Inhibition of NOS enhances pulmonary vascular changes in stroke-prone spontaneously hypertensive rats

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Inhibition of NOS enhances pulmonary vascular changes in stroke-prone spontaneously hypertensive rats. Am. J. Physiol. Lung Cell. Mol. Physiol. 278: L81–L89, 2000.—To determine the effects of chronic nitric oxide (NO) blockade on the pulmonary vasculature, 58-day-old spontaneously hypertensive rats of the stroke-prone substrain (SHRSP) and Wistar-Kyoto rats (WKY) received Nω-nitro-L-arginine (L-NNA; 15 mg·kg−1·day−1 orally for 8 days). Relaxation to acetylcholine (ACH) in hilar pulmonary arteries (PAs), the ratio of right ventricular (RV) to body weight (RV/BW) to assess RV hypertrophy (RVH), and the percent medial wall thickness (WT) of resistance PAs were examined. L-NNA did not alter the PA relaxation, RV/BW, or WT in WKY. Although the PA relaxation and RV/BW in control SHRSP were comparable to those in WKY, the WT was increased (31 ± 2 vs. 19 ± 1%). L-NNA-treated SHRSP showed two patterns: in one group, the relaxation, RV/BW, and WT were comparable to those in the control SHRSP; in the other, impaired relaxation (36 ± 7 vs. 88 ± 4% for WKY) was associated with an increase in WT (37 ± 1%) and RV/BW (0.76 ± 0.05). Thus the abnormal pulmonary vasculature in SHRSP at <10 wk of age is not accompanied by impaired relaxation in PAs or RVH; however, impaired relaxation is associated with increased WT and RVH.

nitric oxide synthase; acetylcholine; Nω-nitro-L-arginine; pulmonary circulation; pulmonary hypertension

ELEVATED PULMONARY ARTERIAL PRESSURE (Ppa) and enhanced pulmonary vasoconstriction to hypoxia have been reported to occur in patients with systemic hypertension (11, 34). Inhibition of angiotensin-converting enzyme and/or blockade of angiotensin II (ANG II) type 1 receptor results in attenuation of hypoxia-induced pulmonary vasoconstriction and pulmonary hypertension in humans and experimental models (15, 16, 28). Spontaneously hypertensive rats (SHR) were bred to be a model of systemic hypertension (32). SHR of the stroke-prone substrain (SHRSP) develop severe systemic hypertension and stroke (30, 33), and the placement of these animals on a high-salt and stroke-prone diet accelerates the natural progression of the disease (33). Interference with the renin-angiotensin system has a protective effect on pathological changes in the brain, heart, and kidneys (38, 39). Nitric oxide (NO), produced by vascular endothelial cells, plays an important role in the modulation of vascular tone and structure via a cGMP mechanism (9, 10) and has been reported to oppose the activities of Ang II (27). Inhibition of NO by chronic administration of a NO synthase (NOS) inhibitor further hastens the disease process in the brain, heart, and kidneys of SHRSP (6, 43). Endothelial dysfunction and impaired bioavailability of NO in the pulmonary circulation have been reported in various forms of clinical and experimental pulmonary hypertension (PH) irrespective of the underlying disease processes (1, 5, 8, 21, 22). Furthermore, exogenous NO administration attenuates both monocrotaline- and chronic hypoxia-induced PH in rats (17, 20). Taken together, these observations suggest that the low availability of bioactive NO plays an important role in the pathogenesis and/or progression of PH.

There are only a few studies that have examined the alterations in the pulmonary vascular system in SHR and SHRSP models of systemic hypertension. SRHs at 16 wk of age develop mild PH (14). Altered vascular reactivity (24) and metabolism (36) in the pulmonary circulation have also been documented in this strain. Because SHRSP treated with 1% saline and a stroke-prone diet rapidly develop severe systemic hypertension and end-organ damage, we hypothesized that these rats would also develop pulmonary hypertensive changes at a very early age, and the inhibition of endogenous NO formation would contribute to the development of pulmonary hypertensive changes and right ventricular (RV) hypertrophy (RVH). To test this, we compared the effect of inhibition of NOS with Nω-nitro-L-arginine (L-NNA) in SHRSP with that in age-matched Wistar-Kyoto rats (WKY) given 1% NaCl and fed a stroke-prone rodent diet. We examined endothelium-dependent, cGMP-mediated relaxation to acetylcholine (ACH) and ADP, endothelium-independent cGMP-mediated relaxation to glyceryl trinitrate (nitroglycerin; GTN), and cAMP-mediated relaxation to isoproterenol in isolated hilar pulmonary arteries (PAs) from these rats. In addition, RVH, left ventricular (LV) hypertrophy (LVH), and medial wall thickening of the resistance PAs were assessed.

