Micro-architecture and composition of artery walls: relationship to location, diameter and the distribution of mechanical stress

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Purpose: We reviewed the structural basis of the mechanical properties of the arterial wall, in order to establish a coherent micro-anatomical basis for the differences in compliance among different arteries and a framework for assessing changes in the mechanical properties of specific individual arteries in relation to changing physical stresses.

Data identification: The data and concepts presented here were derived from both earlier and ongoing work. Features that assure stability and integrity in relation to blood flow (wall shear stress) and pressure (mural tensile stress) were examined. Particular attention was paid to the morphogenetic and biosynthetic means by which arteries adapt to normal or abnormal modifications of these forces, particularly in relation to growth, location in the arterial tree and geometric configuration.

Results and conclusions: Thickness, composition and architecture of the artery wall, including thickness and composition of the intima, are normally determined by the stresses imposed by pressure and flow. Vessel radius is closely associated with flow, so that a normal baseline level of shear stress of about 15 dyn/cm² is maintained or restored. Wall thickness and composition are determined by wall tension in relation to pressure and radius. Baseline levels of tensile stress differ with location but appear to be similar for homologous vessels. Changes in flow that modify the radius also modify wall tension. Changes in wall thickness and composition are likely to cause changes in compliance, due to altered flow and/or pressure patterns; these changes in compliance may be adaptive rather than destructive. Changes in the compliance of specific arteries over time may be used to evaluate the progression and severity of the conditions underlying these changes.

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Introduction

The artery wall is composed of distinct structural elements which function in a coordinated manner to assure stability and resiliency in relation to imposed mechanical forces. The force associated with intraluminal pressure (P) tends to enlarge the lumen radius (r) and extend the artery circumference [1]. Since the wall thickness of elastic arteries and large muscular arteries is small compared with the lumen radius, tangential tension (T) can be estimated from the law of Laplace (T = Pr). Wall shear stress associated with blood flow at the blood–endothelial interface can be estimated from the shear velocity gradient near the wall and fluid viscosity. Smooth muscle cells, elastic fibers and collagen provide the tensile support. Cell attachments to matrix components, configurational relationships among the structural elements and the capacity of the living vessel to adjust its radius, wall thickness and wall composition permit the artery wall to withstand increases, decreases or short-term variations and oscillations in pressure and flow.

As pressure varies between diastole and systole the close association between elastin and collagen fibers provides a variable effective modulus of elasticity, depending on the degree of distension and on the relative quantities, distribution and organization of the two

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matrix fiber elements [2]. The close association in the media of components with a different elastic modulus also occurs in other biological stress bearing materials such as bamboo, wood and bone [3]. In the aorta, collagen fibers normally bear a major portion of the tensile stress and, when drawn taut, prevent excessive distension [7]. The extensible elastin network contributes to tensile support but also provides resiliency by distributing stresses uniformly through the wall. In this manner, disruptive propagation of structural flaws is prevented, a graded mobilization of the media is assured and there is a coordinated recoil of the wall with some return of pulsatile energy to the blood during diastole. The smooth muscle cells provide active tensile support, and may also modulate mural mechanical properties by altering the matrix fiber configuration and orientation [1]. These cells are also responsible for the adaptive biosynthetic response which assures the appropriate quantities and relative proportions of matrix components needed for stability and resiliency [5].

Transmural organization and cohesion

Close study of the infrastructure of the media of large arteries by means of reconstructions from semi-thin light microscopic sections and scanning and transmission ultrastructural preparations has shown that the structure is a composite of subunits, each comprising a group or fascicle of commonly oriented smooth muscle cells surrounded by a similarly oriented array of interconnected elastic fibers [6]. The stacking of these units is readily seen on distended and precisely oriented standard light microscopic sections. In axially directed sections, the bars of the elastin framework are transected in their small-dimension and outline compartments, each containing a fascicle of smooth muscle cells. The smooth muscle cells of individual fascicles are bound together by a continuous intercellular and pericellular basal lamina (type IV collagen) and by a basketwork of fine collagen fibrils (type III), many of which are embedded in the basal lamina. Separately organized, coarser collagen fibers (type I) appear as bundles between adjacent musculo-elastic fascicles and only occasionally within musculo-elastic fascicles [7]. The size, orientation and distribution of the musculo-elastic fascicles in relation to curves and branch regions suggest that they are aligned along lines of tensile force [6]. The fiber bundles are crimped so that configurational rigidity may also contribute resistance to deformation or stretch. Smooth muscle cells are firmly attached to the immediately surrounding elastin bars by a series of firm linear junctions. The collagen bundles are not attached to elastic fibers and are only occasionally attached to cells. This composite of stacked musculo-elastic fascicles results in a transmural distribution of aortic medial elements, not in layers of elastin—cells—elastin, but in layers of elastin—cells—elastin: collagen: elastin—cells—elastin: collagen: elastin—cells—elastin, and so on.

