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Arterial Compliance

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The constituents of the walls of blood vessels make them compliant. Their compliance is demonstrated by the relationship between transmural pressure and vessel diameter. Arteries, in contrast to veins, exhibit a steep pressure/volume relationship indicative of less compliant vessels. The compliance characteristics of these vessels relate to their initial shape and to the components of the wall, including vascular smooth muscle, collagen, elastin, and other interstitial elements. The nonlinear relationship between volume and pressure is indicative of the physical properties of the components and of the heterogeneous nature of the wall. This nonlinearity means that no single number can be utilized to define the compliance characteristics of any blood vessel or any vascular bed.

Changes in vascular compliance can be induced by changes in the tone of vascular smooth muscle; by changes in the mass of the smooth muscle, collagen, or elastin components of the wall; by infiltration of the wall with cellular or interstitial elements; or by a change in tissue fluid in the wall. Since these changes in compliance may independently affect large arteries, small arteries, arterioles, and veins, a change in vascular compliance must be assessed separately in different segments of the vasculature.

The influence of vascular compliance on circulatory integrity is often not adequately emphasized. The conduit arterial system serves as a *Windkessel* that smooths out the pulsatile arterial flow and delivers it in a more continuous fashion into the capillary beds. This Windkessel effect is, in part, accomplished by compliance of the arterial system, which allows expansion of the arteries during systole and release of the stored blood in diastole to maintain diastolic flow. Changes in the compliance of these vessels can have important effects on systolic blood pressure, left ventricular load, and cardiac output. Compliance of the small arteries plays a role in the generation of reflected waves, which add an oscillatory component to the arterial pulse wave and are reflected backward toward the root of the aorta in late systole. These reflected waves may also affect left ventricular load.

This chapter reviews what is known about the factors affecting arterial compliance, the influence of disease processes on vascular structure and tone, techniques used to assess arterial compliance, and the possible impact of changes in arterial compliance on circulatory integrity.

The Arterial Circulation and Arterial Compliance

Physiology of the Arterial System

The arterial circulation is a branching system of conduits that conducts blood from the heart to the capillaries where an exchange of nutrients and waste products occurs between tissue cells and the blood. Since the arterial tree is distensible, it acts as an elastic reservoir that stores part of the energy of cardiac contraction, maintaining pressure and flow during diastole when the heart is not ejecting blood.[1] The smallest arteries and arterioles are the sites of greatest hemodynamic resistance and act in conjunction with the precapillary sphincters to form a variable resistance that controls the rate of blood flow through the tissues.[2] The arterioles also provide a step-down in the hydrostatic pressure within capillaries to prevent excessive loss of blood volume by transudation of fluid across capillary walls. An arterial system composed of elastic conduits and high-resistance terminals constitutes a hydraulic filter that converts the intermittent output from the heart into steady capillary flow.[3] For optimal function, this should be achieved with the least possible energy expenditure.[4] To minimize cardiac work during systole in this pulsatile system, the normal arterial bed provides a low-input impedance or opposition to left ventricular ejection.[5] This is accomplished in the periphery by desirable arterial elastic properties and geometric proportions. The heart has also adapted to the arterial system with its physiologic range of heart rates determined, in part, by arterial properties. Thus, a compromise is reached

between the heart and the systemic circulation to provide optimal coupling so that the left ventricle can supply the amount of blood per unit time necessary for tissue metabolism at minimal energy cost and still be able to adapt quickly to increased metabolic demands.[6]

Compliance and the Arterial System

The pressure generated during left ventricular systole ejects a stroke volume that contributes to arterial distention and forward flow in the arterial circulation. The volume stored in the arteries is dependent on the arterial compliance. The forward flow is dependent on the perfusion pressure and the resistance in the smaller vessels. A normally compliant system can store a considerable volume of blood in the aorta and the large arteries during systole.[7] Compliance in young normal subjects has been measured at approximately 2 mL/mm Hg.[8] As the arterial system becomes less distensible, the storage capacity of the aorta and conduit arteries is diminished for any given pulse pressure. Under these circumstances, a larger fraction of the stroke volume must run off during systole or a greater rise in systolic pressure must occur to accommodate increased volume in the noncompliant arterial tree. If the arteries were totally nondistensible, capillary flow would be limited to systole and stroke volume would be dependent on systolic pressure and arteriolar resistance. The impact of these vascular changes on left ventricular function can be profound.[9] When the ventricle ejects into a compliant system, a slower rise in systolic pressure for a given stroke volume causes a lower wall stress and a lower oxygen consumption. Furthermore, the ventricle should eject more rapidly because of the lower impedance, and the greater rate of reduction in chamber size further reduces wall stress during ejection. Thus, changes in arterial compliance can alter the pulse contour, the dynamics of left ventricular ejection, and the ratio of systolic to diastolic flow into the capillary bed without necessarily affecting mean arterial pressure.[10]

Whereas it is recognized that the proximal aorta and its major branches are the most compliant portion of the arterial circulation,[11] the peripheral vasculature also contributes importantly to circulatory regulation. These vessels have a small storage capacity of their own and act as a major site for reflected waves that reverberate proximally and contribute to pressure phenomena in the arteries.[12] The waveform of pressure and flow transmitted to these vessels is more pulsatile if the proximal arteries are less compliant.[13] If the compliance of these smaller vessels were reduced, it would impair the mechanical damping of the pulse pressure, which has been shown to influence vessel structure and growth.[14] Little is known about the impact of pulsative versus continuous flow into the precapillary and capillary vasculature, but physical materials are more susceptible to fatigue and fracture from intermittent changes in stress than from continuous stress.[15] Applying this observation to the arterial wall, it is possible that excessive pulsatile pressure in the small vessels could accelerate vascular damage.[16]

Clinically, *arterial compliance* has been defined as a change in area, diameter, or volume of an artery or arterial bed for a given change in pressure. Compliance is dependent on vessel geometry as well as the mechanical properties of the vessel wall.[17] Arterial wall properties are different in different vessels, in the same vessel at various distending pressures, and with activation of smooth muscle in the vessel wall. Although no single descriptor of arterial physical characteristics can completely describe the mechanical behavior of the vasculature, arterial compliance represents the best clinical index of the buffering function of the arterial system. Changes in the mechanical behavior of blood vessels, manifested by a reduced arterial compliance, can influence growth and remodeling of the left ventricle, large arteries, small arteries, and arterioles.[18] Clearly, arterial blood vessels can no longer be considered as passive conduits to deliver blood to peripheral tissues in response to metabolic demands. Instead, they should be viewed as biophysical sensors that respond to hemodynamic and neurohumoral stimuli that influence the tone and structure of the systemic circulation.[19]

Studies assessing the compliance characteristics of the arterial system have been hampered by the lack of a gold standard, thus making comparison of results from different laboratories difficult if not impossible. Although an association between reduced arterial compliance and risk factors for vascular disease has been described previously, the results have not been uniformly consistent and may be critically dependent on the methodology used, the patient population under study, and the segment of the vasculature examined.[20] Furthermore, difficulties in drawing firm conclusions from published studies are compounded by confusion surrounding the terminology employed to describe the mechanical behavior of blood vessels, the lack of comparative studies using different techniques with the same patient, and the marked heterogeneity in the response of blood vessels to aging, disease, and therapeutic interventions.

Blood Vessel Structure

The arterial wall is composed of three concentric zones: the tunica intima, tunica media, and tunica adventitia. The *tunica intima* consists of the vascular endothelium and a thin layer of collagen and elastin fibers that anchor it to the internal elastic lamina. The *tunica adventitia* consists primarily of collagen that merges with the surrounding connective tissue.[21] The *tunica media* forms the largest part of the arterial wall and is the principal determinant of the vessel's mechanical properties. It is composed of the elastic materials collagen and elastin in addition to smooth muscle. The distribution of collagen and elastin differs strikingly between the central and the peripheral arteries.[22] In the proximal aorta, elastin is the dominant component, whereas collagen dominates in the more distal vessels.[23] Because the elastic modulus of collagen is much higher than that of elastin, the arteries are stiffer as the distance from the heart increases.[12,24,25]

Arterial blood vessels, therefore, are complex three-dimensional structures whose wall components differ in mechanical, biochemical, and physiologic characteristics. Traditionally, the mechanical strength of blood vessels has been viewed as residing in the media, with elastin fibers playing a major role at lower pressures and collagen fibers bearing most of the mechanical stress at higher pressures.

The potential role of the endothelium in buffering pulsatile pressure in the arterial system has been emphasized.[26,27] As a single monolayer of cells, the endothelium possesses little tensile strength but can profoundly alter the mechanical characteristics of blood vessels through the elaboration of vasoactive substances that influence vascular tone, structure, and growth.[28] Emerging data support the concept that the cardioprotective actions of drug interventions, at least in part, may be dependent on favorably influencing endothelial function and pulsatile arterial function.[29]

Vascular Pressure/Volume Relationship

The relationship between pressure and cross-sectional area or volume in a blood vessel is curvilinear. The slope of a tangent to the pressure-volume curve (dV/dP) is defined as the *compliance*. As transmural pressure in an artery increases, the compliance decreases as a result of the more distensible elastin bearing a greater portion of the load at lower pressures than the less distensible collagen.[25,30,31] This elastic property of arterial walls demonstrates why the compliance of a vessel cannot be described by a single number but rather must be defined for a given distending pressure or volume.