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METHODS

SHRSP and WKY were bred in the Animal Care Facility at New York Medical College (Valhalla, NY). Breeding pairs were obtained from the small-animal division of the National Institutes of Health (Bethesda, MD). All rats in this study (age 49–52 days) had free access to high-salt intake (1% normal saline) and a stroke-prone rodent diet (Zeigler Brothers, Gardner, PA) for 2 wk. The investigation conforms with the Guide for the Care and Use of Laboratory Animals (7th ed.; Washington, DC: Natl. Acad. Press, 1996).

Protocols

Rats were treated twice daily by gavage with L-NNA (15 mg·kg⁻¹·day⁻¹) or isovolumic vehicle (deionized water, 6 ml·kg⁻¹·day⁻¹) starting at 8–8.4 wk of age. The treatment with L-NNA was continued for 8 days. The rats were divided into four groups: group I, control WKY (vehicle treated; n = 10); group II, L-NNA treated WKY (n = 10); group III, control SHRSP (vehicle treated; n = 9); and group IV, L-NNA-treated SHRSP (n = 16). Depending on the relaxation responses to ACh in PAs, L-NNA-treated SHRSP in group IV were subdivided into two groups: those that showed no diminution in the relaxation response to 10⁻⁵ M ACh compared with that in group III (group IV-a; n = 8) and those that showed 2 SD below the mean relaxation response of the control value (group IV-b; n = 8). The rats were weighed twice each week, and systemic blood pressure was recorded with tail-cuff plethysmography.

Systemic and \( P_{ba} \) Measurement

On the last day of treatment, the rats were anesthetized with pentobarbital sodium (65 mg·kg⁻¹ ip) and allowed to breathe freely through a tracheal cannula. Body temperature was maintained at 37°C with a heat lamp. The left femoral artery was cannulated with PE-50 tubing containing heparinized saline (30 IU/ml) for arterial blood pressure measurement with a COBE CDX III fixed-dome transducer connected to a Digi-Med blood pressure analyzer (Micro-Med), which, in turn, was connected to a DPU-411 thermal printer. After a 20-min period of blood pressure measurement, the rat was put on rodent ventilator (breaths 70–80/min, tidal volume 0.83 ml/100 g). The chest was opened through a midline incision. After the rib cage and bleeders were secured, PE-50 tubing with 25-gauge needle was inserted into the RV and advanced to the PA, and the pressure was recorded on Grass polygraph (model 7D, Grass Instruments, Quincy, MA). The PA or RV systolic pressure was defined as \( P_{pa} \). At the end of the pressure measurement, the vascular system was perfused with heparinized normal saline via the femoral artery cannula. The heart and lungs were removed and placed in ice-cold Krebs bicarbonate buffer. Hilar PAs were dissected with care for isolated vessel studies, and the heart and lungs were preserved in 10% neutral-buffered Formalin for lung histology and the assessment of RVH and LVH. A reliable \( P_{pa} \) in group IV-b could not be obtained because the rats in this group developed significant hypotension when placed on the ventilator and a few of the rats died profusely.

Isolated PA Study

Hilar PAs were dissected with care and cut into rings 3 mm in length. In some rings, the luminal surface was rubbed with a pared wooden handle of a cotton-tipped swab to disrupt the endothelial surface. The rings were mounted on steel wire hooks attached to a force displacement transducer (FT03, Grass Instruments), and the changes in isometric force were recorded on a Grass polygraph (model 7, Grass Instruments). The arterial rings were allowed to equilibrate at an optimal basal tension of 2 g in Krebs bicarbonate buffer containing (in mM) 118 NaCl, 4.7 KCl, 1.5 CaCl₂, 25 NaHCO₃, 1.1 MgSO₄, 1.2 KH₂PO₄, and 5.6 glucose in individual 10-ml organ baths (Metro Scientific, Farmingdale, NY) maintained at 37°C and aerated with 21% O₂-5% CO₂-balance N₂ at a pH of 7.4 (18). The rings were allowed to equilibrate in drug-free Krebs buffer for 30 min between the experimental cycles. After the initial incubation of the arterial rings in Krebs buffer for 1 h, a cumulative concentration-response curve with phenylephrine (PE; 10⁻⁶ to 10⁻⁵ M) was obtained. Once a steady state was reached, 10⁻⁶ M ACh was added to assess the integrity of the endothelium. For subsequent experiments, a dose of PE that produced submaximal contraction (50–60% of the maximal contraction) was used. In all experiments, the resting tension was defined as zero. Relaxation responses are expressed as the percent decrease in tone in relation to the active force generated above the baseline by PE. Relaxation responses to ACh, ADP, GTN, and isoprot-eranol were examined. GTN and isoproterenol-induced endothelium-independent relaxation. For the purpose of statistical analysis, the results from endothelium-intact vessels were used.

