Vascular Dilation Responses of Rat Small Mesenteric Arteries at High Intravascular Pressure in Spontaneously Hypertensive Rats

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Background: Hypertension is associated with remodeling and mechanical alterations of resistance arteries. Numerous studies have investigated the mechanical and morphometric properties of small arteries obtained from hypertensive animals and humans. However, the functional properties of resistance arteries from normotensive and hypertensive subjects have only been examined under normotensive conditions. The objective of the present study was to evaluate the dilation responses of small mesenteric arteries (SMA) from spontaneously hypertensive rats (SHR) at various levels of intraluminal pressure.

Methods and Results: SMA segments from Wistar Kyoto (WKY) rats and SHR were pressurized using pressure myography. Endothelium-dependent and -independent dilation responses of the SMA were examined under 3 different intravascular pressures (50, 80 and 120 mmHg). Endothelium-dependent dilation was evaluated by measuring vasodilator responses to increasing doses of acetylcholine or increases in intraluminal flow rate. Endothelium-independent vasodilator function was examined by using sodium nitroprusside. The results indicate that both endothelium-dependent and -independent dilation responses of SMA from WKY progressively decrease with increased intravascular pressure. In contrast, all dilatation responses of the SMA from SHR were enhanced at higher intraluminal pressures.

Conclusions: These findings of differential sensitivity to luminal pressure should be considered during in vitro examination of vessels from normotensive and hypertensive subjects. (*Circ J* 2009; **73:** 2091 – 2097)

Key Words: Acetylcholine; Flow-mediated dilation; Hypertension; Rats; Sodium nitroprusside

Hypertension is a multifactorial, polygenic disease and is an important risk factor for the development of atherosclerosis and cardiovascular diseases.[1–4] It is well established that chronic hypertension is associated with the structural and functional changes in the resistance vasculature that are responsible for the elevated peripheral resistance in hypertension;[1,5,6] such structural alterations are termed "vascular remodeling". In the majority of hypertension models studied, the internal diameter is reduced and the wall/lumen ratio is increased in small arteries as a consequence of increased wall thickness. Vascular remodeling is also associated with altered mechanical properties such as reduced distensibility.[5–7] In addition, the altered balance of vasoconstrictor and vasodilator systems has an important role in augmenting systemic resistance in hypertension.[8,9]

In vitro studies of small arteries from hypertensive animals and humans are widely used in the investigation of hypertension and its complications. Two experimental techniques are commonly used: (1) wire myography and (2) pressurized myography systems.[10,11] The pressurized method has several advantages, including maintenance of the vessel's cylindrical shape and better preservation of the endothelium. The structural and mechanical characteristics of the small arteries of both normotensive and hypertensive rats and humans have been evaluated at different levels of intravascular pressure by the pressurized myography technique.[11–15] In those studies, the small arteries obtained from hypertensive subjects were exposed to intraluminal pressures within a wide range (ie, 3–140 mmHg), and structural and mechanical properties, such as internal and external diameters, cross-sectional area, wall/lumen ratio, distensibility, circumferential wall strain or stress, were evaluated. The results have indicated that small arteries from hypertensive subjects have altered structural and mechanical properties compared with normotensives.

Pressurized small artery preparations also have been used to examine the functional properties of vessels from normotensive and hypertensive rats or humans.[16–21] However, those studies, which investigated the dilatation responses of small arteries to several agonists or flow by pressurized myography, were only performed under normotensive conditions, and the "normotensive" intraluminal pressures differed among them. Small mesenteric arteries (SMA) are usually exposed to pressures of 30 or 45 mmHg,[16–18] whereas small arteries obtained from skeletal muscle are exposed to greater pressures.[19] Pressurized small artery preparations also have been used in several human studies:

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subcutaneous small arteries obtained from hypertensive patients were exposed to 60 mmHg intraluminal pressure and endothelial function was assessed at this pressure state.[20,21] In other words, these pressurized myography studies used a similar level of intraluminal pressure for the small arteries from normotensive and hypertensive subjects, and then examined their functional properties under normotensive conditions.

Chronically elevated blood pressure (BP) induces alterations of vessel wall shape and composition, and these alterations can be considered as an adaptive response.[7,21] Likewise, it is plausible that the functional properties of small arteries also may accommodate to high BP condition in hypertensive patients. Therefore, the functional responses of small arteries from hypertensive subjects may differ when tested in the normotensive or hypertensive state.