A number of models of the arterial wall have been used to explain the relationships among the three main components of the wall and their contributions to arterial compliance.[32–35] A detailed description of these models is beyond the scope of this chapter; however, a brief description of one of these models follows. Figure 85.1 shows a modified Maxwell model of the arterial wall. In this model, smooth muscle is in parallel with collagen and elastin fibers, which combine to make up the parallel elastic component of the arterial wall. Collagen fibers are depicted as hooks that contribute little to arterial wall mechanics when not engaged, but that are quite stiff when recruited.[36] In addition, smooth muscle is in series with connective tissue components (collagen in this example) that compose the series elastic component. When pressure increases, the vessel is stretched and tension increases in the parallel collagen, the parallel elastin, and the combined smooth muscle–series elastic component. Additional collagen fibers are also recruited. When the vessel has little or no smooth muscle tone, the mechanical properties of the artery are almost entirely due to the parallel elastic component's mechanical properties.

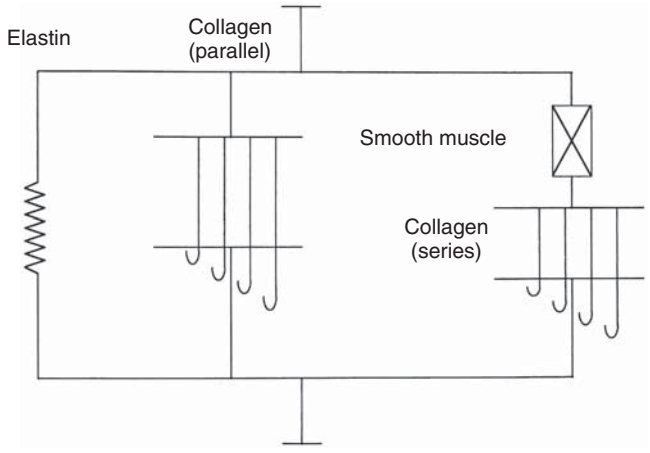

FIGURE 85.1. Modified Maxwell model of the arterial wall. Elastin and collagen (parallel) make up the parallel elastic component. Collagen is represented by stiff springs that are recruited as the arterial wall is stretched (parallel collagen) or as the smooth muscle contracts (series collagen).

Smooth Muscle Relaxation and Arterial Compliance

Whereas the effects of wall structure and distending pressure on vascular compliance are generally agreed on, the effects of smooth muscle tone on vascular compliance are controversial. Detailed reviews of this topic are available elsewhere.[37–41] In isolated vessel and intact animal studies, some investigators have claimed increases[37,42,43] and others decreases[24,38,44] in vessel compliance in response to smooth muscle contraction. Most in vivo studies in humans have demonstrated increases in arterial compliance in response to the systemic administration of vasodilator drugs.[45–48] However, in most studies, there are decreases in blood pressure following systemic drug administration owing to smooth muscle relaxation in resistance vessels. This indirect effect results in a leftward shift along a given compliance-pressure curve. This pressure effect alone improves arterial compliance and makes it difficult to determine the direct effects of the drug on the arterial wall.

In human subjects, several studies have been performed using intravascular ultrasound to assess the direct effects of smooth muscle relaxation on arterial wall mechanics.[49,50] In these studies, the brachial artery transmural pressure was reduced by inflating a cuff surrounding the artery being imaged. Figure 85.2 shows the effects of smooth muscle relaxation with intraarterial nitroglycerin on in vivo brachial artery area, compliance, and incremental elastic modulus in eight normal human subjects.[49] Intraarterial nitroglycerin shifted the pressure-area curve upward in a nonparallel fashion by approximately 22%. It also shifted the pressure-compliance curve upward by approximately 50%. There was no significant change in the incremental elastic modulus with nitroglycerin. These changes in arterial wall mechanics in response to smooth muscle relaxation can be explained based on the arterial wall model described previously. The compliance of a given artery at a given pressure (isobaric compliance) is dependent on two factors: the size of the vessel and the stiffness of the wall. Smooth muscle relaxation can alter both the size of the vessel and the functional stiffness of the wall. Table 85.1 shows the various factors that are altered with smooth muscle relaxation within the arterial wall and the mechanisms responsible for changes in arterial compliance as a result of these alterations. Smooth muscle relaxation decreases smooth muscle tone and thus decreases tension in both the smooth muscle and its associated series elastic component. It also increases vessel size, which alone is an important determinant of arterial compliance.[51] These geometric and stiffness changes increase arterial compliance. An increase in vessel size also results in increased stretch of parallel elastin and collagen fibers and increased recruitment of previously disengaged or coiled

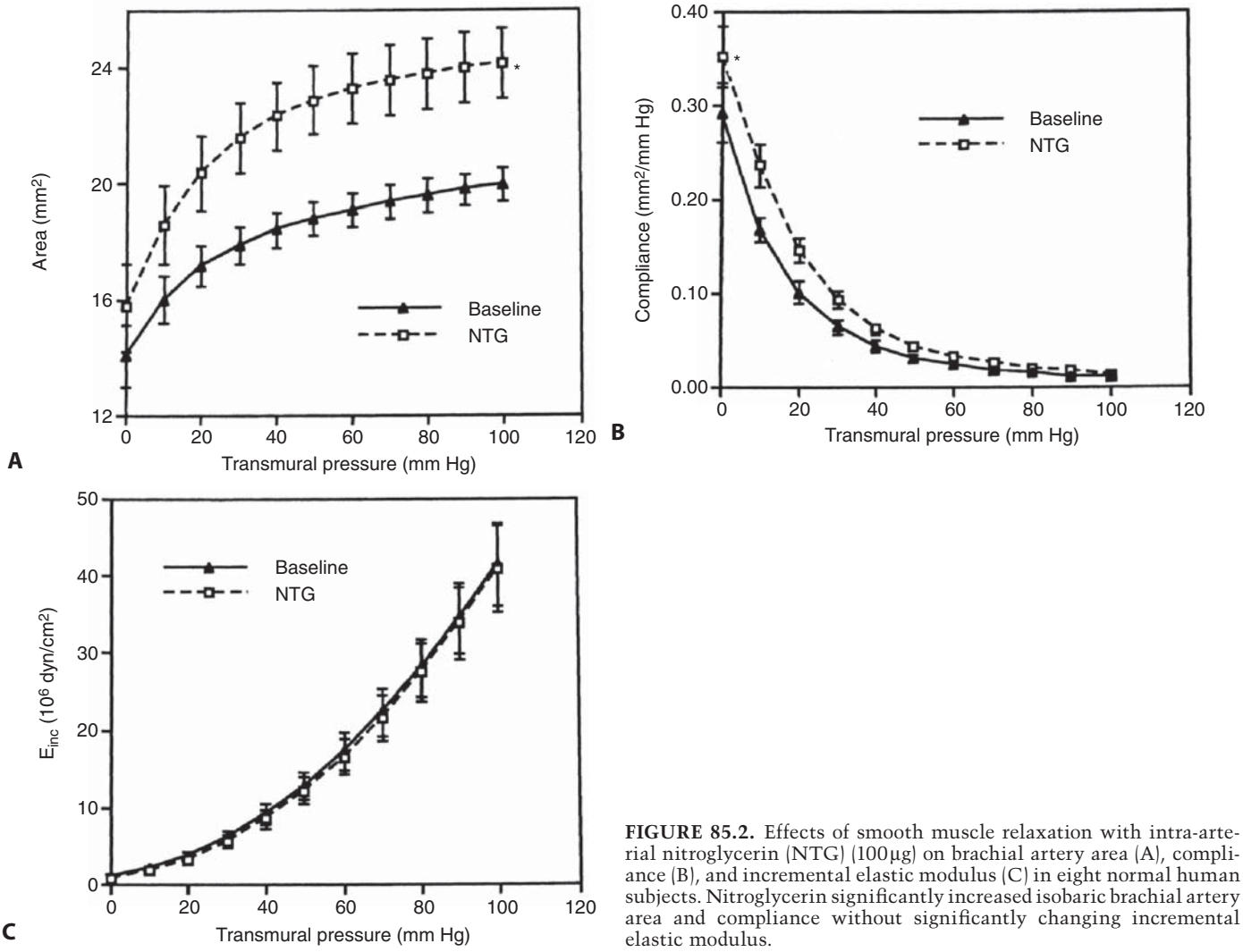

FIGURE 85.2. Effects of smooth muscle relaxation with intra-arterial nitroglycerin (NTG) (100μg) on brachial artery area (A), compliance (B), and incremental elastic modulus (C) in eight normal human subjects. Nitroglycerin significantly increased isobaric brachial artery area and compliance without significantly changing incremental elastic modulus.

collagen fibers. These changes decrease arterial compliance. The direct effect of smooth muscle relaxation on arterial compliance is the net effect of these opposing factors. In the normal subjects described, arterial compliance increased because of an increase in arterial size (geometric effect) in conjunction with no change in arterial stiffness. The incremental elastic modulus, an intrinsic measure of wall stiffness, did not change because the decrease in stiffness owing to decreased smooth muscle-series elastic component tension was balanced by the increase in stiffness owing to increased parallel elastic component tension. Since the effects of a vasodilator drug on arterial compliance are complex and involve a number of competing mechanisms, it is not surprising that studies of arterial compliance in different species, different arteries, or different disease states have produced conflicting results.

