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Impaired Nitric Oxide–Mediated Flow-Induced Dilation in Arterioles of Spontaneously Hypertensive Rats

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Abstract We tested the hypothesis that impairment of flow-dependent dilator mechanisms of skeletal muscle arterioles is one of the underlying reasons for the increased peripheral resistance in hypertension. Isolated, cannulated arterioles (≈55 μm) of gracilis muscle of 12-week-old spontaneously hypertensive (SH) and normotensive Wistar (NW) rats were investigated. At a constant perfusion pressure (80 mm Hg), the active diameters of NW and SH arterioles were 57.7±1.9 and 51.5±3.2 μm, whereas their passive diameters (Ca^{2+}-free solution) were 113.6±2.9 and 101.7±2.9 μm, respectively. Flow-induced dilation was elicited by increases in flow of the perfusion solution from 0 to 25 μL/min in 5-μL/min steps. This response was significantly less in arterioles of SH compared with NW rats. For example, at 25-μL/min flow, the diameter of arterioles of SH rats was ≈56% less ($P<.05$) than those of NW rats. Indomethacin, an inhibitor of prostaglandin synthesis, significantly attenuated the flow-diameter curve in both strains of rats. In contrast, N^{ω}-nitro-L-arginine, a nitric oxide synthase inhibitor, significantly shifted the flow-diameter curve to the right in NW rats, but it did not affect the flow-diameter curve in SH rats. Thus, the present findings demonstrate that in gracilis muscle arterioles of normotensive rats in response to increases in flow (shear stress), prostaglandins and nitric oxide are coreleased, resulting in a dilation. In early hypertension, however, there is a reduced arteriolar dilation to increases in flow that is due to the impairment of the nitric oxide–mediated portion of the flow-dependent arteriolar dilation. (***Circ Res.* 1994;74:416-421.)**

Key Words • microvessels • gracilis muscle • sodium nitroprusside • acetylcholine • nitric oxide • arachidonic acid • N^{ω}-nitro-L-arginine • prostaglandins • indomethacin

In vivo studies of the microcirculation of skeletal muscle in hypertension have demonstrated a variety of structural changes[1-4] that are thought to contribute to the maintenance of increased peripheral vascular resistance.[4] In addition, previous in vitro studies[5-8] demonstrated changes in the vasoactive function of large arteries in various forms of hypertension. For example, a reduced dilation to acetylcholine and to other endothelium-dependent substances was shown to be present in hypertension, indicating an impairment in the function of endothelium to produce dilator factors.[5-8] Although studies investigating the dilator function of microvessels are sparse in hypertension,[9,10] it was demonstrated in skeletal muscle arterioles of Dahl salt-sensitive rats that there is a deficiency in the basal production of nitric oxide,[9] known to be produced in the endothelium of arterioles.[11-14]

It seems well established that the vascular endothelium has an important role in the regulation of skeletal muscle microcirculation via the production and release of dilator factors to a variety of stimuli.[13-16] The presence and importance of a flow-induced dilator mechanism has also been demonstrated in vivo and in vitro in skeletal muscle arterioles of normotensive rats. Furthermore, it was shown that this mechanism depends on the intact function of the endothelium.[15,16] The presence and possible alterations of flow-induced dilation of skeletal muscle arterioles, however, have not yet been investigated in hypertension.

We hypothesized that in hypertension there is an impairment of the flow-sensitive vasodilator mechanism and that impairment of this mechanism could contribute to the enhanced peripheral resistance.

The aim of our in vitro study, therefore, was (1) to establish, in arterioles of gracilis muscle of both normotensive and hypertensive rats, the nature and the mediation of the vascular response after an increase in perfusate flow and (2) to test the hypothesis that flow-dependent dilation is impaired in hypertension, and if so, to delineate the reason for the alteration.

To test our hypothesis, we investigated the changes in diameter as a function of perfusate flow (in the presence of a constant intravascular pressure) in isolated gracilis arterioles of normotensive and spontaneously hypertensive rats. In addition, the possible role of endothelial factors in the development and/or modulation of flow-induced dilation was assessed by the use of pharmacological agents affecting the synthesis of endothelium-derived relaxing factor/nitric oxide and prostaglandins.

