Flow Patterns and Spatial Distribution of Atherosclerotic Lesions in Human Coronary Arteries

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To investigate the potential role of fluid mechanical factors in the localized genesis and development of atherosclerotic lesions in humans, the exact anatomic locations of atherosclerotic lesions and the flow patterns at such sites in left and right human coronary arteries were studied in detail by flow visualization and high-speed cinematographic techniques using five isolated, transparent human coronary arterial trees prepared postmortem. It was found that atherosclerotic plaques and wall thickenings in left and right coronary arteries were localized almost exclusively on the outer wall of one or both daughter vessels at major bifurcations and T-junctions, which left the flow-divider free of lesions, and along the inner wall of curved segments. When flow patterns in such vessels were studied in detail, it was discovered that these sites were where flow was either slow or disturbed with the formation of slow recirculation and secondary flows and where wall shear stress was low. The results indicate that the major hemodynamic factors directly related to the localization of atherosclerotic plaques and wall thickenings in the human arterial system are the low fluid velocity and the resultant low shear stress that acts on the vessel wall. (Circulation Research 1990;66:1045–1066)

Luminal narrowing or occlusion of large arteries through the development of atherosclerotic plaque is the vascular disease responsible for the highest mortality in the form of heart failure or stroke among North American men. Many questions concerning the pathogenesis of atherosclerosis remain unanswered. Various factors, such as heredity, dietary fat content, hypertension, obesity, diabetes, and smoking, are believed to aggravate the disease. Much attention has been focused on the possible correlations between diet and the formation of atherosclerotic lesions since the patchy atheromatous plaques are rich in lipids and can be easily produced experimentally in various animals by feeding them diets containing high levels of cholesterol.\textsuperscript{1,2} Undoubtedly, anomalies in plasma lipid concentration and lipid metabolism by vascular endothelial cells, as in hypercholesterolemia, exert a prominent influence on the genesis and progression of atherosclerosis. However, such a theory cannot account for the second piece of evidence, that is, localization of atherosclerotic lesions in the arterial system. Clinical and postmortem studies indicate that atherosclerotic lesions on human vessel walls do not develop randomly and do not occur throughout the circulation but instead localize at certain selected sites in the arterial tree such as the branching sites and curved segments of large arteries where the blood flow is disturbed and separation of streamlines from the vessel wall and formation of eddies are likely to occur.\textsuperscript{3–5} Thus, it is strongly suspected that arterial hemodynamics play an important role in the genesis, progression, and regression of atherosclerosis.\textsuperscript{6–8}

Among the theories and hypotheses proposed to account for the localization of atherosclerosis, the causative effects of high and low wall shear stresses, which were originally reported by Fry\textsuperscript{9} and Caro et al.,\textsuperscript{4} respectively, almost two decades ago, have received much attention. Since then, a considerable amount of work, both theoretical and experimental, has been carried out by many investigators. The integrated results from studies in animals show that in cholesterol-fed rabbits and swine, early atherosclerotic changes to vessel walls occur preferentially at the flow-divider (high shear region) of branching arteries,\textsuperscript{10,11} giving support to the high-shear hypothesis of atherogenesis. On the other hand, recent postmortem pathological investigations indicate that preferred sites for naturally formed atherosclerotic lesions in humans lie in regions...
of low shear stress. Furthermore, there have been several interesting but scattered reports on the effects of shear stress on the biological functions of endothelial cells that indicate that exposure of endothelial cells to moderate-to-high shear stresses prevents atherogenesis in cholesterol-fed monkeys and enhances the synthesis of prostacyclin and uptake of low density lipoproteins by endothelial cells in culture. Therefore, despite the effort of many investigators, the effects of shear stress on vascular endothelium and the pathogenesis of atherosclerosis remain unclear. Further detailed and systematic studies are required to understand the exact role of hemodynamic factors in the localization of the sites of atherosclerotic lesions in the human arterial tree.

The purpose of the present study was to clarify the possible connection between flow patterns and the exact anatomic locations of atherosclerotic plaques and wall thickenings that formed spontaneously in human coronary arteries. The study was motivated by the fact that despite the high incidence of narrowing and occlusion of vessel lumens through the development of atherosclerotic lesions and the resultant deposition of platelet thrombi, little information is available on either the spatial distribution of atherosclerotic lesions or fluid dynamics in human coronary arteries. The study was carried out with pressure-fixed human coronary arterial trees rendered transparent by a novel technique developed in our laboratory. The transparent natural arteries have, for the first time, permitted a simultaneous study of the exact anatomic locations and sizes of atherosclerotic plaques and wall thickenings as well as the detailed characteristics of the flow prevailing at such sites by directly observing and photographing the behavior of suspended tracer particles flowing in steady or pulsatile fashion through the transparent segments of normal and diseased human coronary arteries. The results obtained from this anatomic and fluid mechanical study are described in detail.

Materials and Methods

Preparation of Transparent Coronary Arterial Trees

Isolated, transparent human coronary arterial trees containing the proximal portion of the ascending aorta and left and right coronary arteries with their major branches were prepared postmortem by a modification of the method described by Karino and Motomiya. Since it is known that most flow in coronary arteries occurs during diastole, which is longer in duration than systole, coronary arterial trees in the present study were constructed so that they represented the vascular geometries in the diastolic period of the cardiac cycle.

Five fresh and intact human hearts with an 8–10-cm long segment of the ascending aorta were obtained at autopsy from four male subjects aged 18, 56, 61, and 75 years and a 51-year-old female subject in all of whom the primary cause of death was not cardiovascular disease. After the heart and aorta were thoroughly rinsed with isotonic saline, the ascending aorta was excised at about 5–7 cm down-stream from the aortic valve and cannulated with a 10-cm long, rigid, plastic cylinder. The other end of the plastic cylinder was connected to an overflow head tank via flexible plastic tubing. The heart was placed in a dissecting pan, and the aorta and coronary arteries were continuously perfused with ice-cooled saline by establishing a recirculatory system between the dissecting pan and the overflow head tank with a roller pump. The left and right coronary arteries and their major branches with diameters of more than 1.5 mm were exposed and separated from the heart to the desired point of cannulation by using fine scissors and pincers to carefully dissect the heart muscles and remove the surrounding tissue. The other smaller branches were ligated with 6-0 Prolene suturing thread at positions that were close to their branching sites but left them attached to their parent vessels and the heart. Each of the major branches then was incised at a location at least 1.5 cm down-stream from its branching site, cannulated with a 2–2.5-cm long, square-cut, thin-walled stainless-steel pipe (made of a hypodermic syringe needle with an outer diameter approximately equal to the inner diameter of the vessel to be cannulated), and firmly tied in place. The other end of the cannula was capped with tightly fitted, short, plastic tubing with a sealed end. Then, the cannulae were affixed to the heart by suturing and tying them onto the heart muscles while maintaining the original configuration of each vessel under a physiological perfusion pressure of ~100 mm Hg.