TABLE 85.1. Smooth muscle relaxation and arterial compliance

Factor	*Mechanism*
Factors that increase arterial compliance	
Decreased smooth muscle tone	Decreased tension in SM and SEC
Increased vessel size	Geometric effect
Factors that decrease arterial compliance	
Increased stretch or recruitment of collagen	Increased tension in parallel collagen Recruitment of coiled or slack collagen
Increased stretch of parallel elastin	Increased tension in parallel elastin

SEC, series elastic component; SM, smooth muscle.

Pressure Pulse Contour and Wave Reflection

The arterial pressure waveform is derived from the complex interaction of the left ventricular stroke volume, the physical properties of the arterial tree, and the characteristics of the fluid in the system. During systole, only the proximal portion of the aorta becomes distended initially because the inertia of blood hinders the passage of the stroke volume to the periphery. The radial stretch of the ascending aorta brought about by left ventricular ejection initiates a pressure wave that is propagated down the aorta and its branches.[2] This pressure wave travels with a finite velocity that is considerably faster than the actual forward movement of the blood itself. There are marked changes in the shape of the arterial pulse wave as it is propagated peripherally[52] (Fig. 85.3). The distortion in the arterial waveform includes a delay in the time of onset of the initial pressure rise, damping of the high-frequency components of the pulse, and a narrowing and elevation of the systolic portions of the pressure wave.[53] In the proximal portion of the diastolic pressure waveform, a hump becomes more prominent as the pulse passes peripherally. These morphologic changes tend to diminish with age as the arteries become less compliant. The damping of the high-frequency components of the arterial pulse is largely due to the viscoelastic properties of the arterial walls. The mechanisms involved in the peaking of the pressure wave are not clearly defined.[54] Several factors appear to contribute, including wave reflections, geometric tapering, resonance, and pressure-dependent transmission velocity.

It is impossible to explain data on pressure wave transmission and changes in pulse pressure contour morphology without considering wave reflection and a type of damped resonance in the system.[55] Tapering and branching of the arteries alter the pulse contour because an incident wave will be reflected at branch points and the pressure wave becomes amplified as it progresses down a tapered tube. Furthermore, the arterial tree will resonate at certain frequencies while other frequencies are effectively damped. The transmission velocity varies inversely with arterial compliance that, in turn, varies inversely with pressure level. Thus, the peak of the pressure curve will tend to catch up with the "foot" of the same curve. Particularly in peripheral arteries, this phenomenon contributes to peaking and narrowing of the waveform. Reflection and resonance, in addition to influencing the peak of the pressure pulse contours, also contribute to the diastolic hump on the same peripheral waveforms.[56]

The traditional view suggests that pulse wave reflection will significantly increase input impedance, peak systolic pressure, pulse pressure, and stroke work, and that the arterial system is designed to minimize wave reflection.[57] This concept assumes that forward and reflected pressure waves interact in a constructive fashion only resulting in an increase arterial blood pressure.[58,59] However, propagating waves are recognized as oscillatory phenomena that can raise or lower pressure.[60,61] Recent work indicates that a significant amount of wave reflection can occur in the arterial system without detrimentally influencing a number of important hemodynamic parameters.[62] This is achieved by an arterial structure with appropriate impedance mismatches, wave velocities, and branch lengths where the balance of constructive and destructive interaction of forward and backward waves minimizes the effect of reflection.[62] Thus the design of the arterial system may serve to minimize the *effects* of wave reflection rather than minimizing reflection per se.

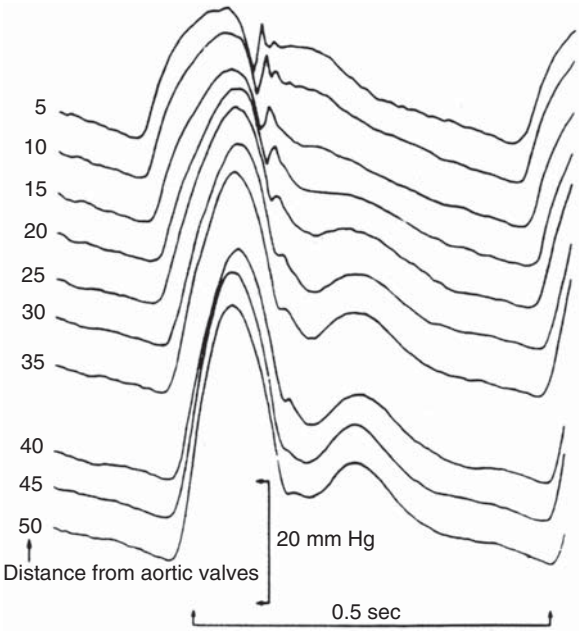

FIGURE 85.3. Pressure waves recorded sequentially at 50-cm intervals between the aortic arch (5 cm from the aortic valve) and the internal iliac artery (50 cm from the aortic valve) in a 16.5-kg wombat through a catheter inserted in the femoral artery.

Techniques for Measuring Arterial Compliance

Table 85.2 depicts the various methods used for estimating arterial compliance along with the advantages and limitations of each technique. These methods are described in the following subsections.

Direct

The most direct way to measure arterial compliance in vivo is by measuring simultaneous pulsatile pressure and diameter (or area) changes within an artery. Pulsatile changes in pressure can be measured either invasively or noninvasively using several techniques, including sphygmomanometry and applanation tonometry. It is critical, however, that the absolute pressure be measured at the same site as the caliber measurement. Accurate measurements of pulsatile changes in arterial diameter or cross-sectional area are more difficult to obtain. A number of techniques have been used in situ or in vivo to assess pulsatile changes in arterial diameter. In animals, ultrasound crystals,[63–66] differential transformers,[67] resistance strain gauges,[68] and photoelectric gauges[62] are some of the techniques that have been utilized to measure arterial diameter. Whereas each of these techniques has its advantages, there are associated problems, including the

TABLE 85.2. Methods used to estimate arterial compliance

Methods	*Advantages*	*Limitations*	*Information*
Direct			
Angiography	Evaluation of different aortic segments	Expensive, invasive, limited clinical application	Regional aortic compliance
Magnetic resonance imaging	Noninvasive, not limited by acoustic window, able to examine multiple segments, not overly operator dependent	Claustrophobia-inducing, expensive, limited availability, remote site of BP measurement	Regional aortic compliance
TTE/TEE TTE	Noninvasive, reasonable availability	Expensive, TTE limited by acoustic window, operator-dependent techniques, TEE invasive, remote site of BP measurement	Regional aortic compliance
Transcutaneous ET/IVUS	Transcutaneous technique non-invasive; both techniques techniques reproducible	Operator dependent, IVUS invasive, remote site of BP measurement with ET, clinical research application	Regional compliance of peripheral arteries
Venous occlusion plethysmography	Noninvasive, reasonable availability	Remote site of BP measurement, clinical research application	Compliance of vascular bed under cuff
Indirect			
Stroke volume/pulse pressure ratio	Noninvasive, reasonable availability	Noninvasive estimate of stroke volume required brachial sphygmomanometer BP measurement	Total arterial compliance
Pulse wave velocity	Noninvasive reasonable availability, reproducible	Limited to larger arteries, errors estimating path length and wave-form distortion with pulse propagation	Segmental arterial compliance
Fourier analysis of pressure and flow waveforms	Standard technique, reproducible	Expensive, invasive, limited to the clinical research arena	Total arterial compliance
Pulse contour analysis	Noninvasive,reproducible, potential for widespread clinical application	Diastolic: estimation of stroke volume Systolic: transfer function	Diastolic: Large artery elasticity (compliance) Small artery elasticity (compliance) Systole: Augmentation index (a function of both large artery and small artery compliance)

BP, blood pressure; ET, echo-tracking; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; IVUS, intravascular ultrasound.

effects of surgery, anesthesia, and hindrance produced by the device used, which can alter mechanical properties of the vessel wall.

In vivo studies of pulsatile arterial diameter changes in humans have been performed using a variety of techniques. Angiography,[69,70] magnetic resonance imaging,[71] transthoracic[72] and transesophageal echocardiography,[73] and intravascular wall motion detectors[74] have been used to assess aortic compliance. Studies of peripheral vascular compliance have utilized plethysmography[75,76] and ultrasound techniques including Doppler velocimetry[77–79] and two-dimensional ultrasound.[80] Since the late 1980s, a number of laboratories have used noninvasive echo-tracking systems to measure arterial diameter as a function of time.[81–84] Figure 85.4A shows an example of the radiofrequency signal obtained from an A-mode image of a normal human brachial artery. The high-amplitude spikes represent the anterior and posterior arterial wall. Markers are placed over these spikes, and the movement of the arterial wall as a function of time is recorded with precision approaching 5 μm.[85] By using simultaneous noninvasive finger plethysmography or radial artery tonometry, pressure waveforms can be obtained simultaneously with the arterial diameter waveforms (Fig. 85.4B) and calibrated based on cuff recordings of blood pressure. If an artery such as the brachial artery is imaged through a water-filled cuff under different cuff using an echo-tracking system, then arterial mechanical properties can be studied over a wide range of transmural pressures.[86] These noninvasive echo-tracking techniques are becoming refined and widely applied to the study of vascular physiology and pathophysiology in human subjects in vivo. Finally, intravascular ultrasound is an invasive technique that has been used to assess human pulmonary,[87] aortic,[88] coronary,[89–92] and brachial[49,50] artery compliance.

