Original Contributions

Blood Flow and the Localization of Atherosclerotic Plaques

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SUMMARY  Saphenous veins used in aortocoronary bypass procedures slowly narrow. The narrowing and atherosclerosis appear to develop in reaction to the new flow conditions present in the saphenous veins. Localization of atherosclerosis in the arterial system also suggests that local flow conditions play a role in atherogenesis; plaques are characteristically found in regions of separated flow. The pattern of separated flow in arteries is influenced by the pulsatility of arterial flow. Stagnation points delimiting flow separations migrate with each systole. An additional motion of blood, angular momentum, produces a corkscrew component to the flow. This added rotary component generates a stress that combines with the stress generated by to and fro motion of stagnation points to produce an area of multidirectional shear stress in the stagnation region. The rapidly reorienting shear stress places a special burden on the region's endothelial cells, producing an area of non-elongated cells, compromising cell internal fluidity, and modifying adhesion to neighboring cells to increase local permeability. The amount of multi-directional force generated in regions of multi-directional shear stress is increased by the flow properties of blood. Studies of blood, particularly in diabetes, will be able to characterize the factors that control the magnitude of permeability-enhancing multi-directional stress and suggest new ways to slow atherogenesis and ultimately prevent atherosclerosis.

A RECENT STEP FORWARD in the surgical treatment of ischemic heart disease has been the introduction of the coronary bypass operation. This procedure follows a number of less successful predecessors by directly enhancing impaired coronary artery blood flow. It utilizes saphenous vein segments to connect the ascending aorta to sites distal to atheromatous blockage in one or more coronary arteries. Commonly, three or four segments of saphenous vein are used to anastomose as many coronary sites. This procedure is more than a decade old and it has now been established that the transplanted saphenous veins develop a progressive diminution in lumen size. The progressive occlusion is due to a combination of intimal thickening, intimal medial sclerosis, and late development of local atherosclerotic plaques. For that reason, it has become more and more common practice in surgical management of ischemic heart disease to use an internal mammary artery rather than a saphenous vein to bypass the coronary site most sensitive to progressive ischemia. The internal mammary artery bypass initially delivers less blood flow than a saphenous vein but it is not subject to progressive narrowing and so gives a better long term result. This lesson from coronary bypass surgery and previous observations about atherogenesis suggest that local arterial conditions of blood flow and pressure gradient determine the site and rate development of atherosclerotic plaques. We will review here current information about the role of pressure and flow in generating atherosclerotic plaques, highlighting the fluid mechanics relevant to atherogenesis.

Blood Pressure Gradient and Arterial Wall Compliance

It is commonly believed that arteries experience greater pressure than veins, but this is not continually true. When one is standing, the force of gravity raises the pressure in the lower segments of saphenous and tibial veins to the same height as that being experienced by the coronary arteries. It is really the pressure gradient, the rate of decline in pressure with distance, that distinguishes arteries from veins. The difference between arteries and veins is illustrated by the inadvertent cutting of a small artery or vein during a surgical procedure. An artery pumps blood out while a vein oozes.

The role of a pressure gradient in regulating vessel wall anatomy can be seen when trauma produces an arteriovenous fistula. Adjacent veins, exposed to an unusually high pressure gradient, become altered in a pattern usually referred to as arterialization. The media increases in thickness as smooth muscle cells proliferate and the internal elastic membrane becomes more distinct. The ability of veins to arterialize led to their use in the coronary bypass procedure. Unfortunately, their effort to arterialize is unsuccessful. The flow changes they experience are abrupt; a very high pressure gradient is suddenly generated. They become rigid tubular structures rather than elastic-walled muscular arteries.

Stiffening of bypass vessels is not unique to veins. When a radial artery is substituted for a vein in an
aortocoronary bypass procedure, it undergoes a similar rigidification. This appears to develop because a muscular artery also experiences a pressure gradient beyond its ability to tolerate when placed at the transplant site.

