlates well with pulse shear rate.

We have followed this protocol on nearly a dozen casts. The aggregate data, which now include over 200 pairs of sites, support the negative correlation that is shown in Fig. 9. A thorough statistical analysis of the data base is under way in an attempt to construct a model of the thickening process.

RELATIONSHIPS BETWEEN GEOMETRY AND HEMODYNAMICS

Let us now turn to the role of arterial geometry in the atherogenic process. To begin with, it seems quite obvious that any fluid mechanical phenomena that might be involved in the pathogenesis of atherosclerosis are themselves influenced by various geometric
First of all, it is clear that the shear stress at any part of geometry on the shear at a site in a bifurcation may be different from what they would be in a simple pipe flow. The third effect on the shear rate at a site in a bifurcation is that of the particular geometric features of that branch. It is the last effect that we are looking for. We identify the geometric features of particular branches that most strongly influence the shear rate by "subtracting out" the effects of cross section and bifurcating geometry and then looking for explanations of the residual shear variability.

To deal with the effect of local cross section, we observe that everywhere in the bifurcation, except immediately upstream of the flow divider tip, the cross section of the lumen is more or less elliptical. If the site were on the wall of a straight elliptical pipe of uniform cross section, then the following simple expression specifies the mean shear rate at the wall:

$$\langle S \rangle = \frac{32 \langle q \rangle}{\pi a^2 b}.$$  \hspace{1cm} (1)

Here, $\langle q \rangle$ is the mean (time-averaged) flow rate through the pipe, and $a$ and $b$ are the axes of the ellipse; the shear rate given by the formula is that at the end of axis $a$. The expressions for maximum and pulse shear rate are much more difficult; therefore, our analysis will be limited to mean shear rate. As might be expected, all three shear rates in Fig. 8 are closely correlated with one another.

We hypothesize that the average effect of the bifurcating geometry on the shear rate can be represented by a multiplicative factor, $P$, which is a function of a normalized longitudinal distance down the branch:

$$\langle S \rangle = \langle S \rangle_0 P \left( \frac{z}{d} \right).$$  \hspace{1cm} (2)

The longitudinal coordinate, $z$, is referenced to zero at the flow divider tip, and the normalizing dimension, $d$, is the equivalent diameter of the parent aorta 1 centimeter upstream of the tip; $d = (ab)^{1/2}$. Combining Eqs. 1 and 2 and rearranging, we get

$$\frac{\pi a^2 b \langle S \rangle}{32 \langle q \rangle} = P \left( \frac{z}{d} \right).$$  \hspace{1cm} (3)

The term on the left, which is nondimensional, will be referred to as the reduced shear at the site.

There is no a priori form for the function $P$, which measures the effect of the bifurcating geometry on the shear rate along the outer wall, so we estimate it by polynomial fitting. The results are shown in Fig. 10, which is based on 52 data points along the outer walls of six casts. Because the vessel cross section and $\langle q \rangle$ change discontinuously on passing from the aorta to the iliac arteries, reduced shear data in the particular site is affected by the local cross section of the lumen at that site. All else being equal, if the vessel is larger, the shear will be less. Second, these sites are in a bifurcating geometry; this will cause the shears to be different from what they would be in a simple pipe flow.
parent and daughters were correlated separately. The data obtained in the aorta do not support a polynomial of degree greater than unity; a quadratic minimizes the standard error of estimate of the data obtained in the iliac arteries. The best-fit polynomials in the figure are taken to represent the effect on reduced shear of the geometry of an average aortic bifurcation, while the effects of the geometry of a particular vessel are reflected in the deviations between the measured shear and that given by the polynomials. To identify the important geometric features affecting the shear rate, we sought geometric explanations of the largest deviations from the polynomial. In particular, we looked at the 11 sites at which the reduced shear deviated from the best fits by more than one standard error of estimate. The serial numbers of eight of those sites are shown in Fig. 11; the locations in the two branches to which they belong are shown in Fig. 11.

By tedious examination of radiographs of the vessels and tracings of the molds and casts, we found that four specific geometric features were sufficient to explain the deviations at all 11 sites. Each of the features can be found in one of the two branches in Fig. 11. A. They are listed below.

1. If the flow divider does not lie along the axis of the aorta but is offset, considerable asymmetry in the flowfield and significant secondary (circumferential) flows are induced. As a result, the shears are raised on the outer wall of the aorta that is farther from the offset tip, while the wall closer to the flow divider tip experiences lower shears than would be expected from the polynomial fit. Such was the case at sites 401, 402, and 406.

2. In most branches, the outer walls curve smoothly away from the parent vessel axis as z increases. In a few cases, a wall curve toward the axis just upstream of the bifurcation and then once again curves outward. This causes a small intrusion into the flow; such an intrusion can be seen at sites 401 and 402 in the figure. Even when it is quite small, the intrusion can elevate the velocities and shears at its site. This effect also contributed to the high shear values at sites 401 and 402. As indicated in footnote 13, this response to small intrusions was also seen in other branches whose flow dividers were not offset.