In the usual thick histologic sections of the media the transmural stacks of musculo-elastic fascicles look, at first sight, to be alternating layers of elastic fibers and cells with intervening collagen fibers of no particular orientation. In homologous mammalian arteries, the width composition and organization of the transmural layers are remarkably similar regardless of species, but the number of layers across the media corresponds closely to the tangential tension imposed on the adult vessel. In the aorta, the structural layers are distinct and similar for most adult mammals, and each layer corresponds to a circumferential tension of about 2000 dyn/cm [8]. In the adult pulmonary trunk, transmural layers are much less distinctly delineated than for the aortic media. Tension per layer is lower, at about 1000 dyn/cm, but again constant regardless of species. Similar studies of renal and coronary arteries have shown that in each case the homologous vessels are similar in overall media structure and that the number of transmural layers corresponds to circumferential tension, in relation to diameter [9]. For very large mammals like cattle and horses, the aortic wall architecture is somewhat different. Prominent smooth muscle bundles form in the outer layers and elastin fibers become much less prominent; the inner 30 layers maintain the same configuration as in smaller species. Vasa vasorum penetrates the media when there are more than about 30 transmural layers and are found only beyond the inner 30 layers [10]. Aortas with fewer than 30 layers have no intramedial vasa vasorum. In aortas with medial vasa, the tensile stress per layer is greater than 2000 dyn/cm even without the above-mentioned departures from a uniform transmural lamellar structure. In addition, even in aortic walls with a uniform cross-sectional structure, the relative proportions of collagen and elastin change with distance from the heart, but the gradient with respect to distance along the vessel differs from species to species [11]. In humans the transmural gradient of relative collagen and elastin content across the aortic wall changes with age [12]. The precise determinants of the specific structural characteristics and composition of homologous arteries have not yet been established. Among the possible factors are distance from the heart, relative growth rate of supplied organs and local differences in flow velocity, flow profile and pressure during the cardiac cycle.

Adaptations that maintain optimal tensile stress

Differential artery wall adaptation to wall tension can be observed during early post-natal growth and in relation to the changes in wall tension [5]. For ex-
ample, under normal circumstances, blood pressure in the pulmonary trunk and the ascending aorta are very nearly equal at birth and are about half the normal adult value. The length, radius, wall thickness and morphology of the pulmonary trunk and ascending aorta are similar. During the post-natal period aortic blood pressure rises to approximately twice the neonatal value, while pressure in the pulmonary trunk falls to less than half its initial value. As growth proceeds, length and radius remain about the same for the two vessel segments, but wall thickness increases much more rapidly in the aorta. The differences in media thickness are mainly due to different rates of accumulation of collagen and elastin. The rates of matrix fiber accumulation for each vessel parallel the increases in wall tension or wall tensile stress. Despite the marked difference between the vessels in absolute values of both tension and matrix fiber content, the number of cells increases at the same rate in both segments. Thus, the rate of production of matrix per cell is markedly different for the two artery segments and a corresponding difference is seen in wall architecture. These findings suggest that arterial smooth muscle cells are capable of a wide range of biosynthetic responses during growth and that the responses are induced and modulated by the tensile stress imposed. If a chronic elevation in pressure is imposed on an adult artery, the basic layered structure of the media may not be altered, but each transmural layer widens and the cross-sectional area of the media increases. In an experimental study of the effects of hypertension on the aorta of the rat [13] the number of transmural layers remained fixed, but the cross-sectional area increased by 0.1 mm² for every 5000 dyn/cm² increase in mural tension. Since the number of layers did not increase, the tension per layer increased above normal levels.

