

Nitric oxide modulates the interaction of pressure-induced wall mechanics and myogenic response of rat intramural coronary arterioles

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Interactions between the biomechanical characteristics and pressure-induced active response of coronary microvessels are still not well known. We tested the hypothesis that pressure-dependent biomechanical characteristics of the coronary vascular wall are modulated by the active myogenic response and local vasodilators. We have utilized data obtained previously in isolated rat intramural coronary arterioles (~100 μm in diameter), in which the diameter was investigated as a function of intraluminal pressure (Szekeres et al.: *J. Cardiovasc. Pharmacol.*, 43, 242–249, 2004). To characterize the magnitude of myogenic response, diameter was expressed as percent of passive diameter as a function of pressure (normalized diameter; ND). In addition, circumferential wall stress (WS) and incremental distensibility (ID) were calculated. In control conditions, after an initial increase between 0–30 mm Hg, ND decreased substantially as pressure increased from 30 to 150 mm Hg. Correspondingly, WS gradually increased as a function of pressure (from 0.3 ± 0.03 to 34.7 ± 4.4 kPa) exhibiting a plateau phase between 40–80 mm Hg. In contrast, ID decreased and reached negative values (min: $-104.9 \pm 21.9 \cdot 10^{-6} \text{ m}^2/\text{N}$ at 50 mm Hg). Inhibition of nitric oxide (NO) synthase by L-NNA decreased basal diameter (~35% at 2 mm Hg), eliminated pressure-induced changes in ND, reduced the slope of pressure-WS curve, and decreased ID at lower pressures. Simultaneous administration of L-NNA and adenosine (which restored initial diameter, i.e. length of smooth muscle) restored – in part – the pressure-induced reduction in ND, reversed the pressure-induced behavior of WS to control, but not that of ID. These results not only confirm that in coronary arterioles wall stress is regulated by the myogenic response, but also suggest that there is interplay between the mechanical behavior of the wall and the myogenic response. Furthermore, the presence of NO seems to be necessary for maintaining a higher distensibility of intramural coronary arterioles allowing increases in diameter to lower pressures, which then activate the myogenic mechanism resulting in constrictions and full development of myogenic tone, as indicated by the presence of negative slope of pressure-diameter curve in the presence of NO.

Keywords: intramural coronary arterioles, rats, isolated vessels, myogenic tone, myogenic response, vascular biomechanics, elasticity, nitric oxide, adenosine

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Coronary arterial vessels represent a significant portion of hemodynamic resistance of the cardiac circulation, thus they are a target for various control mechanisms of coronary perfusion. Their passive and active characteristics can greatly influence the function of myocardium both in normal and in pathophysiological conditions (7, 22, 34, 43). Previous studies described the pressure independent biomechanical properties of rat intramural coronary resistance arteries of different diameter (33, 43). It was shown that passive and active biomechanical characteristics of the vessel wall determine its vasomotor functions (14). The present work aims to elucidate the pressure dependent biomechanical properties of intramural coronary arterioles known to be activating the myogenic mechanism, because less is known regarding the modulation of the biomechanical characteristics of the vessel wall by the myogenic and endothelial mechanisms.

Characterization of wall stress, distensibility and elastic behavior of the vessel wall are important, but only few systematic biomechanical measurements are available in isolated, resistance sized coronary vessels (3, 11, 26, 36, 43). These properties of vessels depend on the network location, vascular diameter, intraluminal pressure and contractile state of the smooth muscle, all of which may change in pathological conditions, such as hypertension and atherosclerosis (3, 5, 16, 42, 43).

The myogenic mechanism is usually well expressed in small arteries and arterioles, and it has an important role in the local regulation of blood flow (4, 17, 30, 41). By eliciting active dilation and constriction of blood vessels in response to a decrease or increase in intravascular pressure, respectively, the strength and characteristics of the myogenic response vary substantially among different species and vascular beds (4, 7, 9, 13, 15, 17, 21, 22, 28, 37, 41, 45). It has been established that small coronary arteries and arterioles exhibit substantial myogenic responses both in animals (4, 12, 21–23, 37, 45) and in humans (28).

