Abstract—We hypothesized that during hypertension, the impairment of mediation of shear stress–induced dilation by nitric oxide (NO) is due to the prevailing hemodynamic forces, and that mediation of this response by NO should still be present in young spontaneously hypertensive rats (SHR). Thus, responses to increases in perfusate flow eliciting increases in wall shear stress were investigated in pressurized (80 mm Hg), isolated arterioles (≈70 to 100 μm) of the left or right gracilis muscle obtained from the same WKY and SHR at 4 and 12 weeks of age. Flow-induced dilations were similar in WKY and SHR at 4 weeks (maximum, 26.5 ± 1.8 and 24.2 ± 2.0 μm, respectively). Also, the middle of the upward portion of the shear stress–diameter curves was similar in arterioles of the 2 strains. Inhibition of NO synthase with Nω-nitro-L-arginine (L-NNA) or inhibition of synthesis of prostaglandins (PGs) with indomethacin elicited an ≈50% reduction in flow-dependent dilation, whereas their combined administration eliminated the responses in both groups. In arterioles of 12-week-old WKY, flow-induced dilation became significantly greater (maximum, 46.1 ± 2.3 μm) than responses of arterioles of 4-week-old WKY and 12-week-old SHR (maximum, 18.3 ± 5.9 μm), which shifted only the shear stress–diameter curve of the 12-week-old WKY significantly to the left. Also, at 12 weeks of age, flow-dependent dilation of arterioles from SHR is mediated solely by PGs. Thus, shear stress–induced arteriolar dilation is mediated by NO and PGs in 4-week-old WKY and SHR. With aging, the release of NO and PGs increases in normotensive rats, whereas the contribution of NO to the regulation of shear stress disappears in 12-week-old SHR, which suggests that this change is probably caused by the increase in intraluminal pressure as hypertension develops. (Hypertension. 1999;34:1073-1079.)

Key Words: arterioles ▪ dilation ▪ nitric oxide ▪ prostaglandin ▪ age ▪ rats, inbred SHR ▪ wall shear stress

Arterial endothelium plays an important role in the regulation of skeletal muscle microcirculation via the production and release of dilator factors such as nitric oxide (NO) and prostaglandins. In vivo and in vitro studies have shown that one of the most important physiological stimuli for the release of NO and prostaglandins is the presence and change in wall shear stress.1–3 Regulation of wall shear stress contributes to the minimization of energy loss in the circulation by adjusting vascular resistance;4 thus, it is important to long-term regulation of blood pressure. Previous morphological studies suggest that alteration in flow during normal or pathological development can greatly influence the diameter and growth of vessels.4,5 Furthermore, shear stress–induced dilation elicited by an increase in intraluminal flow is reduced in isolated skeletal muscle arterioles of spontaneously hypertensive rats (SHR) by the age of 12 weeks.6–8 This alteration is likely to contribute further to the increased peripheral vascular resistance. Studies also have shown that the reason for the reduced response is an impairment of NO-mediated portion of the response, whereas the mediation by prostaglandins is retained.7 These and other findings9,10 suggest that elevated blood pressure is deleterious to the endothelium. Furthermore, recent findings have suggested that acute hypertension in the coronary circulation results in impairment of endothelium11 and that acute elevation of intraluminal pressure in isolated arterioles of normotensive rats elicits an impairment of responses mediated by NO.12

On the basis of these findings, we hypothesized that at an early age when the systemic blood pressure is still not significantly higher than normal, flow-induced dilation in skeletal muscle arterioles of normotensive and hypertensive rats should be present, similar, and mediated by both NO and prostaglandins. Furthermore, it is likely that, with aging and as hypertension develops, the increase in intraluminal pressure or other factors will affect the synthesis and release of endothelial factors that mediate shear stress–induced dilation. These questions have not been studied before. To understand the development of the regulation of wall shear stress under normotensive and hypertensive conditions, it is important to assess the role of genetic and environmental factors.
To test our hypothesis, we characterized, in isolated arterioles of gracilis muscle of normotensive Wistar-Kyoto rats (WKY) and SHR, the magnitude and the mediation of flow-induced response at a prehypertensive age (4 weeks old) and contrasted these responses with those in vessels isolated from the same WKY and SHR at 12 weeks of age, when the systemic blood pressure is significantly higher in SHR compared with WKY.

