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Vascular Mechanics for the Cardiologist

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Many common problems in clinical cardiology are due to disturbances in vascular mechanics. The terminology and basic principles of vascular mechanics, including fundamentals of the relation of stress and strain, are described in this review. Approaches to measuring vessel wall stiffness and the mechanical basis for vascular catastrophes are introduced.

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Many common problems in clinical cardiology and cardiovascular research are due to abnormalities in vascular mechanics. For example, systemic hypertension is almost always associated with altered mechanical properties of the peripheral vasculature (1). The vascular catastrophes of atherosclerotic plaque rupture (a common mechanism of myocardial infarction) and aortic dissection can be viewed as mechanical failures of the diseased vessel. In addition, interventional procedures such as angioplasty are often effective because of mechanical injury to the vessel wall, although the injury itself may lead to restenosis (2). Understanding these mechanical phenomena will assume even greater importance in the future as the cellular and molecular mechanisms for regulating the mechanical behavior of the vessel are unraveled. This review discusses the basic principles and terms of solid mechanics of the vessel wall. (For an introduction to basic cardiovascular fluid mechanics, the reader is referred to the review by Yoganathan et al. [3].)

Stress and strain. It is common clinical jargon to refer to a patient's "stiff arteries." "Stiffness" is a general term to describe resistance to deformation. However, defining the stiffness of the vessel wall can be difficult because no single number can describe the complex mechanical behavior of a vessel. To arrive at useful approximations, it is important to understand the basic relation of stress and strain.

A *stress* is a force acting on a surface divided by the size of the surface and therefore has units of force per area (Fig. 1, Table 1). The surface may be external, such as the lumen of an artery, or internal. On any surface, stress may be applied perpendicular ("normal") to the surface, such as the stress that blood pressure applies to the lumen of the vessel, or may be applied parallel to the surface, called *shear stress*. Normal stresses may be referred to as either compressive or tensile. On the endothelial surface of the vessel, shear stresses exerted by the blood because of complex hemodynamic patterns may disturb the endothelial cell and can influence a wide variety of cell functions. Within the vessel wall there are also shear stresses between the layers of the vessel. Stress may be applied in any direction, so that in the vessel wall we refer to radial, circumferential and longitudinal components of stresses.

The important relation of stresses in a thin pressurized cylinder can be used to demonstrate the directionality of stresses in the arterial wall (Fig. 2). When a cylinder is pressurized, the radial stress of the pressure must be balanced by a circumferential tensile stress in the vessel wall. Under the assumption that the wall of the cylinder is thin relative to the diameter of the vessel, it can be shown that

$$\sigma = Pr/h,$$

where σ is the circumferential wall stress, P the radial wall stress acting at the internal surface (or, more simply, the pressure in the vessel), h is the thickness of the vessel and r is the radius of the vessel. This formula is commonly known as Laplace's law, although it is more correctly attributed to Young (4). Laplace's law explains why abdominal aortic aneurysms rupture at blood pressures that the normal aorta tolerates. As the aorta becomes thin and the radius increases, tensile stresses in the aneurysm wall become very large. It is therefore not surprising that probability of rupture of aortic aneurysms is closely related to the maximal size of the aneurysm (5). The relation of internal pressure to circumferential wall stress is different in the noncylindric structure of the left ventricle (6) or in the complex structure of the atherosclerotic artery (7).

Although *strain* is intimately related to stress, the terms should not be used interchangeably. A strain is an increase (or decrease) in length of a material and is usually expressed as a fraction or percent of the initial length; therefore, unlike stress, strain has no units. A tensile stress on a material such as a rubber band leads to elongation, or a positive strain; for

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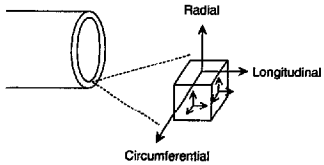

Figure 1. Directions of stresses on one face of a small volume of material in the vessel wall. Because stress is a force per unit area, the direction of the force must be defined. On the top face of the volume, a radially directed stress from the internal lumen pressure is imposed perpendicular to the surface. There might also exist two tangential stresses on this face—a shear stress in both the circumferential and longitudinal directions. The volume also has other surfaces with stresses (**small arrows**), so that in a very small volume, a total of nine stress components exist.