While myogenic responses are generated exclusively by vascular smooth muscle (22, 41), the tone generated by this mechanism can be modulated by factors released from the endothelium (10, 12, 13) and of other tissues. Among others, nitric oxide (NO) has been shown to have a significant effect on coronary blood flow (6, 18), which could be – at least in part – due to modulation of the myogenic mechanism of coronary arterioles (45).

The biomechanical characteristics of coronary arterial vessels may play an important role in the regulation of vascular diameter. Indeed, the effect of NO synthase inhibition has been examined on the elastic properties of the right interventricular coronary arteries (36) and on the distensibility of intramural coronary arterioles of rats (45). In the present study, we have hypothesized that modulation of biomechanical characteristics of isolated intramural coronary arterioles by nitric oxide is necessary for the full development of the myogenic response.

Methods

Isolation of rat coronary arterioles

Twelve-week-old male Wistar rats (weighing 360–400 grams) were anesthetized with pentobarbital sodium (Nembutal sodium, CEVA 50 mg/kg, intraperitoneally). The investigation conforms to the Guide for the Care and Use of Laboratory Animals (USNIH publication No. 85–23, revised 1996). The chest was quickly opened; the heart was removed and placed into cold, oxygenized, modified Krebs solution. Intramural coronary arterioles (~100 μm in diameter) branching from the left anterior descending coronary artery were isolated (32). The superficial layer of cardiac muscle was removed by blunt dissection following the left anterior descending artery from the aortic orifice to the apex. Once the appropriate segment was found, the muscle fibers surrounding the vessels were carefully removed with a microforceps and fine-tip needles (25G). Side branches were carefully identified (down to ~10 μm in diameter) cleaned and tied with individual filaments teased from a 2-0 suture thread, as previously described (32, 41, 43). Then the arteriolar segment was removed and placed in a vessel chamber filled with modified Krebs solution, which contained in mM, 110 NaCl, 5 KCl, 2.5 CaCl_2 , 1 MgSO_4 , 1 KH_2PO_4 , 24 NaHCO_3 and 10 glucose. The vessel was cannulated at both ends with glass microcannulas and extended to its in vivo length (~1 mm). Clotted blood was washed out at low perfusion pressure, and then one of the cannulas was closed. Utilizing a pressure-servo syringe reservoir system (Living Systems, Burlington, VT) arterioles were pressurized in a no-flow condition. Vessels were checked for leaks by the stability of the inlet pressure when the servo function was turned off. Vessels with observable leaks were discarded. The temperature of the chamber was maintained at 37 °C, bubbled with 21% O_2 and 5% CO_2 balanced with N_2 , the pH was kept at 7.4. A continuous superfusion was applied at a rate of 15 ml/min. The inner diameter of arterioles was measured with a calibrated image-sharing monitor (Instrumentation for Physiology and Medicine, San Diego, CA). Perfusion pressure was measured with a Gould pressure transducer, calibrated with a mercury manometer. Data were recorded on a chart recorder (Omega Engineering Inc., Stamford, CT).

Experimental protocols

Arterioles were allowed to equilibrate for ~1 hour at 60 mm Hg intraluminal pressure in the modified Krebs solution. Then pressure was decreased to 2 mm Hg and then increased to 10 mm Hg, then up to 150 mm Hg in 10 mm Hg pressure steps. The steady-state diameter at each step was measured (after ~4 min). N^ω -nitro-L-arginine (L-NNA, 10^{-5}M), an inhibitor of nitric oxide synthase and adenosine (ADO, 5×10^{-5} – $5 \times 10^{-4}\text{M}$) were administered at 60 mm Hg continuous intraluminal pressure into the superfusion fluid. The vessels were incubated with the drugs for 20–30 min. In this protocol, after the control pressure-diameter relationship was obtained, the pressure steps were repeated in the presence of L-NNA and then again in the simultaneous presence of L-NNA and ADO. The concentration of ADO was adjusted to allow the