Indirect

A number of indirect techniques for measuring arterial compliance have been utilized by physiologists and clinical investigators. It is well recognized that a pressure pulse wave is transmitted more slowly in distensible than in rigid tubes. The method most commonly employed in humans to measure pulse wave velocity has estimated the time of travel of the foot of the waveform over a known distance.[93] The *foot* is defined as the point at the end of diastole when the steep rise of the wavefront begins. Mathematical equations have been

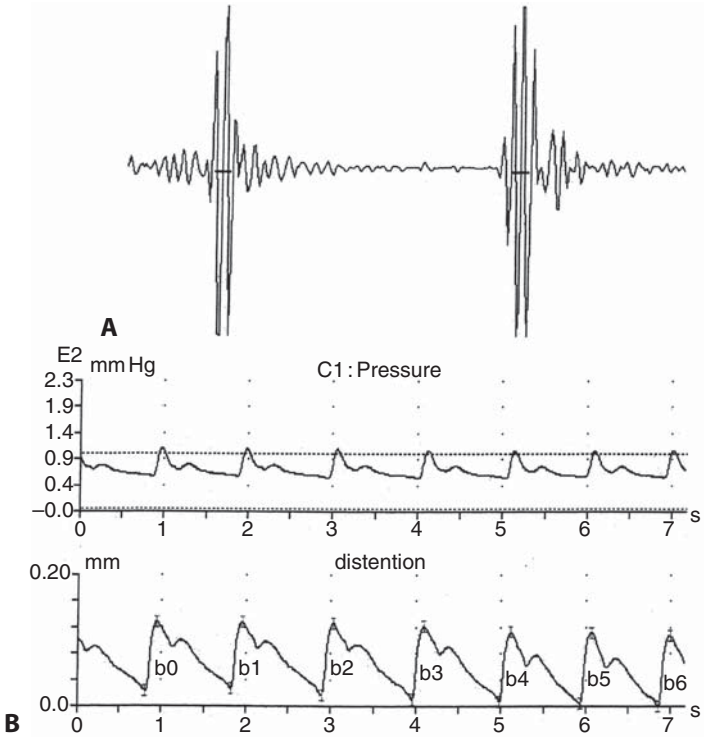

FIGURE 85.4. (A) Radiofrequency signal of the brachial artery in a normal human subject. The first large spike represents the anterior wall of the brachial artery, and the second large spike represents the posterior wall of the artery. Motion of the brachial artery can be measured by tracking the movement of these signals. (B) Simultaneous pressure (above) and diameter (below) waveforms from the brachial artery of a normal human subject. Arterial compliance can be determined by plotting instantaneous arterial pressure versus diameter and calculating the slope of the curve at any given pressure.

proposed by Moens[94] and Bramwell and Hill[95] to quantitatively express the relation between pulse wave velocity and elastic modulus. These formulas assume that the pulse wave velocity depends only on vessel diameter, blood density, and local arterial wall properties. However, pulse wave velocity is also sensitive to changes in heart rate, blood pressure, and wave reflections in the system.[96] The increase in pulse wave velocity with increased stiffness of the arteries does not strictly represent a measure of *compliance of the arteries*, which is defined as an increment in volume produced by an increment in pressure. The use of the Bramwell and Hill formula also assumes that pulse wave reflections are negligible in the system. Although reflections are small for high frequencies corresponding to the wavefoot, it has previously been demonstrated that the propagation coefficients can be modified by reflected waves.[97,98] Neglecting the viscous properties of the blood also introduces small errors in relating pulse wave velocity to arterial compliance. Inconsistencies in the literature also arise from the variable methods employed to define the foot of the pulse contour and accurately describe the distance between the pressure or the flow probes. Finally, pulse wave velocity is proportional to the square root of arterial wall stiffness, and therefore is not particularly sensitive to changes in intrinsic wall properties that influence large vessel compliance. Finally, although pulse wave velocity remains an accepted index of arterial elastic properties, small changes may not be detected because the data generated can often show considerable scatter.[99]

Generalized changes in the physical characteristics of the arterial circulation influence the impedance to left ventricular ejection. Information about the static and pulsatile elements of the impedance load can be quantified by analyzing the altered pressure and flow relationships and pulse contour parameters produced through the effects of disease on the structural and functional components of the arterial system.[100] In the frequency domain analysis of pressure and flow waveforms, characteristic impedance defines a relationship between pressure and flow in an artery when pressure and flow waves are not influenced by wave reflections (Figs. 85.5 and 85.6). It is measured by averaging moduli of high-frequency values of impedance when fluctuations caused by wave reflections are negligible and provides an indirect measure of compliance distal to a site of measurement.[101] However, the values of moduli used are often close to the noise level of the recording instruments. Therefore,

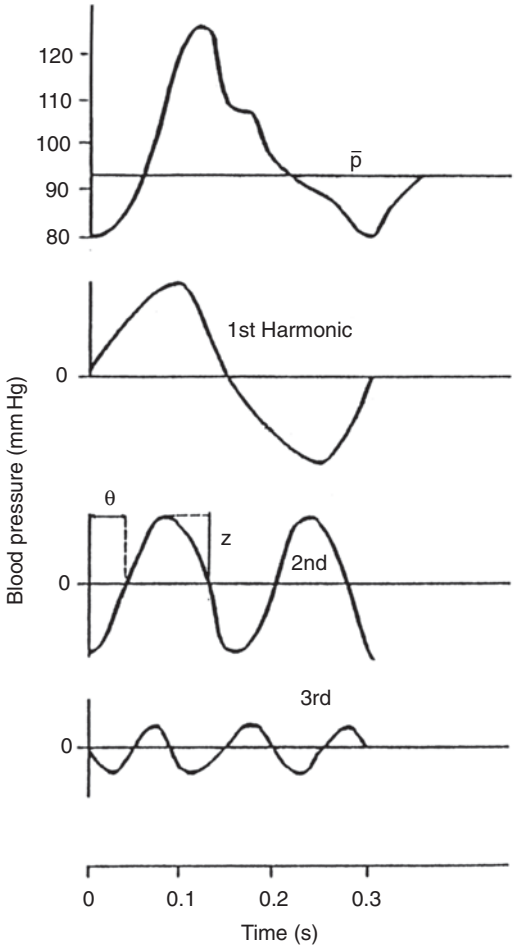

FIGURE 85.5. The Fourier series of the pressure waveform consists of the mean pressure ($\bar{p}$) and a series of sinusoidal waves or harmonics. The first harmonic is at the frequency of the heart rate, the second is twice that frequency, and so on. The amplitude of each harmonic is termed the *modulus* (z), and the timing of each sinusoidal wave in relation to others is called its *phase angle* (θ). The sum of all terms in the Fourier series approaches the original wave in configuration as additional harmonics are computed.

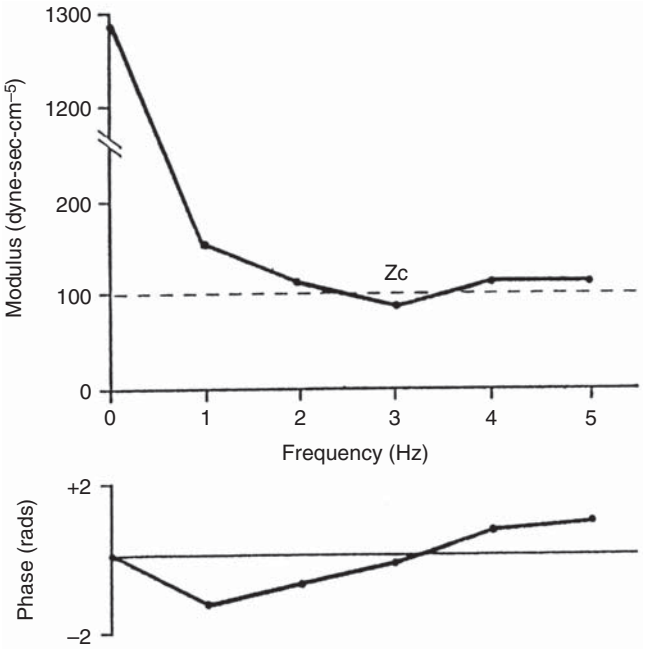

FIGURE 85.6. Hypothetical aortic input impedance spectrum. The impedance modulus values decline from a high value of 0 Hz (i.e., resistance) to a minimum usually between 2 and 4 Hz. This is approximately the same frequency that phase crosses the zero line. Negative phase angles denote that flow leads pressure. Impedance moduli oscillate due to wave reflections around the characteristic impedance, Zc (average of moduli >2 Hz) that is approximately 10% of the resistance.

characteristic impedance, which is not a standardized parameter, can be difficult to calculate and interpret.[102] Clearly, the aortic impedance spectrum contains a great deal of information about the physical state of the arterial circulation, and although it is considered the gold standard for studying the opposition to left ventricular ejection, the utility of the technique is limited by the invasive nature of the procedures involved.

There is a growing interest in the quantitative and descriptive analysis of the arterial pressure pulse waveform in the time domain. During systole, the heart imparts energy into the arterial circulation, producing changing values of pressure and flow at all points in the system. A minor part of the stroke volume is dissipated as forward capillary flow during systole. The remainder is retained by the distensible arteries as potential energy.[103] Closure of the aortic valve prevents further transfer of energy from the heart to the blood vessels. During diastole, this stored energy will passively decay through the arterial tree, and the shape of the end result (the diastolic waveform) will be reflected in the interaction between the input (stroke volume) and the arterial wall properties. Using the technique of pulse contour analysis, arterial compliance values can be estimated by analyzing diastolic arterial pressure decay and employing a modified Windkessel model to interpret the decay of the pressure pulse wave in terms of compliance, inertance, and resistance[104,105] (Fig. 85.7).