Thus, we hypothesized that the vasodilator responses of SMA from spontaneously hypertensive rats (SHR) might be better at higher intraluminal pressures. For this purpose, we evaluated the endothelium-dependent and –independent vascular dilation responses of SMA from SHR and Wistar Kyoto (WKY) rats at progressively increasing intraluminal pressures.

Methods

Animals

SHR (12–15 weeks of age) and age-matched normotensive WKY rats (Harlan Laboratories, USA) were used to obtain SMAs. The animals were housed at 23±2°C on a 12:12 h light–dark cycle and had free access to standard rat chow and drinking water. Systolic BP (SBP) of all animals was monitored daily by tail-cuff method during the week before the experiments. The experimental protocol was approved by the Animal Care and Usage Committee of Akdeniz University and was in accordance with the Declaration of Helsinki and International Association for the Study of Pain guidelines.

Isolation of Mesenteric Resistance Arteries

Rats were anesthetized with an intraperitoneal injection of thiopental sodium (80 mg/kg body weight). The mesenteric bed was removed and placed in a dissecting dish filled with MOPS (4-morpholinepropanesulfonic acid)-buffered physiological saline solution (PSS) containing (in mmol/L) 145.0 NaCl, 4.7 KCl, 2.0 $CaCl_2$, 1.17 $MgSO_4$, 1.2 NaH_2PO_4, 5.0 glucose, 2.0 pyruvate, 0.02 EDTA, and 25.0 MOPS, pH=7.4. A second-order branch of a mesenteric artery was isolated from the mesenteric vascular bed and carefully cleaned of surrounding tissue under a dissecting microscope (SZ61, Olympus).

The isolated arterial segments were transferred to a vessel chamber (CH/1, Living Systems, Burlington, VT, USA) containing 2 horizontal glass micropipettes whose tapered ends were opposed. A servo-controlled roller pump perfusion system (Living Systems) was connected to the proximal pipette, and a similar but manually-controlled roller pump attached to the distal end. The pressure in each pipette was monitored by pressure transducers, and thus the intraluminal pressure in the vessel could be controlled by the servo-perfusion system.

After cannulation of one end of the vessel with a micropipette, the perfusion pressure was raised to 20 mmHg to clear all clotted blood from the lumen, and then the other end of the vessel was mounted on the distal pipette; both ends of the vessel were attached using 11-0 surgical nylon suture. The flow chamber with the arterial segment preparation was placed on an inverted microscope (Eclipse TS100, Nikon) equipped with a charge-coupled device camera (XC73CE, Sony). The camera was connected to a video dimension-analysis system (model V94, Living Systems), which allowed continuous measurement of vessel diameter. Mean intraluminal pressure, pressure gradient, fluid flow rate through the arterial segment, and vessel diameter were continuously recorded via a data acquisition system (MP 100A-CE; BIOPAC Systems) connected to a personal computer.

The arteries were perfused with MOPS-PSS supplemented with albumin (1 g/100 ml) and the axial length of the arterial segment was adjusted by positioning the cannula until the vascular walls were parallel without obvious stretching. Intraluminal pressure was then set to 50 mmHg with the servo-controlled pump and the arterial segment was allowed to equilibrate at this pressure for 60 min at 37°C under no-flow conditions.

Three separate series of experiments were performed in the arterial segments in order to determine acetylcholine (ACh)-, flow- and sodium nitroprusside (SNP)-induced dilation responses at 3 intraluminal pressures (50, 80, 120 mmHg). Prior to the assessment of vascular dilation responses, arteries that did not develop at least 20% spontaneous tone were constricted with phenylephrine. At the end of each experiment, the MOPS-PSS bath solution was replaced with Ca^{2+}-free PSS and the vessels were incubated at least for 30 min to determine their maximal passive diameter at intraluminal pressures of 50, 80 and 120 mmHg.

Determination of Vasodilator Response

Endothelium-Dependent Dilation Endothelium-dependent dilation was evaluated by measuring vasodilator responses to increasing doses of ACh or increases in the intraluminal flow rate.

ACh-Induced Dilation ACh-induced dilation was first assessed at 50 mmHg pressure by adding increasing doses of ACh to the bath solution to achieve levels over the range of 10^{-9} to 10^{-4} mol/L (n=10). The vessel was then washed and the perfusion pressure was increased to 80 mmHg, the vessel incubated at this pressure for 30 min and responses to ACh were obtained. After washing the vessel, the pressure was raised to 120 mmHg for another 30 min and dose–response behavior to ACh was assessed at the increased pressure.

