

# Response of arteries to near-wall fluid dynamic behavior

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Arteries are living tissues which react and adapt to their environment, particularly in relation to changes in the rate of blood flow required to supply peripheral tissues or organs. Medium and small size arteries increase in diameter in response to short-term demands for increased flow and decrease in diameter in the event of diminished demands. Such immediate reactions are regulated primarily by vasoactive substances acting directly on smooth muscle cells of the media or by release of smooth muscle relaxation or contraction factors elaborated by endothelial cells. Chronic or long-term changes in arterial diameter appear to be governed directly by near-wall flow phenomena, e.g. the fluid dynamic wall shear. Recent evidence suggests that the normal tendency of arteries to respond to long-term changes in the shear field can result in intimal thickening and that this response may also favor the development of atherosclerosis. Thus, there appears to be a close relationship between fluid dynamics and the structure of arteries. From the fluid dynamics viewpoint, the pulsatile, three dimensional nature of blood flow requires sophisticated experimental methods in order to provide adequate data for correlation with biological studies. Research within the past decade has led to the conclusion that arteries seek a vessel diameter-blood flow combination which results in a flow-induced mean wall shear stress of approximately 15 dynes/sq.cm. If this value is chronically exceeded, vessel enlargement develops. If normal baseline shear stress is not restored by this increase in radius, the local response may continue. Conversely, reduced wall shear tends to induce intimal thickening in order to reduce lumen radius and thus increase wall shear toward normal levels. Under certain conditions this reaction may progress to the development of atherosclerotic plaques. Despite this knowledge, key points remain to be clarified. Is it the wall shear stress or the wall shear rate which determines the reaction? The former possibility implies that a mechanical shear-related stimulus is at the heart of the biological response mechanisms while the latter suggests a mass transport-related mechanism.

## I. INTRODUCTION

The primary function of arteries is to distribute blood to the tissues and organs of the body. Arteries operate under both fluid mechanics and solid mechanics constraints. Lumen diameters must be adequate to assure sufficient blood flow to tissues under a variety of requirements, while mural structure must withstand the tensile stresses which develop in relation to pressure and radius. While the fluid mechanics and solid

mechanics requirements are not independent, it is the fluid mechanics effects upon which this paper concentrates.

Arteries must adapt to changing conditions, both immediate and long-term. For example, exercise induces a rapid response employing both chemoregulatory and neurogenic mechanisms. The major effect is on the diameter of small arteries and arterioles. In contrast, growth

necessitates increasing blood supply to enlarging organs as the volume of tissue increases. Chronic changes in arterial structure and diameter also occur in the mature adult. Over the past several years we have studied the tendency of arteries to change diameter in response to long-term changes in flow rate. We have also related these phenomena to the focal occurrence of intimal thickening where vessel geometry results in regions of reduced wall shear stress. The presence of specific atherogenic stimuli can lead to the development of pathological states such as atherosclerosis. We have therefore postulated that in many instances atherosclerosis arises as an abnormal extension of the natural response of the artery to local, near-wall, fluid dynamic phenomena. Proof of this hypothesis requires sophisticated fluid dynamic studies, both experimental and theoretical, in association with closely linked biological studies.

## II. FLUID MECHANICS

From the fluid mechanics viewpoint it is useful to conceptualize the arterial flow field as comprising three regimes: (i) a primary flow field; (ii) near-wall flow; and (iii) the fluid-wall interaction region. The primary flow field refers to the major features of the local flow, e.g. velocity profile behavior, flow separation, recirculation, and secondary flow features. The primary field depends upon geometry, pulsatility, wall motion and nonNewtonian blood rheology, and in essentially that order of importance. Excellent results in describing the primary flow field can be obtained by assuming that the artery is rigid and that blood is Newtonian. This was demonstrated by Ku *et al.* (1985) who compared in vitro measurements of pulsatile flow in a plexiglas model of the human carotid artery with noninvasive velocity profile studies in normal human subjects and showed that the basic flow phenomena seen in the model were also found in the actual vessels. Correlations of fluid dynamic measurements in such models with studies of intimal thickness in either experimental animal or human vessels have led to considerable progress in defining those fluid dynamic factors which seem conducive to atherosclerotic plaque development (e.g., Zarins *et al.*, 1983; Friedman *et al.*, 1981). As will be discussed below, such correlations have led to the finding that relatively low wall shear is associated with localization of plaques and relatively high wall shear is related to regions of the artery wall which are spared of disease.

Near-wall flow behavior refers to the fluid mechanics occurring very close to the artery wall. The correlative studies resulting from primary flow field models have been vital in identifying specific fluid dynamic factors which should be investigated further. However, having done this it may be unnecessary to model the entire flow field when studying phenomena occurring in the immediate neighborhood of the artery wall. This allows considerable simplification in experimental and theoretical models of both the fluid mechanics and the biology involved. On the other hand, in the near-wall region it may be presumptuous to assume that wall motion and nonNewtonian effects are negligible, and current studies are underway to evaluate their importance (e.g., Duncan *et al.*, 1988; Davis, 1989).