It has been recognized for many years that qualitatively consistent changes in the arterial pulse contour occur in many disease states and with physiologic and pharmacologic interventions.[106] The pulse contour technique quantifies these changes to provide additional information about arterial wall properties and the load imposed on the heart. The Windkessel, as popularized by Frank,[107] represents a nonpropagative model of the arterial circulation that views the peripheral vasculature as a lumped capacitance in parallel with a terminal resistance. This and other closely related models have been employed to simulate the load on the heart or interpret this load in terms of the mechanical properties of the arterial circulation. Estimates of compliance, like estimates of pulse wave velocity, are sensitive to changes in heart rate and blood pressure.[108] The derived values are also sensitive to wave reflections in the system, and different estimation methods applied to the same data can yield different results. For example, methods that integrate pressure with respect to time during the diastolic interval (area method) specifically minimize the effects of wave reflections in distorting the diastolic pressure decay from a monoexponential form. Conversely, the pulse contour technique is exquisitely sensitive in quantifying the impact of wave reflections in distorting the pressure pulse decay in diastole.

A number of techniques have been described in an attempt to determine central aortic pressure from peripheral arterial waveforms.[109–111] A feature of the central aortic waveform is a late systolic pressure peak that is assumed to represent a reflection from more distal sites.[109] This late systolic peak, therefore, can provide insight into the magnitude of the reflection and its transit time from the reflecting site back to the aortic root. Techniques based on the determination of a pressure transfer function between the radial artery and aorta have been developed to provide a quantitative estimate of central pressure wave reflection.[112,113] In addition to deriving central pressures, this methodology has been utilized to quantify augmentation of systolic pressure within the aorta as a consequence of early pulse wave reflection. Some investigators relate a change in the augmentation index as identifying alteration in arterial stiffness and promote the index as a noninvasive marker of future cardiovascular

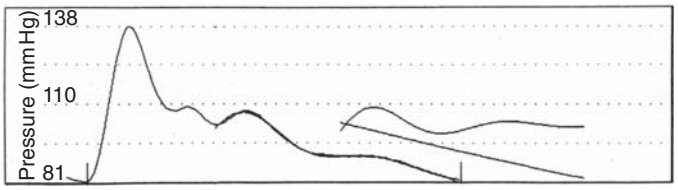

FIGURE 85.7. The passive transient response of the arterial vasculature to the initial loading conditions produced during systole during left ventricular ejection is determined by analyzing the diastolic portion of the pressure pulse waveform. A curve-fit software program utilizes a third-order equation $[A_1e^{-A_2t} + A_3e^{-A_4t} \cos (A_5t + A_6)]$ to represent the time course of the diastolic pressure decay and produce a set of A constants that describe an average waveform that accurately fits each marked pressure pulse contour. The first term in the equation fits to the exponential decay of pressure in diastole and the second term to the oscillatory dicrotic waveform as depicted here. Elements in the modified Windkessel model[155] are calculated from the systemic resistance and the six A constants by equating the A constants with comparable coefficients from the solution to the circuit equations.

risk.[114,115] It has been demonstrated that in patients with end-stage renal disease calculation of the augmentation index may contribute to the prediction of future cardiovascular mortality.[116]

The augmentation index is a composite measure sensitive to changes in myocardial contractility and the timing and amplitude of wave reflection that is influenced by pulse wave velocity, blood pressure, gender, height and most particularly heart rate.[117–119] Clearly, many of the factors that influence augmentation of systolic pressure occur independently of a change in arterial stiffness. A number of studies show a little or no association between the augmentation index and aortic pulse wave velocity (an indirect measure of stiffness) assessed simultaneously in the same patients.[120–122] Furthermore, the accuracy of employing a generalized transfer function to the radial artery pressure pulse waveform to provide estimates of central aortic parameters has also been questioned.[123–126] Wide margins of error comparing centrally measured and centrally derived augmentation index have been noted to the extent that the two measures were not statistically significantly correlated.[126] When calibrated non-invasively, significant underestimation of central aortic systolic pressure is commonly described.[127–129] Indeed, analysis of untransformed radial waveforms appears to produce smaller errors in the estimate of central aortic systolic pressure than those derived using a generalized transfer function.[130] The large number of potential confounders and inaccuracies in deriving central parameters with noninvasive calibration of radial waveforms limits the clinical application of the technique.

Abnormalities of Vascular Compliance in Aging and Disease States

Aging

An understanding of age-related physiologic changes occurring in the vascular system is crucial to appreciate the influence of age on the development of cardiovascular disease and its response to treatment. Although it is recognized that the interindividual variability and the severity of the age-related vascular disease can be substantial,[131] a major problem in studying the effects of age on the cardiovascular system relates to distinguishing age-related from disease-related changes.[132] Adaptations in the arterial vasculature play a critical role in influencing the rise in blood pressure and the left ventricular afterload that accompany advancing age.[133] These changes also contribute to alterations in regional blood flow,[134] atherosclerosis,[135] and the microvascular abnormalities[136] that occur during senescence. The age-related changes in the properties of the arterial system are both structural and functional in nature.

Aging effects involve the arterial intima but are most marked in the media, where there is loss of the orderly arrangement of elastic fibers, which display thinning, fraying, and fragmentation.[137] Elastic degeneration is associated with an increase in collagenous material, often with the deposition of calcium in the degenerating media. In addition, aging (and diabetes mellitus) results in the accumulation of advanced glycation end products that cause cross-linking of proteins in the vessel wall and decreased elasticity.[138] These acute glycation end products may serve as a target for novel therapies designed to selectively break cross-links and improve arterial compliance. The progressive arterial stiffening with aging is more rapid in the central than in the peripheral vessels,[139] so that in the elderly, the aorta and larger arteries exhibit similar stiffness. Studies by Learoyd and Taylor[25] showed that the viscoelastic properties of human arterial walls are altered with age. These authors performed static and dynamic stress-strain studies on arteries removed at autopsy. They concluded that Young's modulus of elasticity increased progressively with increasing distance from the heart and that older vessels (age ≥35 years) had a higher modulus than young vessels (age <35 years). These findings and those of other investigators demonstrate that aging changes do not simply develop in the elderly but are progressive throughout life and are well developed by early adulthood.[140]

Longitudinal and cross-sectional studies of the age-related changes in blood pressure indicate that diastolic blood pressure tends to plateau between 50 and 60 years while systolic blood pressure continues to increase, producing a widening of pulse pressure with age.[141–143] In individuals younger than 60 years diastolic blood pressure may be superior to both systolic blood pressure and pulse pressure in predicting cardiovascular risk.[144,145] Thereafter, systolic blood pressure is the single most important measure for predicting future cardiovascular risk.[144] Some studies show that in patients older than 60 years the measurement of pulse pressure provides added value to systolic blood pressure in assessing long-term cardiovascular mortality.[144–146] This has not been shown in all studies,[147] suggesting that pulse pressure may add to risk assessment in older individuals but perhaps only in certain populations.

Measurement of pulse wave velocity has been the indirect method most commonly employed to evaluate age-related compliance changes in large artery segments.[139,148–150] Change in aortic stiffness with age appears to be similar in both genders until puberty.[151] Thereafter, some studies show that males have a greater decline in aortic stiffness and increased pulse wave velocity than their female counterparts.[151,152] Regional heterogeneity in arterial stiffening with advancing age is well described. Carotid-femoral pulse wave velocity increases substantially with advancing age, whereas an insignificant increase in carotid-brachial pulse wave velocity is described.[153] Mitchell et al.[153] have calculated reflected wave transit time that indicates wave reflection remained unchanged or decreases with increasing age. Based on this work and the findings of others,[154] the authors concluded that the increased central pressure with aging may display a closer relationship with an increase in forward wave amplitude rather than enhanced peripheral pulse wave reflection. They also speculated that increased transmission of pulsatile energy into the microcirculation may have adverse pathophysiologic consequences, resulting in an elevated risk of future vascular events.

Although it has not been extensively studied, functional changes in the properties of the arterial system could influence the compliance characteristics of the blood vessels. The well-recognized reduction in β-mediated adrenergic function with age may make a significant contribution to changes in

vascular tone, vasodilating capacity, and vascular compliance in senescence.[155] Recent data suggest that altered β-adrenergic sensitivity in black individuals may contribute to increased aortic stiffness independent of change in blood pressure.[156]

Age-related changes in the intima of the arterial blood vessels may also contribute to altered smooth muscle tone by influencing the release of endothelium-derived relaxing factors.[157] The clinical implication of the reduction in compliance may reside in a diminished vasodilator reserve and an inability to respond to increased metabolic demands. A decrease in compliance also increases the impedance load opposing left ventricular ejection. Although the results of previous studies are not entirely consistent, it would appear that characteristic impedance increases with age, signifying an increased opposition to pulsatile flow.[158–160] This senescent increase in vascular impedance could provide a stimulus for the increase in left ventricular mass in the aged population. Cardiac morphology studied at autopsy[161] and by echocardiography[162] shows a modest degree of myocardial hypertrophy in advanced years. This adaptive left ventricular hypertrophy is associated with an increased risk of cardiovascular morbidity and mortality and therefore cannot be dismissed as an unimportant manifestation of the aging process.[163,164]

Age-related changes in the vasculature are not confined to the large arteries but involve the small arteries and arterioles as well.[136,165] Peripheral vascular resistance has been employed to estimate hemodynamic adaptations in arterial resistance vessels in previous studies, and a modest increase with aging has usually been documented.[166] This measurement represents a steady-state situation based on continuously fixed pressure and a constant flow model of the circulation in which resistance is calculated from mean arterial pressure and cardiac output. This model ignores pressure fluctuations occurring in the circulation, where the compliance characteristics of the arterial vasculature provide the vital buffering function required to smooth pulsatile outflow from the heart. In these smaller vessels, atherosclerotic changes are much less prevalent and medial arteriosclerotic change is predominant.[167] Furthermore, as the increase in systemic resistance is attributed to medial degenerative changes that rarely produce significant vascular narrowing,[166,165,167] measurement of the compliance characteristics of these vessels may provide important information about senescent changes that are not reflected in flow resistance.