segment to reach its control diameter at 60 mm Hg. Passive diameter (PD) was obtained in Ca^{2+} -free Krebs solution containing 10^{-4}M sodium nitroprusside and 1.0 mM ethylene glycol-bis(b-aminoethyl ether)-N,N,N',N'-tetraacetic acid. The vessels were incubated for 20 minutes in this solution, then step increases in perfusion pressure were repeated as above, and the passive diameter of arterioles at each pressure step was defined.

Salts and chemicals were obtained from Sigma Chemical (St. Louis, MO). Drugs were freshly prepared on the day of the experiment in Krebs solution.

Calculations of biomechanical parameters

Changes in diameter in response to intraluminal pressure were normalized to the corresponding passive diameter and expressed as percent values. In addition, circumferential (tangential) wall stress and incremental distensibility were calculated (26, 43). Circumferential wall stress (WS) was computed according to the Laplace equation: $\sigma_{\theta} = P \cdot r_i / h$, where σ_{θ} is the circumferential wall stress, P is the intraluminal pressure, r_i is the inner radius and h is the wall thickness ($h = r_0 - r_i$). Incremental distensibility $D_{\text{inc}} = \Delta V / V \Delta P$, where D_{inc} is the incremental distensibility, ΔV is the change in vessel lumen volume in relation to the initial volume of V in response to pressure change of ΔP .

Data are presented as means $\pm$ SEM. Statistical significance was calculated with repeated measures ANOVA followed by Tukey's post hoc test. A level of $P < 0.05$ was considered statistically significant. A curve fitting method was applied using Microsoft Excell Software.

Results

Step increases in intraluminal pressure (in the range of 2 to 150 mm Hg) substantially reduced the normalized diameter of rat intramural coronary arterioles. Figure 1 shows that normalized diameter coronary vessels increased in the range of low pressures, whereas higher intraluminal pressures (from 30 to 150 mm Hg) elicited active constrictions, which became maximal at 90 mm Hg. At 60 mm Hg, the active diameter of arterioles was $66.2 \pm 4.4\%$ of their passive diameter $182.2 \pm 7.1 \mu\text{m}$. Administration of the nitric oxide synthase inhibitor L-NNA significantly reduced the initial diameter of arterioles at 60 mm Hg by $\sim 35\%$ compared to control and eliminated both the dilations and constrictions in response to changes in pressure. Additional adenosine (5×10^{-5} to $5 \times 10^{-4}\text{M}$) administration in the presence of L-NNA restored the initial diameter (at 2 mm Hg) present in control conditions, but the dilations in response to lower pressures were absent and the magnitude of constrictions to higher pressures, were greatly reduced as compared to the control. Values of slopes were -0.46 ± 0.05 , -0.08 ± 0.09 , -0.16 ± 0.07 in control, in the L-NNA and in L-NNA+ADO groups, respectively ($p < 0.01$ between control and L-NNA, control and L-NNA+ADO groups, Fig. 1, insert).

The circumferential wall stress of rat intramural coronary arterioles increased monotonically as a function of pressure in passive conditions (Fig. 2, top panel).

