In chronically hypoxic rats, lung tissue expression of mRNA and protein for nitric oxide synthase (NOS) significantly increase as early as 24 h after hypoxic exposure [1]. Immunohistochemistry has shown progressive increases in endothelial NOS (eNOS) expression in pulmonary vessels of internal diameter (ID) <150 μm and in inducible NOS (iNOS) in the vascular smooth muscle of all pulmonary vessels during 1- to 7-d hypoxic exposure [1]. However, the functional significance of the structural up-regulation of NOS during these early phases of chronic hypoxia (CH) has not yet been clarified in the resistance and conduit pulmonary arteries of the rat.

The question about how the endogenous nitric oxide (NO)–mediated regulation of basal pulmonary vascular resistance changes in response to CH has been investigated extensively by measuring the pressure-flow relation in 3- to 4-wk hypoxic rat lungs, and many studies have shown a significant enhancement [2–5]. However, this question has not been studied sufficiently during earlier CH phases. A small [6] or insignificant [7] increase in the NO-mediated basal vascular resistance regulation has been suggested in 1-wk hypoxic rats. Moreover, exactly which pulmonary vascular segments contribute to this regulation remains to be examined.

To resolve these issues, we directly measured ID changes in resistance and conduit pulmonary arteries of 1- and 2-week hypoxic rats and normoxic control rats in response to nitric oxide synthase (NOS) inhibitors in vivo. At 2 weeks of hypoxic exposure, the ID reduction as a result of NOS inhibition was enhanced within the resistance arteries, but not at 1 week of hypoxia. [Japanese Journal of Physiology, 51, 395–398, 2001]

Key words: chronic hypoxia, nitric oxide, basal pulmonary vascular tone.
Pulmonary arterial pressure increased by 1.7–2.7 mmHg in response to the nonselective NOS inhibitor in the present study. Cardiac output has been shown to decrease by 15–40% after nonselective NOS inhibitor injections in normoxic and chronically hypoxic rats [6, 11, 12]. It is therefore possible that the pressure- and flow-sensing mechanisms [13] influenced the ID response pattern during NOS inhibition. To examine this possibility, further preliminary experiments were carried out. We measured the ID changes of 100–700 μm pulmonary arteries in the left lung in response to mechanically induced pulmonary arterial pressure increases of 2 to 3 mmHg or pulmonary blood flow decreases of 20–40%. The right main pulmonary artery was partially occluded by ligation to increase pulmonary arterial pressure of the left lung. The same procedure was employed for the vena cava inferior to decrease pulmonary blood flow. Neither of these procedures, however, induced a significant ID change, suggesting that the possibility is small. The nonselective NOS inhibitor has been shown to cause neuronal NOS inhibition in the brain stem and thus increase sympathetic nerve activity [14]. Therefore there is another possibility that activating pulmonary sympathetic nerve activity or an increase in plasma catecholamine concentration, or both, contributed to the NOS inhibitor–induced ID reduction. However, it has been shown that an autonomic blockade has no effect on the increase in systemic arterial pressure or on decreases in cardiac output and tissue flows caused by NOS inhibitor injection in rats [11]. Moreover, we found that a selective neuronal NOS inhibitor, 7-nitro...
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indazole, had no significant effect on the pulmonary artery ID in both normoxic and chronically hypoxic rats (unpublished data). The data suggest that this possibility is also small.

The recent Northern and Western analyses have shown a ~150% increase in eNOS mRNA and protein in the rat lung tissue at 1 wk of exposure to hypoxia (10% O₂) [1]. Moreover, eNOS and iNOS immunoreactivity in the pulmonary vessels was progressively increased over 1 to 7 d of hypoxia [1]. The present study focused on the issues concerning when and in which pulmonary vascular segment the progressively increased NOS expression during early CH phases enhances the NO-mediated regulation of basal pulmonary vascular tone in the in vivo rat lung. The results suggest that a continuous release of NO regulates the basal vascular tone of both the resistance (100–150 μm) and the small conduit (500–700 μm) pulmonary arteries under normoxic conditions and that the basal release of NO dominantly dilates the conduit arteries compared with the resistance arteries. This agrees well with our previous data in the cat [15]. The NO-mediated regulation was not enhanced at 1 wk of hypoxia (10% O₂ exposure), although it was at 2 wk of hypoxia. This is inconsistent with the above-mentioned up-regulation of NOS and indicates that an increased vascular NOS expression does not correlate with the enhancement of NO-mediated basal vascular tone regulation at 1 wk of hypoxia. One possible reason for this discrepancy is that an increase in NO production in resistance arteries was not significant enough to change their vascular tone despite the structural up-regulation of NOS at 1 wk of hypoxia. Previous findings that perfuse NO-containing compound (NOₓ) concentration significantly increased in lungs isolated from 2-wk, but only slightly from 1-wk, hypoxic rats [16] may support this possibility, although the NOₓ concentration reflects the sum of NO release in all pulmonary vascular segments. It has been shown that 1-wk hypoxic exposure attenuates the ability of sodium nitroprusside to elevate cyclic GMP levels in the rat pulmonary arteries [17], suggesting decreased guanylyl cyclase activity at 1 wk of hypoxia. This may also partly explain the discrepancy.

In the rat resistance pulmonary arteries, especially vessels <150 μm ID, both eNOS and iNOS immunoreactivity increased in response to hypoxia for 2–4 wk, and in the conduit arteries iNOS predominantly increased [1, 18]. In the present study, however, a significant increase in the nonselective NOS inhibitor–induced vasoconstriction at 2 wk of hypoxia was observed locally in the resistance arteries, although there was an increasing tendency of the vasoconstriction in the conduit arteries. It is therefore possible that the contribution of hypoxia-induced iNOS increases in the conduit arteries to the NO-mediated regulation of basal vascular tone is small, if any exists. It is of interest to note that 2-wk hypoxia increased cyclic GMP phosphodiesterase (PDE) activity in the rat conduit pulmonary arteries, but not in the resistance arteries [19]. Therefore in the conduit arteries, an increased production of NO from iNOS may not rise cyclic GMP level because of the hypoxic increase in cGMP PDE, which catalyze cGMP hydrolysis. Our present data of the locally enhanced vasodilator effect of NO in the resistance arteries suggest that this enhancement serves to attenuate hypoxic pulmonary vasoconstriction which occurs chiefly in these arteries [10, 20] and thus inhibit the pulmonary hypertension progress.

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