Materials and Methods

Experiments were conducted on isolated arterioles (≈55 μm) of gracilis muscle of 12-week-old male normotensive Wistar (NW) and spontaneously hypertensive (SH) rats. Systolic blood pressure was measured by the tail-cuff method. Rats were anesthetized with intraperitoneal injections of sodium pentobarbital (Nembutal sodium, 50 mg/kg). The isolation procedure of gracilis muscle arterioles has been described previously.[14,17] Briefly, the gracilis muscle of rats was exposed by an incision in the skin. The muscle then was cut out and placed on a Petri dish containing cold (0°C to 4°C) salt solution

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(pH 7.4) composed of, in mmol/L: NaCl 145, KCl 5.0, $CaCl_2$ 2.0, $MgSO_4$ 1.0, NaH_2PO_4 1.0, dextrose 5.0, pyruvate 2.0, EDTA 0.02, and 3-*N*-morpholino-propane sulfonic acid (MOPS) 3.0. The muscle was pinned to the silicone bottom of the dish and allowed to equilibrate for ≈15 minutes. Rats were euthanized by an overdose of sodium pentobarbital.

With microsurgery instruments and an operating microscope (Olympus), a segment ≈1 mm long of an arteriole branching off from the main arteriole supplying the muscle was isolated from the gracilis muscle and surrounding tissue and transferred to the vessel chamber. The chamber contained a pair of glass micropipettes filled with physiological salt (PS) solution at room temperature. The PS solution used for suffusion and perfusion of the vessels contained, in mmol/L: NaCl 110.0, KCl 5.0, $CaCl_2$ 2.5, $MgSO_4$ 1.0, dextrose 10.0, $NaHCO_3$ 24.0, and EDTA 0.02 and was equilibrated with a gas mixture of 21% O_2/5% CO_2, balanced with N_2, at pH 7.4 (37°C). From a reservoir, the vessel chamber (15 mL) was continuously supplied with PS solution at a rate of 40 mL/min.

After the vessel was mounted on the proximal pipette and secured with sutures, the perfusion pressure was raised to 20 mm Hg to clear the clotted blood from the lumen; then, the other end of the vessel was mounted on the distal pipette. As described previously,[18] both proximal (inflow) and distal (outflow) micropipettes were connected with silicone tubing to a pressure-servo syringe system (Living Systems Inc, Burlington, Vt). The system was arranged to have mirror symmetry, so that the axis of symmetry was located perpendicularly at the middle of the arteriolar segment. Only pipettes with similar dimensions and equivalent resistances to flow were used, as assessed by the changes in perfusion pressure in response to increments of flow by a Harvard perfusion pump. This resulted in equal resistances (R_1 and R_2) of the two sides of the system (from pressure transducer to the tip of the pipette).

To flush the vessel and cannulas, the system was perfused for several minutes. Then, the perfusion pressure was slowly (over ≈1 minute) increased to 80 mm Hg. At this time, the pressure-servo system was placed in the manual mode (ie, no automatic maintenance of pressure) to ascertain that there were no leaks in the system. If no leaks were detected (ie, perfusion pressure remained constant), the pressure-servo system was set in the automatic mode. The temperature was set to 37°C (YSI temperature controller), and the vessels were allowed to equilibrate for about 1 hour.

Experimental Procedure

In all protocols, only those vessels that developed spontaneous tone to pressure were used, since no vasoactive agent was added to the PS solution. After the equilibration period, flow-diameter relations were obtained in control conditions in both strains of rats. Perfusate flow was increased from 0 to 25 μL/min in 5-μL/min steps. Flow was established at a constant intravascular pressure (80 mm Hg) by changing proximal and distal pressures to an equal degree but in opposite directions to keep midpoint luminal pressure constant. The flow was measured by a ball flowmeter (Omega) calibrated by a Harvard perfusion pump in which flow rate was accurate in the range of 0 to 100 μL/min. Each flow step was maintained for ≈5 minutes to allow the vessels to reach steady-state conditions before the diameter of the arterioles was measured. After the flow-diameter relation was obtained, flow was stopped; then, after ≈20 minutes, responses of arterioles to vasoactive agents were tested.

In the first experimental series, the role of prostaglandins in flow-induced dilation of gracilis muscle arterioles was assessed. After control responses were obtained, indomethacin (10^{-5} mol/L) was added to the suffusion solution to inhibit the synthesis of prostaglandins.[13,16,18] After an incubation period of ≈30 minutes, the flow-diameter relations were once more assessed. To assess the efficacy and specificity of this inhibitor, arteriolar responses to arachidonic acid (10^{-5} mol/L) and prostaglandin E_2 (10^{-8} mol/L) were obtained before and after the vessels were exposed to indomethacin.