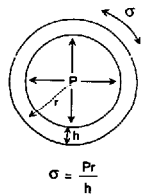

Figure 2. Cross section of an artery demonstrating Laplace's law. The radial pressure (P) in the lumen is balanced by a circumferential tensile stress (σ) in the artery wall. If the wall becomes thin and the radius (r) increases (such as in aortic aneurysms), circumferential stresses can be many times normal, leading to vessel rupture. It is assumed in Laplace's law that the wall thickness (h) is small compared with the vessel radius (thin-wall assumption); more complex equations are required to estimate stresses in thick-walled cylinders.

example, a stress of 5 mm Hg on a rubber band may cause a 3-cm rubber band to elongate to 3.3 cm or to have a strain of 0.1 (10%). In many nonbiologic materials, the relation between stress and strain is constant for small strains:

$$E = \text{Stress/Strain}.$$

The constant E is called the elastic modulus, or the Young's modulus, after the 19th century English physician and physicist Thomas Young. (Shear stresses cause angular deformations of solid materials called shear strains, which will not be considered here.) Over a range of stress, the elastic modulus may be constant; this is called linear elastic behavior. The relation between stress and strain may become nonlinear and E, the stress/strain ratio, is no longer constant. Most biologic materials exhibit *nonlinear* mechanical behavior (Fig. 3). As the stress on a biologic material is increased, the increment of strain for each increment of stress decreases, so that the material becomes stiffer. This may be one reason why percutaneous balloon coronary angioplasty often requires balloon pressures over 50 times greater than mean arterial blood pressure. As the balloon pressure increases (and stress on the vessel wall increases), the vessel wall becomes stiffer; for each increment of vessel dilation, the increment of balloon pressure must be greater.

Table 1. Definitions of Vascular Mechanics

Stress	Force per unit area, such as N/m². Like force, stress is directional
Strain	Increase in dimension (e.g., elongation), usually expressed as a percent of the initial dimension
Stiffness	General term describing resistance to deformation; may be expressed with a variety of variables. A variable describing stiffness may be geometry dependent, static or dynamic
Compliance	Change in volume per change in pressure. In the vessel, it is used as the reciprocal of stiffness
Elastic modulus	Fundamental material property describing the relation of stress and strain
Elastic deformation	When a material changes shape under stress but returns to its initial shape when the stress is removed
Plastic deformation	When a material does not return to its initial shape when a stress is removed
Isotropic	Material with mechanical properties that are independent of the direction of the stress applied; a block of steel is isotropic
Anisotropic	Material with mechanical properties that are dependent on the direction of the stress applied; biologic materials are anisotropic
Viscoelastic	Time dependence of the response to a stress or strain; an important property of biologic materials

Another mechanical property of the material concerns whether or not a material returns to its original length when the applied stress is removed. If it does, the material is considered *elastic*. If not, the material is said to exhibit *plastic deformation*; if subjected to a high level of stress, in excess of what is termed the *yield stress*, the material will no longer return to its initial length if the stress is removed. Plastic deformation indicates that the material has been changed permanently.

If the vessel wall were made of a uniform, incompressible, linear elastic material, a single number (the elastic modulus) could be used to describe its mechanical behavior. However, most biologic materials, including the vessel wall, have complex three-dimensional structures that have different stress/strain relations in different directions. For example, the direction of the grain of wood gives a tree the ability to better withstand stresses in certain directions, and we exploit this property when we build with wood. Similarly, the vessel wall has a three-dimensional structure (such as the circumferential lamellae of the media) that makes the stress/strain relationship (the stiffness) different in different directions. This important property is called *anisotropy*; when a material (such as a block of steel) has the same stress/strain

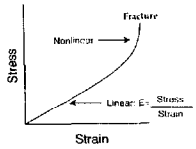

Figure 3. Stress/strain curve demonstrating linear and nonlinear behavior. In a perfectly linear elastic material, each increment of stress leads to a proportional increase in strain. Many nonbiologic materials (rubber, steel) behave this way over large ranges of stresses. Biologic tissues, such as the normal artery or atherosclerotic plaque, have nonlinear stress/strain relations, so that each additional increment of stress leads to a *smaller* strain. Therefore, at higher stresses (such as higher blood pressures), the vessel wall is stiffer. E = elastic modulus.