The root of the ascending aorta was separated from the heart by dissecting the tissue surrounding the aortic valve and then sealed by inserting a tightly fitted plastic disk into the aorta proximal and adjacent to the valve cusps and tying the surrounding aortic tissues over it. To simulate a diastolic condition of the heart and the arterial tree, the right and left ventricles were inflated to approximately their normal diastolic volumes by filling them with small pieces of gauze. Furthermore, to maintain the geometric integrity of the coronary arteries and their major branches after removing all of the heart muscles and tissues, the arteries and aorta were tied at each cannula with a thick suturing thread and firmly affixed onto a three-dimensional stainless-steel frame. The frame had been constructed for this purpose by bending and stretching a 3-mm o.d. stainless-steel pipe around the surface of the heart and aorta so that it crossed and made good contact with all the cannulae of the left and right coronary arterial branches as well as the thick plastic cylinder that had been cannulated into the aorta by winding around it several times.

The coronary arterial tree, which was still attached to the heart, was connected via flexible plastic tubing to a head tank and a collecting reservoir and then fixed by simultaneous perfusion with and immersion in a mixture of 2% glutaraldehyde and 4% formal-
dehydrate in isotonic saline at the physiological mean perfusion pressure of \( \sim 100 \) mm Hg. Then, the arterial tree and the aorta were isolated from the heart, dehydrated for 2–3 days by perfusion with and immersion in ethanol-saline mixtures of progressively increasing ethanol concentration under the same perfusion pressure, and suspended in pure ethanol. Finally, the coronary arterial tree attached to the aorta was filled with and immersed in methyl salicylate (oil of wintergreen) containing 5% ethanol under the physiological mean perfusion pressure necessary to render the vessel transparent.

**Experimental Procedure**

Mounted on a supporting frame, the isolated transparent coronary arterial tree was suspended in oil of wintergreen containing 5% ethanol in a transparent glass chamber and transilluminated with condensed parallel light from a 200-W AC tungsten-filament white lamp through a pair of 16-cm diameter plano-convex lenses aligned in series. The whole arterial tree and segments of interest were observed from various angles by changing the orientation of the arterial tree relative to the direction of the light beams and photographed with a ruler on 35-mm color or black and white films with a Nikon FE 35-mm camera with zoom and close-up lenses.

The arterial tree in the glass chamber then was placed on a vertically movable horizontal stage located in front of the vertically mounted stage of a microscope. The areas of interest on the arterial tree were transilluminated with condensed parallel light provided by a Reichert Binolux twin-lamp assembly (Sargent-Welch Scientific, Montreal, Canada) supplying either low-intensity light from a tungsten-filament lamp or high-intensity light from a 200-W DC mercury arc lamp with a blue filter to eliminate ultraviolet illumination.

The aorta and the cannulated left and right coronary arterial branches were connected via approximately 150-cm long flexible plastic tubing, with an inner diameter approximately the same as the outer diameter of the cannula, to a head tank and a triangular flask used as a collecting reservoir, respectively. Steady and pulsatile flows were obtained using a head tank system in combination with a sinusoidal oscillatory flow pump.

A dilute suspension of a mixture of 50-, 80-, 115-, and 165-\( \mu \)m diameter polystyrene microspheres (density \( \rho \), 1.06 g/cm\(^2\); Particle Information Services, Bremerton, Washington) in oil of wintergreen containing 5% ethanol (density \( \rho \), 1.16 g/cm\(^2\); viscosity \( \mu \), 0.026 g/cm-sec) was substituted for blood. This is based on our assumption that since the estimated mean shear rates in human coronary arteries are well over the critical values of \( \sim 100 \) sec\(^{-1}\), above which the blood behaves as a Newtonian fluid, the non-Newtonian characteristics of the blood would have no effect on coronary blood flow; thus, blood can be replaced by any Newtonian fluid.

After filling the arterial tree and the entire flow system with the suspension, the desired flow rates in the main artery and its branches were established by adjusting the height of the head tank as well as each collecting reservoir. The suspension was subjected to steady or pulsatile flow through the transparent arterial tree, and the behavior of individual suspended tracer microspheres flowing though various regions of the left and right coronary arteries was observed through a zoom lens (magnification, \( \times 1-5 \)) attached to a cine camera and photographed on 16-mm cine films (Kodak double X-negative) with a Hycam 16-mm cine camera (Red Lake Labs, Santa Clara, California) at film speeds of 1,200–1,500 pictures per second.

With respect to the flow conditions in the human coronary arteries, it is known that during strenuous exercise, the heart increases its cardiac output as much as fourfold to sixfold. At the same time, the coronary blood flow also increases fourfold to fivefold to supply the extra nutrients needed by the heart. If it is assumed that the localization of atherosclerotic lesions on the vessel wall is related to an abnormality or disturbance of the flow in that vessel, the effect will be more pronounced at high Reynolds numbers (hence, high flow rates) since the formation of disturbed flows is favored at high Reynolds numbers. Hence, taking all these factors into consideration, we have conducted flow studies at flow rates about twofold to threefold higher than the reported mean values for humans and at a high oscillatory frequency of 2 Hz (120 beats/min) so that the flow mimics the typical coronary blood flow under moderate exercise. Flow studies were conducted by letting flow occur through one (left or right) coronary artery at a time. The outflow rates through each branch were obtained by measuring the volume of suspension expelled in a given time during which filming of the flow patterns was performed. Furthermore, at each branching site studied, the flow rate in each daughter vessel was first adjusted to its geometric flow ratio (flow rate ratio calculated by assuming that the fluid in the parent vessel is distributed into the daughter vessels in proportion to their cross-sectional areas assessed at the apex of the flow-divider) and then shifted to more or less than the control value. In the present study, most of the flow experiments were conducted in steady flow since it is not practical to express the detailed flow patterns observed in pulsatile flow in two-dimensional figures. Only a few experiments were carried out in pulsatile flow (steady plus oscillatory flow) with an oscillatory frequency of 2 Hz and displacement volumes of 0.5 and 1.5 ml to compare the results obtained in steady flow with those in pulsatile flow and determine whether the phenomena observed in steady flow also occur in pulsatile flow. Whenever possible, flow was observed and recorded along two diametric planes that were normal to each other to obtain a better grasp of the complete flow patterns in various regions of disturbed flow along the arterial tree.
Analysis

Subsequently, the developed 35-mm films were projected onto a glass screen with a slide projector and analyzed to obtain geometric data for each segment such as the diameter and length of each segment, the angle of branching, and the sizes and thicknesses of atherosclerotic plaques and wall thickenings located on the inner surface of vessel walls.

The 16-mm cine films were projected onto a drafting table, and the movements of individual tracer particles were analyzed on a frame-by-frame basis with the aid of a stop-motion 16-mm movie analyzer (Vanguard Instrument Corp, Melville, New York) to obtain the detailed flow patterns and distributions of fluid velocity and wall shear stress.

The representative geometric and flow conditions such as the vessel diameter ($D_0$), mean volume flow rate ($Q_o$), mean fluid velocity ($U_o$), and Reynolds number ($Re_o \equiv D_0 U_o \rho / \mu$, where $\rho$ and $\mu$ are the density and viscosity of the flowing fluid, respectively) were evaluated for each main vessel proximal to the site of branching and bending. The velocity distributions at various axial locations were obtained by plotting approximately 100 points of the axial components of particle translational velocities (calculated from tracings of the tracer particle paths that were in good focus and appeared to be located in or close to the median plane of the vessel normal to the viewing axis) against the distance from the vessel wall. Wall shear stresses were determined by multiplying the slopes of the tangents drawn at the vessel wall on the best-fit curves of velocity profiles at various axial locations by the viscosity of the fluid. The locations of separation and stagnation points were determined from the movements of the smallest (50-μm diameter) tracer microspheres that were too small to be traced to obtain the detailed flow patterns but were observable as dust in the picture. Throughout the analysis, special attention was paid to the phenomena occurring near the vessel wall by finding and tracing the behavior of the smallest traceable microspheres located as close as possible to the vessel wall.