In the second series of experiments, after control flow-diameter curves were obtained, the vessels were subjected to N^{ω}-nitro-L-arginine (L-NNA, 10^{-4} mol/L), an inhibitor of nitric oxide synthesis.[19,20] Then, after an ≈15-minute incubation period, changes in diameter in response to step increases in perfusate flow were reassessed. The efficacy and specificity of this inhibitor were assessed by arteriolar responses to acetylcholine (10^{-8} mol/L) and sodium nitroprusside (10^{-7} mol/L), known to be endothelium-dependent and -independent dilator agents, respectively,[11-14] before and after the vessels were exposed to L-NNA. In this experimental series, after control responses and responses in the presence of L-NNA were obtained, indomethacin was administered and the flow-diameter relation was again determined.

Responses to vasoactive agents were tested at 80 mm Hg perfusion pressure in no-flow conditions. All drugs were added to the reservoir connected to the vessel chamber, and final concentrations are reported. After responses to each drug subsided, the vessel chamber was flushed with PS solution. 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 PS solution that contained sodium nitroprusside (10^{-4} mol/L) and EGTA (1.0 mmol/L). The vessels were incubated for 10 minutes, then the passive diameter of arterioles at 80 mm Hg perfusion pressure was obtained. The diameters of vessels and peak responses in various experimental conditions were measured with an image shearing monitor (model 907, IPM, San Diego, Calif) and recorded with an X-Y recorder (Multicorder, MC6625).

All salts and chemicals were obtained from Sigma Co or Aldrich Co and were prepared on the day of the experiment. Changes in diameter in response to vasoactive agents were normalized to the corresponding passive diameter and expressed as percent changes. Results are presented as mean±SEM. N and n refer to the number of rats and vessels, respectively. Statistical analyses were done by analysis of variance, followed by Tukey's post hoc test, regression analysis, and paired and grouped Student's *t* tests, as appropriate. A value of $P<.05$ was considered significant.

Results

The systolic blood pressures of NW and SH rats were 105.0±3.1 (N=6) and 200.0±2.9 (N=7) mm Hg, respectively, showing a significant increase in blood pressure in hypertensive compared with normotensive rats.

The active diameters of arterioles of NW and SH rats obtained in the presence of constant intravascular pressure (80 mm Hg) and static flow conditions were not significantly different (57.7±1.9 and 51.5±3.2 μm, respectively). In the same conditions but in Ca^{2+}-free solution, the passive diameter of each arteriole was also obtained (see "Materials and Methods"). We found that the mean passive diameters of NW and SH vessels were significantly different (113.6±2.9 and 101.7±2.9 μm, respectively; $P<.05$), but the active vessel diameters, expressed as a percent of passive diameter, were not different in the two strains of rats (50.9±1.4% and 50.7±2.5%).

Fig 1 demonstrates the changes in the diameter of arterioles of NW and SH rats in response to step increases in flow in control conditions. From 5-μL/min perfusate flow, the diameter of arterioles of SH rats started to deviate significantly ($P<.05$) from that of NW, and at 25-μL/min flow, the diameter of SH arterioles was ≈56% less than that of NW. Also, the significant difference in the slope of flow-diameter curves indicates

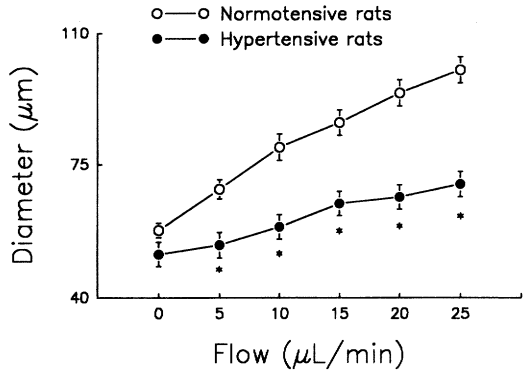

FIG 1. Graph showing arteriolar diameter (mean±SEM) of normotensive Wistar (N [rats]=11/n [vessels]=12) and spontaneously hypertensive rat (N=12/n=12) gracilis muscle as a function of perfusate flow. The slopes of the regression lines are significantly different: NW, $y=1.69x+59.9$ ($r=.993$) and SH, $y=0.77x+51.2$ ($r=.989$). *Significant differences ($P<.05$) between hypertensive and normotensive rats.