Whereas it is generally accepted that the structural and functional changes associated with aging impair the buffering function of the arterial circulation, most studies have been confined to the large conduit arteries and have emphasized that changes in pulsatile function do not progress in a uniform or consistent manner.[168,169] Prior studies employing pulse wave velocity to estimate the stiffness of arterial segments indicate that the aorta stiffens progressively at an accelerated rate compared with other arterial segments. Echo-tracking technology has revealed that age-related changes in pulsatile function are inhomogeneous within localized arterial segments of elastic and muscular arteries and that the compliance characteristics of the radial artery may paradoxically increase with age. Distensibility and compliance of the elastic common carotid artery decreases linearly with age from the third decade onward, with a reduction in compliance being less steep than a reduction in distensibility. The smaller decrease in compliance is explained by the increase in arterial diameter observed with increasing age.[170–172] While distensibility of the common femoral artery is reduced in older age, mechanical properties of the brachial artery and the deep and superficial femoral arteries do not change significantly.[173,174] Even within the same arterial segment loss of distensibility with increasing age is not homogeneous. In the carotid artery, the carotid bulb is more severely affected by age-related change than the remainder of the arterial segment.[175]

Whether these changes in arterial wall composition can be held responsible for the loss of arterial distensibility with aging remains a matter of debate. Recent studies in rats indicate that by the changes in collagen or elastin content or density or in the degree of collagen, cross-linking cannot account for changes in arterial wall properties with increase in age.[176] It has been proposed that the relative loss of glycosaminoglycans and proteoglycans may be responsible, at least in part, for age-related changes of arterial stiffness.[177] In contrast to the marked heterogeneity in the physical characteristics of localized arterial segments with aging, consistent and predictable changes occur in the arterial pulse contour, regardless of the site of measurement.

McVeigh et al.[178] examined the effects of aging on the compliance characteristics of the arterial circulation, applying the pulse contour analysis technique to waveforms recorded invasively and noninvasively from the brachial and radial arteries, respectively. Consistent age-related reductions in arterial compliance estimates were found regardless of measurement site or method employed. The decline in small artery compliance with aging was significantly greater that estimates recorded for large arteries. As the smaller arterial vessels are generally free from atheroma and the decline in small artery compliance with aging was independent of changes in blood pressure, this estimate may reflect the effects of the degenerative aging process per se in altering pulsatile arterial function. One plausible explanation for our findings may reside in impaired endothelial function, which is known to accompany advancing age and may negatively affect pulsatile arterial function.

Atherosclerosis

Atherosclerosis and the increase in mean arterial pressure that occurs with advancing age could account, at least in part, for alteration in arterial wall properties. Changes in arterial stiffness have been documented with atherosclerosis, but the findings have not been consistent. Farrar and coworkers[179,180] in experimental atherosclerosis in the rhesus monkey demonstrated the loss of aortic distensibility by pulse wave velocity with the development of atherosclerosis and the improvement of aortic distensibility with regression of atherosclerosis. Recent work links changes in vascular compliance with the extent and severity of coronary atherosclerosis and subclinical aortic atherosclerosis in humans. By contrast, in vitro studies of human aortas failed to show any difference in distensibility attributable to atherosclerosis when comparing atheroma-filled and atheroma-free specimens.[181] Similarly, studies of pulse wave velocity change in populations with a high and low prevalence of atherosclerosis failed to show any difference between groups.[140]

Some studies, but not all, support a relationship between coronary artery disease and aortic stiffness, and pulse wave velocity estimates have been proposed as a useful surrogate for atherosclerosis in the coronary bed.[182–186] If atherosclerotic disease in the arterial vasculature progressively stiffened blood vessels, the accompanying change in the mechanical properties of the vessels could serve as a surrogate marker for subclinical atherosclerosis.[187] Furthermore, the surrogate marker of aortic stiffness could hold predictive value for the occurrence of cardiovascular and coronary events.[188] However, atherosclerosis alters the morphology of diseased arterial tissue in a highly variable and complex fashion that defies straightforward characterization, and localized interrogation of mechanical wall properties of vessels around predominantly lipid-laded plaques reveals a decrease, rather than an increase, in arterial wall stiffness.[189]

In a prospective, population-based cohort study in elderly men, carotid artery plaque burden was a strong and independent predictor of all-cause and cardiovascular mortality. The additional predictive information conveyed by measures of carotid artery stiffness appeared limited in this group.[190] Zureik et al.[191] reported that echogenic, but not echolucent carotid plaques, were associated with an increase in aortic stiffness. Prospective studies have failed to show that echogenic plaques are independently associated with future cerebral vascular events.[192–195] The authors suggested that assessment of both plaque morphology and arterial stiffness would permit better identification of high-risk subjects.[195] These data raise interesting questions about the relationship between morphology (i.e., vessel wall characteristics and plaque burden) and function (i.e., selected measures of elasticity and stiffness). Data on aortic pulse wave velocity suggest that changes in this measure probably identifies more extensive calcific disease distributed throughout the arterial system.[196] Lipid-laden plaques that are prone to fissuring and rupture are not likely to be identified by changes in pulse wave velocity. Therefore, even if close linear correlation did exist between the severity and extent of atherosclerosis and the change in pulse wave velocity, the recognition that most coronary events occur in patients with only mild to moderate disease with a predominance of lipid-rich plaques suggests this measure has limited utility for risk prediction in asymptomatic populations.[187,197]

Plaque Rupture and Myocardial Infarction

The mechanical properties of atherosclerotic coronary arteries are important factors influencing the likelihood of plaque rupture and resultant unstable angina or myocardial infarction. Coronary arteries with circumferential disease have decreased distensibility that is inversely related to wall thickness.[92] Distensibility is significantly greater in vessels with noncircumferential disease as compared with vessels with circumferential disease. In vessels with noncircumferential disease, the plaque portion of the wall is about four times less distensible than the more normal part of the wall. The decrease in wall distensibility of the plaque is related to the presence, size, and intrinsic characteristics of the plaque.[198]

The majority of acute myocardial infarctions occur as a result of plaque rupture. Cracks begin in the fibrous cap of an atherosclerotic coronary artery at areas of stress concentration. Finite element analysis models of plaques[199,200,201] have shown that stress concentration occurs at the shoulder of the fibrous cap, the location of approximately 60% of plaque ruptures.[199] Changes in the stiffness of arterial components such as the lipid pool, the fibrous cap or the vessel wall may result in a shift of stress concentration to a new area, in some cases away from the dangerous shoulder region. Crack propagation and ultimate rupture may be explained, in biomechanical terms, as a chronic fatigue process resulting from millions or billions of cycles (heart beats) of low-level stress imposed on the plaque.[198] A more detailed understanding of the mechanical properties of the atherosclerotic coronary artery and the mechanical forces imposed on it should result in better strategies for reducing the load on the plaque and creating a more benign biomechanical environment, less conducive to fatigue failure, plaque rupture, and myocardial infarction.

Hypertension

Hypertension is a common and chronic age-related disorder associated with an increase in blood pressure and cardiovascular and renal complications.[202] Guidelines continue to be refined, incorporating and reflecting new evidence, that provide recommendations for the classification of blood pressure and selection of treatment goals that vary with disease state or the presence of target-organ damage.[203] The relationship between blood pressure and risk of vascular events is continuous and independent of other risk factors. However, it is recognized that high blood pressure is typically associated with other risk factors that modify cardiovascular risk.[204] The aggregation of metabolic, inflammatory, and procoagulant risk factors impact on the development of vascular complications regardless of the operational blood pressure thresholds used for diagnosis.

End-organ damage powerfully influences cardiovascular risk and the benefits of therapeutic interventions.[203] Vital organs such as the kidney, heart, and brain represent well-recognized preferential targets in the hypertension syndrome. Unfortunately, by the time symptoms develop or events occur as manifestations of target-organ damage, the disease process is already at an advanced stage. Although not traditionally viewed as an end-organ, it is accelerated disease in the arterial circulation that is responsible for the morbid and mortal events in hypertension.[205] Hypertension, therefore, should be viewed as a syndrome that mediates its effects by altering the structure, properties, and function of wall and endothelial components of arterial blood vessels.[206]

Structural and functional changes in arterial blood vessels have been described at the earliest stages in hypertension and act not only as a marker for the hypertensive disease process but also as a risk factor for accelerated disease development.[207] The ability to detect and monitor subclinical damage, representing the cumulative and integrated influence of risk factors in impairing arterial wall integrity, holds the potential to further refine cardiovascular risk stratification and enable early intervention to prevent or attenuate disease progression. The importance of assessing arterial wall integrity has been highlighted by studies demonstrating that impairment in the mechanical properties of large arteries represents an independent risk factor for future cardiovascular events.[208] Thus much attention has been directed toward the development of novel techniques that provide

more direct information in relation to changes in arterial wall integrity in the hypertension syndrome.