Histological Examinations

After completing all the flow studies, the transparent coronary arterial trees were put back into ethanol and used for histological examinations to determine the major components of the atherosclerotic plaques and wall thickenings found in these vessels. Several short segments were removed from each arterial tree. The approximate anatomic locations were the distal portion of the left main coronary artery (LMCA), the proximal portion of the left anterior descending coronary arterial branch (LAD), the proximal portion of the left circumflex arterial branch (LCx), and the major bends of the right coronary artery (RCA). The tissue samples were embedded in paraffin, sectioned, and stained with hematoxylin and eosin or Masson trichrome for differential staining of connective tissue fibers and cells.

Results

As already described in detail, five isolated, transparent human coronary arterial trees were prepared postmortem by cannulating the aorta and the major branches of the left and right coronary arteries, fixing them under physiological pressure, dehydrating them with ethanol, and finally suspending them in oil of wintergreen containing 5% ethanol. Photographs taken during and at the end of the preparation process show the detailed anatomy of the arterial tree (Figures 1 and 2). Photographs of sections of these human coronary arteries prepared after completing all the flow studies are shown in Figure 3. Careful examination of the stained sections revealed that virtually all the plaques and wall thickenings observed without magnification as dark-colored patches and elevated intimal layers on transparent coronary arterial trees were atherosclerotic lesions mainly composed of collagen and ground substances with some deposits of calcium. There were many empty spaces in the tissue sections; these were considered to be sites of lipids and foam cells before they were extracted by ethanol and oil of wintergreen. The plaques that appeared as nontransparent spots were composed of very dense, unorganized, acellular materials containing numerous calcium deposits; hereafter, they are referred to as calcified plaques. It was also found that, in most cases, the intimal thickenings were still coated with a layer of endothelial cells after being treated with ethanol and oil of wintergreen to render the vessel transparent.

The prepared transparent arterial trees lost the elasticity of natural living artery during the process of fixing, dehydrating, and rendering them transparent. However, the method ensured the preservation of the complex three-dimensional configuration of the natural coronary arteries. Moreover, they became transparent without any optical distortion, even in the presence of atherosclerotic thickening of the vessel wall, although the areas of calcification remained as nontransparent dark spots (Figure 1D). Thus, it was possible to make observations and measurements of the exact locations of atherosclerotic lesions and the flow in both normal and diseased vessels from any direction without the errors that arise from optical distortions (due to the difference in the refractive index between the vessel wall and the flowing liquid) and that are inevitable when glass models and plastic casts are used. The transparent arterial trees were used first to study the exact anatomic locations of atherosclerotic lesions and then to study the detailed fluid mechanical characteristics of the flow at such sites. Here, the anatomic location of the vessel wall in branching arteries and arterial bends was specified using the simple terminology assigned to particular areas or segments of the artery as shown in Figure 4. The results are described in detail for each location along the arterial tree.

Left Main Coronary Artery

As shown in Figures 1A, 1B, 2A, and 2B, the relatively straight LMCA arose with a bell-shaped
Asakura and Karino
Flow Patterns in Human Coronary Arteries

Figure 1. Photographs taken during and at the end of the preparation of the isolated transparent human coronary arterial trees showing (panel A) a coronary arterial tree exposed, cannulated, and firmly fixed on a solid three-dimensional stainless-steel frame but still attached to the heart (photograph taken just before fixation while the arterial tree was perfused with isotonic saline under physiological pressure), (panel B) an isolated coronary arterial tree after fixation with a mixture of 2% glutaraldehyde and 4% formaldehyde in isotonic saline under the physiological mean pressure of ~100 mm Hg, (panel C) an isolated transparent coronary arterial tree prepared from an 18-year-old male subject (arterial tree suspended in a glass chamber filled with oil of wintergreen containing 5% ethanol), and (panel D) an isolated transparent coronary arterial tree prepared from a 75-year-old male subject who had severe atherosclerotic lesions.
Figure 2. Photographs of various segments of transparent human coronary arteries showing the exact anatomic location of atherosclerotic wall thickenings and calcified plaques at (panel A) the hips of a trifurcation of the left main coronary artery (top view), (panel B) the lower wall of the left anterior descending branch (right lateral view of the artery shown in panel A), and (panel C) the inner wall of curved segments (top view) of the right coronary artery in an arterial tree prepared from a 61-year-old male subject.

entrance from the distal end of the aortic sinus. Close observation of the anatomic structure of the entrance region revealed that curvatures of the vessel wall were very gentle on the upper (pericardial side) wall but rather sharp like the flow-divider at branching sites on the lower (myocardial side) wall. When viewed laterally, the measured angles (acute toward the heart) between the axes of the LMCA and the ascending aorta were between 25° and 60° in the four older subjects (51-75 years old) and 70° in the younger (18-year-old) subject. Moreover, when observations were made along the axis of the ascending aorta, the axis of the LMCA was skewed toward the RCA with angles of deviation from the diametric plane of the ascending aorta, which passed through the center of the orifice of the LMCA between 50° and 70°. The internal diameter of the LMCA, measured at the midportion of its entire length, was between 3.8 and 4.1 mm in the four older subjects and 5.3 mm in the younger subject.

Atherosclerotic lesions were found in three regions. In four of five segments, atherosclerotic wall thickenings were observed on the right upper wall (relative to the direction of the flow) opposite the sharp leading edge of the lower wall. In these four cases, two cases were calcified plaques. The second preferred site was located on the lower right lateral wall just downstream of the lower leading edge of the LMCA. In three cases, mild wall thickening was found at this site. The third preferred site was the
Figure 3. Histological preparation of transverse sections of the human coronary arterial tree prepared from a 51-year-old female subject showing the exact circumferential locations and the extent of atherosclerotic wall thickening formed at four standard locations. Panel A: Distal portion of the left main coronary artery; panel B: proximal portion of the left anterior descending branch; panel C: proximal portion of the left circumflex branch; panel D: acute bend in the proximal portion of the right coronary artery; panel E: magnified (original magnification, ×50) view of vessel wall taken from area indicated by circle in panel D. Deformation of the vessel wall and cracking of the plaque in panels A and B are artifacts created during the preparation of the sections. Myoinimal thickenings were composed mainly of acellular fibrous materials and calcium deposits. In regions of atherosclerotic plaques, there were many empty spaces, which appeared to be the sites where lipids and foam cells were located before they were extracted by ethanol and oil of wintergreen. PC, pericardial side; MC, myocardial side; L, left; R, right (relative to the direction of blood flow); IW, inner wall of bifurcation; OW, outer wall of bifurcation; I, intima; M, media; A, adventitia. Stains were hematoxylin and eosin (panels A–C) and Masson trichrome (panels D and E). Original magnification of panels A–D, ×5.
mation of a backflow region along the lower right lateral (myocardial side) wall between the separation point S and stagnation point P, where a wall thickening was found in three vessels as described earlier. This was the only region in which disturbed flow was observed in the LMCA. Distributions of fluid velocity were calculated from the velocity of tracer particles. As is evident from Figure 5B, velocity distribution in the LMCA was skewed toward the lower wall at the entrance but quickly reversed within a short distance (less than 1 diameter) from the lower leading edge and skewed toward the upper wall, creating a low wall shear stress region along the upper wall at the entrance and at the lower wall farther downstream. Comparison of these results with the anatomic study of the sites of atherosclerotic lesions indicates that preferred sites for the formation of atherosclerotic plaques and wall thickenings are located in regions of slow flow and low wall shear stress.