Compliance of the vessel wall may be important to the ability of a vessel to resist atherosclerosis. The pulmonary artery is the most compliant vessel in the body. When it is exchanged in site with the stiffer abdominal aorta in hypercholesterolemic dogs, the aorta in the pulmonary circulation develops plaques but the pulmonary artery segment placed below the renal arteries remains plaque-free.7

The ascending aorta expands about 11% in circumference with each heartbeat,6 responding appropriately to the abrupt delivery of 70 ml of blood. An internal mammary artery shifted to the coronary bed probably remains patent because it continues to take its origin from the subclavian artery several centimeters downstream from the aortic graft site. The distally transplanted internal mammary artery experiences a later compliance.

Declining aortic compliance and a sharpening of the systolic pressure gradient are characteristic features of aging. The ability of the arterial system to accept the systolic volume is so great in childhood that the systolic arterial pressure is lower in the legs than the arms.8 By the time adolescence is reached, the systolic pressure gradient between arm and leg disappears. As the adult vascular pattern is established, a considerable part of the blood delivered into the iliofemoral arteries from the aorta actually reverses flow after systole and returns toward the aorta. Upper aortic compliance, quite high in childhood, becomes impaired in late adult life. But stiffening with aging does not affect all the arteries equally; the compliance of the muscular arteries in the lower extremity actually rises.9 As the aorta stiffens, its branch arteries experience a more abrupt systolic delivery of blood. They appear able to accommodate to this progressive burden by increasing their compliance.

Atherosclerotic Plaque Sites

It has been observed for decades that atherosclerotic plaques are usually found in certain arterial areas.10 They develop near the origin of arteries that arise from the aorta and at sites where muscular arteries, including the carotid, branch or change direction. An example of the latter is the femoral artery in the adductor canal. But the curving axillary artery and the division of the brachial artery into the radial and ulnar arteries are not often subject to plaque formation. The branching of the popliteal artery into the anterior and posterior tibial arteries and the peroneal artery is predisposed to plaque formation principally in diabetics. The spared arterial sites have lower blood flow rates than affected sites; it is interesting to note that diabetics often have an unusually high blood flow to their feet.11

Predilection of certain sites to atherosclerosis has generated interest in the possibility that blood flow might play some role in plaque formation. In the late 1960's, Donald Fry and his group at the National Heart Institute noted that the dog and pig develop cholesterol-containing plaques when fed an unusually high cholesterol diet. The same arterial sites that develop plaques on a high cholesterol diet were stained when Evans blue dye was injected into the bloodstream. They knew that Evans blue was bound to plasma albumin and recognized that macromolecule permeability was unusually high at the arterial sites that develop plaques when cholesterol is fed. They hypothesized that local shear stress, the force being applied by flowing blood, was elevated in these regions and conducted an experiment in a dog to test this hypothesis.12 The experiment consisted of placing a cylinder in the aorta. The cylinder was slotted, forcing blood to flow down a narrow channel next to the aortic wall. The experimental maneuver increased local penetration of Evans blue dye; the endothelium actually became eroded in some areas. They used a simplified equation to calculate local shear stress and concluded that a shear stress of 400 dynes/cm² or more was associated with an increase in vessel wall permeability and that a shear stress of 1000 dynes/cm² could actually wash away endothelial cells. More recent experiments support the concept that high shear stress increases albumin entry into arterial walls.13 An increase in permeability was found when shear stress exceeded 100 to 200 dynes/cm², lending support to the concept that shear stress and arterial wall permeability can be linked. Fry's concrete approach to atherogenesis attracted the interest of investigative groups whose background included fluid mechanics or fluid dynamics.

Separated Blood Flow at Plaque Sites

Fluid scientists were familiar with the concept of separated flows (see fig. 1). They began to question cardiologists about whether plaques formed on the upstream or downstream wall of an arterial branch. They reasoned that separated flows usually occurred on the upstream side and were not associated with particularly large shear stresses. As more information became available, the wall found to be more predisposed to atherogenesis was the separated flow wall. Separated blood flows develop because, when a fluid turns, its inertia is overcome by the development of local pressure gradients. The downstream side of the branch vessel is exposed to an increased shear stress and the upstream side develops a separated flow. The pressure-flow relations and flow paths are shown diagrammatically in figure 1. In the separated flow the upstream wall is exposed to flow and shear stress that are reversed in direction. Beyond the separated flow, downstream directed flow and shear stress become progressively re-established.

