Assessment of endothelial function of large, medium, and small vessels: a unified myograph

Xiao Lu¹ and Ghassan S. Kassab¹,²,³,⁴

Departments of ¹Biomedical Engineering, ²Cellular and Integrative Physiology, and ³Surgery and ⁴Indiana Center for Vascular Biology and Medicine, Indiana University Purdue University Indianapolis, Indianapolis, Indiana

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Lu X, Kassab GS. Assessment of endothelial function of large, medium, and small vessels: a unified myograph. Am J Physiol Heart Circ Physiol 300: H94–H100, 2011. First published November 12, 2010; doi:10.1152/ajpheart.00708.2010.—Endothelial dysfunction precedes the development of morphological atherosclerotic changes and can also contribute to lesion development in cardiovascular diseases. Currently, there is a lack of a single method to determine endothelial function of the entire range of vessel dimensions from aorta to arterioles. Here we assessed endothelial function of a large range of size arteries using a unified isovolumic myograph method. The method maintains a constant volume of fluid in the lumen of the vessel during contraction and relaxation, which are characterized by an increase and a decrease of pressure, respectively. Segments of six aortas, six common femoral arteries, and six mesenteric arteries from rats; six carotid arteries from mice; and six coronary and carotid arteries from pigs were used. The endothelium-dependent dose-response vasorelaxation was determined with endothelium-dependent vasodilators while arterial preconstriction was induced with vasoconstrictors at a submaximal dose. The circumferential midtension during vasoreactivity varied from 43.1 ± 7.9 to 2.59 ± 0.46 mN/mm (from large to small arteries), whereas the circumferential midstress showed a much smaller variation from 217 ± 23.5 to 123 ± 15.3 kPa (in the same range of vessels). We also found that overinflation and axial overelongation compromised endothelium-dependent vasorelaxation to underscore the significance of vessel preload. In conclusion, an isovolumic myograph was used to unify arterial vasoreactivity from large to small arteries and shows the uniformity of wall stress and %tension throughout the range of vessel sizes.

Address for reprint requests and other correspondence: G. S. Kassab, Dept. of Biomedical Engineering, Indiana Univ. Purdue Univ. Indianapolis, Indianapolis, IN, 46202 (e-mail: gkassab@iupui.edu).

VASCULAR ENDOTHELIAL DYSFUNCTION is widely considered to be a consequence, a biomarker, and a mediator of the adverse effects of cardiovascular risk factors (2, 4, 5, 11, 15, 18, 21). Endothelial dysfunction precedes the development of morphological atherosclerotic changes and can also contribute to lesion development and later clinical complications (15, 23, 24). Endothelial dysfunction has also been shown to be a predictor of adverse outcomes in patients with coronary artery disease (10, 11, 20). Although endothelial dysfunction may be indicated by several biomarkers such as the expression of endothelial nitric oxide (NO) synthase, the expression of cyclooxygenase, and the production of nitric oxide or prostacyclin, the vasodilation of blood vessel in response to endothelium-dependent agonists is the gold standard. The wire and pressure myographs have been used extensively to study the vasoreactivity and pharmacology of large and small vessels, respectively (7–9, 12–16, 19, 26). The applicability of wire myograph is in vessels with a diameter range from large vessels (aorta) down to about 500 µm. The attachment of vessel rings to hooks, however, causes endothelial injury and leads to a nonphysiological geometry and loading (7, 8). The pressure myograph, on the other hand, employs a vessel segment that can be pressurized and hence preserves the geometry of the vessel under physiological loading. Unlike the high sensitivity of the wire myograph, which records tension under isometric conditions, the pressure myograph records diameter changes under isobaric conditions. The diameter changes are quite large in small muscular artery (arteriole) but relatively small in elastic arteries such as aorta. Hence, the pressure myograph is primarily used for small vessels that have substantial vasoreactivity. Furthermore, it is uncertain whether the %relaxation in small artery, which is computed from geometry (pressure myograph), is equivalent to the %relaxation in larger artery, which is computed from force (wire myograph). There is currently no unified myograph that applies to small as well as large vessels under equivalent conditions using the same metric.

