Smooth Muscle Relaxation
Effects on Arterial Compliance, Distensibility, Elastic Modulus, and Pulse Wave Velocity

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Abstract—Compliance, distensibility, incremental elastic modulus ($E_{inc}$), and pulse wave velocity are all terms used to describe the mechanical properties of arteries. Previous studies assessing the effects of smooth muscle relaxation on each of these parameters have produced conflicting results. Our laboratory has previously demonstrated that intrabrachial infusion of nitroglycerin in normal human subjects results in a large increase in brachial artery compliance without changing arterial wall stiffness as measured by $E_{inc}$. In the present study, the relationships among compliance, distensibility, $E_{inc}$, and pulse wave velocity under different levels of vascular tone are shown using data acquired by intravascular ultrasound as well as theoretical curves. We demonstrate that the effects of smooth muscle relaxation can be depicted as 2 separate steps: (1) a rightward shift to a new theoretical curve describing the relationship between 2 of the above elastic parameters that is solely due to changes in vessel geometry and (2) a shift along the new curve that is dependent on changes in wall stiffness. (Hypertension. 1998;32:356-359.)

Key Words: arteries ■ compliance ■ elasticity ■ vasodilation ■ muscle, smooth

A number of different terms are used to describe the mechanical properties of arteries. These include compliance, distensibility, incremental elastic modulus ($E_{inc}$), and pulse wave velocity (PWV), among others. The effects of smooth muscle relaxation on these parameters are complicated and controversial. For example, smooth muscle relaxation has been reported to decrease $E_{inc}$, increase $E_{inc}$, increase distensibility, and increase compliance. There are a number of potential explanations for these conflicting results, including isobaric versus isometric analysis of data, different techniques and research conditions, and direct versus indirect (systemic) effects of drugs in the various studies. One additional possible source of difficulty in interpreting the effects of smooth muscle relaxation on arterial mechanical properties relates to the terms used. It is often assumed that a directional change in 1 of these measures of arterial elasticity after an intervention (such as drug therapy) necessarily implies an automatic and predetermined directional change of another. For example, an increase in compliance of an artery after administration of a smooth muscle vasodilator is assumed to result in a decrease in arterial $E_{inc}$ because these terms are inversely related.

We have previously reported that in vivo human brachial artery smooth muscle relaxation with nitroglycerin results in a large (≈50%) increase in arterial compliance without any significant change in $E_{inc}$. In the present study, we determined brachial artery compliance, $E_{inc}$, distensibility, and PWV in normal human subjects in vivo using a recently described intravascular ultrasound technique. We then generated theoretical curves to describe the relationships among these 4 variables at baseline and after smooth muscle relaxation with intra-arterial nitroglycerin. We demonstrate that smooth muscle relaxation can be viewed as 2 separate effects. The first is a rightward shift to a new theoretical curve describing the relationship between the 2 variables that is proportional to the magnitude of the vasodilation and is solely a geometric effect. The second is a shift along the new curve that is dependent only on the change in vessel stiffness.

Methods

Study Population
Brachial artery elastic mechanics were measured in 8 normal human subjects of mean ± SD age 37.5 ± 4.4 years (range, 22 to 51 years). These subjects were without significant medical problems as assessed by history, physical examination, ECG, and routine blood tests. Written informed consent was obtained from all subjects. This study was approved by the Institutional Research Board at the University of Minnesota.

Intravascular Ultrasound
The details of this technique, including reproducibility of the measurements, have been previously described. The brachial artery was imaged using a commercially available intravascular ultrasound (IVUS) system (HP Sonos Intravascular Imaging System, Hewlett Packard Co). Briefly, a 3.5F or 4.0F monorail IVUS catheter with a 30-MHz mechanical rotating transducer (Boston Scientific Corp) was placed through a sheath into the brachial artery. Simultaneous intrabrachial artery pressure and IVUS images were obtained so that arterial pressure, cross-sectional area, and wall thickness could be determined off-line at any point in the cardiac cycle. Transmural pressure was reduced by inflating a pressurized upper arm cuff.
overlying the IVUS catheter and was defined as intra-arterial minus cuff pressure. Bolus infusions of nitroglycerin (100 μg) were administered through a sidearm of the arterial sheath at doses that altered brachial artery smooth muscle tone without producing changes in blood pressure or other systemic effects. This technique allowed the study of brachial artery elastic properties over a wide range of transmural pressure and smooth muscle tone. Brachial artery images were captured and analyzed using a Macintosh Hci personal computer, framegrabber (Data Translations-QuickCapture), and the NIH Image program.

Arterial Elastic Parameters
Compliance at any given pressure was calculated as the tangent or first derivative of the pressure-luminal area curve (dA/dP). Distensibility was defined as the compliance at a given pressure divided by a reference area. Wall stress was calculated using Laplace’s Law as transmural pressure multiplied by midwall radius divided by wall thickness (h). Strain was calculated as radius at a given pressure divided by effective unstressed radius (vessel radius at 0 mm Hg transmural pressure). E_{inc} was defined as 0.75 multiplied by the tangent or first derivative of the stress-strain curve. PWV was calculated according to the Moens-Koertewig equation\(^1\), where \(\rho\) is blood density and \(\pi\) is vessel inner radius. Pressure-area and stress-strain data were fit to an arc tangent equation, with all individual curves resulting in \(r\) values of 0.96 or greater.