Flow-Mediated Dilation (FMD) FMD was assessed using various flow rates between 7 and 63 μl/min while intraluminal pressure was kept constant by the pressure servo-control system (n=10). That is, the speed of the peristaltic pump connected to the distal end of vessel was manually adjusted to generate the required flow rate with the desired intraluminal pressure maintained by the servo pump at the proximal end. Each intraluminal pressure was maintained for 30 min with no flow prior to measuring FMD, with each flow rate maintained for 5 min to allow the vessel to reach a steady diameter. After obtaining FMD responses of vessels at 50 mmHg, the vessel was washed, the pressure raised to 80 mmHg, and FMD was assessed at that intraluminal pressure. After washing, the pressure was raised to 120 mmHg and the procedure repeated.

Endothelium-Independent Dilation Endothelium-independent dilation was assessed by adding increasing doses of SNP to the bath solution at concentrations over the range

Table. Maximal Passive Diameter and Initial Tone of Small Mesenteric Arteries From WKY and SHR at 50, 80 and 120 mmHg Intraluminal Pressure

	WKY			SHR		
	50 mmHg	80 mmHg	120 mmHg	50 mmHg	80 mmHg	120 mmHg
Passive diameter (μm)	385.1±9.5	406.2±8.9	417.7±9.0	337.8±7.3***	358.9±7.7***	374.6±8.2**
Initial tone (%)	34.9±1.5	30.9±1.3	23.1±0.9	42.1±1.3***	39.7±1.1***	36.5±1.1***

Values are means±SE.
WKY, Wistar Kyoto; SHR, spontaneously hypertensive rats.
**P<0.01, ***P<0.001; difference from WKY group.