We have recently introduced a modification of the pressure myograph, called the isovolumic myograph, to study endothelial function in ex vivo vascular segments. This approach retains the sensitivity to contractile force of a wire myograph while providing a physiological geometry and loading similar to a pressure myograph (16). Here we show that the method can be used to assess endothelial function for the diameter range of arteries from 300 µm up to over 5 mm. We also show that the %change of pressure may be a good surrogate for the %relaxation to quantify endothelial function. Finally, we show that the physiological loading (circumferential and axial) significantly affects endothelial function, and hence the preservation of physiological geometry and loading conditions are essential for a functional endothelial assay.

MATERIALS AND METHODS

The animal experiments were performed in accordance with the guidelines of the Institute of Laboratory Animal Research Guide, Public Health Service Policy, and Animal Welfare Act and were approved by the Indiana University School of Medicine Institutional Animal Care and Use Committee.

Animals and tissue preparation. Wistar male rats were obtained at 3 mo of age (Charles River). Six aortas, six femoral arteries, and six mesenteric arteries were harvested from 18 rats. The animals were acclimated to the facility for approximately 1 wk before the start of the study. On the day of termination, the animal was first anesthetized with pentobarbital sodium (80 mg/kg ip) and euthanized by an overdose of anesthesia with pentobarbital sodium (300 mg/kg ip). Either aorta, common femoral artery, or mesenteric artery were marked with water-resistant ink on their surface, and the distances between two given markers were measured. The arteries were excised...
quickly and placed in ice-cold physiological saline solution (PSS) containing (in mmol/l) 119 NaCl, 4.7 KCl, 25 NaHCO3, 1.17 KH2PO4, 1.17 MgSO4, 1.6 CaCl, and 5.5 dextrose, gassed by 95% O2-5% CO2. The distances between the same two markers were measured again, and the ratio of in vivo and ex vivo length was determined as the stretch ratio that was used to stretch the artery to in vivo length in the isovolumic myograph. Six carotid and right coronary arteries were harvested from pigs, and six carotid arteries were harvested from mice. Each artery was carefully cleaned from adjacent tissue with the aid of a stereo-dissection microscope. The branches on the artery were ligated, and the artery was allowed to warm up to room temperature (22°C) slowly in 10–15 min. The artery was transferred to the chamber of isovolumic system and cannulated with connectors and secured with 8-0 suture twice to avoid any leakage. The artery was warmed up to 37°C slowly (20–25 min) and equilibrated for 40 min at a transmural pressure of 15 mmHg before agonist and antagonist stimulation.

**Isovolumic myograph.** The isovolumic system consisted of a chamber with two connectors that bridge the blood vessel and rigid tubes. One tube was connected to a 50-ml flask with PSS, and the flask was pressurized with a regulator to inflate the vessel at the desired pressure. Another tube was connected to a solid-state pressure transducer (SPR-524, Microtip catheter transducer, Millar) to monitor the transmural pressure and a volume compensator to compensate for water transport across the vessel wall. The outlet of the tube was blocked to achieve isovolumic conditions. The PSS aerated with mixed gas (22% O2-5% CO2-73% N2) filled the chamber and tubes before vessel cannulation. A CCD camera on a microscope transferred the image of the vessel to a computer that digitized the external diameter of the vessel. Since the outlet was closed off, there was no flow in the vessel and the vessel was merely pressurized. To achieve isovolumic state, a clamp placed on the tube between the pressurized flask and the connector was closed and the PSS in the lumen of the vessel and tubes was sealed, i.e., constant volume. The vascular contraction or relaxation during chemical stimulation was characterized by significant changes of intraluminal pressure.

**Volume compensation due to fluid filtration.** Although a fairly constant volume of the solution can be achieved in the lumen of the vessel, it is not strictly constant since the PSS may be transported across the vessel wall (water flux) driven by the transmural pressure. Although the rate of water flux is very small (<1 nl/min) and no visible reduction of diameter is seen during the duration of the experiment (<1 h), a pressure drop (drop in baseline pressure) is still measurable (0.6 to 3 mmHg/min). To stabilize the baseline pressure, a volume compensator was connected in parallel with the pressure transducer. The volume compensator comprises a gastight connector, a microsyringe (maximum volume, 25 μl), a microsyringe pump (UltraMicroPump III, World Precision Instruments), and a microsyringe pump controller (Micro 4, World Precision Instruments). The criteria for the compensatory rate of the microsyringe pump controller was to maintain the transmural pressure at the desired baseline value (variation < ±0.2 mmHg/min). There was no measurable change of vessel diameter during compensation. If the leak rate was > 1 μl/min, the specimen was discarded as the vessel wall was damaged.