**Left Anterior Descending Branch and Left Circumflex Branch Junction and Proximal Portions**

As shown in Figures 1, 2A, and 2B, within 2–3 diameter distances after stemming off the aortic sinus, the LMCA divided into two major branches with approximately equal diameters (LAD and LCx); often, a third intermediate branch was formed. In the present study, three of five vessels had the intermediate branch. After branching off the LMCA, the proximal portion of the LAD gently curved toward the lower wall along the curved surface of the myocardium. The measured branching angle between the axes of the LAD and LCx ranged from ~70° in two subjects (including the 18-year-old) to 105° in the other three subjects.

Atherosclerotic lesions were found at two distinct locations at the branching site as shown in Figure 2A by a photograph of the arterial tree prepared from a 61-year-old man. In all of the five transparent arterial trees prepared and studied, atherosclerotic wall thickenings were located almost exclusively along the outer wall (hip) of the bifurcation or trifurcation. To be more specific, they were formed along the lower lateral walls of the bifurcation and extended distally to the lower (myocardial side) walls of the LAD and LCx. Calcified plaques also were found at these sites as a part of the wall thickening (on the LAD side in three subjects and on the LCx side in one subject). As an extension of these two lesions, the lower wall of the distal LMCA also was thickened. In all cases, the flow-divider and upper (pericardial side) walls were minimally affected by atherosclerotic lesions.

In the proximal portion of the LAD, atherosclerotic plaques and wall thickenings were found along the right lateral and lower walls (inner wall of the curved segment). It was also noted that atherosclerotic lesions in the LAD were confined to the initial few centimeters from the junction of the LAD and LCx. No atherosclerotic plaque was found on the upper wall, not even in the most severe case encountered.
In the proximal LCx, atherosclerotic wall thickenings were found in the four older subjects along the lower lateral wall as an extension of the one formed at the hip of the LAD-LCx junction. No atherosclerotic change was found along the inner wall of the bifurcation or trifurcation. Except for one severely calcified case, no atherosclerotic plaque was found on the upper wall. In the one severely calcified case mentioned above, several small calcified plaques were found in an area where the LCx curved toward the upper wall (inner wall of a gently curved segment).

It was also noted that the frequency and degree of severity of the atherosclerotic lesions decreased with increasing distance from the origin of the artery.

The results from flow studies showed that, in three vessels prepared from the older subjects (51, 56, and 61 years old), spiral secondary and recirculation flows formed in one or both daughter vessels of the LMCA near the hips of the bifurcation or trifurcation at the exact sites of atherosclerotic plaques and wall thickenings. Figure 6 illustrates the detailed flow patterns, which have been traced from the movements of tracer microspheres, and distributions of fluid axial velocity and wall shear stress observed in steady flow at the trifurcation of the LMCA in an arterial tree prepared from a 61-year-old male subject. As shown in Figure 6A, flow separation occurred at the hips of the bifurcation (indicated by S), creating wide regions of separated flow. Then, the regions of separated flow were filled with the spiral and recirculation flows that formed as a result of a strong deflection of the flow from the LMCA at the obtuse-angled flow-divider. Due to the particular anatomic structure of the trifurcation (e.g., slight bending of the LAD and LCx toward the lower walls at the branching site) as well as the skewing of the approaching velocity (higher along the upper wall) in the distal LMCA, the deflection of flow at the flow-divider was not symmetrical about the common median plane (curved plane parallel to the pericardium) of the LMCA and its two major daughter vessels. The deflection of flow was much stronger in the lower half of the common median plane in both the LAD and LCx and resulted in the formation of spiral secondary and recirculation flows along the lower lateral walls of the trifurcation. To confirm this, observations were also made laterally. Figure 6B illustrates the flow patterns observed when the viewing axis was aligned with the common median plane of the LMCA and LAD, which was parallel to the pericardium (right lateral view of the flow shown in Figure 6A). As shown, a long, thin-layered recircu-
\begin{align*}
\text{Left anterior descending branch} & \quad D_0 = 4.13 \text{ mm} \\
\text{Left main coronary artery} & \quad Q_0 = 334 \text{ ml/min} \\
\text{Left main coronary artery} & \quad \bar{U}_0 = 416 \text{ mm/sec}
\end{align*}
lotion zone was formed adjacent to the lower right lateral wall of the LMCA just downstream of the lower leading edge where a mild wall thickening was found. Going farther down, flow was deflected at the flow-divider on both sides of the common median plane, but the movements of tracer microspheres were more complicated near the lower wall, where atherosclerotic lesion was also severe, than near the upper wall. The axial velocity distributions in the median plane of both the LMCA and LAD, normal to the pericardium, were calculated from the paths of tracer particles located close to each diametric plane; the results are shown in Figure 6C. As is evident, the velocity distribution skewed toward the upper wall in both the distal LMCA and proximal LAD. The long and wide atherosclerotic wall thickening was located along the lower wall where both fluid velocity and wall shear stress were much lower.

The above results were compared with those obtained in another arterial tree prepared from a healthy 18-year-old man who died in an automobile accident. As shown in Figure 7A, it was found that the pathological and fluid mechanical phenomena occurring at the junction were basically the same as those observed in the previous two cases. However, it was evident that the flow patterns were much simpler than those observed in older subjects, and no recirculation zone was formed in this trifurcation. Figure 7B illustrates the distributions of fluid axial velocity and wall shear stress calculated along the common diametric plane parallel to the pericardium. As is evident in the common median plane, the velocity distribution flattened proximal to the flow-divider, slightly skewed toward the outer walls at the flow-divider, and then gradually shifted toward the inner walls with increasing distance from the flow-divider. The calculated wall shear stresses were higher along the inner walls than the outer walls of the trifurcation. The hips, sites of a slight thickening of the vessel wall, were the regions of low wall shear stress. The velocity profile in the diametric plane normal to the pericardium (not shown) was flattened over a long distance from the flow-divider. Due to the short length of the LMCA, the wall shear stress at the proximal LAD was higher on the lower wall near the flow-divider but gradually reversed with increasing distance from the flow-divider and eventually became higher on the upper wall. Also, the velocity profile changed from a flat to a more parabolic shape with distance.

Middle and Distal Left Anterior Descending Coronary Artery and Its Major Branching Sites

In the middle and distal portions of the LAD, the degree of severity of atherosclerotic lesions was greatly reduced. Except for the severely calcified case shown in Figure 1D, most atherosclerotic lesions were confined to branching sites. Atherosclerotic plaques and wall thickenings in the middle and distal LAD were found along the hips of one or both daughter vessels of the bifurcation and along the inner wall of curved segments. It was also noticed that the stem of the LAD was more tortuous in the older subjects than in the younger one. In such tortuous vessels, atherosclerotic wall thickenings were found along the inner wall of each curved segment.