Although somewhat artificial, it is convenient to differentiate the arterial circulation into proximal and distal compartments based on the architecture, structural components of the vessel walls, and primary function of the two compartments.[209,210] The arterial media is composed of elastic materials, elastin and collagen, in addition to smooth muscle. In the proximal aorta elastin predominates, whereas the collagen-to-elastin ratio is reversed in the more peripheral arteries where collagen predominates. The characteristics, amount, and chemical modification of collagen along with fraying and fragmentation of elastin changes the mechanical properties of the aorta with aging, and this process is accelerated in patients with hypertension.[210]

As pressure rises, more of the stress on the vessel wall is borne by the collagen fibers of the central arteries. Thus a reduction in distensibility of the aorta, but not necessarily of peripheral muscular arteries, is observed, reflecting intrinsic alterations in the mechanical properties of the aorta.[211] The reduced distensibility of the vessel wall increases the velocity of the pressure pulse and decreases the transit time of wave reflections. These pathologic changes lead to augmentation of the systolic pressure and an increase in pulse pressure. The altered hemodynamics impact detrimentally on ventricular-vascular coupling, and the increase in pulsatile stress may predispose to rupture of atheromatous plaques.[210] The structural changes in the central arteries, recognized as a relatively late manifestation of disease, contributes to the phenotype of isolated systolic hypertension predominantly found in older individuals.

By passively increasing the distending pressure on vessel walls, high blood pressure will impair the mechanical properties of the arterial system. Whether impairment in the mechanical properties of arteries is a consequence of the elevated pressure or represents an intrinsic alteration in wall properties has been the subject of considerable controversy.[208] A number of groups have provided evidence that measures of increased stiffness in large arteries are due predominantly to an increase in distending pressure rather than hypertension-associated changes in the structural properties of wall materials.[212–215] Bussy et al.[216] provided evidence for increased stiffness of the elastic carotid artery in young but not middle-aged or older hypertensive patients and suggested that deleterious effects of aging and hypertension are not additive.

There is likely a progressive decline in the mechanical properties of the central aorta with distensibility affected to a greater extent than compliance due to the compensatory dilation of the aorta in hypertension. Systolic blood pressure is recognized as an important and powerful predictor of future cardiovascular risk especially in older populations.[217] Pulse pressure may provide added value in risk assessment but this has not been confirmed in all studies.[218] Recent studies employing carotid-femoral pulse wave velocity, as an indirect measure of vessel stiffness, predicted all-cause cardiovascular mortality and coronary events in patients with hypertension independent of systolic blood pressure.[219] Although the absolute number of events was small, these data provide support that added predictive value, beyond blood pressure measurements, can be gained by assessment of the mechanical properties of arteries.

Microcirculation is a collective term for the smallest segments of the vascular system and is a major site of control of vascular resistance.[209] It includes arterioles and capillaries and is considered a continuum rather than a distinct site of resistance control. The primary function of the microcirculation is to optimize nutrient and oxygen supply to tissues in response to variation in demand and avoid fluctuations in the hydrostatic pressure. Importantly, it is recognized as a site where the earliest manifestations of cardiovascular disease, especially inflammatory processes, occur.[220]

Microcirculatory abnormalities are extremely prevalent in hypertension and may arise as a consequence of the disease or be primarily involved in pathogenesis and thus represent a potential target for therapeutic interventions. Alteration in vasomotor tone, with a propensity to enhanced vasoconstriction, anatomic alterations with an increase in vessel wall–to-lumen ratio, and a reduction in density of arterioles or capillaries (rarefaction) are recognized abnormalities in the microcirculation associated with hypertension.[221] One study provided compelling evidence that alterations in small resistance artery morphology, followed by endothelial dysfunction, represent the earliest forms of target organ damage in hypertension.[207] Similar changes are noted in scleroderma and syndrome X, suggesting that an increase in blood pressure is not a prerequisite for the development of structural and functional microvascular abnormalities.[221] Furthermore, epidemiologic studies suggest that a microcirculatory abnormality may predispose to the future development of hypertension in adulthood, as blood pressure could be predicted by a combination of birth weight and placenta weight.[221] However, a direct role for structural changes as a primary cause of hypertension remains the subject of debate.[222]

Organ-specific microvascular complications associated with hypertension include nephropathy, retinopathy, lacunar infarction, and microvascular angina. The hemodynamic hallmark of essential hypertension is an increase in total peripheral resistance that is determined by structural and functional alterations at a microvascular level. Diastolic blood pressure is often employed as an indirect surrogate for an increase in peripheral resistance in the clinical setting. Epidemiologic studies confirm that in younger populations diastolic blood pressure appears superior to systolic and pulse pressure in predicting cardiovascular risk.[217] While reflective of an abnormality in microvascular beds, an elevated diastolic blood pressure primarily acts as a harbinger for macrovascular events, including stroke and myocardial infarction, in patients with hypertension. Important recent data provide evidence for the prognostic significance of altered small-artery structure in predicting fatal and nonfatal cardiovascular events in hypertension. Rizzoni et al.[223] demonstrated that structural alteration in subcutaneous resistance arteries predicted future cardiovascular events, independent of other cardiovascular risk factors, indicating an important direct role for the microcirculation in the development of heart disease, stroke, and renal disease. Evidence derived from analysis of arterial pulse waveforms provides further support for the importance of microcirculatory abnormalities in individuals at risk for atherosclerotic events.[224]

The resistance calculation reflects the changes in tone, capillary density, or wall thickness/lumen ratio that influence blood flow. However, the dynamic structural and func-

tional adaptations in which diameter and wall thickness of the microcirculation change in response to neurohumoral and hemodynamic stimuli alter more than flow and resistance. Changes in the physical properties and diameters of microcirculatory beds also influence the distensibility and compliance characteristics of the blood vessels.[225] Although arterial compliance is considered primarily a function of large blood vessels, the ability of microcirculatory beds to dilate and constrict will alter compliance, irrespective of a change in wall properties, as compliance depends on geometry and structure of the vasculature. Thus flow resistance and the compliance characteristics of the microvasculature change in a dynamic fashion to both acute and chronic stimuli.[226] Indeed, the ability of a vessel or network to distend in response to a pressure load may be more sensitive than a caliber change in identifying abnormal structure or tone in the microcirculation.[208]

The changes in steady-state (flow resistance) and pulsatile function (arterial compliance) influence mean arterial pressure and the pattern of wave reflection and can be identified by a change in the shape or morphology of the pressure pulse waveform.[210] Dilation of the microvasculature, by reducing mean arterial pressure and wave reflection, decreases the passive distending pressure on more central arteries and favorably impacts on pulsatile phenomena in this section of the arterial circulation. The reduction in distending pressure enables more efficient buffering of the pulsatile cardiac output by central arteries and reduces pulsatile stress transmitted to the microcirculation. If smaller vessels of the microvasculature have impaired compliance characteristics, the inefficient damping of pulsatile pressure will have consequences for this section of the vasculature.[226] It is clear the biophysical properties of microvascular networks play a pivotal role in modulating the propagation and reflection of pressure and flow in the circulation that contributes to the initiation, maintenance, and amplification of blood pressure. Therefore, normalization of microvascular structure and function should be regarded as an important target for drug interventions.[216]

Antihypertensive Drugs and Arterial Wall Properties

The therapeutic benefits of antihypertensive drugs on the cardiovascular system comprise two major effects: the effects due to blood pressure lowering and the direct effect of the drug in the vessel wall.[227] Drug therapy that lowers blood pressure in hypertensive patients improves clinical outcome. Whether further improvements in outcome depend on how the blood pressure is lowered (by influencing both pulsatile and steady-state hemodynamics) or by favorably influencing the arterial wall (through direct effects on endothelium and wall properties) remains to be established. Antihypertensive agents lower blood pressure by dilating the microvasculature, and the favorable effects on the mechanical properties of large arteries are mediated to a major extent via these actions rather than by direct effects on central arteries.[226]

The arterial blood pressure is not the only factor determining vascular structure, design, and function in hypertension.[222] Furthermore, blood pressure reduction in response to antihypertensive therapy is not necessarily accompanied by a change in vessel structure and function.[222] Schiffrin et al.[228] have shown that small artery remodeling and endothelial dysfunction were corrected with angiotensin II receptor blockade but not beta-blockade despite a similar reduction in blood pressure with treatment.[228] The beneficial actions may relate to involvement of the renin-angiotensin system and oxidative stress in accelerated aging and the development of atherosclerosis.[206] The reduction in inflammatory mediators, restoration of endothelial function, and improvement in vessel wall mechanics would be expected to confer vasculoprotective benefits beyond blood pressure reduction. The chronic actions of drug therapy in reversing vessel and network structural abnormalities and restoring endothelial function may be a more important goal in the long-term treatment of hypertension than promoting vessel dilation.[221]