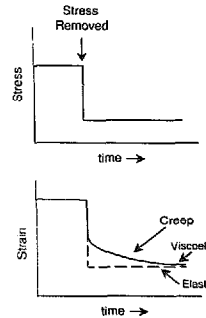

Figure 4. Viscoelasticity, an important time dependence of the stress/strain relation. When stress is removed, strain in a perfectly elastic material will immediately decrease, and the material will assume its new shape (**dashed line**). Strain in a viscoelastic material will gradually decrease over time, a phenomenon known as *creep* (**solid line**). In some studies of percutaneous coronary angioplasty, this phenomenon has been called *elastic recoil*.

relation in all directions, it is called *isotropic*. The anisotropic nature of the vessel means that describing the mechanical behavior of the vessel with a single elastic modulus is a gross oversimplification. In fact, to describe completely the biomechanical behavior of an anisotropic material with a three-dimensional structure, over 20 variables would have to be specified (8). Although several of the most critical variables have been measured in animal and normal human arteries over the past several decades, few measurements have been made in diseased human arteries.

Viscoelasticity. In addition to the three-dimensional and nonlinear behavior of the vessel wall, an important time factor must be considered in the stress/strain response. If a material is perfectly elastic, the stress/strain response occurs immediately or in a negligible time. Biologic tissues rarely behave this way. If a constant tensile stress is placed on a biologic tissue, the tissue will continue to elongate (that is, the strain will increase) for some period of time until a new equilibrium strain is reached; this time dependence of the stress/strain response is called *viscoelasticity* (Fig. 4). One example of arterial viscoelasticity in action occurs in percutaneous balloon angioplasty. Interventional cardiologists know that some lesions will open only during prolonged balloon inflations. These prolonged stresses allow vessel wall strains to increase until the critical fracture point is reached. If the vessel were perfectly elastic instead of viscoelastic, strains would be immediately achieved by the initial inflation, and no benefit from prolonged inflation would be observed. (Some of this time-dependent behavior may also be due to plastic deformation.) Similarly, a component of the coronary restenosis phenomenon has been described as "delayed elastic recoil" (9). This can be observed as a relaxation of the vessel to a smaller diameter within hours or days after the angioplasty; some element of relaxation over time is expected with viscoelastic materials. The term "elastic recoil" is a misnomer because, by definition, this type of biomechanical behavior is viscoelastic, not elastic.

There are several ways to describe the viscoelasticity of the vessel wall. For example, when an angioplasty balloon is deflated from a constant pressure of 4 atm, stresses applied to the vessel wall are suddenly reduced to levels of arterial pressure. The gradual "recoil" is called *creep*, and numerous mathematical models have been used to characterize this process. In one simple model, the length of the material fits an exponential decay toward the final dimension, and the time course of creep can be estimated by an exponential decay constant.

Viscoelasticity also can be described by considering the effects of a periodic stress, such as the systolic pressure wave. If a stress is applied to the vessel wall and then quickly removed, the vessel wall may not have time to reach its new equilibrium strain before the stress is removed. Stresses imposed periodically (dynamic stress) will therefore cause smaller strains than stresses imposed constantly, and the vessel wall therefore appears stiffer during pulsatile flow. The ratio of stress to strain under pulsatile conditions is called the *dynamic stiffness* and is generally higher than static stiffness.

Measuring vascular stiffness. It is clear that complexities of the vascular wall, such as anisotropy, nonlinear behavior and viscoelasticity, make simple estimates of vascular stiffness hazardous. In fact, even imaging techniques with higher resolution than those currently available would not allow us to completely characterize the three-dimensional mechanical behavior of the vessel in vivo. Although it is not possible to measure the actual elastic moduli of the vessel wall components (or a number of other variables) in vivo, some general

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expression of the overall "stiffness" of the vessel is useful. Several approaches have been described that use clinically available methods for characterizing the stiffness of the vessel wall in vivo. The ability to measure vascular stiffness has been improved by recent imaging advances, such as high frequency intravascular ultrasound (10,11).