Methods
In the present study, male normotensive WKY \((n=16)\), and SHR \((n=13)\) (Charles River Laboratories, Mass) were used. The procedures followed were in agreement with institutional guidelines. Systolic blood pressure was measured by the tail-cuff method. Rats were anesthetized with intraperitoneal injections of sodium pentobarbital (Nembutal sodium, 50 mg/kg). Experiments were conducted on arterioles isolated from gracilis muscle (left and right) of the same rats at 4 and 12 weeks of age \((\sim 70 \text{ and } 100 \mu\text{m} \text{ in diameter})\), respectively. The isolation procedure of gracilis muscle arterioles has been described previously.\(^6\) Briefly, when rats were 4 weeks old, the left gracilis muscle of each rat was exposed by an incision of the skin. A selected portion of the gracilis muscle was then cut out and placed on a Petri dish containing cold \(4^\circ\text{C}\) physiological salt solution \((\text{PSS}1; \text{pH } 7.4)\), which was composed of \((\text{in mmol/L})\) 145 NaCl, 5.0 KCl, 2.0 CaCl\(_2\), 1.0 MgSO\(_4\), 1.0 NaH\(_2\)PO\(_4\), 5.0 dextrose, 2.0 pyruvate, 0.02 EDTA, and 3.0 MOPS. The piece of muscle was pinned to the silicone bottom of the dish and allowed to equilibrate for \(\sim 15\) minutes. Rats were treated with an antibiotic (ampicillin 6 mg/kg IM, BID for 3 days; Pfizer Animal Health) and an analgesic (Buprenex 0.3 mg/kg IM, BID for 3 days; Reckitt and Colman Pharmaceuticals Inc). The skin was closed with sterile suture, and rats were allowed to recover from anesthesia. At 12 weeks of age, arterioles either from the right gracilis muscle of the same rats or from another group of rats were used.

With the use of microsurgical instruments and an operating microscope (Olympus, a \(1 \text{-mm}\)-segment) of a first-order arteriole was isolated from the gracilis muscle and surrounding tissue and transferred to the vessel chamber. The vessel chamber contained a pair of glass micropipettes filled with physiological salt solution \((\text{PSS}2)\) at room temperature. The PSS2 solution used for suffusion and perfusion of the vessels contained \((\text{in mmol/L})\) 110 NaCl, 5.0 KCl, 2.5 CaCl\(_2\), 1.0 MgSO\(_4\), \(24.0 \text{NaHCO}_3\), 5.0 dextrose, 2.0 pyruvate, 0.02 EDTA, and 3.0 MOPS. The piece of muscle was connected with silicone tubing to a pressure-servo syringe system (Omega) that was calibrated by a Harvard perfusion pump in the range of 0 to 100 \(\mu\text{L/min}\). Each flow step was maintained for \(\sim 5\) minutes to allow the vessels to reach a steady-state condition before the diameter of the arterioles was measured. After control flow-diameter curves were obtained, we subjected the vessels to \(N^\circ\text{-nitro-L-arginine (L-NNA; }10^{-4} \text{ mol/L})\), an inhibitor of NO synthesis.\(^2\) Then, after an \(\sim 15\)-minute incubation period, changes in diameter in response to step increases in perfusate flow were reassessed. The role of prostaglandins in flow-induced dilation of gracilis muscle arterioles was also assessed. To inhibit the synthesis of prostaglandins, indomethacin \((\text{INDO}; 10^{-4} \text{ mol/L})\) was added to the PSS2 containing L-NNA. After the incubation period \((\sim 30\) minutes\), the flow-diameter relationships were once more assessed. In separate experiments, INDO was given before the administration of L-NNA to exclude the effect of possible interaction between NO and cyclooxygenase.

All drugs were added to the reservoir connected to the vessel chamber, and final concentrations are reported. To assess the active tone generated by the arterioles in response to intravascular pressure, at the conclusion of each experiment, the suffusion solution was changed to a Ca\(^{2+}\)-free PSS2 that contained sodium nitroprusside \((10^{-4} \text{ mol/L})\) and EGTA \((1.0 \text{ mmol/L})\). Vessels were incubated for 10 minutes, and then the passive diameter of arterioles at 80 mm Hg perfusion pressure was obtained.