Flow studies were conducted at some major branching sites of the LAD. It was found that the flow patterns at each branching site in steady flow were greatly affected by the nature of the flow proximal to the branching site (e.g., whether the approaching flow was laminar or already disturbed). In general, flow was disturbed to some extent at all of the major bifurcations of the LAD. Much stronger and more pronounced disturbed flows were observed when two large-diameter side branches came off the LAD at the same location.

Figure 8 illustrates the detailed flow patterns observed in steady flow at the branching site of the second diagonal branch in one of the arterial trees with a moderate degree of atherosclerotic wall thickening and tortuosity in the LAD. As is evident, a recirculation zone was formed in the second diagonal branch adjacent to the hip of the bifurcation at the exact site of an atherosclerotic wall thickening. The inner wall of each curved segment was also a preferred site for atherosclerosis.

Left Circumflex Artery and Its Major Branching Sites

The anatomic structure of the LCx varied considerably among subjects. The LCx was also tortuous in the older subjects. Thus, there was no particular region where atherosclerotic lesions were concentrated. In general, the lesion was more severe in the proximal portion than in the middle (region of the branching site of the obtuse marginal branch) and distal portions. Atherosclerotic lesions were found at the inner wall of curved segments and along the hips of bifurcations.
FIGURE 7. Detailed flow patterns (A) and distributions of fluid axial velocity and wall shear stress (B) (as in Figure 5) at the trifurcation of the left main coronary artery (LMCA), proximal left anterior descending branch (LAD), and left circumflex branch (LCx) in an 18-year-old male subject's arterial tree in which wall thickening was minimal. Panel A shows the formation of double helicoidal flows in each major daughter vessel along the hips of the trifurcation where slight wall thickening was found. Wall shear stress was low along the hips of this vessel from a young subject, as it also was in the vessel from the previous, older subject. Arrows at S indicate separation points. $Re_o$, Reynolds number; $D_o$, vessel diameter; $Q_o$, mean volume flow rate; $U_o$, mean fluid velocity; IB, intermediate branch.
Figure 8. Detailed flow patterns (as in Figure 5) observed in steady flow at the branching site of the second diagonal branch from the left anterior descending branch in a vessel prepared from a 61-year-old male subject. The formation of disturbed flows with a recirculation zone and double helicoidal flows is shown. Atherosclerotic wall thickenings were localized at the hips of the bifurcation and along the inner wall of curved segments where fluid velocity and wall shear stress were low. Arrows at S and P indicate separation and stagnation points, respectively. $Re_o$, Reynolds number; $D_o$, vessel diameter; $Q_o$, mean volume flow rate; $U_o$, mean fluid velocity.

Figure 9 illustrates the detailed flow patterns observed at the branching site of the obtuse marginal branch (OM). As is evident, the approaching flow in the LCx proximal to the flow-divider was already disturbed due to the irregularly bending nature of the LCx. The approaching velocity distribution was skewed toward one side of the wall in both the common median plane parallel to the pericardium and the median plane normal to it (not shown). In this particular vessel, the left lateral wall of the LCx corresponded to a region of separated flow. Particles in the slowly moving spiral flow (indicated by the dashed lines in the figure) located adjacent to the lower (myocardial side) wall passed through this region. The particles then traveled along the left lateral and upper walls of the LCx and approached the flow-divider. After being deflected at the flow-divider near the upper wall, they split into two groups, one entering the OM and the other trailing down along the upper wall of the LCx. Flow separation occurred at the sharp bend of the OM opposite the flow-divider (indicated by S). The particles located near the lower wall close to the right lateral wall entered this region from the far end and then moved backward along the outer wall of the bifurcation before suddenly changing direction and being entrained by the rapid flow from the LCx. In this manner, a recirculation zone was formed downstream of the sharp bend between the separation point S and the stagnation point P, at the entrance of the OM. A pronounced atherosclerotic wall thickening was found at the sharp bend (hip of the bifurcation) where a triangular-shaped recirculation zone was formed.

**Entrance Region of Right Coronary Artery**

As in the case of the left coronary artery, the RCA arose with a bell-shaped entrance from the distal end.
of the aortic sinus. When viewed laterally, the measured angles (toward the heart) between the axes of the RCA and the ascending aorta were between 75° and 95° with a mean value of 88°. The mean angle (away from the LMCA) of deviation from the diametric plane of the ascending aorta that passed through the center of the orifice of the RCA was about 2°, indicating that the RCA stemmed from the aorta almost symmetrically. The internal diameter of the RCA, measured in its entrance region, ranged from 3.3 to 3.8 mm in the five coronary arteries studied.

In all five RCAs, atherosclerotic wall thickenings were found at the entrance region within 1 cm from the origin of the RCA. In most cases, the vessel wall was not thickened just on one particular side but equally all around the intima. In only one case was the intimal thickening found at the left lateral wall as shown in Figure 2C. The flow in the entrance region of the RCA was laminar in all cases.

**Major Bends of Right Coronary Artery**

From the origin of the artery to the branching site of the posterior descending branch in the proximal and middle portion of the RCA, the vessel diameter remained almost constant (Figure 2C). Except for one case in which the conus branch was unusually large (Figure 1C), the diameters of the side branches in the proximal and middle portions of the RCA were quite small. The artery was tortuous with a series of asymmetrically arrayed sharp and gentle bends. Atherosclerotic wall thickenings were found at the inner wall of the curved segments in an alternating fashion and at the hips of the major bifurcations and T-junctions of the RCA. In one vessel with severe atherosclerotic lesions, calcified plaques were found scattered over the proximal and middle portions of the RCA. However, even in such severe cases, the frequency and degree of severity of atherosclerotic lesions tended to decrease with increasing distance from the origin of the artery.

The results from flow studies showed that even though there are fewer bifurcations and T-junctions in the RCA than the LCA due to the presence of sharp and gentle bends, the flow in the RCA was by no means simpler than that in the LCA. Formation of strong secondary flows and standing recirculation

**Figure 9.** Detailed flow patterns (as in Figure 5) observed at the branching site of the obtuse marginal branch along the left circumflex branch in an arterial tree prepared from a 61-year-old male subject. Note that the formation of disturbed flows are affected not only by geometric factors such as the branching angle and the radius of curvature at the hips of a bifurcation but also by the nature of the approaching flow proximal to the flow-divider. Atherosclerotic wall thickening was localized at the hip of the bifurcation adjacent to the region of a recirculation flow. Arrows at S and P indicate separation and stagnation points, respectively. Re, Reynolds number; D, vessel diameter; Q, mean volume flow rate; U mean fluid velocity.
Asakura and Karino  Flow Patterns in Human Coronary Arteries

 zones were observed in most of the bends as shown in the following three examples.

First, Figure 10 illustrates the typical flow patterns observed in steady flow in the arterial bends in the proximal portion of the RCA prepared from a 61-year-old male subject. As shown, flow separation occurred at the inner wall of the first bend (indicated by S). At the outer wall of the bend, the fluid elements in the mainstream, having high momentum, were strongly deflected sideways and resulted in the formation of thin-layered spiral secondary flows adjacent to the vessel wall. The region of separated flow along the inner wall was filled by the peripheral secondary flows. A part of the secondary flows moved backward along the inner wall of the bend before suddenly changing direction and rejoining the mainstream on the median plane of the bend after describing a single orbit. Thus, a very thin-layered region of slow reverse flow (recirculation zone) was formed along the inner wall of the curved segment.