The *velocity of a pulse wave* is accelerated in patients with increased vascular stiffness. It follows that by measuring the velocity of the pulse wave during a single cardiac systole, the stiffness of the vessel could be estimated. The problem of wave velocity in a tube dates back to Isaac Newton, but the most commonly used formula was described in the 19th century and is called the Moens-Korteweg equation (8):

$$c = \sqrt{\frac{Eh}{2r\rho}},$$

where c is the velocity of the pulse wave, h the vessel thickness, r the radius of the vessel, ρ the density of blood, and E the elastic modulus of the vessel. Pulse wave velocity has been used by many investigators to estimate vascular stiffness (12), but improved noninvasive imaging techniques have made direct measurement of vessel wall motion more common. Note that pulse wave velocity is proportional to the square root of vessel stiffness, so that pulse wave velocity is not particularly sensitive to changes in vessel stiffness. In addition, the contour of the arterial pulse changes during propagation down the vessel due to wave reflection and other effects, so that measuring the pulse wave velocity may be technically difficult.

One of the first noninvasive measurements was the *percent variation in diameter* of the artery (%D) (13):

$$\%D = \frac{\Delta D}{D},$$

where D is the diastolic internal diameter and ΔD the difference between systolic and diastolic internal diameters. Percent variation in diameter is approximately equal to the circumferential strain in the vessel wall and has no units. Typical %D measurements in the arterial circulation are 7% to 14%, depending on the age range of the subjects and other factors (14). Because this variable does not consider the magnitude of stress required to increase the arterial diameter during systole, it is only useful for comparison between vessels with similar pulse pressures.

To compare vessels with different pulse pressures, the *pressure/strain elastic modulus* may be used:

$$\text{Pressure/strain elastic modulus} = \frac{(\Delta P)D}{\Delta D},$$

where D is the diastolic internal diameter, ΔD the difference between systolic and diastolic internal diameters and ΔP the pulse pressure. The pressure/strain elastic modulus is derived by dividing the pulse pressure by percent variation in diameter; it has the advantage over percent variation in diameter of considering the magnitude of stress placed on the vessel wall. Although this variable has units of stress similar to an elastic modulus, it is different from the elastic modulus of the vessel because the pressure in the lumen is not the same as the tensile stress of the vessel wall. In the human peripheral arteries, the pressure/strain elastic modulus is in the range 350 to 700 mm Hg. The lower measurements are found in younger subjects, reflecting less stiff arteries in the young (14). It should be noted that using the pressure/strain elastic modulus to compare vascular stiffness between patients assumes that the vessel is linear elastic, so that a blood pressure of 100/60 mm Hg would cause the same percent variation in diameter as a blood pressure of 180/140 mm Hg. However, studies have shown that the arterial wall is not linear elastic and that the elastic modulus can change significantly with pressure (15,16).

The *circumferential elastic modulus* of the artery (E_θ) can be estimated when the thickness of the vessel wall can be measured (17):

$$\text{Circumferential elastic modulus} = \frac{(\Delta P)(r)(D)}{h(\Delta D)},$$

where D is the diastolic internal diameter, ΔD the difference between systolic and diastolic internal diameters, ΔP the pulse pressure, h the wall thickness and r the midwall radius. Unlike %D and the pressure/strain elastic modulus, the vessel thickness is required because this method attempts to estimate average vessel wall stress using the thin-wall cylinder formula (see Laplace's law, described earlier). Thus, if two vessels distend by the same amount from the same pulse pressure, the thicker vessel will have a lower E_θ. Typical values for E_θ in the peripheral arteries are 400 to 3,000 mm Hg; the wide range probably reflects the variation in the architecture of different arteries (14). When measurement of vessel thickness is difficult, the pressure/strain elastic modulus is probably preferable as a more reproducible index of general vascular stiffness.