Fluid-wall interaction refers to phenomena involved at the fluid-artery interface and within the arterial wall. Clearly, these require application of fluid dynamics at the cellular level. Here, the very low Reynolds numbers involved are advantageous to the fluid dynamicist, but the complexity of the cellular and molecular activity (in contrast to passivity) is tremendous. A subsequent paper in this session (Weinbaum) will undoubtedly deal with some of the very interesting phenomena occurring in this regime.

## III. BIOLOGICAL EVIDENCE

### PHYSIOLOGIC BEHAVIOR

During angiogenesis and growth, modifications in vessel diameter are related to flow rate demands. In embryonic development, vascular channels with high flow enlarge while those with low flow become smaller and atrophy. Keenan and Rodbard (1973) observed that when two arteries supply the same tissue segment, one tends to enlarge while the other declines and ultimately disappears. In adult mammals, arteries establish a diameter which, in conjunction with their normal flow rate delivery, results in a mean fluid dynamic wall shear stress in the range from 10 - 20 dynes/sq.cm. Table I presents data from several studies in which the shear stress was derived by estimation using measured mean flow rates and arterial diameters while assuming the vessels are long straight tubes.

TABLE I. Estimated Fluid Dynamic Wall Shear Stress for the Arteries of Several Species

Author	Artery	Wall Shear Stress (dynes/cm <sup>2</sup> )
Kamiya and Togawa (1980)	Dog Carotid	15
Whitmore (1968)	Dog carotid, femoral	20
	Dog muscular arteries	22
	Dog terminal arteries	14
Lipowsky and Zweifach (1974)	Cat mesenteric capillary	10
Smaje (1970) Eriksson (1972)	Rat muscle capillary	15-20
Nerem and Seed (1983)	Human coronary arteries	12-17
Bharadvaj, <i>et al</i> (1982)	Human common carotid	16

Several investigators have shown that if the flow rate is altered from its physiologic state for a long period, the arterial diameter seems to respond by changing in such a way

as to recover this physiologic range of shear. Zarins et al. (1987) studied the adaptive response of the arterial wall to increased blood flow by constructing an arteriovenous fistula between the right iliac artery and vein in a series of six cynomolgus monkeys using the left iliac artery as a control. The animals were fed an atherogenic diet containing 2% cholesterol and 25% peanut oil for a period of six months. Blood flow and pressures were measured in the animals at the time of induction and of termination of the study. By connecting the artery with the adjacent vein a large, high flow shunt was created due to the great pressure difference. After six months blood flow in the right iliac artery was 10 times greater than in the left, and the right side vessel had increased its diameter over twofold. While the wall shear stress could not be measured directly in these animals, estimates of the time-averaged values were made from the measured diameters and flow rates using Womersley flow assumptions. These estimates resulted in the same values for wall shear stress ( $16 \pm 4$  dynes/sq.cm for the right iliac,  $15 \pm 2$  dynes/sq.cm for the left) despite the great differences in flow and diameter. Shear stress in the abdominal aorta was  $12 \pm 2$  dynes/sq.cm.

Langille and O'Donnell (1986) studied the effects of decreased flow in the carotid arteries of rabbits and showed that the arterial diameter decreases in response to chronically reduced flow rates, but these authors did not estimate wall shear. Their results strongly suggest that the change in diameter was dependent upon the endothelial cells lining the artery wall since the diameter reduction did not occur when these cells were removed.

The above studies, along with other similar investigations, imply that fluid dynamic wall shear regulates the diameter of arteries. However, it is not yet established whether it is the wall shear stress which is important or the wall shear rate, since the evidence to date cannot distinguish between these, one being simply proportional to the other. A shear stress - related mechanism implies that mechanical forces acting on the artery wall are involved, while a shear rate - related mechanism implies that mass transport between the blood and wall is the key factor. The search for specific mechanisms is ongoing in several laboratories.

## PATHOLOGIC BEHAVIOR

The development of atherosclerosis, at least in its initial stages, may be related to the physiologic response of arteries to wall shear on a localized basis. One of the interesting features of atherosclerosis is that it occurs mainly at specific sites about arterial branchings and bifurcations. The carotid bifurcation and segments of the coronary arteries near branch points are particularly susceptible to plaque development, as are areas around the orifices of small branches coming off the aorta and the aortic bifurcation. These localization patterns have led to a variety of hemodynamic theories of atherogenesis, including high shear stress, low shear rate, high pressure, low pressure and turbulence. Careful observations of the relationships of fluid dynamics with human disease, however, have been rare.