**Tension, stress, and %relaxation.** The circumferential tension and stress were computed based on the following:

\[ T = \sigma \times r_{\text{int}} \]

\[ \sigma = \frac{P \times r_{\text{int}}}{h} \]

\[ r_{\text{int}} = \sqrt{\frac{2 \times \sigma}{15}} \]

where \( T \) is the circumferential tension and \( P \) is the intraluminal pressure measured by a pressure transducer. \( r_{\text{int}} \) is the internal radius of the blood vessel computed by the incompressibility assumption (Eq. 1C) from the external radius, which is measured by the diameter tracking system. \( \sigma \) is the circumferential stress and \( h \) is wall thickness, both of which are computed. \( A \) is the cross-sectional wall area of the vessel at a no-load state (zero intraluminal pressure), which is measured from the images of arterial cross-sectional view. Finally, \( \lambda \) is the axial stretch ratio that is determined by the measurement of the in vivo and ex vivo length between the two markers.

A dose-response vasocostriction and vasodilation in response to vasoconstrictors and vasodilators were carried out under isovolumic conditions. Phenylephrine and acetylcholine (ACh) are the vasoconstrictor and vasodilator of the arteries except for coronary artery, respectively. ACh is vasconstrictor and bradykinin is vasodilator of coronary artery, respectively. Briefly, the artery was stimulated to contract with vasoconstrictor from 10⁻¹⁰ to 10⁻⁵ mol/l to determine the maximal dose at maximal contraction. The artery was then rinsed and equilibrated for 30 min. The artery was contracted with a submaximal dose of vasoconstrictors and relaxed with vasodilators by a series of doses: 10⁻¹⁰ to 10⁻⁵ mol/l in the PSS. The relaxation results in the reductions of intraluminal pressure and circumferential tensions, which was computed using Eq. 1. The calculation of percent relaxation (%R) was based on intraluminal pressure (%Rp), tension (%Rτ), and stress (%Rσ) for comparison:

\[ \% R_p = \frac{(P_d - P_i)}{(P_{\text{max}} - P_i)} \times 100 \]  \hspace{1cm} (2A)

\[ \% R_\tau = \frac{(T_d - T_i)}{(T_{\text{max}} - T_i)} \times 100 \]  \hspace{1cm} (2B)

\[ \% R_\sigma = \frac{(\sigma_d - \sigma_i)}{(\sigma_{\text{max}} - \sigma_i)} \times 100 \]  \hspace{1cm} (2C)

where \( P_d \), \( P_i \), and \( P_{\text{max}} \) are the intraluminal pressures at each dose (Pa), inflation pressure (Pi), and maximum pressure (Pmax) at 0 mol/l of ACh, respectively. \( T_d \), \( T_i \), and \( T_{\text{max}} \) (\( \sigma_{\text{max}} \)) are the circumferential tension (or stress) at every dose (\( \sigma_d \) or \( \sigma_i \)).

**Table 1. Outer diameter, wall thickness, midtension, and midstress of various arterial segments at physiological pressure**

<table>
<thead>
<tr>
<th>Segment</th>
<th>Outer diameter, mm</th>
<th>Wall thickness, mm</th>
<th>Midtension, mN/mm</th>
<th>Midstress, kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>E Carotid artery of pig</td>
<td>5.2 ± 0.50</td>
<td>0.22 ± 0.041</td>
<td>43.1 ± 7.9</td>
<td>202 ± 36.1</td>
</tr>
<tr>
<td>M Coroay artery of pig</td>
<td>3.1 ± 0.24</td>
<td>0.17 ± 0.028</td>
<td>25.1 ± 3.7</td>
<td>148 ± 15.7</td>
</tr>
<tr>
<td>M Aorta of rat</td>
<td>3.9 ± 0.24</td>
<td>0.12 ± 0.023</td>
<td>28.9 ± 3.6</td>
<td>217 ± 23.5</td>
</tr>
<tr>
<td>M Femoral artery of rat</td>
<td>1.03 ± 0.062</td>
<td>0.059 ± 0.005</td>
<td>7.72 ± 0.93</td>
<td>130 ± 13.9</td>
</tr>
<tr>
<td>E Carotid artery of mouse</td>
<td>0.89 ± 0.079</td>
<td>0.042 ± 0.005</td>
<td>7.75 ± 0.81</td>
<td>185 ± 20.3</td>
</tr>
<tr>
<td>M Mesenteric artery of rat</td>
<td>0.31 ± 0.026</td>
<td>0.021 ± 0.003</td>
<td>2.59 ± 0.46</td>
<td>123 ± 15.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. E, elastic artery; M, muscular artery.
Effects of overstretch on endothelial function of femoral artery. The loading perturbation was superimposed on the femoral artery of rats. Briefly, after the test of endothelium-dependent relaxation, the femoral artery was incubated in fresh PSS for 90 min to restore endothelial function. The femoral artery was then exposed to mechanical perturbation with either axial overelongation (stretch ratio of 1.3 to 1.53, 18% increase) or overinflation (pressure of 90 to 162, 80% increase). The stretch ratio of 1.3 was the length ratio of in vivo to ex vivo since the excised vessel shrinks approximate 30%. In axial overstretch, the vessel was stretched to a ratio of 1.53 and inflated to a physiological pressure of 90 mmHg. The vasoreactivity was performed according to the above protocol. In overinflation, the vessel was inflated to 162 mmHg and stretched to a physiological stretch ratio of 1.3. Sodium nitroprusside (SNP)-induced vasorelaxation was applied to evaluate the endothelium-independent vasorelaxation.