Arterial structure and vascular stiffness. Although the artery is divided into the intimal, medial and adventitial layers, the mechanical properties of normal arteries are dominated by the structure of the media. The intima is a single layer of vascular endothelium with a proteoglycan-rich matrix; in the absence of intimal thickening, this layer probably bears little of the stress load. The endothelial layer is exposed to shear stresses due to the viscous effects of blood flow. In general, these stresses are much smaller than arterial pressures, although the magnitude of these stresses varies over a wide range because of variations in velocity profiles and vessel geometry. The media comprises concentric layers of smooth muscle cells, collagen and elastin with extracellular matrix proteoglycans. The proportions of these components vary from artery to artery. The adventitia is relatively loose connective tissue that helps anchor the artery in the surrounding connective tissue, particularly in the longitudinal direction.

Elastin, which can be stretched to up to 300% of its length at rest without rupturing (18), behaves mechanically closer to a linear elastic material like rubber than other connective tissue components. This property is due to proline- and glycine-rich helical regions that stretch easily. When elastin fibers are stretched and released, they return promptly to their original state. The tensile modulus of an elastin fiber is ~750 mm Hg, relatively low for a connective tissue fiber (18). Elastin fibers fracture at very low stresses. Although elastin is an important contributor to the normal pulsatile behavior of the vessel, it is probably much less important in determining the overall strength of the vessel. Collagen fibers, in contrast, are much stiffer. The tensile modulus of individual collagen fibers may be as high as 3.7×10^6 mm Hg, or 5,000 times that of elastin (19). Individual collagen fibers are much stronger than elastin fibers and can resist stresses >100 times the fracture stress of elastin fibers but are much less extensible, fracturing at strains of ~10% (20). With age, elastin content decreases, whereas collagen increases in human arteries, one reason why vascular stiffness increases with age (14).

In some tissues, interstitial matrix proteoglycans play a critical role in determining the mechanical properties of the tissue. The sulfated glycosaminoglycans on the protein core of the proteoglycan are negatively charged. These negatively charged structures influence the flow of extracellular fluid and contribute to the viscoelastic behavior of tissues. For example, articular cartilage mechanical behavior is dominated by large aggregates of the proteoglycan aggrecan with the large carbohydrate chain of hyaluronic acid. The highly negatively charged aggregates, in combination with a collagen network, give cartilage the mechanical properties necessary for protecting the joint against enormous stresses (21). Vascular tissues also have interstitial proteoglycans, although the role of these complex molecules in determining vascular stiffness is unclear (22). One species of aortic chondroitin/dermatan sulfate proteoglycan (similar or identical to the fibroblast proteoglycan versican) is secreted by smooth muscle cells, can form aggregates with hyaluronic acid and may have some role in determining vascular biomechanical behavior (23). Smaller proteoglycans, such as decorin and biglycan, are also synthesized by vascular smooth muscle cells (24). These small proteoglycans do not form large aggregates and have only one (decorin) or two (biglycan) glycosaminoglycan side chains, so they probably do not contribute directly to vascular stiffness. However, the small proteoglycans may participate in the overall organization of the matrix, including collagen fibril formation.

The smooth muscle cell of the arterial media is a fundamental contributor to vascular stiffness. Medial smooth muscle cells are the major source of vascular extracellular matrix, including collagen, elastin and proteoglycans, in addition to their direct contribution to mechanical behavior through contraction. Smooth muscle cells are oriented circumferentially in the vessel, and their contractile state may change the stiffness of the vessel. The mechanical properties of vascular smooth muscle (and other muscles) depend not only on the force/length relation (as with all other constituents of the wall), but also on the muscle's physiologic state, so that no single elastic modulus can be assigned to smooth muscle cells (25). Experimental studies have indicated that vascular smooth muscle cells from several species all generate maximal stresses of 750 to 1,500 mm Hg. The vascular smooth muscle cell contractile state is influenced by a variety of agents that may alter vascular stiffness.