The linkage of atherogenesis to separated flows led to a concept opposite the one introduced by Fry. Low wall shear stress came to be considered uniquely important in atherogenesis. It was suggested that low shear stress-related phenomena, such as flow stagnation and resulting platelet adhesion or hypoxia, could be involved in plaque formation.13 A controversy
formed between the high and low shear stress alternatives. Histologic studies were utilized to determine the actual local flow conditions associated with atherogenesis.

**Endothelial Cell Orientation and Atherogenesis**

Arterial endothelial cells, observed from the lumen, tend to form elongated rather than equilateral polygons. The long axis of these polygons regularly parallels the direction of blood flow. The nuclei of arterial endothelial cells are flattened on their abluminal side, suggesting additional streamlining to reduce the drag arterial endothelial cells experience. Fry's group at the National Heart Institute showed that endothelial cell flow orientation was re-established when a square segment of the aortic wall was removed, rotated 90 degrees and sutured back in its original position. Within a week, the endothelial cell orientation had also rotated 90 degrees. More recently, Gimbrone et al. have shown that endothelial cells in tissue culture will orient to the flow when exposed to small but steady shear stress (about 10 dynes/cm²).

Fry's group had noted that endothelial cells at the sites stained by Evans blue dye were not elongated and were perplexed by their observation. The orientation of endothelial cells at sites of early atherogenesis in humans became a test to compare the high shear stress and low shear stress hypotheses. Endothelial cells are not elongated at sites of early human atherosclerosis, and this fact has been interpreted as evidence supporting the low shear stress hypothesis. But for arterial flow, a more attractive explanation exists.

**The Complexity of Separated Arterial Flows**

The separated flow figure (fig. 1) presents this pattern statically and in two dimensions. No changing flow velocity or fluid motion into or out of the plane of the paper on which it is printed is considered. In the real world, no separated flow exists as simply as shown in figure 1. Three dimensions are present and they allow more complex flow patterns. Flow is reflected off the wall more pronouncedly in the center than at the sides of curved vessel areas causing the fluid near the axis to flow away from the reflection point, creating two secondary flow vortices.

The stagnation point forms the boundary between the separated flow and the re-attachment of the main flow to the wall. Arterial flow is pulsatile in nature. When blood flow accelerates as systole reaches the vessel, the stagnation point moves downstream. This movement may be as much as several millimeters; it is characteristically greater in stiffer arteries. Greater systolic expansion of the artery wall allows it to accept a larger fluid volume with a lower forward flow veloc-

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**Figure 1.** The pattern of separation associated with a splitting of flow is diagrammed here. The pictured structure contains a symmetrical laminar flow, represented by a velocity parabola, coming from the top. As the flow passes downward toward the branch to the right, part of it is deflected to the side channel. The remainder continues downward. In both divisions, laminar flow develops and increases in symmetry as the fluid passes away from the branch point. The complex curvilinear flow at the branch is mediated by the development of local pressure gradients. The pressures develop in response to fluid inertia through altered momentum. The flow pattern separates from the wall at the beginning of the branch point and becomes attached again beyond a point called the stagnation point. Upstream from the stagnation point the flow near the wall is retrograde. At the stagnation point local flow disappears. Particles placed in a stable separated flow tend to remain in it for extended periods; A particle moves very slowly when it is on either side of the stagnation point.
ity. Areas of the wall under a moving stagnation point experience retrograde shear stress during systole and forward shear stress during diastole. But by itself reversal of shear stress direction does not appear to cause endothelial damage. Large areas of arterial wall in the lower extremities are exposed to a to and fro pattern of shear stress in adults because arterial blood normally flows backward during diastole.

Secondary vortical flows are not the only effect created in three dimensions by fluid inertia and vessel geometry. An additional factor important in causing endothelial compromise is produced by retained angular momentum. Angular momentum is generated by an asymmetry in the origin of a branch vessel from the aorta and by the rotational component of cardiac systole itself. Angular momentum causes arterial flow to have a corkscrew component that passes into and through areas of separated flow. The retained angular momentum changes the simple to and fro shear stress pattern under the migrating stagnation point to a rotating shear stress. Near this point, the local shear stress angle continually changes direction as the forward and backward components are added to an often pulsating sideward angular momentum component. The local rotating shear stress exposes each endothelial cell under the migrating stagnation point to multidirectional shear stress.