A biosynthetic response by smooth muscle cells to cyclic stretch in cell culture has also been demonstrated [14]. In these experiments, rabbit aortic smooth muscle cells were grown on purified elastin membranes which were subjected to cyclic stretching at 52 cycles/min for 4-8 days. Compared to cells grown on stationary or agitated membranes, those grown on cyclically stretched membranes produced two to four times more collagen. Cell proliferation was not differentially altered by any of these procedures. Furthermore, the cyclically stretched cells showed fewer degenerative changes and their cytoplasmic features were consistent with the level of biosynthesis.

**Structure of the adventitia**

The composition and structure of the adventitia also vary for homologous vessels and may change with changing mechanical conditions [9]. In the coronary arteries of young animals there are adventitial layers composed of distinct collagen and elastin fibers. Fibroblasts are present but are not a striking feature. Circumferential intimal thickening is an early development, particularly in human coronary arteries, and there is corresponding progressive simplification and relative reduction in prominence of the adventitial fibro-elastic layers. In the main renal arteries, adventitial fibro-elastic layers are similarly prominent at birth, but in contrast to the coronary arteries, remain prominent throughout life. Meanwhile, intimal thickening is very unusual in the renal arteries, even as intimal thickening and/or atherosclerosis progress elsewhere in the arterial tree [16]. Differences in the structure of the adventitia probably correspond to differences in the degree and variation of pulsatile tensile stresses transmitted to the perianterstitial tissues from the media. Vessel-wall tethering at branchings, bending and buckling during the cardiac cycle, and the motion of adjacent structures and of the organs being supplied with blood may also contribute to adventitial structural changes. The importance of axial tension on the renal arteries, possibly attributable to stretch exerted by the kidneys, is evident in the frequent formation of axially oriented smooth muscle bundles in the adventitia.

**Adaptations that maintain optimal shear stress**

Alterations in wall shear stress due to changes in the flow rate induce adaptations that tend to restore normal baseline levels of wall shear stress. For example, an arteriovenous fistula results in increased flow in the artery proximal to the shunt and therefore in a marked initial increase in wall shear stress. Over time, the radius of the artery increases until the wall shear stress is restored to the normal level of about 15 dyn/cm² [17,18]. Conversely, when the wall shear stress is reduced, smooth muscle cell proliferation generally occurs in the intima and the resulting thickening reduces the lumen radius and increases flow velocity until the normal wall shear stress is restored [19,20]. The process is self-limiting if the baseline wall shear is restored to normal. The thickened intima then organizes and elaborates matrix fibers in a configuration that imitates the underlying structure of the media. We have called this form intimal fibrocellular hypertrophy [20]. When flow velocity is not sufficiently increased by intimal thickening, due to obstructions or to geometric configurations that maintain abnormal local levels of wall shear stress, the process may proceed to pathological stenosis or obliteration of the lumen. The morphology of this form differs from the stabilized, adapted, self-limiting form in that the component cells are not oriented and matrix fibers are scant. When an artery is enlarged in response to increased flow, the wall tensile stress is increased. The intima may also thicken to
provide sufficient wall thickness to restore normal wall tensile stress [21].

**Effects of changes in pressure**

When the artery wall is stretched by cyclic changes in pressure or by an increase in pressure, the interwoven fine collagen fibers surrounding the smooth muscle cell fascicles change orientation, tightening about the muscle group in the manner of a 'Chinese finger trap' to preserve cohesion of the fascicles [22]. With further increases in wall tension, cohesion of the media is assured by the tight, relatively pliable, pericellular basal lamina, reinforced by its fine basketwork of collagen fibrils. When an artery is hyperdistended by abnormally high pressures, the smooth muscle cells are drawn out to form attenuated projections at their points of insertion on the elastin fibers. Fractures occur across cell bodies and evidence of rents and recoil is seen in the basal laminae, but the separated cell fragments remain attached to elastin at their points of insertion [22]. The degree to which the integrity of the wall is restored after such an injury is not clear.

In summary, the artery wall is organized as a composite of musculo-elastic fascicles. The size, composition and orientation of these units appears to be related to the spatial distribution of tensile stresses. Architecture and composition as well as the thickness of artery walls are related to artery location and to the stresses imposed by blood pressure and flow. The reactions at the cellular and molecular level that determine the adaptive changes and the structural similarities in homologous vessels of different sizes remain to be determined. A characterization of the basis for the interactions between pressure and flow in determining vessel architecture, thickness and compliance should permit discrimination between adaptive and pathologic degrees of change.

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