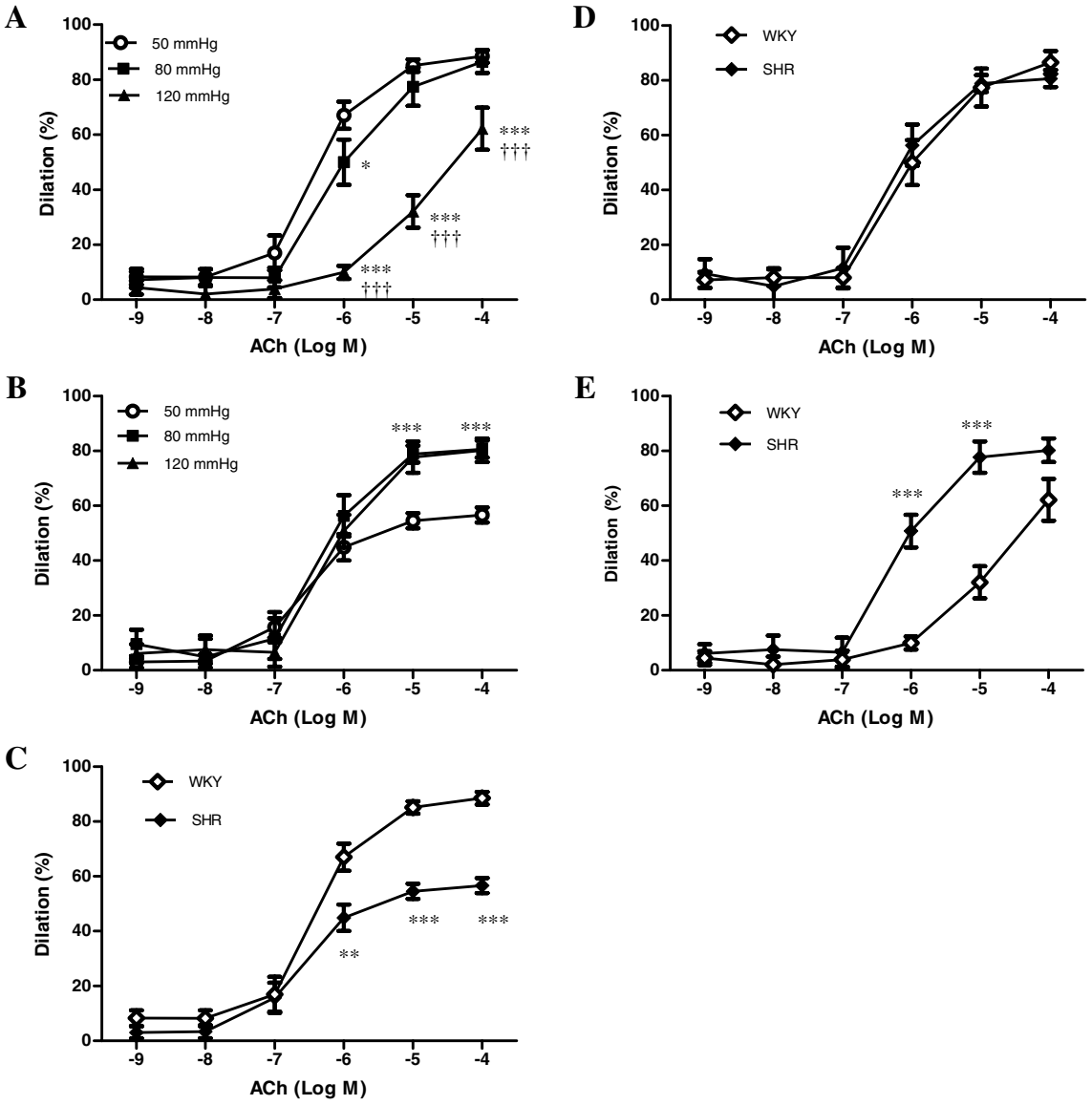

Figure 1. Acetylcholine (ACh)-induced dilation responses of small mesenteric arteries (SMA) from Wistar Kyoto (WKY) and spontaneously hypertensive rats (SHR) at 50, 80 and 120 mmHg intraluminal pressure. (**A**) Normotensive rats (WKY); (**B**) hypertensive rats (SHR). Comparison of the dilation responses of the 2 groups at 50 mmHg (**C**); 80 mmHg (**D**) and 120 mmHg (**E**). Values are means±SE. *P<0.05, **P<0.01, ***P<0.001, difference from 50 mmHg or WKY; †††P<0.001, difference from 80 mmHg.

of 10^{-9} to 10^{-4} mol/L (n=9). The relaxation responses to SNP were obtained at the 3 different intraluminal pressures (ie, 50, 80 and 120 mmHg) using the same procedure as before.

Statistical Analysis

All values are given as means±SE. Vasodilatation, as percent maximal response, was calculated as $(D_d - D_b)/(D_p - D_b) \times 100$, where D_d is the measured diameter for a given dose, D_b is the baseline diameter before an interven-