All salts and chemicals were obtained from Sigma Chemical Co or Aldrich Co and were prepared on the day of the experiment. The diameter of vessels, under various experimental conditions, were measured with an image-sherwing monitor \((\text{IPM}, \text{model} 907)\) and recorded with an X-Y recorder \((\text{Multicorder, MC6625})\). The wall shear stress was calculated according to the following equation: \(\tau = Q \eta / A\), where \(Q\) is perfusate flow, \(\eta\) is viscosity of the perfusate \((\sim 0.007 \text{ poise at } 37^\circ\text{C})\), and \(r\) is vessel radius. Data are presented as mean\(\pm\)SEM; \(n\) indicates number of rats. Statistical analyses were done by ANOVA followed by the Tukey post hoc test or regression analysis as appropriate. A value of \(P < 0.05\) was considered significant.

Results
The systolic blood pressures of 4-week-old normotensive WKY and SHR were 122.8\(\pm\)3.3 and 121.5\(\pm\)4.7 mm Hg \((n=8)\), respectively, whereas at 12 weeks of age, they were 133.3\(\pm\)2.3 and 193.5\(\pm\)8.1 mm Hg \((n=8)\), respectively, which shows a significant increase in blood pressure in 12-week-old SHR.

Flow-Dependent Dilation of Arterioles From 4-Week-Old Rats
The active diameters of arterioles of 4-week-old WKY and SHR, obtained in the presence of constant intravascular pressure \((80 \text{ mm Hg})\) and under static flow conditions, were significantly different \((74.0\pm2.8\) and 63.4\(\pm2.2 \mu\text{m}, \text{respectively;}\) \(P<0.01\)). After conclusion of the experiments and under the same conditions but in Ca\(^{2+}\)-free solution, the passive diameter of each arteriole was also obtained (see Methods). We found that the mean passive diameters of 4-week-old WKY and SHR were also significantly different \((148.8\pm4.2\) and 122.7\(\pm2.4 \mu\text{m}, \text{respectively;}\) \(P<0.05\)), but the arteriolar tone, expressed as the percentage of passive diameter, was not different in the 2 strains of rats \((49.8\pm1.3\) and 51.7\(\pm1.5\)%).

Figure 1, top, shows the changes in the diameter of arterioles from 4-week-old WKY and SHR in response to step increases in flow in control conditions. From 2 \(\mu\text{L/min}\) perfusate flow, the diameter of arterioles from 4-week-old WKY and SHR increased significantly. The increase in diameter at 14 \(\mu\text{L/min}\) flow was similar in arterioles of...
4-week-old WKY and SHR. Also, no significant difference existed in the slope of flow-diameter curves, which indicates that arterioles of WKY and SHR exhibit similar dilations to increases in perfusate flow.

Figure 1, bottom, shows the changes in the diameter of arterioles from 4-week-old WKY and SHR in response to step increases in wall shear stress in control conditions. From 5 dyne/cm² of shear stress, the diameter of arterioles from 4-week-old WKY and SHR increased substantially, which delayed the increase in shear stress as flow increased. The middle portion of the shear stress–diameter curves and also the slopes of these curves were similar in arterioles of 4-week-old WKY and SHR.

Next, we investigated the endothelial mechanisms responsible for the mediation of flow-induced dilation of arterioles of WKY and SHR at 4 weeks of age. INDO, a blocker of prostaglandin synthesis, did not affect basal diameter (48.8±2.0 to 46.7±3.6 and 50.7±2.6 to 49.1±1.3 μm) but significantly reduced the dilation to increases in perfusate flow in arterioles of both strains of rats (Figure 2, top and bottom). In 4-week-old WKY, the reduction of the maximum response was ≈62%, whereas in 4-week-old SHR, it was ≈45% (at maximal flow rate).

L-NNA, a NO synthase inhibitor, similarly and significantly reduced basal diameter of arterioles from the 2 strains of 4-week-old rats (48.8±2.5 to 42.8±2.5 and 54.0±2.6 to 46.5±3.6 μm in WKY and SHR, respectively; P<0.05). In addition, in 4-week-old WKY and SHR, L-NNA significantly reduced flow-induced arteriolar dilation (Figure 2, top and bottom). For example, at 14 μL/min flow, the diameter of L-NNA–treated arterioles of 4-week-old WKY and SHR was ≈44% and ≈46% less than that of control, respectively. Also, the slopes of flow-diameter curves were significantly different between control and in the presence of L-NNA. In the presence of L-NNA, administration of INDO elicited a further significant reduction of flow-induced responses and practically eliminated the dilation to increases in perfusate flow in both 4-week-old WKY and SHR (Figure 2). Figure 3 summarizes the effects of INDO and L-NNA on the calculated wall shear stress–diameter curves of these arterioles. The inhibitors had similar effects on responses of arterioles, and as a result, the maintained shear stress shifted to the right in both 4-week-old WKY and SHR (Figure 3). In the presence of both L-NNA and INDO, shear stress did not induce arteriolar dilation either in WKY or SHR (Figure 3); thus, shear stress increased to a high level (≈250 dyne/cm²).
Flow-Dependent Dilation of Arterioles From 12-Week-Old Rats