Data analysis and statistics. The relation of the %R between circumferential tension (%RT) and transmural pressure (%Rp) measurements were expressed by %Rp = α%RT + β. Similarly, the relation of the %R between circumferential tension (%RT) and stress (%Rσ) measurements were expressed by %Rσ = χ%RT + δ, where α, β, χ, and δ are empirical constants that were respectively determined with a linear least squares fit and a corresponding correlation coefficient R^2. In a Bland-Altman scatter diagram (1), we plotted the ratio differences between the two measurements (%RT - %Rp)/%RT against their means (%R0 + %Rσ)/2 and (%RT - %Rσ)/%RT against (%R0 + %Rσ)/2. In the scatter diagram, the precision and bias of the method were quantified. Any significant differences between two groups were determined by a Student’s t-test. Significant differences between the dose-dependent groups were determined by use of analysis of variance between groups. A probability of P < 0.05 was considered to be indicative of a statistically significant difference.

RESULTS

The isovolumic myograph was used to determine vascular reactivity of various diameter vessels in a standardized manner throughout the range of vessels (Table 1), as opposed to the wire and pressure myographs that would invoke different methodologies for the various vessels (Fig. 1). Since the vessel wall is permeable to water, intraluminal pressure results in a water flux across the vessel wall (filtration), which causes a gradual drop of baseline pressure in the isovolumic myograph. A microsyringe was used to compensate for the filtration to maintain a constant baseline pressure. Figure 2 shows the changes in intraluminal pressure determined with the isovolumic condition in a femoral artery segment with volume compensation at 38 nl/min to offset the fluid filtration. When a vessel was distended to a higher pressure, a higher compensatory rate was needed to maintain a uniform baseline pressure. A thinner-walled vessel requires a higher compensatory rate because of the increase in filtration. The typical vasoreactivity tracing curves of aorta, femoral artery, and mesenteric artery of rats are shown in Fig. 3. At physiological pressures of aorta, femoral artery, and mesenteric artery, respectively, the contraction generated from vascular smooth muscle in the three types of arteries caused an increase in intraluminal pressure of 30 to 40 mmHg in response to phenylephrine at 10^{-5} mol/l. The dose-response vasorelaxations to ACh were clearly observed by the stepwise reduction in intraluminal pressure (Fig. 3).

A large vascular reactive circumferential tension was expected in large diameter of arteries (Fig. 4A) since tension is proportional to vessel diameter. Since intraluminal pressures of large arteries were similar to small arteries during vascular reactivity, the variation of over 10-fold was observed in the circumferential tension from large to small arteries (Fig. 4A, and Table 1). The circumferential stress, which is tension...
normalized by wall thickness, showed a much smaller variation in the same range of vessels (Fig. 4B, and Table 1). Furthermore, the changes of stress during dose-response vascular relaxation were similar in all arteries (Fig. 4B). The %relaxations of the stress of the arteries are shown in Fig. 4C, which appears similar to vascular relaxation curves. The %relaxations of the tension and intraluminal pressure were approximately identical to that of the stress (data not shown).