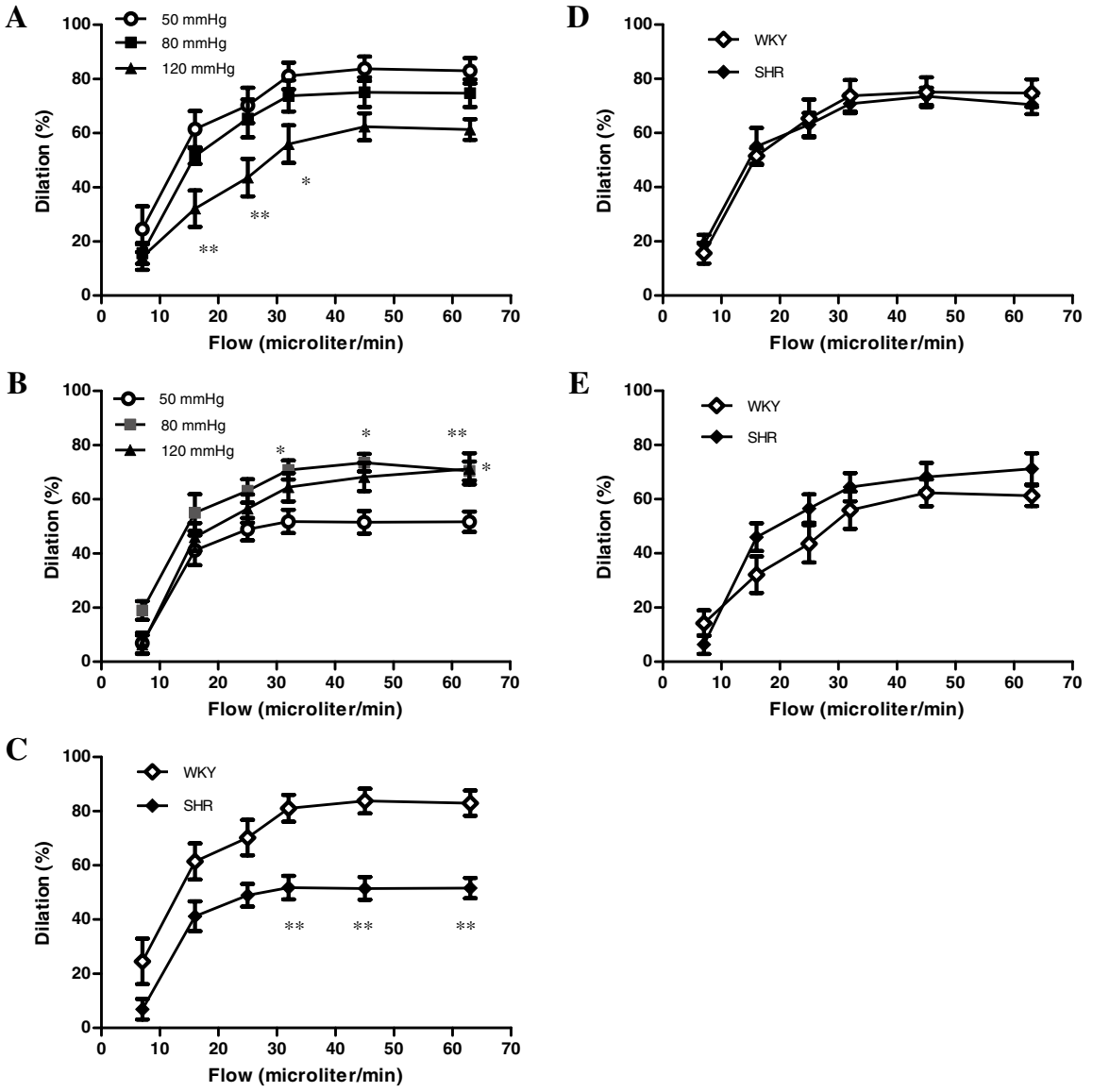

Figure 2. Flow-mediated dilation (FMD) responses of small mesenteric arteries (SMA) from Wistar Kyoto (WKY) and spontaneously hypertensive rats (SHR) at 50, 80 and 120 mmHg intraluminal pressure. (**A**) Normotensive rats (WKY); (**B**) hypertensive rats (SHR). Comparison of the dilation responses of the 2 groups at 50 mmHg (**C**); 80 mmHg (**D**) and 120 mmHg (**E**). Values are means ± SE. *P<0.05, **P<0.01, difference from 50 mmHg or WKY.

tion was started, and D_p is the maximal passive diameter. Initial tone is expressed as a percentage of maximal passive diameter. ACh, flow and SNP responses are expressed as a percentage of maximal possible vasodilatation. P<0.05 was considered significant.

Between-group differences in BP, maximal passive diameter and the initial tone of vessels from WKY and SHR rats were assessed using Student's t-tests for unpaired observations. Two-way ANOVA with repeated measures followed by the Bonferroni test were used for comparison of the response curves.

Results

SBP was significantly higher in SHR compared with WKY rats (SBP_{SHR} 189.6±1.4 mmHg; SBP_{WKY} 132.6±2.8 mmHg; P<0.001). Maximal passive diameter and initial tone of vessels are shown in **Table**. Passive diameters for SHR were approximately 12% smaller (P<0.001 for 50 and 80 mmHg, P<0.01 for 120 mmHg), whereas initial tone was significantly higher (20% at 50 mmHg, 30% at 80 mmHg, 60% at 120 mmHg, all P<0.001).

Endothelium-Dependent Dilation

ACh-Induced Dilation **Figure 1** illustrates the responses to ACh at the 3 different intraluminal pressures for SMA from the WKY and SHR rats.

