WHAT ARE THE DETERMINANTS OF PLAQUE INSTABILITY AND ITS CONSEQUENCES?

Data from adult human carotid and aortic studies indicate that atherosclerotic plaques tend to occur in regions of low or oscillating wall shear stress, whereas relatively high shear rates and unidirectional, laminar flow patterns tend to be associated with sparing. Coronary arteries are exposed to greater fluctuations in flow direction and amplitude during systole than are other systemic arteries, and increases in heart rate result in decreased diastolic time whereas systolic time remains nearly constant. Individual differences in the relative involvement of the coronary arteries compared with other vessels in the same arterial tree have therefore been attributed to differences in heart rate. Both experimental and clinical studies tend to indicate that elevated heart rate is a risk factor for coronary artery disease.

Although intimal reactions such as advanced atherosclerosis and obstructive intimal hyperplasia underlie clinically significant interferences with flow, well-organized focal and diffuse fibrocellular intimal thickening occur frequently without lipid accumulation or occlusion. Just as increased flow results in artery enlargement until baseline shear stress levels of about 15 dynes/cm² are restored, artery enlargement could result in intimal thickening to reestablish normal levels of tensile stress. Conversely, reduced flow could stimulate intimal thickening to reduce effective diameter and increase wall shear stress to more normal levels. Such intimal reactions are usually self-limiting in bypass grafts, at anastomoses between vessels or between vessels and prosthetic grafts, and about geometric modifications associated with radial or axial artery enlargement and tortuosity. Even advanced and extensive atherosclerotic disease is associated with artery enlargement, widely patent artery lumens, and persistence of adequate flow until about 40% or more of the potential luminal area is occupied by plaque. Also, despite the formation of complex, eccentric plaques, lumen shape nearly always remains circular. The impression that uncomplicated plaques bulge into the lumen on cross-section is nearly always based on artefacts of preparation. Modeling of the plaque, incorporation and organization of mural thrombi, and development of a circumferentially structured fibrous cap are also suggestive of adaptive reactions designed to maintain artery wall and plaque stability.

Plaque fractures, disruptions, or ulcerations may nevertheless result in exposure of plaque components to the circulation, thereby engendering occlusive or embolizing thrombi and may also be associated with sudden obstruction caused by plaque hemorrhage even when plaques are not markedly stenotic. Thus despite the apparent capability of arteries to adjust to and compensate for hemodynamic deviations, both focal and regional, to maintain adequate levels of laminar flow, mural integrity, and plaque stability, arteries do become obstructed and in some cases aneurysmal and fragile. The nature and limits of artery adaptability and plaque stability therefore need to be defined, particularly in relation to hemodynamic and other mechanical forces.

Suggestions have been forthcoming from investigations conducted in cell culture with systems designed to subject cells to measurable degrees of mechanical stress. These studies provide data of interest with respect to cell biology and may furnish clues to the manner in which mechanical forces modify the function of artery cells and could affect the architecture and composition of blood vessel walls and plaques. However, these data should direct us to devise corresponding studies in arteries to ascertain the extent to which human arteries adapt to alterations in flow and pressure to cope with the occurrence and enlargement of atherosclerotic lesions. Application of current techniques to the study of the natural history of plaques should permit us to delineate the degree to which mechanical factors influence plaque composition and growth and to determine which structural or compositional features determine whether a plaque is likely to stabilize or tend to disrupt or whether stenoses or aneurysms are likely to develop.

Regardless of extent of involvement, critical lumen narrowing and plaque complications are the significant determinants of clinical severity rather than percent stenosis. Percent stenosis is usually evaluated from angiograms by comparing the diameter of a narrowed lumen segment on axial projection with a presumably uninvolved or less involved adjacent region. Although the absolute diameter at the narrowing is likely to be the best index of the degree of actual or potential obstruction to flow, it is not a reliable indicator of the extent of the disease process. Nor is there adequate information on angiograms concerning the composition of plaques, in either a narrowed or relatively wide segment. Newer means of in vivo visualization promise to provide sufficient resolution and discrimination to establish plaque and wall thickness, cross-sectional area and density, and some details of plaque composition. These data should permit better clinical studies of plaque growth rate and plaque composition. Histologic preparations of artery cross-sections do provide reliable information on artery size, as well as on plaque area, composition, and the distribution of plaque components, provided that the vessels are prepared with sufficient attention to fixation under conditions of distention by suitable levels of intraluminal pressure. In such material percent stenosis is defined as the extent to which the area encompassed by the internal elastic lamina is occupied by plaque, assuming that the internal elastic area represents the potential lumen area.

The susceptibility of plaques to disruption, fracture, or fissuring is likely to be associated with plaque structure, composition, and consistency. Plaques may be relatively soft and pliable, friable or cohesive, densely sclerotic or
calcific, and brittle. Some have well-formed fibrous caps, similar in architecture and thickness to a normal artery wall, thereby effectively sequestering the plaque and its contents from the lumen, whereas others are separated from the lumen by a narrow zone of connective tissue or by endothelium alone. Advanced plaques with intact, well-organized fibrous caps would be expected to present smooth and regular luminal surfaces to the bloodstream, but abnormal levels of wall shear stress and departures from laminar, unidirectional flow may favor local accumulation, adhesion, and deposition of thrombocytes, monocytes, and fibrin. These are likely to occur distal to stenoses, at foci of endothelial surface irregularity or extrinsic mechanical trauma, and in regions of softened plaque consistency. Three-dimensional reconstructions from sequential sections will be required to provide new knowledge concerning plaque organization and the precise location of regions vulnerable to disruption. These features should then be related to geometry and presumed or measured flow field characteristics. Local mechanical stresses resulting from sudden changes in pressure, flow, or pulse rate or torsion and bending in relation to organ movements may precipitate disruption of friable or brittle plaques. Conversely, changes in vessel configuration associated with plaque progression and stenosis may create conditions favoring the development of complex flow instabilities and vibrations. Plaques in experimental animals that are located immediately distal to a region of moderate narrowing have been shown to be more complex in structure and composition than those that occur in the same region in the absence of a proximal stenosis. The likelihood of turbulence is also enhanced as vessels enlarge and become tortuous with age or when multiple plaques occur in the same vessel in close axial proximity.

In conclusion, we now have sound information concerning the distribution of intimal thickenings and atherosclerotic plaques at clinically important sites in humans. Low or oscillatory wall shear stress is the associated hemodynamic condition at these locations. It is also evident that artery walls may compensate for hemodynamic changes and the development of atherosclerotic disease and maintain luminal diameters and configurations consistent with adequate flow. Obstruction occurs when the adaptive processes do not keep pace with plaque enlargement or when plaques are disrupted. Future investigations must therefore include studies of plaque growth and composition in relation to variations in geometric configuration, pulse rate, and flow velocity. Until the disease can be prevented it is necessary to identify those features of plaque composition and configuration that underlie susceptibility to instability and to characterize the hemodynamic and other mechanical circumstances that may induce plaque disruption, as well as those features that favor the maintenance of an adequate and stable channel. Such studies place renewed emphasis on the fact that the artery wall and atherosclerotic plaque are living tissues, capable of healing and adaptive restructuring, as well as degeneration and disruption.

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REFERENCES


DIAGNOSTIC APPROACHES

During the past 20 years there have been dramatic advances in the diagnostic approaches to peripheral arterial disease. Although there was considerable opposition to the introduction of some of these methods, I believe there is