Multi-directional shear stress in separated flow areas has considerably smaller magnitude than originally proposed by Fry. It will not produce endothelial cell orientation but it can enhance local endothelial permeability. To understand this capability, the nature of the attachment of endothelial cells to each other and to the underlying intima must be considered.

**Active Adhesion by Endothelial Cells**

Endothelial cell anchoring involves both cell-cell and cell-connective tissue adhesion. The forces involved in both kinds of adhesion are linked to a physical proximity attraction referred to as electrodynamic force. 

Adjacent endothelial cells are stabilized by applied shear force by this proximity force and by the macromolecular bondings seen in freeze-fracture preparations and referred to as tight junctions. These structures are particularly numerous in retinal and cerebral microvessels. Tight junction macromolecules are usually located somewhat below the luminal surface of adjacent cells. The abluminal surface of each endothelial plasma membrane is attached by the protein fibronectin to networks of Type 4 collagen molecules in the subendothelium. And each endothelial cell has the ability to influence the state of its cytoplasm to help control its susceptibility to shear stress. When the rat is made hypertensive, its arterial endothelial cells develop actin microfilaments near their tight junctions. These actin filaments indicate that the cell is actively responding to external forces by reducing some of its cytosol’s ability to flow. In experimental hypertension, the affected microvessels are exposed to large but directionally uniform shear stress. The applied shear force tugs hardest at the upstream apex of each endothelial cell, where it is attached to its two upstream neighboring cells. Ability to create solid behavior in the environment of the apex is important to each endothelial cell, allowing it to remain anchored to its neighbors. The solid cytosol elements redistribute cell deformation at the apex allowing a small increase in local gap distance with neighboring cells to generate the necessary stress to compensate for the fluid-mediated tugging.

At separated flow sites multi-directional shear stress, even though smaller in magnitude, creates a special problem for the endothelial cell. Multi-directional shear stress causes several endothelial cell apices to need defense. Local endothelial cells appear to respond to the unusual flow burden by a mixture of actin filament or gel formation and increased plasma membrane separation. The proximity force between plasma membranes is compensated at normal separation, but acts to compensate for applied force when the gap distance is slightly increased. The more the membrane separation that is needed, the greater will be local macromolecule permeability. But if actin solids form over a substantial part of the cell volume, organelle and cytosol motion vital to cell survival are disrupted. The multi-directional shear stress-exposed endothelial cell appears to compromise by allowing more plasma membrane separation and increased local permeability.

**Rheology of Blood and its Role in Atherogenesis**

Until quite recently, little attention has been paid to the role of the flow properties of blood in atherogenesis. This has been due in good part to blood’s complexity as a fluid. Blood has flow properties that are not yet fully understood. It is much easier to analyze simple fluids than blood, and it has been suggested that little or no difference should occur. But experiments done by Moravec and Liepsch indicate that there is a substantial difference. They studied flow in arterial models using a polyacrylamide solution that, like blood, is more viscous at low shear rate than at high shear rate. They observed a striking disparity between the behavior of the polyacrylamide solution and glycerol added to water, the simple fluid usually used in such studies. Flow separations were observed to be more numerous and sheer stress near the separations was larger. Their studies indicate that the blood flow-mediated force in arterial plaque areas is larger than previously predicted.

**Blood Viscoelasticity and Thixotrophy**

Solids and fluids have one essential difference. When one applies a force to a solid it resists this force by deforming elastically. When we sit in a chair we apply a force to it and it deforms slightly, countering our weight. If we apply a similar force to a simple fluid it offers resistance only while it is moving. But many fluids, including blood, behave in a more complicated manner. These fluids have elastic (solid) properties and are called viscoelastic fluids. Elasticity is conveyed to blood by its red cells. Red cells deform
during flow and then restore themselves to their original shape once flow ceases. They also become shear-oriented as the flow develops and gradually lose this orientation in the absence of flow. The need for flow orientation produces a property called thixotropy. The word is from the Greek and describes the ability to change by touching. An extra shear stress price is paid during the initiation of flow to cause the red cells to orient.