SMA from WKY rats exhibited a rightward shift of the concentration–response curve with the increases in intraluminal pressure (**Figure 1A**). Compared with the results obtained at 50 mmHg, the dilation response at 10^{-6}–10^{-4} mol/L ACh was significantly decreased at 120 mmHg (P<0.001). In addition, Ach-induced dilation was also significantly impaired at 80 mmHg for dose of 10^{-6} mol/L

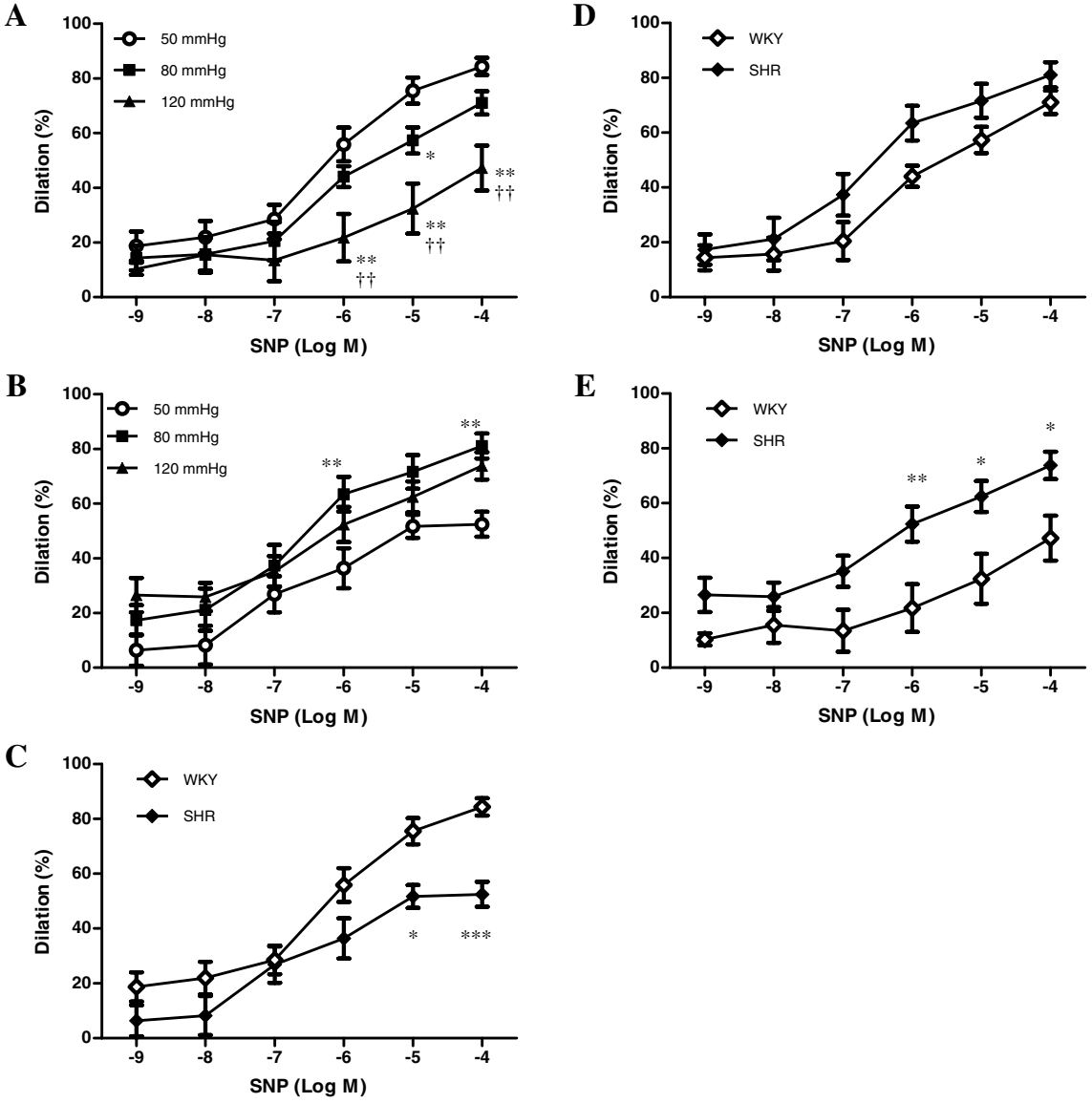

Figure 3. Sodium nitroprusside (SNP)-induced dilation responses of small mesenteric arteries (SMA) from Wistar Kyoto (WKY) and spontaneously hypertensive rats (SHR) at 50, 80 and 120 mmHg intraluminal pressure. (**A**) Normotensive rats (WKY); (**B**) hypertensive rats (SHR). Comparison of the dilation responses of the 2 groups at 50 mmHg (**C**); 80 mmHg (**D**) and 120 mmHg (**E**). Values are means ± SE. *P<0.05, **P<0.01, ***P<0.001 difference from 50 mmHg or WKY; ††P<0.01, difference from 80 mmHg.