Theoretical Curves
Brachial artery compliance, distensibility, \(E_{inc}\), and PWV were measured or calculated over a wide pressure range (between 0 and 100 mm Hg transmural pressure). In the present study, only the data acquired at a mean transmural pressure of 95 mm Hg were used. Theoretical curves describing the relationship between compliance and \(E_{inc}\) under different levels of smooth muscle tone were generated as follows. The mean pressure-area relationship of the brachial artery in the 8 normal subjects was assumed to be linear between 90 and 100 mm Hg, and wall cross-sectional area was assumed to be constant. Actual compliance and \(E_{inc}\) were first measured at transmural pressures of 90 and 100 mm Hg under baseline conditions. The theoretical relationship between compliance and \(E_{inc}\) at a mean pressure of 95 mm Hg was then calculated for any value of inner radius at 100 mm Hg (i.e., any hypothetical change in vessel size in response to this 10-mm Hg pressure increment). By substituting a wide range of values of inner radius at 100 mm Hg for the actual measured values and calculating the new compliance and \(E_{inc}\) for each value, we determined the theoretical baseline compliance-\(E_{inc}\) relationship for this vessel at a mean pressure of 95 mm Hg. Theoretical curves demonstrating the relationships among the other variables under baseline conditions were made using the same approach.

Intra-arterial nitroglycerin resulted in an \(~10\%\) increase in brachial artery radius. The above process was used to generate the theoretical curves describing the relationships among the variables under this new condition. Finally, curves were generated assuming a 20% increase in brachial artery radius after vasodilator administration.

Statistics
Effects of nitroglycerin on arterial elastic parameters were analyzed using paired \(t\) tests. Statistical significance was accepted at \(P<0.05\). Data are presented as mean±SEM.

Results
Measured compliance and \(E_{inc}\) at 95 mm Hg were \(0.010±0.001\) mm\(^3\)/mm Hg and \(38±6\times10^6\) dyne/cm\(^2\) for baseline and \(0.015±0.001\) mm\(^3\)/mm Hg and \(37±6\times10^6\) dyne/cm\(^2\) for nitroglycerin conditions. These points are plotted in Figure 1. Nitroglycerin resulted in a significant increase in brachial artery radius of 10% \((P<0.001)\) and compliance of 50% \((P<0.05)\) without change in \(E_{inc}\). The relationship between compliance and \(E_{inc}\) at 95 mm Hg is shown by the theoretical curves that run through the measured data points under baseline and 10% dilation conditions. An additional theoretical curve is also shown assuming 20% increase in radius after vasodilator administration. As one would expect, under conditions of constant smooth muscle tone, there is an inverse relationship between \(E_{inc}\) and compliance that is curvilinear and has the \(x\) and \(y\) axes as asymptotes. Smooth muscle relaxation produces an upward and rightward shift of the \(E_{inc}\)-compliance curve, with the magnitude of the shift directly proportional to the magnitude of the vasodilation. The vasodilated vessel is more compliant than the vasoconstricted vessel at the same \(E_{inc}\). The vasodilated vessel also has a higher \(E_{inc}\) at the same compliance.

Measured distensibility at 95 mm Hg did not significantly change with nitroglycerin (5.05±0.86 versus 5.80±0.55 \(10^{-6}\)mm Hg) but PWV significantly decreased \((P<0.05)\) from 15.1±1.1 to 13.2±0.7 m/s at 95 mm Hg. Figure 2 shows curves of compliance versus 1/distensibility and compliance versus PWV under baseline, 10% dilation, and 20% dilation conditions. As in the \(E_{inc}\)-compliance curves, the measured data points are marked on the theoretical curves. Figure 3 shows measured data points and theoretical curves for other combinations of the 4 parameters assessed in this study. Of note, \(E_{inc}\)-distensibility curves and compliance-PWV curves under each of the 3 levels of smooth muscle tone are almost superimposable. In contrast, all other curves show a dose-dependent rightward shift with smooth muscle relaxation.

Discussion
The present study demonstrates that brachial artery vasodilation with nitroglycerin in normal human subjects results in a significant increase in compliance and decrease in PWV without producing any significant changes in arterial \(E_{inc}\) or distensibility. By use of measured data and theoretical curves, the relationships among these 4 variables are depicted. These
curves emphasize that smooth muscle relaxation results in changes in vessel stiffness and geometry. The net effect of smooth muscle relaxation depends on the balance of these stiffness and geometric effects. Measuring a change in a given mechanical parameter after smooth muscle relaxation does not necessarily allow one to infer the direction or magnitude of a change in a different parameter.