Mechanics of vascular catastrophes. The structural failure of the diseased vessel is frequently catastrophic. Atherosclerotic plaque rupture appears to be a common early event in acute myocardial infarction; potential mechanisms of plaque rupture have been reviewed by Davies (26) and McIsaac et al. (27). It is possible that plaque rupture is a mechanism of stepwise plaque growth in asymptomatic patients because ruptured coronary plaques may be seen in patients without acute coronary syndromes (26). Both plaque rupture and rupture of aortic aneurysms may be due to circumferential tensile stress failure, a common mechanism of structural failure of a pressurized cylinder (Fig. 5). Pressure in a cylinder causes tensile circumferential stress in the wall of the cylinder. If a small crack develops in the cylinder, the tensile circumferential stress can cause the crack to extend through the wall. In the thin fibrous cap over a lipid pool and the severely diseased aorta, circumferential stresses can reach levels much higher than those in the normal vessel wall (28).

A second important mechanism of structural failure of the vessel is shear failure (Fig. 5). Shear failure occurs when vessel layers separate and slide relative to one another and when the extracellular matrix, which functions as the glue holding these layers together, cannot withstand the shear stress. Shear failure is the likely cause of acute aortic dissection, when the intima tears loose from the media. In addition, shear failure may be an important mechanism of percutaneous balloon angioplasty. As the balloon inflates, the stiffer atherosclerotic plaque resists circumferential elongation more than the normal artery, and high shear stresses are generated at their interface. This leads to a shear stress between the plaque and the artery, causing the plaque to tear away from the artery, leading to dissection. This mechanism causes the wedge-shaped lesions of dissected, thickened intima that protrude into the lumen after angioplasty (29). Both shear stress and circumferential tensile stress may participate in the same vascular catastrophe. In fact, computer models of vessels indicate that regions with high shear stresses are frequently found at locations with high circumferential tensile stresses.

Biology of vascular mechanics. The body of knowledge describing the ability of cells to respond to mechanical stresses at the molecular level is rapidly growing. The delicate endothelial lining is sensitive to changes in shear stress, which may lead to changes in cell shape, growth, production of matrix elements and a wide variety of gene regulatory events (30). Stress-induced changes in endothelial

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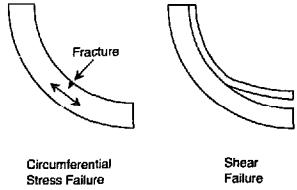

Figure 5. Two common mechanisms of vascular catastrophes. Circumferential stress failure is due to high tensile circumferential stresses in the vessel wall. A small fracture in the wall grows as the tensile forces pull at the edges of the fracture. This may be a common mechanism of atherosclerotic plaque rupture and aortic aneurysm rupture. Shear failure occurs when two layers of the vessel slide against each other, causing a delamination. This is most likely the dominant mechanism of aortic dissection.

function may explain why low and oscillating shear stresses at certain locations in the vasculature (such as the abdominal aorta and carotid sinus) are particularly prone to atherosclerosis (31,32).

Like endothelial cells, vascular smooth muscle cells also sense their mechanical environment and respond with metabolic changes (mechanotransduction). Contact with the extracellular matrix modifies smooth muscle cell responsiveness to growth factors (33). In addition, cyclic stretching of vascular smooth muscle cells leads to changes in extracellular matrix synthesis and cell growth (34). Although the precise mechanism or mechanisms by which stress alters cell function is still under investigation, stretch-activated membrane ion channels may transduce the mechanical signal to the cytoplasm (30). Smooth muscle cells have a variety of extracellular matrix receptors, including the beta-1 integrins, which bind to collagen (35). These heterodimeric cell surface matrix receptors, which are involved in the pathogenesis of inflammation, thrombosis and neoplastic metastasis, may provide anchors to allow transduction of mechanical stress signals to the cytoskeleton (36). Integrins binding to their extracellular ligands cluster on the cell surface membrane at areas called focal adhesion complexes (37); this process triggers intracellular signalling events that are currently under investigation.

The ability of cells to repair their tissues in a structurally organized manner is crucial to the organism. For example, the cells of the dermis normally repair small wounds rapidly and efficiently, and the subsequent scar will not fail. The cells of the vessel wall share a similar vital task of maintaining mechanical integrity. Vascular cells also use changes in shape, migration, extracellular matrix secretion, matrix remodeling and other mechanisms to respond to mechanical stresses. Further understanding of the molecular basis of vascular mechanics will help cardiologists to answer an important question: Why do the cells of the diseased artery sometimes fail to maintain structural stability, allowing mechanical vascular catastrophes?

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