ACh compared with 50 mmHg (P<0.05). However, unlike the WKY rat vessels, the dilation response to ACh of the SMA from SHR increased at higher intraluminal pressures: compared with the results at 50 mmHg, Ach-induced dilation was significantly greater at 10^{-5} and 10^{-4} mol/L ACh for 80 and 120 mmHg (**Figure 1B**, P<0.001).

The ACh-induced dilation responses of the SMA from SHR were significantly lower than those of WKY rats at 50 mmHg (**Figure 1C**). In contrast, the responses of SHR vessels were significantly increased compared with WKY vessels at 120 mmHg (**Figure 1E**). No significant differences were detected between the 2 groups at 80 mmHg intraluminal pressure (**Figure 1D**).

FMD **Figure 2** shows the FMD responses of SMA to increases in perfusate flow at 50, 80 and 120 mmHg intraluminal pressures.

FMD responses were attenuated with increased intraluminal pressure in SMA from WKY rats (**Figure 2A**). Although there were decreased dilatation responses at 80 and 120 mmHg, significant impairment vs 50 mmHg was only seen at 120 mmHg and at 3 intermediate flow rates (16, 26 and 32 μl/min; P<0.01, P<0.01 and P<0.05, respectively).

In contrast, the dilation responses to flow were improved at higher intraluminal pressure in vessels from SHR (**Figure 2B**). FMD was significantly increased at 80 mmHg compared with 50 mmHg flow rates of 32, 45 and 63 μl/min (P<0.05, P<0.01 and P<0.05, respectively). However, at 120 mmHg a significantly increased FMD response was only obtained at 63 μl/min.

The comparison of FMD responses of WKY vs SHR is shown in **Figures 2C–E**. Responses did not differ between

groups at 80 and 120 mmHg (**Figures 2D** and **E**, respectively). However, flow-induced vasodilation in SHR vessels was significantly impaired at 50 mmHg compared with the WKY group (**Figure 2C**).

Endothelium-Independent Dilation

Figure 3 illustrates vasodilator responses of SMA to SNP and it is clear that the response in WKY rats reduced with increased intravascular pressure (**Figure 3A**). Dilation responses decreased at 120 mmHg compared with both 50 and 80 mmHg over the range of 10^{-6}–10^{-4} mol/L SNP ($P<0.001$ and $P<0.01$, respectively), with the dilation response to 10^{-5} mol/L SNP significantly attenuated at 80 mmHg compared with 50 mmHg ($P<0.05$). Unlike the SMA from WKY rats, SNP-induced dilation for vessels from SHR increased with intravascular pressure (**Figure 3B**), with significant increases at 80 mmHg for 10^{-6} and 10^{-4} mol/L SNP ($P<0.01$).

Vasodilatory responses to SNP did not differ between groups at 80 mmHg (**Figure 3D**). However, SNP-induced dilation was significantly decreased in SHR vessels at 50 mmHg, but there was a significantly improvement in dilation response in those vessels at 120 mmHg pressure, compared with the WKY vessels (**Figures 3C** and **E**, respectively).

Discussion

In this study, the dilatation responses of SMA from WKY and SHR rats under progressively increasing intraluminal pressures were examined. Our results indicate that both the endothelium-dependent (ie, ACh, flow) and endothelium-independent (ie, SNP) dilation behavior of WYK and SHR SMA respond differently to increased intraluminal pressure. Flow mediated, ACh-induced and SNP-induced dilatation responses were maximal at 50 mmHg for WKY vessels and all these responses were impaired at 80 and/or 120 mmHg to various degrees. Conversely, both endothelium-dependent and -independent dilation responses of SMA from SHR were greater at 80 and/or 120 mmHg compared with 50 mmHg intraluminal pressure.

Acute or chronic elevations in BP, the main determinant of vessel wall stretch, can instigate important adaptive alterations by modifying the morphology and function of the vessels.[22–24] Acute changes in BP correlate with transient adjustment in vessel diameter. In addition, it has been demonstrated that acute and transient high intravascular pressure cause endothelial dysfunction in vessels from normotensive subjects.[25,26] In a previous study we examined vascular dilation responses of SMA from normotensive Wistar rats under progressively increasing intraluminal pressures and we found that increases in intraluminal pressure impair both endothelium-dependent and- independent dilation responses;[27] the results presented herein for normotensive WKY rats are thus in agreement with our earlier report.