In a series of studies (Zarins et al., 1983; Ku et al.,

1985) we have searched for relationships between hemodynamic behavior and the localization of atherosclerotic plaques in the human carotid artery using a laboratory model for fluid dynamic experiments and data obtained from the carotid arteries of fresh cadavers. The fluid dynamics investigations comprised steady and pulsatile experiments in which laser Doppler velocimetry (LDV) was employed to measure velocity profiles and to estimate wall shear in a large scale plexiglas model which was anatomically representative of the human carotid bifurcation. Figure 1 presents the geometry of the model and the stations at which axial and circumferential velocity components were measured with the LDV system. Transient flow separation occurred along the outer sinus wall, resulting in a zone of wall shear

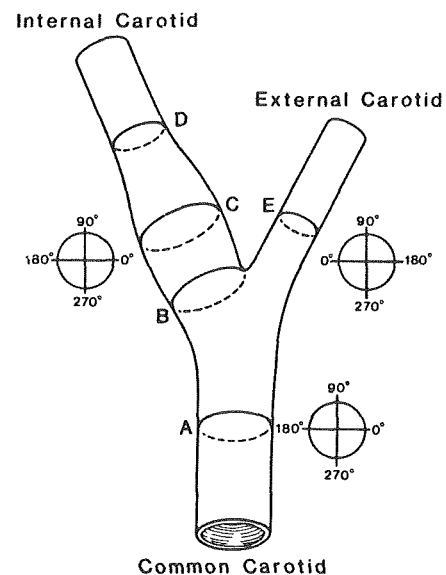


Figure 1. Schematic representation of the axial levels at which wall shear stress measurements from the model and intimal thickness data from human carotid arteries were compared. The orientation for the polar coordinate description of the circumferential sites studied is shown for each level. For the proximal (B), midsinus (C), and distal (D) internal carotid levels, and for the external carotid level (E), the  $0^\circ$  location is defined by the center of the flow divider wall. For the common carotid level (A), the  $0^\circ$  location is on the side corresponding to the origin of the external carotid.

whose magnitude was low but whose direction oscillated during the cycle. This region also was one in which there was a relatively long residence time of tracer particles near the model walls.

The associated pathological studies included extensive mapping of the intimal thickness of human carotid specimens as a function of axial and circumferential location (Figure 2).

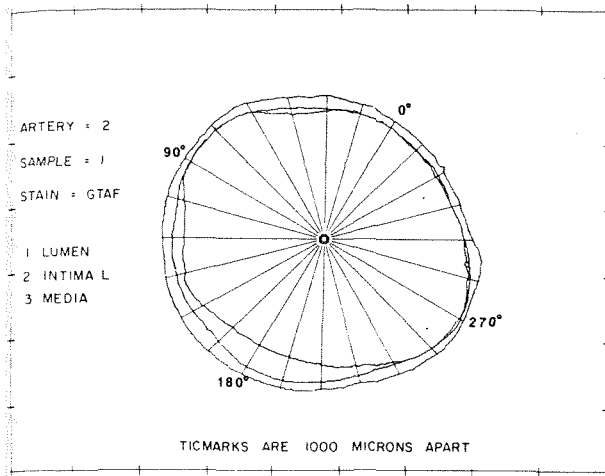


Figure 2. Printout of a typical contour tracing showing polar coordinate intervals at which intimal thickness was computed. 0° = centerpoint of the inner wall of the branch vessel at the flow divider. 180° = center position of the outer wall opposite the flow divider. 90° and 270° are at the intermediate anterior and posterior positions.

Early atherosclerotic plaques appear as localized areas of intimal thickening in cross-sectional slices of the artery. There was an obvious tendency for the areas of intimal thickening to be predominantly along the outer wall of the carotid sinus. We correlated several parameters related to wall shear with the values of intimal thickening measured from the cross-sections (Table II). The correlations showed that intimal thickness was greatest where wall shear was relatively low, and regions of the wall where the wall shear was relatively high tended to be spared of disease. It was

Table II. Correlation of Shear Stress Variables with Intimal Thickness at the Human Carotid Bifurcation

Hemodynamic Variable	r	P
Maximum shear	-0.69	NS
Mean shear	-0.63	NS
1/Maximum shear	0.90	<0.0005
1/Mean shear	0.82	<0.001
Oscillatory shear index (OSI)*	0.82	<0.001

\*For the definition of OSI, refer to Ku, et al. (1985)

also noted that the low wall shear regions in pulsatile flow tended to have oscillations in direction, so that we were unable to separate any correlations between mean shear and

intimal thickening from those relating oscillatory shear and intimal thickening (Figure 3).