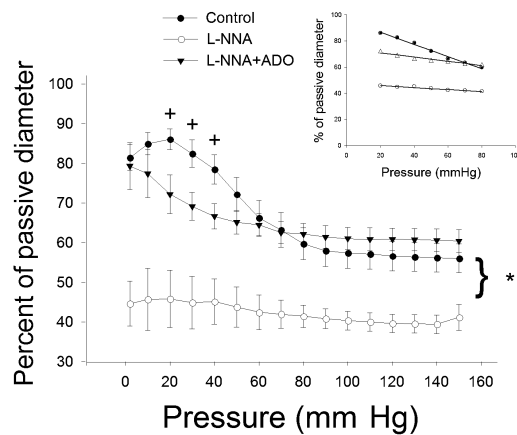


Fig. 1. Steady-state arteriolar diameter of rat intramural coronary arterioles expressed as percent values of passive diameter as a function of intraluminal pressure ($n=10$), in control condition, in the presence of N^G -nitro-L-arginine (L-NNA) and in the simultaneous presence of L-NNA and adenosine (ADO). Mean $\pm$ SEM values. Asterisk and cross indicate statistical significance ($p<0.05$) between control and L-NNA and between control and L-NNA+ADO, respectively. Insert: regression lines of pressure-normalized diameter curves between 20–80 mm Hg in control, in L-NNA and L-NNA + ADO groups were as follows: $y = -0.46x + 95.75$, $R^2 = 0.99$; $y = -0.08x + 47.46$, $R^2 = 0.95$; $y = -0.16x + 74.12$, $R^2 = 0.94$, respectively

In the presence of Ca^{2+} in the superfusion solution wall stress was greatly reduced and a plateau developed between 40 to 100 mmHg pressure. Interestingly, wall stress was significantly less in the presence of L-NNA compared to control (Fig. 2, middle panel, $p<0.05$ above 40 mm Hg). Additional application of ADO restored the initial diameter at 2 mm Hg to control and pressure-wall stress curve approached the characteristics of control curve, but without the presence of a plateau phase. The differences in the shape of curves can be seen in Figure 2, bottom panel. Values of slopes were 0.12 ± 0.04 , 0.11 ± 0.02 , 0.23 ± 0.03 in control, in the L-NNA and in L-NNA+ADO groups, respectively ($p<0.05$ between control and L-NNA+ADO, L-NNA and L-NNA+ADO groups).

In control condition, the incremental distensibility of coronary arterioles was high at low pressures and rapidly decreased with increasing pressure (Fig. 3, upper panel). Values between 2–20 mm Hg were significantly different from zero in the positive direction, whereas the negative values of incremental distensibility became significantly different from zero in the range of 40–80 mm Hg, and the minimum value was $-104.9 \pm 21.9 \cdot 10^{-6} \text{ m}^2/\text{N}$ at 50 mm Hg. The distensibility curve obtained in passive conditions continuously decreased as a function of pressure and remained in the positive range. Administration of L-NNA significantly reduced the initial high value of incremental distensibility (at 2 mm Hg) and the portion of pressure-distensibility curve between 30–70 mm Hg shifted to the positive range. At 50 mm Hg the difference between control and L-NNA, control and L-NNA+ADO values became significant.