Endothelium-Dependent cGMP-Mediated Relaxation Responses

To assess the endothelium-dependent NO-related relaxation, the rings were precontracted with 10⁻⁶ M PE. Once the steady state was reached, concentration-dependent responses to ACh (10⁻⁴ to 10⁻⁵ M) and ADP (10⁻⁵ to 10⁻⁴ M) were obtained.

Endothelium-Independent cGMP-Mediated Relaxation Responses

To assess the endothelium-independent relaxation, the rings were precontracted with 10⁻⁶ M PE, and dose-response curves to GTN (10⁻⁹ to 10⁻⁶ M) were obtained.

cAMP-Mediated Relaxation Responses

To assess cAMP-mediated relaxation, dose-response curves to isoprotenerol (10⁻⁶ to 10⁻⁵ M) were obtained after the arterial rings were precontracted with PE as described in Endothelium-Independent cGMP-Mediated Relaxation Responses.

Assessment of RVH and LVH

Each heart was trimmed of the atrial appendages, and the atria were removed. The free wall of RV was separated from the LV and the septum and weighed. The ratio of the weight of each ventricle in milligrams to body weight (BW) in grams (RV/BW and LV/BW) was calculated to express RVH and LVH, respectively. The ratio of the weights of the RV to the LV could not be used to express RVH in this study because SHRSP displayed significant LVH.

Histology of Lung Vessels

The lungs were processed for analysis by light microscopy. Briefly, the lungs were embedded in paraffin blocks, and 4-µm sections were cut and stained with hematoxylin and eosin and elastic van Gieson to distinguish the elastic laminae. Morphometric analysis was performed as previously described (19, 25). The PAs were identified as vessels with two clearly defined elastic laminae with a layer of smooth muscle cells between the two laminae. The thickness of the medial
Table 1. Age, BW, SAP, Ppa, and LVH in Wistar-Kyoto rats and stroke-prone spontaneously hypertensive rats

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV-a</th>
<th>Group IV-b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, days</td>
<td>69 ± 1</td>
<td>67 ± 1</td>
<td>70 ± 1</td>
<td>67 ± 1</td>
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<td>(n = 10)</td>
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<td>(n = 9)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
</tr>
<tr>
<td>BW, g</td>
<td>257 ± 7</td>
<td>255 ± 9</td>
<td>238 ± 6</td>
<td>187 ± 8*†‡</td>
<td>202 ± 4*†‡</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 9)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
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</tr>
<tr>
<td>SAP, mmHg</td>
<td>96 ± 4</td>
<td>142 ± 9*</td>
<td>196 ± 8*†</td>
<td>204 ± 15*†</td>
<td>201 ± 13*†</td>
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<tr>
<td>(n = 8)</td>
<td>(n = 5)</td>
<td>(n = 8)</td>
<td>(n = 5)</td>
<td>(n = 7)</td>
<td>(n = 7)</td>
</tr>
<tr>
<td>Ppa, mmHg</td>
<td>18 ± 0.9</td>
<td>19 ± 1.4</td>
<td>20 ± 1.9</td>
<td>20 ± 0.2</td>
<td>NA</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>(n = 6)</td>
<td>(n = 7)</td>
<td>(n = 5)</td>
<td>(n = 7)</td>
<td></td>
</tr>
<tr>
<td>LV/BW, mg/g</td>
<td>2.50 ± 0.03</td>
<td>2.70 ± 0.06</td>
<td>3.15 ± 0.09*†‡</td>
<td>3.63 ± 0.12*†‡</td>
<td>4.04 ± 0.02*†‡</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 9)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
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</tr>
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</table>