**FIGURE 10.** Detailed flow patterns (as in Figure 5) observed at some bends of the proximal and middle portions of the right coronary artery in an arterial tree prepared from a 61-year-old male subject (shown in Figure 2C). Shown are the strong deflection of main flow at sites of confrontation with the outer wall of the arterial bends, the development of peripheral secondary flows, and the formation of slow recirculation flows adjacent to the inner wall of the first bend where atherosclerotic wall thickening was localized. Arrows at S and P indicate separation and stagnation points, respectively. $Re$, Reynolds number; $D_0$, vessel diameter; $Q_w$, mean volume flow rate; $U_w$, mean fluid velocity.

![Diagram of Right Coronary Artery and Aortic Sinus](image)

**FIGURE 11.** Detailed flow patterns (as in Figure 5) observed at a bend of the proximal portion of the right coronary artery from an 18-year-old male subject. Arrows at S and P indicate separation and stagnation points, respectively. $Re_w$, Reynolds number; $D_0$, vessel diameter; $Q_w$, mean volume flow rate; $U_w$, mean fluid velocity; S-A, sinoatrial.

![Diagram of Right Coronary Artery and Aortic Sinus](image)
where atherosclerotic wall thickening was found. Similar flow patterns were observed on the second bend where a much wider area of the inner wall of the bend was covered by a thick layer of atherosclerotic lesion. However, due to the technical difficulty in focusing on the smallest dustlike particles traveling along the vessel wall of the two connected bends that were not on the same plane, it was not possible to confirm the presence of a thin-layered reverse flow along the inner wall of the second bend. The above finding raised the question of whether the recirculation zone was created as a result of the formation of an atherosclerotic wall thickening. Thus, studies were also carried out with a coronary arterial tree prepared from a young subject.

Second, Figure 11 illustrates the detailed flow patterns observed in an arterial bend in the proximal portion of the transparent RCA prepared from the 18-year-old male subject. As is evident, formation of a recirculation zone at the inner wall of an arterial bend was observed even in the artery from a young subject in which the degree of wall thickening was minimal. A slight but noticeable wall thickening was found at the inner wall of the bend in the region of a standing recirculation zone. The results clearly indicate that the exact locations of atherosclerotic wall thickening are closely related to the regions of disturbed flow with flow separation and the formation of slow secondary and recirculation flows.

Third, Figure 12A gives another example of flow patterns observed in an arterial segment with multiple bends located in the middle to distal portions of the RCA prepared from the 61-year-old male subject. As shown, although there was no side branch, due to the presence of a series of sharp and gentle bends that were not located on one plane, flow patterns in this arterial segment were very complex. Flow separation occurred at the inner wall of the middle and distal bends. The regions of separated flow were filled with the fluid from the peripheral thin-layered secondary flows that traveled along the vessel wall all the way from the outer wall of each bend. In the middle bend where observations were focused, a thin-layered standing recirculation zone was formed along the upper (pericardial side) inner wall just distal to the apex of the sharp bend where atherosclerotic wall thickening was localized. To identify the regions of high and low wall shear stress,

**FIGURE 12.** Detailed flow patterns (A) and distribution of fluid axial velocity (B) (as in Figure 5) observed in the common median plane (parallel to the pericardium) of an arterial segment with multiple bends located in the middle to distal portions of the right coronary artery from a 61-year-old male subject. Shown are the development of secondary flows, the formation of a recirculation zone adjacent to the inner wall of the middle bend, and the changes in velocity distributions along the arterial segment. Note that the location of atherosclerotic wall thickening is closely related to the region of recirculation flow where both the fluid velocity and wall shear stress are low. Arrows at S and P indicate separation and stagnation points, respectively. $Re_o$, Reynolds number; $D_o$, vessel diameter; $Q_o$, mean volume flow rate; $U_o$, mean fluid velocity.
attempts were made to obtain the distributions of fluid axial velocity (axial component of the fluid linear velocity) across the lumen of the arterial segment. The results are shown in Figure 12B. Due to difficulty in focusing the zoom system, which was attached to a cine camera, on the median plane of the multiple bends that were not located on one common plane, as well as the complexity of the flow that did not allow tracer particles to stay in good focus because of the continuous change of distance from the median plane (focal plane), it was not possible to make accurate measurements from cine films. Thus, the results shown here are only rough estimates of fluid velocity and wall shear stress in this arterial segment. Nevertheless, the results showed some interesting characteristics of the flow in arteries with multiple bends. As is evident from the figure, velocity distribution drastically changed within a few diameter distances between the locations proximal and distal to the apex of each bend. In the proximal portion of a bend, velocity distributions were skewed toward the inner wall, thus facilitating flow separation and formation of a recirculation zone along the inner wall distal to the apex of the bend. Just distal to the apex of the first bend, the peak in velocity distribution gradually shifted toward the outer wall of the first bend and, hence, toward the inner wall of the second bend, again favoring flow separation at the inner wall of the second bend. Atherosclerotic wall thickenings were localized in an alternating manner at the inner wall of each bend with a maximum thickening occurring in regions of recirculation flows where fluid velocity and wall shear stress were low.

**Major Branching Sites of Right Coronary Artery**

At the major bifurcations and T-junctions of the RCA, atherosclerotic plaques and wall thickenings were found almost exclusively on the hip of one or both daughter vessels. In no cases were flow-dividers affected by atherosclerotic lesions.

Flow studies were focused on several bifurcations and T-junctions along the RCA. Figure 13 shows the detailed flow patterns at the bifurcation of the posterior descending branch and the RCA observed in an arterial tree prepared from a 61-year-old male subject. The bifurcation was located just distal to a bend; thus, the RCA formed an S-shaped double bend. Due to this, the flow in the parent vessel was
already disturbed, as is evident by the formation of a clockwise peripheral secondary flow adjacent to the left lateral and upper (pericardial side) walls. Furthermore, the velocity distribution in the parent vessel (not shown) was skewed toward the right lateral wall, which became a part of the inner wall of the distal bend of the RCA. Flow separation occurred in the RCA at the hip of the bifurcation. The region of separated flow was filled with the slow peripheral flow from the lower (myocardial side) wall of the RCA. Particles that entered this region exhibited irregular movements; some of them moved backward and then suddenly changed direction and rejoined the rapidly passing mainstream. Thus, a thin-layered recirculation zone was formed adjacent to the lower wall of the RCA just downstream of the separation point indicated by S, though the exact size of the recirculation zone was not measurable. In the posterior descending branch, neither flow separation nor the formation of a recirculation zone occurred. However, there was a thin-layered slow peripheral secondary flow from the lower wall of the RCA toward the hip and the outer wall of the bifurcation. Atherosclerotic wall thickenings were found at the hips of the bifurcation and along the inner wall of the distal bend of the RCA where both the fluid velocity and wall shear stress were expected to be low.