In the presence of 80-mm Hg perfusion pressure (no flow), the active diameter of arterioles from WKY and SHR was 97.0±4.0 and 109.0±5.7 μm, respectively, whereas the passive diameter of arterioles from WKY and SHR was 177.4±7.5 and 185.9±6.7 μm, respectively. The arteriolar tone expressed as the percentage of passive diameter was not different in the two 12-week-old strains of rats (54.2±1.2% and 58.6±2.4%, respectively).

Figure 4, top, shows the changes in the diameter of arterioles of 12-week-old WKY and SHR in response to step increases in flow in control conditions. From 5 μL/min perfusate flow, the diameter of arterioles of 12-week-old SHR started to deviate significantly (P<0.05) from that of 12-week-old WKY, and at 25 μL/min flow, the change in diameter of 12-week-old SHR arterioles was ≈60% less than that of 12-week-old WKY. Also, the significant difference in the slope of flow–change in diameter curves indicates that in arterioles of 12-week-old SHR, the dilation to increases in perfusate flow is markedly reduced compared with the arterioles of 12-week-old WKY. Similarly, the shear stress–diameter curves (Figure 4, bottom) clearly show that the maintained shear stress is significantly lower in arterioles of 12-week-old WKY.

In arterioles of 12-week-old WKY and SHR (data from our previous study6 indicated by dotted line), INDO did not affect basal tone (55.1±1.6% versus 59±2.4% and 52.5±2.8% versus 52.9±3%, respectively) but significantly reduced the dilation to increases in perfusate flow in arterioles of both strains of rats (Figure 5, top and bottom). In 12-week-old WKY, the reduction of the maximum response was ≈53% (Figure 5, top), whereas in SHR (Figure 5, bottom), INDO eliminated the dilation.6 In 12-week-old WKY, L-NNA significantly reduced basal tone (54.8±1.1% versus 48.7±2.8%) and flow-induced arteriolar dilation (Figure 5, top). For example, at 25 μL/min flow, the change in diameter of L-NNA–treated arterioles of 12-week-old WKY was ≈42% less than that of control. Also, the slopes of flow–diameter curves were significantly different between control and in the presence of L-NNA. In contrast, in arterioles of 12-week-old SHR, L-NNA did not significantly affect basal tone (48.8±4.4% versus 45.8±4.2%) or the arteriolar dilation in response to step increases in perfusate flow (Figure 5, bottom; data from our previous study are given for comparison6). In the presence of L-NNA, administration of INDO eliminated the dilation to increases in perfusate flow in both strains of rats (Figure 5).

In Figure 6, the wall shear stress–change in diameter curves in arterioles of 4- and 12-week-old WKY and SHR are depicted to compare the changes in sensitivity of arterioles to wall shear stress as a function of age. In arterioles of WKY, the upward portion (maintained shear stress) of shear stress–diameter curves shifts to the left significantly from 4 to 12 weeks of age (Figure 6, top). In contrast, in arterioles of 4- and 12-week-old SHR, the shear stress–diameter curves are not different (Figure 6, bottom).
Discussion

The new findings of this study of isolated gracilis muscle arterioles are (1) that shear stress–induced dilations elicited by increases in perfusate flow are similar and are mediated by both NO and prostaglandins in young (4-week-old), prehypertensive SHR as well as WKY, and (2) that during development from 4 to 12 weeks of age, shear stress–dependent dilation became enhanced in WKY as a result of an increased contribution of both NO and prostaglandin, whereas in SHR, shear stress–dependent dilation is significantly attenuated because of reduced NO mediation, while the response is mediated solely by prostaglandins.

Several studies suggest that an altered function of vascular endothelial cells is intimately involved in the pathogenesis of hypertension. However, it is not clear whether alterations in the function of endothelium are primary or secondary to the development of hypertension. Also, no extant studies address the mechanisms of microvascular endothelial changes as a function of age and the development of hypertension. The changes in microvessels could be different from those of large vessels, because the myogenic response, by preventing increases in intraluminal pressure in distal segments of the peripheral circulation, may provide for a protection of microvascular endothelium, at least in the early phase of hypertension.