Values are means ± SE; n, no. of observations. BW, body weight; SAP, systemic arterial pressure; Ppa, pulmonary arterial pressure; LV/BW, left ventricular weight-to-final BW ratio; group I, control Wistar-Kyoto rats (WKY); group II, N-nitro-l-arginine (L-NNA)-treated WKY; group III, control spontaneously hypertensive rats of stroke-prone substrain (SHRSP); group IV-a, L-NNA-treated SHRSP that showed no diminution in relaxation response to 10⁻⁵ M acetylcholine; group IV-b, L-NNA-treated SHRSP that showed 2 SD below mean relaxation response; NA, not available. All rats were maintained on 1% NaCl in drinking solution starting at 49–52 days of age and were subsequently treated with 15 mg·kg⁻¹·day⁻¹ of L-NNA or vehicle for 8 days. Significant difference (P < 0.05) from: * group I; † group II; ‡ group III.
not reach the level of significance. In group IV-b, the relaxation response to 10^{-5} M ADP was significantly impaired compared with the responses in the other groups (Fig. 2). At 10^{-6} M, the relaxation responses in groups IV-b and II were significantly lower compared with those in the SHRSP groups (groups III and IV-a). At 10^{-5} M, however, the relaxation responses in L-NNA-treated WKY (group I) were not different compared with those in groups I, III, and IV-a.

Endothelium-Independent cGMP-Mediated Relaxation

The relaxation response to 10^{-6} M GTN was not impaired in any of the SHRSP groups (Fig. 3). At a concentration of 10^{-8} M GTN, the relaxation response in group I was significantly lower compared with that in the SHRSP groups (groups III and IV-a) and at a concentration of 10^{-7} M, relaxation in group I was significantly lower compared with that in group IV-a.

cAMP-Mediated Relaxation

cAMP-mediated relaxation to isoproterenol was not different in WKY and SHRSP. Treatment with L-NNA did not influence the relaxation responses in any of the groups tested (Fig. 4).

RVH

WKY given L-NNA did not exhibit RVH. There was no evidence of RVH in the control SHRSP (group III) or...
in one subgroup of SHRSP given l-NNA (group IV-a). However, there was significant RVH in the second subgroup of SHRSP treated with l-NNA (group IV-b) as shown in Fig. 5. Because rats in the SHRSP groups had LVH, a ratio of RV to LV weights could not be used to assess RVH. The data for RV to LV weights were as follows: group I, 0.25 ± 0.01 (n = 10 rats); group II, 0.23 ± 0.01 (n = 10 rats); group III, 0.19 ± 0.01 (n = 9 rats); group IV-a, 0.17 ± 0.01 (n = 8 rats); and group IV-b, 0.19 ± 0.01 (n = 7 rats). The absolute RV weights in the experimental groups were as follows: group I, 155 ± 4 mg (n = 10 rats); group II, 156 ± 8 mg (n = 10 rats); group III, 141 ± 4 mg (n = 9 rats); group IV-a, 115 ± 5 mg (n = 8 rats); and group IV-b, 153 ± 8 mg (n = 7 rats).

LVH

Table 1 shows LV/BW as an expression of LVH. The treatment of WKY with l-NNA did not induce LVH despite increased blood pressure. As expected, control SHRSP (group III) exhibited significant LVH compared with that in control WKY (group I). l-NNA treatment significantly increased LVH in SHRSP (P < 0.05 for group IV-a vs. group III), and there was a further increase in LVH in group IV-b, but it did not reach significance (Table 1). Absolute LV weights in the experimental groups were as follows: group I, 646 ± 22 mg (n = 10 rats); group II, 686 ± 31 mg (n = 10 rats); group III, 750 ± 31 mg (n = 9 rats); group IV-a, 671 ± 10 mg (n = 8 rats); and group IV-b, 809 ± 29 mg (n = 7 rats).