The terms compliance, PWV, E_{inc}, and distensibility are all used to describe mechanical properties of arteries. At a given vessel geometry (radius and wall thickness), it is clear that compliance, for example, is directly related to distensibility and indirectly related to E_{inc} and PWV. However, once vessel geometry is changed by vasodilation, the relationships among these variables change. Because the arterial wall is essentially incompressible,\textsuperscript{12,13} wall cross-sectional area is a constant, and thus wall thickness can be calculated for any change in vessel radius. Figure 1 shows the relationship between compliance and E_{inc} at a mean pressure of 95 mm Hg under 3 conditions: baseline, 10% vasodilation, and 20% vasodilation. Ratios of radius to wall thickness under the 3 conditions are 10.0, 12.0, and 15.1, respectively. Smooth muscle relaxation results in 2 separate effects. The first is a rightward shift to a new compliance versus E_{inc} curve. This new curve describes the relationship between compliance and E_{inc} under the new ratio of radius to wall thickness and is due solely to a change in vessel geometry. The second effect is a shift along the new compliance versus E_{inc} curve. This shift is solely a result of the effect of the vasodilator drug on arterial stiffness and is independent of geometry.

The magnitude of the rightward shift of the new compliance-E_{inc} curve is directly related to the magnitude of the vasodilation. The shift along the new compliance-E_{inc} curve is a result of a number of different factors that occur as a result of smooth muscle relaxation and that have an impact on arterial stiffness. Smooth muscle relaxation decreases arterial stiffness by reducing tension generated by the smooth muscle itself. In addition, tension generated by the connective tissue elements in series with the smooth muscle is reduced. On the other hand, smooth muscle relaxation increases arterial stiffness by “engaging” stiff collagen fibers that have previously been slack\textsuperscript{14} and by tensing elastin fibers, both of which are in parallel with the smooth muscle in the arterial wall.

Figure 4 shows a close-up of the compliance-E_{inc} curves at baseline and after a 20% increase in brachial artery radius. Following smooth muscle relaxation, a number of different possible effects can occur. A shift to any point in quadrant 1 (point A) results in an increase in E_{inc} and a decrease in compliance. A shift to any point in quadrant 3 (point C) results in a decrease in E_{inc} and an increase in compliance. However, a shift to any point in quadrant 2 (point B) results in an increase in both E_{inc} and compliance.

In this last situation, the vessel has become more compliant yet stiffer. Although this at first appears to be a mistake, it is not. The geometric advantage gained by the vessel during vasodilation “outweighs” the increase in stiffness that occurs, and the net result is an increase in compliance. Compliance, like PWV, is a term that is dependent on both vessel geometry and stiffness. In contrast, distensibility and E_{inc} are terms that describe the stiffness of the vessel wall and are independent of geometry. If one measures a parameter that incorporates geometry and stiffness (compliance or PWV) before and after vasodilation, then the effect of vasodilation on the other parameter can be predicted. If one measures a stiffness parameter (E_{inc} or distensibility) before and after vasodilation, then the effect of vasodilation on the other stiffness parameter can be predicted. This is shown in Figures 2 and 3, where compliance-PWV and E_{inc}-distensibility curves are nearly superimposable regardless of the magnitude of the vasodilation. In contrast, one cannot predict the directional effect of

Figure 2. Theoretical curves of compliance versus 1/distensibility and compliance vs pulse wave velocity (PWV) at 95 mm Hg transmural pressure under different levels of vascular tone. Vasodilation results in a rightward shift of the compliance-1/distensibility curves but not of the compliance-PWV curves.

Figure 3. Theoretical curves depicting the relationships among incremental elastic modulus (E_{inc}), pulse wave velocity (PWV), and distensibility at 95 mm Hg transmural pressure under different levels of vascular tone. Vasodilation produces a rightward shift of the curves in the first 2 graphs but not in the third.
vasodilation on Einc or distensibility by measuring compliance or PWV.

Measured data and theoretical curves shown in this study depict relationships among the variables at 95 mm Hg transmural pressure only. However, curves can be generated for isobaric smooth muscle relaxation at any pressure, and they will show similar effects. Curves can also be generated to depict the relationships among the variables that follow smooth muscle contraction. Smooth muscle contraction will simply result in a leftward shift of the curves shown that is proportional to the magnitude of the vasoconstriction. Shifts along the new curve will be dependent on alterations in vascular stiffness.

In summary, we demonstrate that intra-arterial nitroglycerin directly increases brachial artery compliance and decreases PWV without altering arterial Einc or distensibility in normal human subjects. Compliance increases and PWV decreases due to vasodilation and geometric effects, not as a result of changes in arterial wall stiffness. The separate effects on geometry and stiffness can be visualized by plotting theoretical curves that describe the relationships among the variables in compliance, distensibility, Einc, and PWV under different conditions of smooth muscle tone. An increase in arterial compliance or a decrease in PWV with smooth muscle relaxation can potentially occur in concert with an increase, a decrease, or no change in vessel wall stiffness.

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References
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