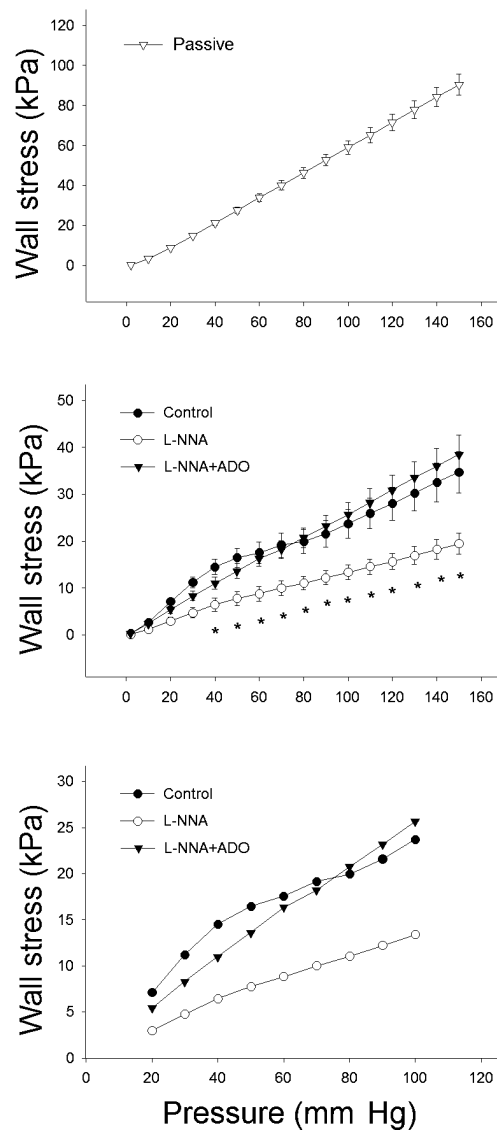


Fig. 2. Average circumferential wall stress of rat intramural coronary arterioles as a function of intraluminal pressure (n=10) in passive condition with Ca^{2+} -free solution (top panel), in control condition, in the presence of N^{G} -nitro-L-arginine (L-NNA) and in the simultaneous presence of L-NNA and adenosine (ADO, middle panel). Mean $\pm$ SEM values. Asterisk indicates statistical significance ($p < 0.05$) between control and L-NNA treatments. Mean values of wall stress between 20–100 mm Hg (bottom panel). The regression lines (not shown) of pressure-wall stress curves between 50–80 mm Hg were as follows: in control, L-NNA and L-NNA+ADO groups, respectively: $y = 0.12x + 10.45$, $R^2 = 0.98$, $y = 0.11x + 2.19$, $R^2 = 0.99$, $y = 0.23x + 2.05$, $R^2 = 0.99$

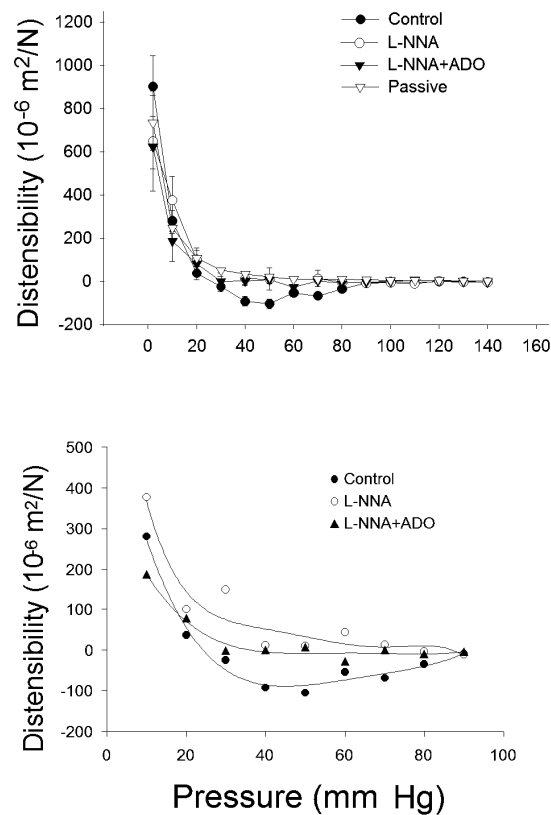


Fig. 3. Incremental distensibility of rat intramural coronary arterioles as a function of intraluminal pressure ($n=10$) in control condition, in the presence of N^G -nitro-L-arginine (L-NNA), in the simultaneous presence of L-NNA and adenosine (ADO) or in passive condition with Ca^{2+} -free solution. Mean $\pm$ SEM values (top panel). Lower panel: curve fitting method was applied on control and L-NNA vs. pressure curves. Curve fitting equations were as follows: in control: $y = 5E-05x^4 - 0.0119x^3 + 1.1672x^2 - 49.246x + 661.83$, $R^2 = 0.98$, in L-NNA: $y = -2E-06x^5 + 0.0006x^4 - 0.0629x^3 + 3.2661x^2 - 84.489x + 942.9$, $R^2 = 0.9$, in L-NNA+ADO: $y = 3E-05x^4 - 0.0072x^3 + 0.6675x^2 - 27.189x + 400.37$, $R^2 = 0.97$. Values of control curve were significantly different from zero in the range of 40–80 mm Hg intraluminal pressure

Although, additional ADO after L-NNA, restored the initial control diameter at low pressures, the initial high level of incremental distensibility was not restored. In addition, in the presence of L-NNA+ADO incremental distensibility did not reach negative values. Figure 3 lower panel shows that there is a significant upward shift in the pressure-distensibility curve in the presence of L-NNA, which is not reversed by the administration of ADO.