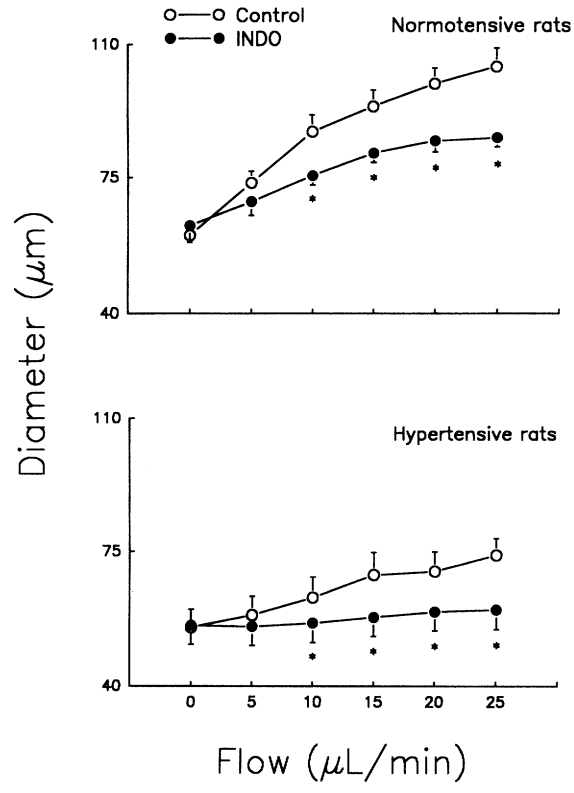

FIG 2. Top, Graph showing arteriolar diameter (mean±SEM) of normotensive Wistar rat gracilis arterioles (N [rats]=5/n [vessels]=5) as a function of perfusate flow in control conditions and in the presence of indomethacin (INDO, 10^{-5} mol/L) in the suffusate. The slopes of regression lines are significantly different ($P<.05$): control, $y=1.7x+64.6$ ($r=.975$); INDO, $y=0.96x+64.6$ ($r=.973$). Bottom, Graph showing changes in diameter (mean±SEM) of spontaneously hypertensive rat gracilis arterioles (N=5/n=5) as a function of perfusate flow in control conditions and in the presence of indomethacin (INDO, 10^{-5} mol/L) in the suffusate. The slopes of regression lines are significantly different ($P<.05$): control, $y=0.76x+55.4$ ($r=.98$); INDO, $y=0.19x+55.1$ ($r=.960$). *Significant changes from control ($P<.05$).

that arterioles of SH rats have a reduced dilation to step increases in perfusate flow compared with the arterioles of normotensive rats.

Next we investigated the endothelial mechanism(s) responsible for the mediation of flow-induced dilation of arterioles of NW and SH rats. First we examined the role of prostaglandins in the flow-induced dilation by obtaining this response in the presence of indomethacin. We found that dilator responses of arterioles to arachidonic acid and prostaglandin E_2 were not significantly different in SH compared with NW rats (Table). The efficacy and specificity of the inhibition of cyclooxygenase by indomethacin is indicated by the elimination of the dilation to arachidonic acid in both strains of rats, whereas the dilation to prostaglandin E_2 was not affected (Table). Indomethacin did not affect basal diameter but significantly reduced the dilation to increases in perfusate flow in arterioles of both strains of rats (Fig 2, upper and lower panels). In NW rats the reduction of the maximum response was 48%, whereas in SH rats it was 79%.

To examine the involvement of nitric oxide in the flow-induced response, we used an L-arginine analogue after obtaining control responses. In control conditions, we found that dilator responses of arterioles to acetylcholine and sodium nitroprusside were not significantly different in SH compared with NW rats (Table). L-NNA inhibited nitric oxide synthase, as indicated by the significant suppression of the dilation to acetylcholine but not to sodium nitroprusside in both strains of rats (Table). L-NNA also significantly reduced the basal

Effect of L-NNA and Indomethacin on Arteriolar Responses to Various Agents in NW and SH Rats

Conditions	Strain	ACh	SNP	AA	PGE_2
Control	NW	32.8±1.6	26.9±3.4	22.2±1.8	22.4±2.4
	SH	31.4±1.8	22.3±0.8	22.8±1.0	24.1±3.4
L-NNA	NW	23.6±1.5*	26.0±2.9		
	SH	23.4±1.5*	22.9±1.0		
Indo	NW			−1.2±0.3*	23.0±1.9
	SH			−0.5±0.2*	22.9±3.9