Sustained hypertension induces alterations of vessel wall shape and structure, with the most obvious being an increase in wall thickness and a decrease in lumen diameter. These structural changes are quite pronounced in SHR, and hence this animal model is used to simulate human essential hypertension.[28,29] It has been confirmed by a number of studies that SMA from SHR have a smaller lumen, as well as an increased media to lumen ratio and cross-sectional area of media.[12,13,16] In agreement with previous studies,[30,31] our results indicate that the passive diameter of SHR arteries is significantly reduced and the initial tone significantly increased at all pressures measured (ie, 50, 80 and 120 mmHg).

The structure of small arteries is, at least in part, determined by pressure-dependent mechanisms and in hypertension, vascular smooth muscle cells undergo hypertrophy/hyperplasia and synthesize extracellular matrix proteins. Consequently, increased wall thickness and rigidity tend to normalize the circumferential tensile stress that is experienced by the vessel wall.[28,32] In the other words, structural remodeling of small arteries is an adaptive response to the altered mechanical conditions that occur in hypertension. There is accumulating evidence that reactive oxygen species (ROS) production is induced by high intravascular pressure and that ROS-coupling intracellular signal pathways are involved in this remodeling process.[23,33] The structural and mechanical properties of small resistance arteries obtained from animals and humans have been studied,[12–16] and in such studies, intravascular pressure was increased gradually and the characteristics of arteries from normotensive and hypertensive subjects examined at various pressures; results indicated that under isobaric conditions, small arteries from hypertensive subjects have different structural and mechanical properties than those of normotensive animals. Such findings thus lend support to the suggestion that small arteries undergo in vivo adaptive remodeling as a consequence of exposure to higher BP in the hypertensive subject.

On the other hand, it has also been shown that the functional properties of resistance arteries in hypertension are also altered, with several studies suggesting that the endothelium-dependent dilation responses of small arteries are impaired in hypertension.[16–21] However, such studies have a potential problem: dilation responses of small arteries from hypertensive subjects have been examined under normotensive pressure in order to provide experimental conditions identical to those for the normotensive control groups. Because it is plausible that the functional properties of resistance arteries may differ at high intravascular pressures because of in vivo adaptation, assessing the properties of hypertensive resistance arteries under normotensive conditions may provide accurate yet non-relevant information.

The actual pressures to which small vessels are exposed can be estimated by extrapolation from several animal studies. Investigations that have measured BP in small vessels in a mesenteric bed indicate that 36–55% of the total pressure drop occurs in these small arteries,[34,35] and thus small artery intraluminal pressure in the rat has been estimated at approximately 50% of SBP.[36] Measurement of BP in the SMAs of hypertensive rats report pressures higher than normotensive animals: BP measured in second-order mesenteric arteries was approximately 50–60 mmHg in normotensive and approximately 85–95 mmHg in hypertensive rats.[35,37] We therefore chose to use intravascular pressures of 50, 80 and 120 mmHg in the present study because these probably encompass the intravascular pressures in both normotensive and hypertensive rats.

Comparison of the dilation responses of SMA from normotensive and hypertensive animals revealed that although both endothelium-dependent and -independent dilation responses of SHR vessels were significantly impaired at 50 mmHg compared with WKY vessels, this difference disappearing at 80 mmHg. Furthermore, both ACh- and SNP-induced dilation responses were significantly higher at 120 mmHg in SHR vessels than in those from the WKY

rats. Thus, it appears that the optimal intraluminal pressure applied to vessels obtained from normotensive and hypertensive subjects should not be identical. This point may be critically important for in vitro myography studies that compare the vessels from normotensive and hypertensive subjects. Although our investigation does not provide mechanistic information, to our knowledge it is the first to investigate the responsiveness of small arteries obtained from hypertensive rats under different intraluminal pressures.

In conclusion, the results of this study indicate that the dilatation responses of SMAs from genetically hypertensive rats are enhanced at higher intravascular pressures. Possible causes may be associated with the vascular adaptive processes that occur during high in vivo BP conditions. Because of this adaptive response, the functional properties may also differ for normotensive vs hypertensive conditions. This differential sensitivity to luminal pressure should be considered during in vitro examination of vessels from normotensive and hypertensive subjects. On the other hand, further studies are required to reveal the underlying mechanisms of this altered dilation response to intraluminal pressure in resistance arteries of hypertensive subjects.

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