Since the diameter does not change significantly under isovolumic conditions, we verified that %changes in pressure were nearly equivalent to %changes in tension. Figure 5A shows a comparison of %relaxation based on tension and pressure relative to an identity line. A linear least squares fit shows a highly significant correlation with $R^2 = 0.99$. A Bland-Altman plot is shown in Fig. 5B (average of two measurements vs. difference), and the data are seen to scatter randomly within 2SD of the mean of the difference. The root mean square is 20.9% of the mean value of the two methods. This analysis shows that pressure is an appropriate surrogate of tension in the calculation of %R and simplifies the measurements and analysis of vasorelaxation. We also analyzed the %change between tension and stress. A linear relationship between %R$_T$ and %R$_T$ is shown in Fig. 5C ($R^2 = 0.97$). A Bland-Altman plot is shown in Fig. 5D. The root mean square is 11.7% of the mean value of two representations of tension and stress.

In Fig. 6, we determined the effect of loading perturbation on endothelial-dependent vasodilation in both circumferential
overinflation and overelongation caused an immediate decrease of endothelium-dependent vasorelaxation. The latter findings underscore the significance of physiological loading on the assessment of endothelial function as ensured in the isovolumic myograph.

The compensation of filtration of blood vessel in the isovolumic myograph is a significant improvement, which stabilizes the baseline of pressure (Fig. 2). The transluminal pressure, vessel wall thickness, and surface area of the blood vessel can significantly affect the filtration rate. Vascular tone may also affect filtration. Tarbell and colleagues (14) demonstrated that vascular tone is proportional to filtration in arterioles since the filtration induces shear stress on arteriolar smooth muscle which contributes to myogenic tone. Although there is no data on the relation between vascular tone and filtration in conduit arteries, it is reasonable to anticipate that vascular filtration may be affected by tone. A constant compensatory rate is set up by maintaining constant pressure before the administration of vasoconstrictor/vasodilator. Since transmural pressure, wall thickness, surface area, and tone may be altered during vascular reactivity induced by agonist/antagonist, we expect this change to be very small, particularly for larger vessels. This is supported by the fact that the baseline pressure is maintained throughout the study. If there was a net filtration, the baseline pressure would change since we do not change the compensatory injection rate. It is likely that transmural pressure during vasoreactivity tends to increase the filtration, whereas the increase in wall thickness and decrease in surface area during vasoreactivity tends to decrease it. The opposing factors likely minimize the changes in the filtration rate relative to the baseline on the time scale of contraction in myography. Under a physiological tone of much larger time scales, this issue clearly remains unclear. In practice, the pressure returned to the baseline (~ ± 6%) after the vessel was exposed to a cycle of maximal contraction and relaxation. If this did not occur, the vessel was excluded from analysis as there was damage of vascular tissue or leakage due to unseen branches.

An interesting observation is that the circumferential stress varied relatively little from large to small arteries (Fig. 4B) compared with the large (an order of magnitude) change of circumferential tension (Fig. 4A, and Table 1). The stress reflects the vascular relaxation in unit-wall thickness as it normalizes the tension. Since the results showed that circumferential stresses are relatively similar in various arteries (Fig. 4B), it implies that a single vascular smooth muscle layer has a similar vasoreactive property. Hence, the vascular reactivity can be standardized and is comparable from large to small arteries. An additional interesting observation was that the circumferential stresses in either elastic arteries (aorta and carotid artery) or muscular arteries (coronary, femoral, and mesenteric arteries) were relatively similar (Fig. 4B) and the stresses in elastic arteries were larger than those in muscular arteries despite the order of magnitude difference in the diameter of either elastic or muscular arteries (Table 1), respectively. Given the significant structural differences between elastic and muscular arteries, this implies that the vascular structure may contribute to vascular reactivity.

In an analysis of passive biomechanical properties, Wolinsky and Glagov (28) found that the average circumferential tension per lamellar unit of an aortic media is fairly constant. This holds over a large variation in aortic diameter ranging

**DISCUSSION**

We experimentally validated that the isovolumic myograph has equal sensitivity in a wide range of arteries, which provides a unified assay for a functional biomarker of endothelial function in response to agonists (Fig. 1). This approach provides a consistent standardized testing protocol for all vessels sizes and allows for comparisons of different vessels with either circumferential tension or stress. We also showed that
from mouse (~1 mm) to pig (~20 mm) since the total number of medial lamellar units is proportional to the aortic diameter; i.e., there are more lamellar in thicker-walled vessels (28). The present study extends this principle in various arteries under contraction.