Data are mean±SEM of percent changes in arteriolar diameter in response to acetylcholine (ACh, 10^{-8} mol/L), sodium nitroprusside (SNP, 10^{-7} mol/L), arachidonic acid (AA, 10^{-5} mol/L), and prostaglandin E_2 (PGE_2, 10^{-8} mol/L) in control and after treatment with N^{ω}-nitro-L-arginine (L-NNA, 10^{-4} mol/L) and indomethacin (Indo, 10^{-5} mol/L) of normal Wistar (NW; N=6/n=7) and spontaneously hypertensive (SH; N=7/n=7) rats. *Significant changes from control ($P<.05$).

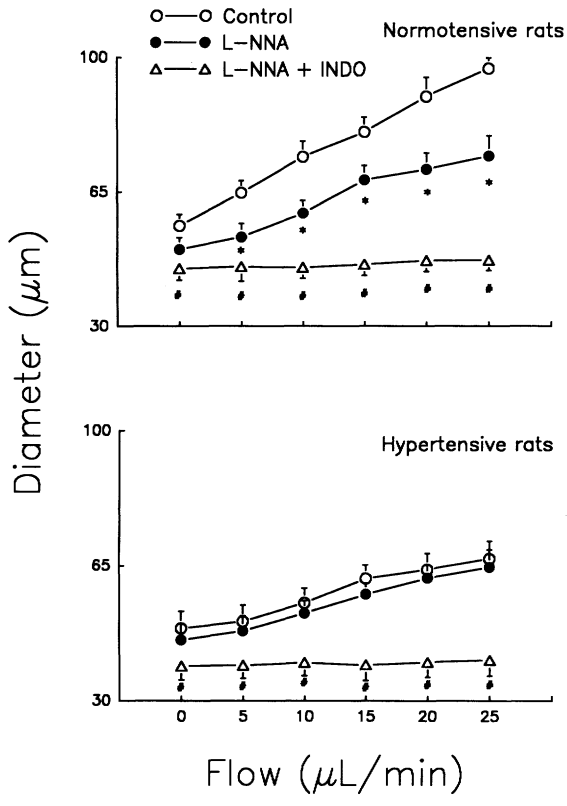

FIG 3. Top, Graph showing arteriolar diameter (mean±SEM) of normotensive Wistar rat gracilis arterioles (N [rats]=6/n [vessels]=7) as a function of perfusate flow in control conditions, in the presence of N^{ω}-nitro-L-arginine (L-NNA, 10^{-4} mol/L), and in the simultaneous presence of L-NNA and indomethacin (INDO) in the suffusate. The slopes of the regression lines are significantly different ($P<.05$): control, $y=1.6x+56.6$ ($r=.999$); L-NNA, $y=1.1x+49.5$ ($r=.986$); L-NNA+INDO, $y=0.09x+44.8$ ($r=.947$). Bottom, Graph showing changes in diameter (mean±SEM) of spontaneously hypertensive rat gracilis arterioles (N=7/n=7) as a function of perfusate flow in control conditions, in the presence of L-NNA (10^{-4} mol/L), and in the presence of L-NNA and INDO. The slope of the regression line of L-NNA+INDO is significantly different from control and from L-NNA, above. Control, $y=0.78x+48.1$ ($r=.987$); L-NNA, $y=0.80x+45.1$ ($r=.995$); L-NNA+INDO, $y=0.05x+39.0$ ($r=.864$). *Significant changes from control; #significant changes from both control and L-NNA ($P<.05$).

diameter of arterioles in a similar manner in both strains of rats (by ≈9% and ≈6% in NW and SH rats, respectively).

In normotensive rats, L-NNA significantly reduced flow-induced arteriolar dilation (Fig 3, upper panel). For example, at 25-μL/min flow, the diameter of L-NNA–treated arterioles of NW rats was ≈43% less than that of control. Also, the slopes of flow-diameter curves were significantly different in the control condition and in the presence of L-NNA. In contrast, in arterioles of SH rats, L-NNA did not significantly affect the arteriolar dilation in response to step increases in perfusate flow (Fig 3, lower panel). In the presence of L-NNA, administration of indomethacin caused an additional decrease in basal diameter (by ≈20%), elicited a further significant reduction of flow-induced responses in normotensive rats, and practically eliminated the dilation to increases in perfusate flow in SH rats (Fig 3). Thus, the inhibitory effect of indomethacin on flow-induced arteriolar dilation was observed both in the presence and the absence of L-NNA and in both NW and SH rats (Figs 2 and 3).