**Flow Patterns Observed in Pulsatile Flow**

Observations of flow were also conducted in pulsatile flow by superimposing a sinusoidal oscillatory flow with a frequency of 2 Hz and displacement volumes of 0.5 and 1.5 ml on steady flow. Studies were focused on two locations along the left coronary artery—the branching site of the LAD and LCx in the vessel shown in Figures 2A and 6A and the branching site of the second diagonal branch from the LAD—and on three locations along the RCA—the double bend of the proximal and middle portions of the RCA in the vessel shown in Figures 2C and 10, the multiple bends of the middle to distal portions of the RCA in the vessel shown in Figure 12, and the branching site of the posterior descending branch from the RCA in the vessel shown in Figure 13. The cine films that recorded the behavior of tracer microspheres revealed that in all vessels chosen for flow studies, the observed phenomena were qualitatively the same as those found in steady flow. At a small displacement volume of 0.5 ml, at which the flow field was still dominated by steady flow component, the secondary and recirculation flows observed in steady flow persisted throughout the entire cycle of pulsation. However, at a higher displacement volume of 1.5 ml, which created a condition nearing a temporal arrest of the main flow at the end of the receding period of pulsation (which corresponded to the peak point of the systolic period in the cardiac cycle), both the secondary and recirculation flows vanished when the main flow velocity attained a minimum in each cycle of pulsation. It was also found that the degree of flow disturbance judged from the size and the velocity of the formed recirculation flows was much higher in pulsatile than steady flow when compared with the same Reynolds numbers (hence, flow rates), and it appeared to be the highest just after the main flow velocity reached a maximum in each cycle of pulsation, though none of these variables was measurable with accuracy from the motion picture.

**Discussion**

The transparent natural vessels used in the present study are especially well suited to the studies of fluid dynamics in the cardiovascular system in relation to the localization of vascular diseases since they allow the simultaneous study of the exact anatomic structure of the vessels, of the locations and sizes of diseased areas on the vessel wall, and of the detailed flow patterns existing at such sites. Unfortunately, it was not possible to render blood vessels transparent while maintaining the elasticity of normal living blood vessels. Thus, there are certain limitations in the application of the present results to the real situation where vessel walls are elastic and undergo a considerable degree of geometric deformation during each cardiac cycle due to the contraction and relaxation of cardiac muscle. However, due to the following reasons, it was assumed that the flow patterns in coronary arteries are not affected significantly by the elastic nature of the vessel wall. First, most blood flow in coronary arteries occurs during the diastolic period of the cardiac cycle when both the heart and coronary arteries are fairly well inflated and stretched close to their maximum sizes. Therefore, under such conditions, the changes in vessel diameter and length during the diastolic period alone will not be so large as to change the flow patterns. Second, judging from the histological data for the dog, coronary arteries are the least elastic vessels compared with other major arteries, such as the aorta and the carotid and femoral arteries. Thus, the changes in the diameter of the coronary arteries are likely to be quite small, even over the entire cardiac cycle. The results from some angiographic assessments indicate that the changes in proximal coronary artery diameter are either undetectably small or within the range of measurement errors. Finally, in most of the older subjects, the coronary arterial walls are thickened and hardened to some extent through the development of atherosclerotic lesions. Thus, in such vessels, the vessel wall elasticity would be greatly reduced.

The results from the present study revealed several interesting and unique features of flow in the human coronary arterial tree and the intimate relation between the regions of disturbed flow and the preferred sites for atherogenesis on the vessel wall. It was demonstrated convincingly that complex secondary flows and standing recirculation zones form in many regions of human coronary arteries. In both steady and pulsatile flow, the general flow patterns observed at each branching site and bend of human coronary arteries were similar to those found in various glass models and plastic casts of arteries.
However, due to the asymmetrical and complex structure of the bifurcations, T-junctions, and bends in natural blood vessels, the exact flow patterns in these vessels were highly asymmetrical and far more complex than those observed in model vessels. Furthermore, the flow patterns at each location of the arterial tree were dependent not only on the local anatomic structure of the vessel wall but also on the nature of the entering flow (i.e., whether the flow entering the region was laminar or already disturbed), and the velocity distribution was axisymmetric or skewed toward a particular side of the vessel wall due to the presence of side branches and bends immediately upstream of the region of interest. Thus, the observed flow patterns were highly specific to the particular anatomic structure of each coronary artery studied.

Due to the large variations in the anatomic structure of human coronary arteries, it is difficult to generalize these findings to all the cases encountered in the human coronary arterial tree and to describe the detailed characteristics of the flow at each location on the arterial tree. However, if attention is focused on the regions of disturbed flow in any arterial tree, certain common characteristics of the flow at such sites can be found. It was shown that disturbed flows were formed in many regions of the coronary arterial tree by one or a combination of the following three mechanisms: 1) a flow separation caused by the irregularity of the vessel wall, 2) the development of strong secondary flows (as a result of flow deflection) caused by sudden changes in the direction of flow, and 3) mismatching of the flow rate entering each daughter vessel at the branching sites, which forces the backflow of excess fluid entering a particular branch due to the inertia of the fluid. Thus, at bifurcations and T-junctions, complex spiral secondary flows and recirculation zones were formed in the junction region by a combination of the above three mechanisms. Formation of such disturbed flow was largely affected by the inflow Reynolds number (flow rate), the flow ratios in the daughter vessels, the curvature of the walls at the flow-divider and the bend opposite to it, and the branching angle. Except for the branching vessels with very asymmetrical structure relative to the common median plane of the main and side daughter vessels, disturbed flows always were formed in a paired structure, symmetrical about the common median plane. In sharp bends, strong secondary flows and a recirculation zone were formed along the vessel wall in paired structures symmetrical about the median plane of the bend (from the outer to the inner walls of the curved segment and just distal to the point of flow separation at the apex of the curvature of the inner wall, respectively) by a combination of the first two mechanisms. However, in neither case was the recirculation zone in the form of a closed vortex. Thus, even in regions of recirculation flow, there was continuous inflow of fluid and particles from the mainstream, thereby ensuring the exchange of material between the region of recirculation flow and the mainstream as it has been demonstrated previously in various models of arterial bifurcations and T-junctions.

The wall shear stresses evaluated at various locations of the coronary arterial tree studied were, in general, much higher than estimated values for humans at rest (~15 dynes/cm²). However, this is due to the fact that the present study was carried out at flow rates about twofold to threefold higher than the reported mean values for humans assuming the conditions of moderate exercise. As for the values of local wall shear stress, no comparison could be made since there were no comparable data available in the literature. However, the general tendency of velocity profile skewing at some curved segments of the LAD and RCA was the same as that reported by others.

Flow studies conducted with a sinusoidal wave pulsatile flow, although strictly speaking it did not mimic the physiological pressure waveform for the arteries, showed no difference in the qualitative findings from steady flow experiments. This is in good agreement with findings obtained from various model studies.

The significance of the present findings lies in the fact that there was a certain positive correlation between the sites of abnormal and disturbed flow and the preferred sites for atherogenesis in human coronary arteries. As has been shown in studies of human coronary arteries and carotid artery bifurcations with conventional pathological techniques, it was also shown in the present study that atherosclerotic plaques and wall thickenings in both left and right coronary arteries were formed almost exclusively on the hip of one or both daughter vessels at major bifurcations and T-junctions and along the inner wall of curved arterial segments. Furthermore, when the flow patterns were studied in detail in these vessels, it was found that these regions were the very places where flow was either slow (low shear region) or disturbed with formation of slow secondary and recirculation flows. In no instance were atherosclerotic lesions found at and around the flow-divider of branching vessels where flow was fast and wall shear stress was high. These findings are quite different from those of Flaherty et al. and Roach and coworkers, who reported that atherosclerotic (sudanophilic) lesions in cholesterol-fed rabbits and swine tend to develop along the distal leading edge (flow-divider) of the branching site of intercostal arteries and other major arteries of the descending aorta where wall shear stress is elevated. This suggests that initiating mechanisms for atherosclerosis differ between humans in whom lesions were formed slowly and spontaneously over many years and experimental animals in which lesions were induced artificially and acutely by diets containing unusually high levels of cholesterol.