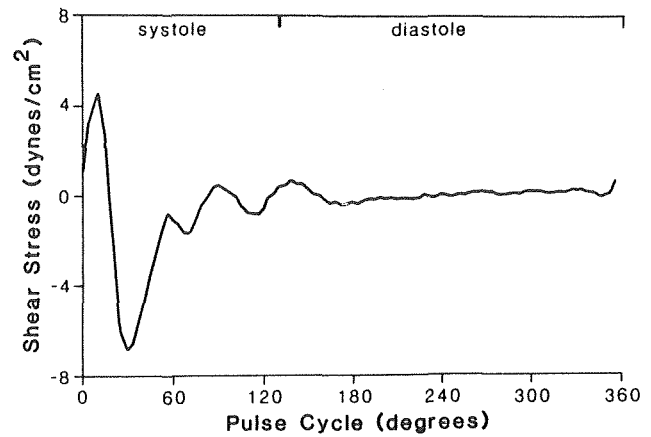


Figure 3. Wall shear stress at the outer wall of the carotid sinus (level B). This curve was derived from near-wall velocity data measured by laser Doppler velocimetry. Values are scaled to correspond to human carotid flow and diversions.

Interestingly, wherever the mean value of wall shear stress exceeded approximately 10 dynes/sq.cm there was a normal intimal thickness. This finding suggests the possibility that early atherosclerotic plaque localization may be an abnormal extension of the otherwise physiologic response of arteries to decrease diameter if the wall shear is below that range required for homeostasis. Since bifurcations have a very nonuniform distribution of wall shear due to the complex three-dimensional fluid dynamic patterns, the artery wall may respond focally to the wall shear it experiences, leading to regions of normal intimal thickening closely adjacent to regions where the physiological response to low shear demands a reduction in diameter and a consequent reaction to thicken the intima.

Evidence for such a model for atherogenesis is available from studies of the human coronary artery reported by Glagov et al. (1987), who noted that human coronary arteries enlarge as atherosclerotic plaques increase in size. In this manner an adequate lumen cross-sectional area is maintained until plaque area is quite large. The mechanism is not understood, but the enlargement may be related to locally elevated wall shear, since as the usually eccentric plaque enlarges, the lumen tends to narrow, resulting in higher velocity. This may induce a dilatational reaction in the uninvolved sector of the artery wall in an attempt to re-establish baseline shear conditions.

#### IV. DISCUSSION

Correlations between fluid dynamic near-wall behavior in

anatomically representative models of various human and animal arteries and the distribution of intimal thickening in actual vessels have demonstrated that there can be dramatic effects of flow upon the living artery wall. These effects can occur with or without the accompaniment of atherosclerosis. While a great deal of new knowledge has resulted from joint studies by fluid dynamicists and biological scientists, much remains to be determined.

We do know that arteries adjust their diameter in response to chronic changes in flow and that this adjustment yields in a mean wall shear stress in the range from 10-20 dynes/sq.cm. These arterial changes can result from natural growth or from experimental manipulations in animals. It is not known, however, whether it is shear stress or shear rate which is the actual stimulus, nor are specific mechanisms known at the cellular level. Endothelial cells may play a role as sensors, since they are the source of a variety of signals that regulate other cells.

Atherosclerosis is a disease process, but it may be induced in relation to an apparently physiologic response to low shear, particularly at sites about branches and bifurcations, if additional stimuli such as circulating atherogenic substances, hypertension or smoking are present. Studies of the human carotid bifurcation revealed a strong correlation among low mean wall shear, oscillating shear, intimal thickening and plaque formation. Investigations of the human aortic bifurcation and coronary arteries led to similar conclusions (Friedman et al, 1986). Regions of relatively high wall shear are usually spared, at least until advanced stages of the disease are reached. After plaques have formed, high shear may contribute to complications such as plaque disruption and embolization.

There is no evidence that turbulence, thought by some to be an atherogenic factor, contributes to plaque initiation. The Reynolds numbers in the vessels involved are sufficiently low to prevent turbulence under normal conditions in the coronary, carotid or femoral arteries, i.e., at the sites of usual selective involvement. Once plaques evolve to a more advanced state, when stenosis reaches a sufficient degree, turbulence can occur. This phenomenon is employed routinely in noninvasive diagnosis of carotid bifurcation disease. The effect is, however, a consequence of atherosclerosis, not a cause.

The biologic processes which regulate arterial responses, both physiologic and pathologic, occur at the cellular and molecular level. Fluid mechanical factors may be viewed as direct inducers or triggers of these processes and also in relation to the transport of humoral agents which are necessary for the tissue reaction to occur. In this sense, fluid mechanics sets boundary conditions for arterial wall structure and function, and plays a primary role in mediating biological events. Yet to be resolved is the question of whether the near-wall flow behavior provides a mechanical shear-stress related or a mass transport-related effect, or both, in regulating arterial wall responses to changes in flow.

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