3. If the daughter vessel makes a very large angle with the parent, as is the case for the right-hand branch in Fig. 11, extremely low shears are found along the outer wall of that daughter in the neighborhood of the bifurcation; this feature explains the low (actually negative) mean shears at sites 806, 810, and 812.

4. If one of the branch vessels departs from the parent at a large angle while the other daughter vessel lies more or less along the axis of the parent, the geometry of the bifurcation is more like that of a continuing parent vessel with a side arm. In such cases, the shear stresses along the outer wall of the continuing parent opposite the side arm are reduced. This was the case at sites 803A and 805.

Figure 10 — Reduced wall shear rate measured in casts versus normalized longitudinal distance. The z axis is coincident with the approximate centerline of the terminal aorta; z = 0 at the flow divider tip and increases downstream. The normalizing diameter is that of a circle whose area is the same as that of the aorta at z = -1 centimeter. The several symbols, which are tagged to designate the left and right sides of the original vessel, identify data obtained in the six casts. The serial numbers of the sites identified in Fig. 11 are shown adjacent to the corresponding data points.

Figure 11 — Tracings of the luminal molds of two vessels used in this study. Arrows point to sites at which the reduced shear rates deviated from the best fits in Fig. 10 by more than one standard error of estimate. The offset in the upper branch can easily be seen by placing the eyes near the plane of the figure and sighting along the aortic axis.
Many of these effects will not surprise students of fluid mechanics. What is important here is the demonstration that in real arteries these geometric features vary enough to cause significant variations in the hemodynamics at the vessel wall. With this list, we now have a basis on which to suggest some possible geometric risk factors.

GEOMETRIC RISK FACTORS

First, the caveats. The premise under which these risk factors are identified is that low shear stresses are bad for the vessel wall. This premise is based on two assumptions. The first, which so far is supported by our data, is that thicker intimas are associated with lower shears. The second, less certain, is that a thicker intima signifies a greater likelihood of developing obstructive atherosclerosis.

With these assumptions, we can use our research results to identify some possible geometric risk factors. The most obvious one is a large cross-sectional area. Clearly, if all else is equal, including flow rate, then the shear at the wall of a large vessel is less than that in a small one. An offset flow divider is a fairly good candidate; however, its influence on shear stress is greater on the wall farther from the tip (where it causes shears to be higher), and it is not a cause of extraordinarily low shear stresses. A large angle between parent and daughter lowers the shear stress on the outer wall of the daughter, and branch angle asymmetry has that effect on the side of the parent across from the side arm.

Having these candidates and a means for identifying others, we are now setting up some studies to validate them. One way in which we are doing this is by retrospective analysis. We are collecting autopsy material, characterizing its geometry in a variety of ways (including parameters that could be risk factors), and then correlating the data with the morphology of the specimens.

What is there to be gained by identifying these largely uncorrectable hazards to your health? However speculative we get at this point, the scientific value of such knowledge and the search for it is not arguable. The research done to identify these risk factors and the knowledge that would be gained by identifying them—and ultimately, the mechanism through which they act—will unquestionably further our understanding of the atherosclerotic process, with all the implications that that has for therapy, prevention, and the like. In addition, a considerable amount of epidemiological data has been gathered to elucidate the effects of other variables on the incidence of vascular disease. Some of those variables have already been identified as risk factors, as noted earlier. If geometry is influential in determining risk, it becomes an uncontrolled variable in these epidemiological studies, and if that can be taken into account, it may allow us to extract additional information from the epidemiological data.

The clinical implications are much more speculative. It is fairly safe to assume that the quality of instruments for imaging internal organs will continue to improve. By the time we identify the first geometric risk factor with reasonable certainty, technology may well have progressed to where one could screen for such a factor in a noninvasive, painless, routine fashion. But what do you do if you look inside somebody and find that his angles are wrong? For one thing, you could warn such a person against other risk factors. As indicated earlier (see Fig. 2), possessors of multiple risk factors are at greater hazard of disease than individuals who have only a single risk factor; thus, a person found to be "geometrically at risk" should be cautioned against other risk factors to which he might be subject. The response some day might be corrective surgery. One must really be convinced that a serious hazard exists before considering such a response, although it could be claimed that such surgery is done today when congenital vascular defects or malformations are corrected; of course, the effect of failure to correct these problems is much more overt than in the present case.

To close on a more practical note, remember the risk factors that we can control today. Watch your weight, stop smoking, eat right, exercise, stay on your blood pressure medication, and—for the time being—let your arterial geometry be.

REFERENCES and NOTES

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13 The two branches in the figure were selected because they are the fewest that together demonstrate all four features described in the text. Fewer features were found in other branches, and each feature was solely responsible for an extreme shear at at least one of the 11 sites.
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