Discussion

The salient finding of this study is that in young, spontaneously hypertensive rats, the flow-dependent dilation of arterioles is significantly reduced compared with that of normotensive rats. This reduced response to flow seems to be due primarily to the impairment of the nitric oxide–mediated portion of flow-dependent dilation.

Previous investigation of the microcirculation of hypertensive animals revealed morphological changes in the vascular wall as well as changes in the structure of the arteriolar network.[1-4] These changes were used to explain the enhanced peripheral resistance that accompanies hypertension.[3] Recent studies, however, support the idea that an altered function of vascular endothelial cells is intimately involved in the development of hypertension. For example, studies of ring preparations of rat aorta[6] and mesenteric arteries[7,8] of hypertensive animals demonstrated that responses to the endothelium-dependent dilator agent acetylcholine were reduced or reversed to constriction, whereas those to endothelium-independent dilator agents remained unaltered. It was also shown that the changes in the function of endothelium of large vessels in hypertension might be linked to changes in the synthesis of nitric oxide or arachidonic acid metabolites or the production of superoxide anions.[7,22] Only a few studies, however, suggest a possible role for the altered function of microvascular endothelium in the development of hypertension.

It was suggested previously that endothelium can contribute to circulatory homeostasis by the shear stress–dependent regulation of vascular resistance that can be stimulated by increases in blood flow.[18,23] Flow-dependent dilation of arterioles has not yet been investigated in hypertension, preventing the assessment of the importance of this mechanism in the development of the chronic elevation of blood pressure. Therefore, the question that our study addressed was whether alterations in the function of arteriolar endothelium and/or smooth muscle affect the magnitude of flow-induced dilation in isolated arterioles of young, genetically hypertensive rats.

Arterioles of rat gracilis muscle were chosen for the present study because the microcirculation of skeletal muscle is responsible for a sizable fraction of peripheral resistance.[24] Also, we used second-order arterioles, vessels in which the elevation of intravascular pressure in hypertension is likely to be less than in larger arterioles and arteries.[25,26] As a control, we used NW rats because in preliminary studies we found that gracilis muscle arterioles of Wistar-Kyoto rats responded poorly or not at all to a variety of vasoactive stimuli and as such could not be used as the appropriate control for SH rats.[27,28] To avoid the interference of other local mechanisms that regulate arteriolar diameter, the presence of and changes in flow-dependent responses were investigated in isolated cannulated arterioles in the presence of constant intravascular pressure.[17] To minimize structural changes in the arteriolar wall, we used relatively young, 12-week-old rats, an age at which SH rats

already have a significantly elevated systemic blood pressure.

We found that the active and passive diameters of arterioles of NW rats were slightly larger than those of SH rats, but only the passive diameters of NW and SH rats differed significantly. Also, the magnitude of the myogenic tone in normotensive and hypertensive gracilis arterioles was similar (≈51% of passive diameter). These findings are in accord with in vivo data obtained in cremaster[1,2,25,26] and spinotrapezius[29] muscle of normotensive and hypertensive rats, tissues in which no significant differences in average basal diameter of arterioles were found, corresponding with the finding that blood pressure is close to normal in small arterioles of hypertensive rats.

Impairment of Flow-Induced Dilation in Hypertension

In response to increases in perfusate flow, arterioles of hypertensive rats exhibited a reduced dilation compared with normotensive rats, as indicated by the significant shift in the slope of the flow-diameter curves of SH arterioles compared with those of NW arterioles (Fig 1). Similar conclusions were reported in human coronary[30] but not in the brachial[31] circulation of patients with essential hypertension. Because previous studies showed that flow-dependent dilation of skeletal muscle arterioles is mediated by endothelial factors,[15,18,32] we hypothesized that changes in the function of the endothelium of hypertensive arterioles are responsible for the observed reduction in flow-induced dilation. To elucidate the role of endothelial factors in the mediation of flow-induced dilation in NW and SH rats, we used inhibitors of nitric oxide[16,19-21] and prostaglandin synthesis.[11-13,18]

Role of Nitric Oxide and Prostaglandins in Flow-Induced Dilation

In normotensive rats, inhibition of either nitric oxide or prostaglandin synthesis alone significantly reduced the dilation to flow. Combined application of these two inhibitors nearly completely eliminated flow-induced dilation of NW arterioles. These findings demonstrate that in arterioles of rat gracilis muscle, both nitric oxide and prostaglandins are involved in the endothelial mediation of dilation after increases in perfusate flow.[32] In gracilis muscle arterioles, this proportion seems to be ≈41% and ≈48%, respectively, accounting nearly completely for the mediation of the response.