Lung Histology

SHRSP displayed medial thickening of PAs (Fig. 6B), and the pulmonary veins also showed thickening (Fig. 6C) as described by Aharinejad et al. (2) in older SHR aged 14–18 wk. There was no evidence of pulmonary hemorrhage in this group. In WKY, arterial and venous abnormalities were not observed. PAs in group IV-a (SHRSP + l-NNA) showed medial wall thickening that

![Fig. 5. Ratio of right ventricular (RV) weight to body weight (RV/BW), an index of RV hypertrophy (RVH) in group I (n = 10 rats), group II (n = 10 rats), group III (n = 9 rats), group IV-a (n = 8 rats), and group IV-b (n = 7 rats). There was significant RVH in group IV-b compared with that in the rest of the groups, *P < 0.05 vs. groups I, II, III, and IV-a.](http://ajplung.physiology.org/)

![Fig. 6. Micrographs obtained from elastic van Gieson-stained slides of lungs (×10 magnification). A: thin-walled pulmonary artery (arrow) from a control WKY. B: thick-walled pulmonary artery (arrow) from a control SHRSP. C: eccentric hypertrophy of a pulmonary vein (arrow) in lung section from a control SHRSP. Unlike artery, vein does not have an internal elastic lamina.](http://ajplung.physiology.org/)
was comparable to that observed in the SHRSP control group. However, in group IV-b (SHRSP + L-NNA), pulmonary medial wall thickening was significantly increased compared with that in group III, group IV-a, and the WKY groups (Fig. 7). WKY given L-NNA did not exhibit pulmonary arterial or venous abnormalities.

Regression Analysis for Parameters in Group IV

Linear regression analysis of the data in groups IV-a and IV-b revealed a highly significant correlation between the percent relaxation response to $10^{-5}$ M ACh in the PAs and the RV/BW ($P < 0.005; r = 0.48$) and also between the relaxation response and the %WT ($P < 0.001; r = 0.68$). There was no correlation between the relaxation response and the LV/BW ($P > 0.10; r = 0.17$).

DISCUSSION

The present study shows that by 10 wk of age, SHRSP develop abnormal anatomic changes in the pulmonary vasculature such as medial wall thickening of resistance PAs and focal thickening of the venous walls. These changes were not accompanied by PH or RVH at this age. Similarly, increases in pulmonary arterial WT and venous abnormalities have been described in older SHR (2). These changes in the absence of PH may reflect intrinsic vascular differences and/or hormonal alterations. For example, cultured pulmonary vascular smooth muscle cells from Fawn-Hooded rats, another genetic model of systemic hypertension that develops PH, proliferate at a much higher rate compared with cells from Sprague-Dawley rats and also show much higher binding of epidermal growth factor (13). An abnormally high rate of proliferation of cultured aortic vascular smooth muscle cells has been observed in older SHR (12). ANG II plays an important role in cell cycle regulation and has been reported to stimulate the proliferation of human pulmonary arterial smooth muscle cells (7, 29). Marked increases in ANG-converting enzyme immunoreactivity have been detected in endothelial cells and in the subendothelial neointimal region of elastic PAs from patients with primary PH (37). There is also evidence to suggest that ANG II plays a role in the pathogenesis of hypoxia-induced PH and monocrotaline-induced PH associated with increased pulmonary flow (28, 31). Thus the pulmonary vascular changes observed in this study in the control SHRSP may be due to intrinsic vascular abnormalities and/or to hormonal factors such as ANG II.

L-NNA-treated SHRSP showed two distinct patterns of endothelium-dependent relaxation responses to ACh and ADP in PAs. Relaxation responses in group IV-a were not impaired, and, not surprisingly, these rats did not develop PH or RVH. Pulmonary arterial medial WT was also comparable to that in the control SHRSP. PH in group IV-b could not be documented because these rats were unstable during the surgical procedure used to measure $P_{pa}$. Despite this, group IV-b exhibited an impaired endothelium-dependent relaxation to ACh in the isolated PA, concomitant with significant medial wall thickening of PAs and RVH, which suggests that PH may also have been present. Overall, the endothelium-dependent NO-mediated relaxation response in hilar PAs from L-NNA-treated SHRSP was directly related to %WT and RVH because there was a significant correlation between the percent relaxation response to $10^{-5}$ M ACh and either %WT or RV/BW. In contrast, the endothelium-independent relaxation to GTN was not impaired in group IV-b. Thus although the endothelial response was impaired in this group, the smooth muscle cells were capable of responding to NO. These observations are consistent with the diminished availability of endogenous NO in this group. NO has been shown to decrease the proliferation of cultured vascular smooth muscle cells (10) and to suppress the function of endothelin-1 (4) and ANG II type 1 receptors (27). Thus it is likely that the decreased availability of bioactive NO in group IV-b may promote vascular remodeling due to the combined effect in the intrinsic actions of a deficit of NO and the abnormal influence of other humoral factors that promote vessel wall thickening. Whether the further increase in %WT after L-NNA treatment is secondary to hyperplasia or hypertrophy of the smooth muscle cells could not be determined. The association of diminished relaxation response and increased %WT in group IV-b supports the concept that low availability of bioactive NO due to either the inhibition of NO production or its rapid degradation contributes to the pathogenesis or progression of PH. Group IV-b was also the only group that exhibited RVH. Although BW was diminished in group IV-b, this did not differ from the BW in group IV-a, and yet RV weight was increased only in group IV-b. Thus RVH was evident in group IV-b on the basis of both increased absolute RV weight and increased RV/BW. In contrast, there was no correlation between relaxation responses and either LV/BW or systemic blood pressure. Thus the differences in pulmonary response to L-NNA in SHRSP do not appear to be related to the level of systemic blood pressure or BW changes because