Discussion

The findings of the present study demonstrate that biomechanical characteristics of intramural coronary arterioles changes as a function of intraluminal pressure. In passive condition, circumferential wall stress increased as pressure increased, a response, which was greatly reduced in the active condition (Ca^{2+} is present) and further reduced significantly by the presence of NO synthase inhibition. Wall distensibility reached negative values in active conditions, whereas in the absence of NO the negative values were not observed. The above findings confirm that an increase in wall stress has a significant role in initiating an active myogenic constrictor response, which in turn reduces wall stress. Whereas, the novel finding of the present study is that in the absence of NO the development of pressure-induced changes in the diameter of rat intramural coronary arterioles are greatly diminished as indicated by the absence of negative slope of pressure-diameter curve. Moreover, in the absence of NO the distensibility is reduced at low pressure reducing thereby the pressure-induced increase in wall stress, the stimulus of the myogenic mechanism.

Biomechanics of coronary arteriolar wall

Passive and active biomechanical characteristics of the vessel wall, such as wall stress, distensibility and elasticity are importantly determine the capability of vessels to change in their diameter in various conditions (29, 31, 43), and thus regulate blood flow and tissue perfusion. Alteration of the biomechanical characteristics of the vessel wall in certain physiological and pathological conditions can greatly affect the function of vessels. Biomechanical characteristics of large arteries isolated from animals and humans have been previously described (8, 29, 31). Yet, investigation of wall biomechanics of arterioles and small arteries of various tissues (1, 3, 11, 24, 36, 43, 46), such as coronary resistance arteries and arterioles (11, 26, 36, 43) are still relatively scarce in the literature.

Previously it has been shown that in mechanically preconditioned conditions (with repeated pressure-cycles), when the pressure sensitivity of vessels is diminished, the biomechanical characteristics of coronary arterial wall depend primarily upon the diameter of the vessel and contractile state of smooth muscle (36, 43). In the present study, the vessels were not mechanically preconditioned in order to keep the myogenic mechanism active.

Wall biomechanics in the presence of myogenic response

Intramural coronary arterioles isolated from rat heart exhibited a substantial myogenic response, as also described previously (45). Similar myogenic responses have been described in isolated, cannulated microvessels from several vascular beds (4, 9, 12, 13, 21, 37, 41). In the present study, changes in normalized diameter of vessels show that stepwise increases of intraluminal pressure – after a substantial initial dilations at low pressures – elicited constriction between 30–100 mm Hg, and the maximum tone

developed at 60 mm Hg pressure (~70%). This tone was maintained up to 150 mm Hg intraluminal pressure. The range of maximum myogenic responsiveness (the portion of the curve with the steepest slope) was between 40–70 mm Hg, as also indicated by the negative values of incremental distensibility (Figs 1 and 3).

The characteristics of intraluminal pressure-circumferential wall stress curve (Fig. 2) reveal that in passive condition wall stress of intramural coronary arterioles increased linearly with increasing pressure. In the presence of Ca^{2+} there was a significant reduction in the slope of pressure-wall stress curve. Moreover, a plateau phase could be observed between 30–70 mm Hg, that is, despite the increase in pressure wall stress remains relatively constant, which was due to the active myogenic constriction. These findings suggest that myogenic response regulates wall stress.