Previous studies showed that endothelium can contribute to circulatory homeostasis by shear stress–dependent regulation of vascular resistance that can be stimulated by increases in blood flow. Flow-dependent dilation of arterioles has not yet been investigated in young hypertensive rats, at which time systemic blood pressure is not significantly different in WKY and SHR, which prevents assessment of the possible role of adaptation or changes of this mechanism as a function of age during normal development and the development of hypertension. Therefore, we aimed to clarify whether flow–induced dilation is present in arterioles of young normotensive and genetically hypertensive rats and, if so, what endothelial factors mediate the response. arterioles of WKY and SHR gracilis muscle were chosen for the present study, and flow–dependent responses were investigated in isolated cannulated arterioles in the presence of constant intravascular pressure. We found that at 4 weeks of age, the systemic blood pressure of WKY and SHR was not significantly different, but at 12 weeks of age, systemic blood pressure was significantly elevated in SHR. Note that the tail-cuff plethysmography used to assess systemic blood pressures of rats in the present study is not highly accurate; thus, small differences or periodic increases in systemic blood pressure of animals may not have been detected. The basal and passive diameters of

---

**Figure 5.** Top, Change in diameter (mean±SEM) of WKY-12w gracilis arterioles (n=16) as a function of perfusate flow under control conditions (○), in the presence of L-NNA (●) or INDO (▲), or in the simultaneous presence of L-NNA and INDO (●) in the suffusate. Slopes of the regression lines are significantly different from control or the use of single inhibitors. Control, y=4.9x+2.6 (r=0.98); L-NNA, y=2.7x+0.54 (r=0.99); INDO, y=2.2x+0.62 (r=0.99); L-NNA+INDO, y=0.0x+0.33 (r=0.00). Bottom, Change in diameter (mean±SEM) of SHR-12w gracilis arterioles (n=7) as a function of perfusate flow under control conditions, in the presence of L-NNA, or in the presence of L-NNA and INDO. Slopes of the regression line of L-NNA+INDO are significantly different from control and from the use of L-NNA. Control, y=0.78x−0.73 (r=0.99); L-NNA, y=0.82x−0.74 (r=0.99); L-NNA+INDO, y=0.0x+0 (r=0.00). Significant changes from control or from the use of L-NNA (P<0.05).

---

**Figure 6.** Change in diameter (mean±SEM) as a function of wall shear stress in gracilis arterioles of 4-(○) and 12-(▲) week-old age–matched WKY (top, n=16 and 16, respectively) and SHR (bottom, n=13 and 7, respectively). *Significant differences (P<0.05).
Flow-Induced Dilation at 4 Weeks of Age

At 4 weeks of age, in response to increases in perfusate flow, arterioles of WKY and SHR exhibited similar dilations, as indicated by the slope of the flow-diameter curves of SHR and WKY arterioles (Figure 1). In both normotensive and hypertensive rats, inhibition of either NO or prostaglandin synthesis alone significantly reduced the dilation to flow. Combined application of these 2 inhibitors nearly completely eliminated flow-induced dilation of WKY and SHR arterioles. These findings demonstrate that at a prehypertensive age in arterioles of rat gracilis muscle, both NO and prostaglandins are involved in the endothelial mediation of dilation after increases in perfusate flow. This proportion seems to be \( \approx 41\% \) and \( \approx 48\% \), respectively; these 2 endothelium-derived factors are responsible for the full mediation of the response. These findings also indicate that flow-induced NO and prostaglandin release are present in arterioles of young SHR. Others also have found NO-dependent vasodilation in young SHR.\(^{18}\) In agreement with these functional data, previous studies already demonstrated that the level of endothelial NO synthase (eNOS) protein was similar in the aorta of 4-week-old SHR and WKY.\(^{21}\)

Flow-Induced Dilation at 12 Weeks of Age

In arterioles of 12-week-old WKY, we found that flow-dependent dilation is significantly enhanced compared with that in 4-week-old WKY and that this dilation is mediated by endothelium-derived NO and prostaglandins. In contrast, in 12-week-old hypertensive rats, the magnitude of flow-induced dilation is similar to what was observed at 4 weeks of age. Therefore, the dilation to increases in flow is reduced compared with 12-week-old normotensive rats. Inhibition of NO synthase by L-NNA did not reduce the response, whereas INDO treatment nearly completely eliminated flow-induced dilation\(^{6}\) in 12-week-old SHR. The findings suggest that increases in perfusate flow do not elicit an NO-mediated dilation of these arterioles but do stimulate the synthesis of prostaglandins that are responsible for the dilation in response to increases in flow in arterioles of hypertensive rats.