In a wire myograph, a vessel ring is loaded by hooks to make the loading uniaxial and planar in the circumferential direction while the axial tension is zero. The loading direction in a wire myograph is approximately at the maximal contractile direction of vascular smooth muscle, which mimics the contractile studies in striated muscle. The endothelium-dependent vasorelaxation in a wire myograph is computed as the %ratio of dose-response tension to maximal contractile tension. In contrast to the tension in a wire myograph, the vessel diameter is the measurement variable in the pressure myograph (19). The endothelium-dependent vasorelaxation in the pressure myograph is computed as the %ratio of the dose-response changes of diameter to the maximal change of diameter from contraction to dilation. The contractile tension of a muscle depends on the number of activated actin-myosin filaments, whereas the contractile dimension depends on the movement between actin and myosin fiber. Based on Hill’s equation (tension-velocity relation), the relation between tension and diameter is highly nonlinear during contraction (16). Although the %relaxations from wire myograph (tension measurement) and pressure myograph (diameter measurement) are dimensionless, they are inherently not comparable.

The present myograph expresses %relaxation in terms of tension or pressure (if the diameter is constant). This is not unlike the wire myograph, albeit under the physiological conditions of a pressure myograph. The major advance here is that both small and large vessels can be quantified in the same way based on the same definition of %relaxation, which is currently not possible with pressure and wire myographs. The %relaxation index normalizes the differences among samples and therefore has an advantage in reducing statistical variability. On the other hand, %relaxation does not reflect some of the information in the original measurements (dimension and/or tension). This is true for all myographs.

In order for a vascular assay to garner utility, it must be simple and easy to use. Accordingly, we addressed the question, Can pressure replace tension to eliminate the need for microscope and only require a pressure transducer? The answer is positive since Fig. 5B shows a 20.9% root mean square error between the two measures with no systemic bias. Hence, the pressure can be used interchangeably with tension, which simplifies future experiments and allows the testing of multiple parallel vessels. The change of pressure will provide a higher throughput for vascular assessment compared with the need to track diameter in the pressure myograph.

There is no doubt that physical loading influences the reactivity of blood vessel and the response of the endothelium (7, 8). Ideally, the loading and geometry of vessel segment should mimic physiological conditions. The importance of maintaining the blood vessel at physiological load is that the wall tension of an artery may influence vasoreactivity in two ways: vascular smooth muscle and endothelial cells. The alteration of wall tension may activate or inactivate the contraction of vascular smooth muscle and the signal pathways of endothelial cells mediated by mechanotransductions such as integrins and G protein-coupled receptors (9, 17, 25, 26). It has been suggested that the change in distension or stretch affects vascular reactivity (3, 6, 22, 27). In the present study, we extended the pressure and stretch to a pathological range (e.g., hypertensive pressures or stretches) and verified that the effect on the vasorelaxation of blood vessel is substantial (Fig. 6). The vessel segment in the wire myograph is tension-free axially compared with an in vivo vessel that is stretched axially with the extent of which can vary in hypertension, aging, and vessel disease. Our method provides direct evidence that either acute axial overelongation or intraluminal overinflation causes immediate endothelial dysfunction mediated by a decrease in NO (Fig. 6).

The evaluation of ex vivo vasoreactivity of blood vessels, including wire, pressure, and present isovolumic myographs, provide a well-controlled and detailed method to understand the physiopathological, pharmacological, and active biomechanical properties of blood vessels. The limitations of these ex vivo systems, however, should be noted. The cross talk between endothelium and blood flow and between adventitia and adjacent tissue are disturbed under ex vivo conditions. Furthermore, various growth factors, hormones, inflammatory and neural transmitters, mechanical interactions, etc., are difficult to mimic in an ex vivo preparation. The measurements in various myographs reflect the general function of the endothelium and vascular smooth muscle. The ex vivo data, however, cannot reflect the precise state of in vivo endothelial and vascular smooth muscle cells. These limitations warrant consideration in the interpretation of the data.

In summary, we tested the vasoreactivity of aorta and carotid, femoral, and mesenteric arteries in mice, rats, and pigs using an isovolumic myograph method under physiological geometry and loading. The isovolumic myograph has equivalent sensitivities in various arteries and provides an approach to unify the measurement of all size of arteries under the same conditions. We anticipate this approach to have significant utility in investigations of endothelial function in various disease models, as well as to assess the possible therapeutics at the early stage of drug discovery.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

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