It is clear at this point that hemodynamic factors are involved in the pathogenesis, progression, or prevention of atherosclerosis in the human arterial...
tree. What is not clear is what factor or factors exercise control on this phenomenon. As has been described, atherosclerotic plaques and wall thickenings were usually localized in regions of disturbed flow that contained the points of both flow separation and reattachment (stagnation). Thus, it may be hypothesized that separation and reattachment points play a specific role in atherogenesis as previously proposed by some investigators.\textsuperscript{39–41} However, it is not likely that the presence of these two points is an absolute requirement for this phenomenon since atherosclerotic lesions were formed even in branching arteries with very small branching angles (hence, very gentle curvature at the outer walls) and in arterial bends with very gentle curvature, as in the LAD in the left coronary artery, in which neither flow separation nor the formation of secondary and recirculation flows was observed under various flow conditions. In such regions, the only noticeable anomaly in hemodynamic factors was the skewing of the velocity distribution away from the vessel wall where atherosclerotic changes occurred. In other words, the only hemodynamic factor associated with this wall thickening was the low fluid velocity in the vicinity of the suffering vessel wall and the resultant low shear stress on the vessel wall. This implies that, in the arterial system, low fluid velocity (hence, low wall shear stress) and high fluid velocity (hence, high wall shear stress) play pathogenic and preventive roles, respectively, in atherosclerosis. This may explain the gradual decrease in frequency and degree of severity of atherosclerotic lesions with increasing distance from the origin of coronary arteries observed in the present study and reported by several other investigators.\textsuperscript{3,12} Simple calculations performed by applying Poiseuille’s law to the flow in transparent human coronary arterial trees show that both the fluid mean velocity and wall shear stress increase gradually up to about 1.5-fold in moving from the proximal to the distal portions of the left and right coronary arteries, as has been shown by Nerem and Seed.\textsuperscript{36}

It is also noteworthy that, as it has been shown by other investigators as well,\textsuperscript{13,15,42–44} the wall thickening at the hip of bifurcations and the inner wall of curved segments did not occur suddenly and irregularly but did occur very gradually and very smoothly in both longitudinal and circumferential directions, with the maximum thickening appearing around the point of flow separation if any existed. The cross sections of the wall thickening appeared as eclipsed lunar shapes with their points of maximum thickness located close to the bisector plane of the wall thickening that contained the points of flow separation and reattachment (stagnation) if there were any. Thus, the stereoscopic structure of the wall thickening appeared as if it reflected the spatial distribution of some hemodynamic factors such as wall pressure, fluid velocity, or wall shear stress. This suggests that redistribution of accumulated atherosclerotic materials might take place within the vessel wall and might be controlled by a hemodynamic factor that is characterized by a gradually and continuously varying nature such as wall pressure.

If it is assumed that local fluid velocity and high blood pressure prevailing in the arterial system play a key role in atherogenesis, the phenomena at the blood-endothelium boundary would be envisaged as follows. Due to the fact that every atherogenic lipoprotein particle (hereafter referred to as particles) has a certain finite size, their translational velocity will not be zero even when they are in contact with the endothelium. Thus, their movements over the endothelium will be largely affected by the fluid velocity in the immediate vicinity of the endothelium. In regions of slow flow, since the vessel wall (hence, the endothelium itself) is permeable to water, solute, and macromolecules, the radial component of the fluid velocity in fluid layers adjacent to the endothelium may become about the same order or even greater than the longitudinal component, resulting in the arrest or permanent adhesion and concentration of the particles on the endothelium—even though both the particles and endothelium are charged negatively, and their interaction is hampered by electrostatic repulsive force. This may in turn result in the enhanced infiltration and uptake of the particles by endothelial cells through concentration-induced endocytosis. The low fluid velocity and the resultant low wall shear stress prevailing in regions of recirculation flow may provide especially favorable conditions for the particles for prolonged interaction and adhesion onto the endothelium, which are the most important steps for internalization of the particles by the endothelial cells by means of endocytosis and junctional infiltration. In this way, the accumulation of particles within the intima will continue.

However, since their further penetration into the adventitia of the vessel wall is obstructed to some extent by the fine structure of the underlying media, especially the elastin layers, it is necessary for the particles to diffuse or migrate laterally within the intima. If there is any regional difference in pressure on the endothelium and within the intima, they will migrate toward the lower pressure region (which usually occurs at the point of flow separation), resulting in the highest accumulation of the particles, thus thickening of the vessel wall, at such sites. In this way, the lumen becomes narrower and narrower at the point of minimum pressure on the endothelium, thereby further promoting flow separation and formation of recirculation flows. The slower the velocity and the higher the blood pressure, the higher and faster the accumulation of the particles in the vessel wall. The fact that the severest lesions were located in regions of separated flow where the particle velocity was the lowest gives strong support to this view. In such regions, it has been shown by Karino and Goldsmith\textsuperscript{45,46} that the transport of blood cells to the vessel wall is enhanced by the radially directed flow along the curved streamlines existing in the vicinity of the reattachment (stagnation) point. Thus, it is possible that, since the fluid velocity and wall shear stress
in such regions are very low and the endothelium is permeable, not only the atherogenic lipoproteins discussed above but also the platelets and monocytes may have a greater opportunity to interact for longer periods with the endothelial cells than elsewhere. This, in turn, may lead to and enhance the deposition of platelets and monocytes on the endothelium and the release of certain chemical agents such as the platelet-derived growth factor for smooth muscle cells in such regions. What is not clear at present is how much the infiltration and uptake of the atherogenic lipoproteins by endothelial cells are affected by the nature of the individual cells located in different regions of the vessel wall.

It has been shown that vascular endothelial cells are susceptible to flow and exhibit certain morphological changes corresponding to the direction and magnitude of the shear stress.47–49 Thus, in arterial bifurcations, the endothelial cells located on the inner wall distal to the flow-divider (where the shear stress is high) were found to be elongated in the direction of flow, whereas those cells located on the outer walls opposite the flow-divider (where secondary and recirculation flows may form and the shear stress is much lower) were not elongated but were oriented in a random fashion.50,51 Such local difference in the morphology of endothelial cells may provide different permeability to water, solutes, and macromolecules. It is also possible that endothelial cells located in different regions and subjected to different levels of shear stress may have different biological and biochemical functions. It is now important to concentrate our research on transport phenomena at the blood-endothelium boundary to determine the effects of fluid velocity and wall permeability on the deposition and accumulation of atherogenic lipoproteins on the endothelium. It is also necessary to further investigate the effects of shear stress on the morphology and metabolic function of endothelial cells and on the permeability of the endothelium to atherogenic lipoproteins. Only after that may a full explanation for the localization of atherosclerotic lesions in the human arterial tree be found.

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