Thus, in normotensive rats, the synthesis of NO and prostaglandins increases with age and elicits augmented flow-induced dilation in older (12-week-old) rats. Previous findings showed that expression of eNOS is markedly increased in proliferating cultured bovine aortic endothelial cells, which suggests that similar events take place in normotensive WKY during development.\(^{22}\) The underlying reason for the enhanced appearance of eNOS could be the continuous presence of wall shear stress, which may also increase with the increase in blood pressure in WKY. In SHR, the greater increase in blood pressure (and, hence, wall shear stress) leads to the impairment of NO mediation, whereas the synthesis of prostaglandins is not affected. Indeed, during the development of hypertension, a decline in the activity and expression of eNOS has been shown in the rat aorta.\(^{21}\) In addition, a reduced release of NO was accompanied by depressed eNOS activity in thoracic aorta.\(^{23}\) Other studies showed that the decline of eNOS protein is accompanied by an increase of inducible NOS expression in Wistar rats and an increased plasma concentration of nitrate and nitrite.\(^{24}\) Contrary to these findings, the plasma concentration of serum nitrate/nitrite is reduced in individuals with essential hypertension,\(^{25}\) whereas Bonnaradex et al.\(^{26}\) showed no association of the eNOS gene with human essential hypertension. However, at present, we do not know whether alterations in wall shear stress are linked to NO release by inducible NOS and what the cellular origin of NO in the plasma in this condition may be.

Notably, studies measuring NO synthase and gene expression were done on endothelial cells either in tissue culture or in those isolated from large conduit vessels. These results may not be applicable to microvascular endothelial cells because they are likely to undergo a different process of adaptation. Our recent studies show that an acute increase in intraluminal pressure from 80 to 160 mm Hg (for 30 minutes) in isolated arterioles attenuates flow-dependent dilation as a result of enhanced production of superoxide\(^{12,27}\) interfering with NO. We can safely assume that in these vessels eNOS was present, because before pressure treatment, NO mediation was intact. Furthermore, application of superoxide dismutase and catalase, scavengers of reactive oxygen species, prevented the impairment, which suggests a primary role for hemodynamic forces in the impairment of the endothelial L-arginine pathway.

To reconcile some of the divergent results, one has to take into account the fact that the final physiological response, namely the dilation, depends not only on the presence of the specific gene, message, or protein, but also on a host of other factors, such as substrate availability, cofactors (tetrahydrobiopterin, Ca\(^{2+}\), and calmodulin), and levels of superoxide dismutase and superoxide.\(^{28,29}\) Nevertheless, it remains an intriguing question as to why in hypertension an impairment occurs in the signal transduction that links alterations in shear stress to NO release but not to prostaglandin release. The pathological consequences of inappropriate regulation of wall shear stress is that arterioles tend to promote increases in peripheral resistance and elevation of blood pressure.\(^{29}\) Higher blood pressure increases blood flow velocity, which in the presence of reduced vascular diameter further increases wall shear stress; this then can set up a pathological positive feedback mechanism. Regulation of wall shear stress at higher values not only would impose an extra burden on cardiac function but could further impair endothelial function.

In conclusion, the new findings of the present study are that in young normotensive and genetically hypertensive rats, shear stress–induced dilation of arterioles are present and are not different. This dilation increases with age in normotensive
rats because of the increased release of NO and prostaglandins, whereas this dilation reduces with age in hypertensive rats as a result of an absence of NO mediation. Furthermore, the present findings suggest that in hypertension, elevated hemodynamic forces rather than genetic factors are primarily responsible for the development of impaired endothelial regulation of wall shear stress in skeletal muscle arterioles.

Acknowledgments
This work was supported by National Institutes of Health grants HL-46813 and HL-43023, AHA grant 9930244N, and AHA NY state affiliate grant 9830015T. We appreciate the excellent secretarial assistance of Mary Browne and Miriam Nunez.

References
Development of Nitric Oxide and Prostaglandin Mediation of Shear Stress–Induced Arteriolar Dilation With Aging and Hypertension
Akos Koller and An Huang

Hypertension. 1999;34:1073-1079
doi: 10.1161/01.HYP.34.5.1073

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/34/5/1073

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/