![Fig. 7. Percent wall thickness (%WT) in pulmonary arteries in group I (n = 8 rats), group II (n = 10 rats), group III (n = 7 rats), group IV-a (n = 5 rats), and group IV-b (n = 8 rats). Group II showed normal %WT. Groups III, IV-a, and IV-b had significantly increased %WT compared with group I. Group IV-b showed a further increase in %WT. *P < 0.005 vs. groups I and II. #P < 0.05 vs. groups III and IV-a.](http://ajplung.physiology.org/)
the L-arginine-NO pathway has been reported to be fully established. In this context, it is worth noting that the mechanism that is subsequently lost once hypertension is considered to be a compensatory mechanism that is responsible for the development of cardiac hypertrophy in SHRSP (41). Thus the enhanced ACh-induced relaxation in the PAs from young SHRSP may also be part of a compensatory circulatory response to offset the developing pulmonary vascular changes. Although the response to ADP appeared greater in SHRSP compared with WKY, this was not significant. The relaxation to smaller doses of GTN was higher in the control SHRSP compared with the control WKY. The cAMP-mediated relaxation to isoproterenol was not modulated by L-NNA treatment in any of the groups. This is consistent with the previous finding by Mathew et al. (18) that in rat hilar PAs, the endothelium does not modulate the contractile response to PE. SHRSP at 10 wk of age displayed significant systemic hypertension and LVH compared with those in WKY. LVH is considered to be an adaptive mechanism to compensate for cardiac overload. Chronic treatment of saline-drinking SHRSP with L-arginine for 1 mo had no effect on either cardiac hypertrophy or blood pressure (40). However, Matsuoko et al. (23) have shown that chronic treatment of water-drinking SHR with L-arginine for 3 mo attenuates cardiac hypertrophy without altering blood pressure. In the present study, SHRSP on L-NNA treatment developed significant LVH that was not accompanied by a further increase in blood pressure. At the end of 8 days of L-NNA treatment, WKY developed only moderate systemic hypertension (142 ± 9 mmHg), which was not accompanied by LVH. Relaxation responses to ACh, GTN, and isoproterenol in hilar PAs were not impaired in this group. Nor were there any histological changes in the lungs, PH, or RVH. LVH has been observed only in a small number of WKY that exhibited severe systemic hypertension after 8 wk of treatment with an NOS inhibitor (3). Thus in WKY, the magnitude and duration of hypertension appear to be the factors that determine the presence or absence of ventricular hypertrophy. In contrast, a defect in the L-arginine-NO axis plays a significant role in the development of cardiac hypertrophy in SHRSP where systemic hypertension has already been established.

In summary, SHRSP at a relatively young age show anatomic abnormalities in the pulmonary vasculature that are not associated with impaired endothelium-dependent relaxation responses or RVH. The enhanced relaxation response to low concentrations of ACh in isolated PAs could be a compensatory response to the developing pulmonary vascular histological abnormalities in this model. Impaired endothelium-dependent relaxation after 8 days of L-NNA treatment in SHRSP is associated with increased medial thickening of resistance PAs and RVH. Thus the development of pulmonary vascular abnormalities in SHRSP does not appear to be related to an impairment in endogenous bioavailability of NO. In contrast to SHRSP, L-NNA treatment for the same period of time had no effect on pulmonary arterial WT or RV weight in WKY. These findings suggest that although the SHRSP have pulmonary vascular abnormalities, NO plays an important role in protecting against the development of pulmonary vascular changes in this group.

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