Modulation of biomechanical characteristics of coronary arteriole by nitric oxide

Although, the myogenic mechanism is initiated in the vascular smooth muscle, endothelial factors, such as nitric oxide have been suggested to play a role in the modulation of vascular tone (6, 18). Previous studies in isolated coronary resistance arteries and arterioles showed an enhanced coronary vascular tone in the absence of nitric oxide (36, 44, 45, 47). The present study however indicates, that NO is an important factor in modulating the biomechanical characteristics of intramural coronary arteries. Inhibition of NO synthesis induced a substantial decrease in diameter, wall stress and distensibility at 2 mm Hg (Figs 1–3). Furthermore, in the absence of NO both the initial dilation to low pressure steps and the active constriction in response to higher pressure steps were absent. These suggest that the initial dilation is a prerequisite of the following active myogenic constriction. Smooth muscle cells could be sensitive to the extent or to the rate of the change in length initiated by passive forces (30, 35). We have found that inhibition of NO synthesis reduced the diameter of coronary vessels at low pressures, which likely by increasing wall thickness, reduced the circumferential wall stress (Figs 1 and 2), which in turn inactivated smooth muscle cells. Thus, in the absence of NO, the initial value of wall stress is reduced, and the whole curve is shifted downward. Thus, reduction of the stimulus, i.e. wall stress is likely to be responsible for the absence of vigorous myogenic constriction. In addition, in the absence of NO the circumferential active shortening of smooth muscle is close to the theoretical limit for contraction of smooth muscle providing further explanation for the lack of pressure sensitive constriction.

In active condition, the incremental distensibility of intramural coronary arterioles gradually decreased as pressure increased and showed negative values in control condition, indicating that an active myogenic response is initiated by increases in wall stress. Similarly, previous findings showed that the distensibility of coronary arteries decreases with increasing pressure (26, 43). However, the characteristics of intraluminal pressure – wall stress curve (Fig. 2) reveal that in the presence of L-NNA, increases in wall stress during the first steps of pressure rises are not sufficient to activate stretch-induced constriction. The pressure-incremental distensibility curve (Fig. 3) revealed that in the presence of L-NNA, the initial high distensibility is reduced and it is not restored

by the simultaneous administration of the vasodilator adenosine. This may be responsible for the loss of the negative portion of the curve, which corresponds to the active myogenic constriction. Thus, it seems that NO has a specific effect to maintain an appropriate distensibility of the arteriolar wall leading to dilation and forthcoming active myogenic constriction.

Other investigators found, that an NO donor agent decreased the stiffness of coronary arteries (36). Because distensibility decreased in the absence of NO at low pressures, NO seems to limit the pressure-induced stretch of coronary arteriolar wall. NO may affect the distensibility of vascular smooth muscle by modulating Ca^{2+} -related mechanisms (19, 27). Collectively these findings suggest that absence of NO, by decreasing distensibility, limits the pressure-induced adjustments of coronary vascular tone.

Clinical relevance

Biomechanical characteristics of vessel wall may have important clinical relevance (26). Several clinical studies showed that biomechanical characteristics of vessels, such as vascular compliance, capacitance, distensibility and elastic modulus determined in vivo by ultrasound techniques can have a great insight in revealing arterial functions and helping to diagnose various arterial diseases (2, 5, 20, 25, 38–40, 42). Moreover, adjustments of the biomechanical properties of artificial graft and host segments in coronary bypass surgery recently moved in the focus of research (3) indicating their clinical importance.

In conclusion, we found that the biomechanical characteristics of rat intramural coronary arterioles changes substantially as a function of intraluminal pressure. Nitric oxide seems to be important, not only as a vasodilator, but as also an agent, which is able to maintain an appropriate distensibility of coronary arterioles, allowing the full development of active myogenic tone. Thus, we propose that NO plays an important role in modulating the biomechanical characteristics of coronary arterioles, in part by maintaining proper vascular elasticity and distensibility. Further studies are needed to reveal the molecular mechanism responsible for the specific role of NO in the modulation of biomechanical properties of coronary arterioles.

Acknowledgments

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