**Properties of Blood and Separated Flows**

The effect of blood’s complex flow behavior on separated flows cannot yet be specified. Direct measurements have not been made under appropriate flow conditions. But a reasonable picture can be generated by visualizing a single red blood cell as it passes through an artery near the flow separation boundary represented by the upper dashed line in figure 1. Erythrocytes above the flow separation boundary recycler in the separated flow while those below the separation boundary pass downstream. On either side, the erythrocyte close to the boundary line near the center of the artery is moving very rapidly. But it slows considerably as it moves toward the stagnation point. As it passes beyond the stagnation point to flow either upstream or downstream, our representative red cell accelerates again. In addition to the temporary slowing, our erythrocyte experiences fluid shear force that falls markedly to a very low level near the stagnation point and then rises again as flow accelerates. Erythrocytes rotate in a tank-tread fashion when they flow in rapidly shearing plasma. They are extended into elongated ellipses and the plasma membrane on both sides of the cell is sheared by the adjacent fluid to give it a continuous rolling motion. As our model erythrocyte moves toward the stagnation point it loses its elongated shape and tank-treading motion. Its dimple can reappear if it is exposed to a low shear rate. In addition to returning toward its normal resting shape for a brief period, our representative erythrocyte can actually aggregate with adjacent red cells if it is given about a tenth of a second. As the representative red cell and its neighbors change in shape, orientation, and local contact, they modify substantially the force actually being applied to the arterial wall. In a simple fluid, shear stress builds up slowly in either direction from a value of zero at the stagnation point. Blood viscosity elasticity causes the area on both sides of the stagnation point to experience a shear stress altered in both magnitude and direction. This occurs because viscosity elasticity creates a shear stress memory that is expressed in a direction based on flow history. Blood thixotropy affects flow away from the stagnation point, either upstream or downstream. It will increase the shear stress experienced at the wall in those areas by an as yet unknown amount.

How can we put the separated flow facts together to gain more useful information about atherogenesis? First of all, a series of non-invasive techniques has recently been developed. They can be applied particularly easily to the carotid artery in the detection of early plaques. As the technology improves further we may actually be able to obtain information about angular momentum and stagnation point movement. Since the precision of these measurements may never meet our needs, the study of arterial model systems capable of more detailed analysis is essential. Finally, an improved ability to measure the transient flow behavior of blood should allow us to estimate more precisely the force being applied to endothelial cells near flow separations. This requires that new techniques be developed. We are now working on more rapid transient blood viscometry. Diabetes forms an unusually attractive model for hemorheologic study; diabetics have an increased predilection to atherogenesis, especially at some sites. They also have increased blood thixotropy and a well-defined abnormality of erythrocyte deformability. By looking at diabetic blood’s flow properties, we may unmask some key features of atherogenesis, allowing improved early detection of people at risk for serious occlusive arterial disease and leading ultimately to prevention of atherosclerosis.

**References**

Delay in Referral of Patients With Ruptured Aneurysms to Neurosurgical Attention

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SUMMARY  Aneurysmal subarachnoid hemorrhage is a neurosurgical emergency. Early medical intervention is axiomatic for minimizing rebleeding and ischemia from vasospasm and achieving optimum results. The purpose of this study was to document the length and causes of the delay in referral which occur in patients following aneurysmal subarachnoid hemorrhage. The case histories of 150 consecutive patients admitted to The University of Iowa with proven ruptured aneurysms were studied. Medical records from The University of Iowa and referring hospitals were reviewed, and patients, families, and referring physicians interviewed. Overall, only 36% were referred within 48 hours of their first clear-cut, recognizable sign or symptom of subarachnoid hemorrhage. Median time to referral was 3.6 days. Delay was due to physician diagnostic problems in 37%, delayed referral policy in 23%, unstable patient condition in 7%, failure of patients to recognize severity of illness in 8%, and logistical reasons in 12%. These data suggest that a large proportion of patients have a delay in achieving definitive neurosurgical care following aneurysm rupture, and that for the most part this delay is avoidable. More emphasis must be placed on public health and primary physician education regarding subarachnoid hemorrhage.

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