Diabetes Mellitus

The altered metabolism associated with diabetes mellitus produces structural and functional changes in the arterial vasculature and accounts for the increased cardiovascular morbidity and mortality found in diabetic subjects.[229,230] Large vessel disease represents a major threat to health in patients with diabetes.[231] Although the pathogenesis remains unresolved, it is generally considered to be of atherosclerotic origin.[232] Angiographic[233] and autopsy studies[234] have demonstrated that diabetic patients have more severe and diffuse atheromatous disease than do age-matched controls. However, it is now recognized that a specific vascular process can occur in diabetic patients to produce large vessel damage. In contrast to the distribution of atherosclerosis, which is often confined to particular vessels and territories, diabetic macroangiopathy represents a constellation of changes that affect the entire arterial system.[235] The histologic findings include the accumulation of periodic acid-Schiff–positive substance, connective tissue membrane components such as fibronectin, and type IV collagen, as well as deposition of calcium in the arterial media.[236] The term *diabetic microangiopathy* usually includes arteriolosclerosis and thickening of capillary walls. *Arteriolosclerosis* refers to concentric hyaline thickening of the arteriolar walls and is recognized as a generalized change in diabetes mellitus.[237] The development of microangiopathy involves capillary basement membrane thickening,[230] nonenzymatic glycation of long-lived tissue proteins, abnormalities of endothelial cells and platelets, and perhaps increased blood vessel damage by free radicals.[238] The functional consequences of these changes involve an increased permeability of capillary networks and, eventually, acellular capillaries, resulting in a decreased microvascular density.[239] These changes in the vessel wall affect vessel elasticity.[240] With such widespread changes occurring in both large and small arterial vessels, one would expect these changes to influence the arterial compliance characteristics in diabetic subjects.

Previous work has documented stiffer arteries in patients with type 1 and type 2 diabetes with different degrees of diabetic complications, across various age ranges, at different arterial sites and using different methodologies and measurement techniques.[241–268] However, the data are not entirely consistent, and diabetes is not associated with abnormal arterial wall properties in all arterial territories studied. Monnier and colleagues[267] found an increase in aorta-femoral

pulse wave velocity in patients with long-standing insulin-dependent diabetes versus nondiabetic controls only if they had retinopathy. However, this measurement reflects the stiffness of large artery segments, and the higher blood pressures recorded in the diabetic subjects with retinopathy could have accounted for their findings. Scarpello and coworkers[266] reported an increase in pulse wave velocity in the popliteal to posterior tibial arteries only in diabetic subjects with neuropathy and active or healed foot ulceration. In the upper limbs, pulse wave velocity was similar for all groups. In a recent study, arterial stiffness was evaluated by measuring pulse wave velocity at four different sites, and diabetes was significantly associated with an increase in pulse wave velocity in the central arteries, whereas other factors including age, blood pressure, and gender impacted on the measurement in peripheral arterial regions.[268] These confounding factors and the use of an array of devices, each producing results pertaining to different aspects of vascular structure and function, has produced conflicting data in relation to the effect of diabetes in altering the mechanical properties of arteries.[241–243]

Because consistent abnormalities in the arterial pressure pulse contour have been recognized for many years in diabetic patients, there has been a growing interest in quantifying changes in the pulse contour to provide information about the status of the vasculature in diabetes.[269–271] In the original studies the principal change in the arterial wave shape, found in both small or digital and larger conduit arteries, consisted of a shortening and dampening of the oscillatory diastolic wave. In our own studies, our model-based analysis interpreted diastolic waveform change as indicating a reduction in small but not large artery compliance in patients with type 2 diabetes compared to age- and sex-matched controls.[272] Importantly, no differences were found in peripheral vascular resistance between groups. A reduction in small artery compliance was noted when the patients exhibited one or more complications of the disease, suggesting that the estimate may represent a sensitive marker for early vascular abnormalities occurring in diabetes. Previously, a different approach utilizing arterial transfer functions for the derivation of central aortic waveform characteristics has been employed to provide information on the status of the vasculature in diabetic patients. Lacy et al.[269] found no difference in the augmentation index between patients and control subjects despite increased pulse wave velocity and blood pressure in the diabetic cohort. Although the lack of change in aortic augmentation did not appear to lie with the use of the transfer function, a recent study suggests the use of general transfer functions for derivation of the augmentation index in patients with type 2 diabetes mellitus may be inappropriate.[244]

Heart Failure

Cardiac performance is dependent not only on heart function but also on the interaction of the heart with the systemic vasculature: ventricular-arterial coupling. In many patients with either systolic or diastolic heart failure (particularly older patients), ventricular vascular coupling is abnormal.[270] The failing heart is exquisitely sensitive to arterial loading conditions.[271,272] Although many studies have demonstrated the importance of altering the nonpulsatile left ventricular load (systemic vascular resistance), there is less information on the pulsatile load faced by the failing heart. Determinations of ascending aortic impedance or central pulsatile load using either invasive or noninvasive pressure and flow measurements have shown both reduced[273,274] and normal[275,276] impedance in patients with heart failure. The carotid artery, another central elastic artery, demonstrates impaired compliance in patients with heart failure.[277] Studies of muscular artery mechanical properties under baseline conditions have resulted in conflicting results, with some studies showing abnormalities in patients with heart failure[278,279] and others showing no major differences[273,280,281] between heart failure patients and normal control subjects. Although Ramsey and associates[282] did not find differences in baseline pulse wave velocity or distensibility in patients with idiopathic dilated cardiomyopathy, they demonstrated that changes in arterial elastic properties in response to endothelium-dependent stimuli were blunted. Impairments in arterial elastic properties have been shown to correlate significantly with impaired flow-mediated vasodilation, a measure of endothelial function.[283] Pulse contour analysis studies in heart failure have demonstrated abnormalities of oscillatory but not proximal arterial compliance.[284] Although the mechanisms of abnormal arterial compliance have not been extensively investigated, possible etiologies include increased vessel smooth muscle tone as a result of neurohumoral activation, increased sodium or water content of blood vessels, and structural abnormalities of the vessel wall. Several studies have now demonstrated structural abnormalities in the vessel wall of patients with heart failure including increased carotid artery wall thickness[277] and increased brachial artery wall–to-lumen ratio.[280] Of note, abnormalities in arterial elastic properties occur at early stages of left ventricular dysfunction or heart failure in some animal models,[285,286] and these abnormalities may precede increases in peripheral vascular resistance.[285]

Acute drug administration has been demonstrated to alter pulsatile loading conditions in patients with heart failure. Both nitroprusside[287] and dobutamine[288] can decrease aortic characteristic impedance in patients with heart failure, although the effects of nitroprusside on characteristic impedance are not uniform. There is general agreement, however, that nitroprusside decreases the frequency of the first harmonic of the impedance spectrum, probably as a result of decreased wave reflection.[289,290] Acute angiotensin-converting enzyme inhibition with intravenous enalaprilat substantially increases carotid artery compliance and decreases carotid artery stiffness in patients with idiopathic dilated cardiomyopathy.[291] Chronic angiotensin-converting enzyme inhibition improves radial arterial compliance in patients with heart failure at rest[278] or in response to increased blood flow.[281]

Many studies of drug effects on arterial elastic properties in patients with heart failure have involved systemic administration of drugs. These drugs can have a number of effects, including decreases in blood pressure, changes in autonomic reflexes, and changes in heart rate. It is thus difficult to separate the indirect effects of the drug (e.g., improved compliance due solely to decreased blood pressure) from the direct effects on the arterial wall.

Definitions

A number of different definitions have been used in the literature for the terms describing vascular elastic properties. The following is a summary of these terms and their definitions. Definitions are given using cross-sectional area (A) as the parameter describing vascular dimension; however, blood vessel diameter or volume can be used interchangeably.

Compliance (C): the change in cross-sectional area (ΔA) for a given change in pressure (ΔP). The compliance of an artery can be determined as the slope of a tangent to the pressure-area curve (dA/dP) for that blood vessel.

Distensibility (D): the fractional change in area ($\Delta A/A$) for a given change in intravascular pressure (ΔP). Distensibility, thus, is the quotient of compliance ($\Delta A/\Delta P$) and area (A). This term refers to the relative extensibility of a vessel and serves to facilitate comparison between blood vessels of different sizes.

Wall tension (T): the circumferential force in the vessel wall per unit of vessel length. The relationship between tension and radius *(R)* for a thin-walled vessel is often referred to as the law of Laplace: $T = PR$.

Pulse wave velocity: the distance traveled by a pressure or flow wave divided by the time required to travel that distance. Pulse wave velocity is inversely related to vascular compliance because wave travel is slower along compliant vessels.

Impedance: the total opposition to flow offered by the arterial system.

Input impedance: the ratio of pressure and flow at a given site, which is considered the input to the vascular tree distal to that site.

Characteristic impedance: the ratio of pressure and flow in an artery when pressure and flow waves are not influenced by wave reflection.

Stress (σ): the force per unit area that produces a change in arterial cross-sectional area. Stress is, therefore, wall tension *(T)* divided by wall thickness *(h)* or PR/h.

Strain (ε): the ratio of change in area (ΔA) to the *initial* area *(A)*.

Elastic modulus: the change in stress ($\Delta\sigma$) for a given change in strain ($\Delta\varepsilon$). Because the relationship between stress and strain in an artery is nonlinear, the term *incremental elastic modulus* is used and is defined as the slope of a tangent to the stress-strain curve ($d\sigma/d\varepsilon$). A single incremental elastic modulus cannot be determined for a blood vessel, but rather the value must be reported at a specific distending pressure or cross-sectional area. Unlike compliance, the incremental elastic modulus is an intrinsic characteristic of the vessel wall materials and independent of vessel geometry.

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