Lack of Nitric Oxide–Mediated Dilation to Flow in Hypertensive Rats

In hypertensive rats, in which the flow-induced dilation is already reduced compared with normotensive rats, inhibition of nitric oxide synthase by L-NNA did not further reduce the flow-induced response, whereas indomethacin treatment nearly completely eliminated the impaired flow-induced dilation. These findings suggest that in hypertensive arterioles increases in perfusate flow do not elicit a nitric oxide–mediated dilation but do stimulate the synthesis of prostaglandins that are responsible for the remaining dilation in response to increases in flow.

In contrast to the impaired flow-induced dilation, we found no significant impairment in dilation of SH arterioles to acetylcholine and arachidonic acid, responses that are mediated by endothelium-derived nitric oxide and prostaglandins,[11-13,20] respectively. Arteriolar responses to sodium nitroprusside and prostaglandin E_2 were also not affected in SH rats. These findings indicate that agonist-induced endothelium-derived relaxing factor/nitric oxide and prostaglandin synthesis is preserved in arterioles of young SH rats. Interestingly, in Dahl hypertensive rats arterioles of rat spinotrapezius muscle showed an impairment in the basal release of nitric oxide in resting flow conditions but no appreciable change in the dilator response to acetylcholine.[9] In static flow conditions in the present in vitro study, we found a similar effect of inhibitors of either nitric oxide or prostaglandin synthesis on the diameter of NW and SH arterioles.

Our findings support the hypothesis that in skeletal muscle arterioles of young genetically hypertensive rats, the endothelial synthesis of nitric oxide to agonists is preserved but the sensitivity of arterioles to flow (shear stress), coupled to the synthesis of nitric oxide, is impaired. It is quite possible that this early change in the vasoactive function of arteriolar endothelium precedes the structural changes of the arteriolar wall in various forms of hypertension, similar to what was suggested in a recent study of the function of arterial endothelium of prehypertensive SH rats.[22] The reason for the observed changes, therefore, could be genetically determined or a result of the prevailing hemodynamic conditions[33] (increased flow velocity or pressure, etc) to which these arterioles are exposed in hypertension. Whatever the reason, it seems that in hypertension there is an impairment in the "rheoreceptors" that link the increase in shear stress to nitric oxide synthesis but not in those that link it to prostaglandin synthesis. Previous studies indicate that increases in flow may activate a potassium channel that is coupled to a pertussis toxin–sensitive G protein, eliciting enhanced nitric oxide synthesis.[34-36] Therefore, it is tempting to speculate that perhaps this pathway of signal transduction is impaired in hypertension.

Effect of Impaired Flow-Induced Dilation on Autoregulation

Two of the important vascular mechanisms that regulate arteriolar diameter are stimulated by the changes in pressure and flow (shear stress). Because they have opposite effects on diameter, they are able to maintain an adequate vascular resistance. The impairment of flow-dependent dilation in hypertension could result in an imbalance of these mechanisms favoring the development of a positive feedback cycle to promote (together with other abnormal mechanisms) increases in arteriolar resistance. Such an increase in vascular tone may also be responsible for functional rarefaction observed in skeletal muscle microcirculation in hypertension.[1-3] It is likely that changes similar to those described here occur in arterioles of a variety of vascular beds. Therefore, the lack of a nitric oxide–mediated flow sensitivity in hypertension can, via an increase in peripheral resistance, predispose the circulatory system to an elevation of blood pressure,[37] regardless of whether this mechanism is a target or a cause of hypertension.

In conclusion, the present study is the first to demonstrate a reduced flow-induced dilation of arterioles of

genetically hypertensive rats; this reduction is due to an impairment of the nitric oxide–mediated flow-dependent dilation, whereas the prostaglandin-mediated portion of the dilation seems to be intact. Thus, the present findings suggest an important role for the altered vasoactive function of arteriolar endothelium in skeletal muscle arterioles in the pathogenesis of hypertension.

Acknowledgments

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