Chronic O₂ exposure enhances vascular and airway smooth muscle contraction in the newborn but not adult rat

J. Belik, R. P. Jankov, J. Pan, and A. K. Tanswell

Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada M5G 1X8

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Belik, J., R. P. Jankov, J. Pan, and A. K. Tanswell. Chronic O₂ exposure enhances vascular and airway smooth muscle contraction in the newborn, but not adult rat. J Appl Physiol 94: 2303–2312, 2003. First published January 31, 2003; 10.1152/japplphysiol.00820.2002.—Neonatal rats exposed to 60% O₂ for 14 days develop lung changes compatible with human bronchopulmonary dysplasia and pulmonary hypertension. Our aim was to evaluate and compare the newborn and adult rat pulmonary vascular and airway smooth muscle force generation and relaxation potential after exposure to 60% O₂ for 14 days. Vascular and airway intrapulmonary rings 100 μm in diameter were mounted on a myograph and bathed in Krebs-Henseleit solution bubbled with air-6% O₂ at 37°C. Significant age-dependent changes in intrapulmonary arteries and their neighboring airway muscle properties were observed. Whereas hyperoxia enhanced force in neonatal vascular and airway muscle, the opposite was seen in adult samples. No changes in endothelium-dependent vascular relaxation were observed at either age, but the dose response to an endothelium-independent NO donor was altered. In the newborn experimental animals, the relaxation was reduced, whereas, in their adult counterparts, it was enhanced. After O₂ exposure, the bronchial muscle relaxation response to epithelium-dependent and -independent stimulation was not altered in either age group, whereas the epithelium-dependent response was decreased only in the adult. The antioxidant Trolox, or an endothelin-A and -B receptor antagonist, reversed the vascular and airway muscle’s hyperoxia-induced changes. We conclude that chronic O₂ exposure in the newborn rat results in enhanced lung vascular and airway muscle contraction potential via a mechanism involving reactive oxygen species and the endothelin pathway. The present findings also suggest that the newborn was more susceptible to airway hyperresponsiveness after chronic O₂ exposure.

pulmonary hypertension; airway reactivity; chronic hyperoxia

CHRONIC O₂ EXPOSURE INDUCES pulmonary vascular remodeling and pulmonary hypertension in the newborn rat (26). The mechanisms responsible for these changes are not fully understood, but recent evidence from our laboratory indicates that endothelin-1 and possibly 8-isoprostane are involved in its pathogenesis (20, 21). Inhibition of macrophage influx, or combined blockade of endothelin-A and -B receptors, prevented right ven-tricular hypertrophy and pulmonary vascular remodeling in this model. However, it had no effect on the O₂-induced lung parenchymal changes (20), suggesting that the two pathological processes have a distinct inducing mechanism.

Aside from their putative role in the process of vascular remodeling, isoprostanes (22, 23) and endothelin-1 (12, 13, 40) are potent constrictors of pulmonary vessels and airways. This potential dual effect raises the question of whether the maintenance of a high pulmonary vascular resistance in the chronic hyperoxia-induced pulmonary hypertensive newborn rat is secondary to pulmonary vascular muscle contraction or remodeling.

In this respect, the lung histological findings of increased vascular smooth muscle in the newborn rat exposed to chronic hyperoxia are not necessarily indicative of a greater potential for vasoconstriction. In the ligated ductus arteriosus fetal sheep model of pulmonary hypertension, where muscle hypertrophy is observed, our laboratory showed that the pulmonary arterial smooth muscle had a reduced potential for contraction and endothelin-independent abnormal relaxation properties (3). Similar findings have also been described for the monocrotaline-induced adult rat model of pulmonary hypertension (1).

We reasoned that exposure to chronic hyperoxia may also induce airway smooth muscle changes. Our laboratory has previously reported that newborn rats exposed to chronic hyperoxia for 14 days have histological evidence of a bronchopulmonary dysplasia-like lung morphology (16). In human infants with bronchopulmonary dysplasia, an increased incidence of airway hyperresponsiveness has been described (29). Furthermore, an association between pulmonary hypertension and airway hyperresponsiveness has been reported in children (41) but not adults.

Little is known about the effect of 60% O₂ exposure for 14 days in the adult rat. The only reported study utilizing this concentration and duration of O₂ exposure was limited to evaluating the animal lungs at 7 days, and only minimal histological changes were observed and mostly limited to the vascular endothelium (18). Adult primates exposed for 14 days to this O₂

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concentration were reported to only develop chronic lung epithelial injury (11), but the functional properties of the vascular and airway smooth muscle were not studied.

In this study, we chose to evaluate and compare the pulmonary arterial and airway smooth muscle mechanical properties of the newborn and adult rat after 60% O2 exposure for 14 days. We hypothesized that chronic exposure to 60% O2 induces pulmonary vascular and airway muscle mechanical property changes via reactive oxygen species (ROS) formation, and these are of greater magnitude in the newborn, compared with the adult, rat. In addition, we hypothesized that chronic hyperoxia alters the endothelium- and epithelium-dependent nitric oxide production.

METHODS

Institutional review. All procedures involving animals were conducted according to criteria established by the Canadian Council for Animal Care. Approval for the study was obtained from the Animal Care Review Committee of the University Health Network, Toronto Western Hospital, and Hospital for Sick Children Research Institute.

Exposure system. Pathogen-free, timed-pregnant, or non-pregnant female adult Sprague-Dawley rats (250–275 g) were obtained from Charles River (St. Constant, Quebec). Experiments were conducted as paired exposures, with one chamber receiving 60% O2 and the other receiving air. O2 and CO2 concentrations, temperature, and humidity were continuously monitored, recorded, and regulated by a computer with the use of customized software (AnaWin2 Run-Time, version 2.2.18, Watlow-Anafaze, St. Louis, MO). Gas delivery was regulated by customized hardware (Oxycycler model A84XOV, Biospherix, Redfield, NY) and software (AnaWin2 Run-Time, Watlow-Anafaze) to maintain an O2 concentration of 0.1% of the set point. O2 sensors were calibrated weekly. On the anticipated day of delivery, each dam was placed in a 80 × 60 × 50-cm plastic chamber with 12:12-h light-dark cycles and with the temperature maintained at 25 ± 1°C, humidity ~50%, and CO2 concentration <0.5%. Equal litter sizes (10–12 pups) were maintained between paired chambers. Food and water were available ad libitum. Dams were exchanged daily between chambers to prevent maternal O2 toxicity. Pups were maintained in the chambers (air and O2) for a 14-day exposure period. Adult rats were subjected to the same above-described protocol of chronic hyperoxia. Air-treated animals served as controls. At the termination of each exposure period, animals were killed by an overdose of pentobarbital sodium (40 mg/kg ip).

Organ bath studies. Fourth- or fifth-generation (adult) left lung intralobar bronchi and neighboring pulmonary arterial ring segments (average diameter 100 µm and length 2 mm) were dissected free and mounted in a wire myograph (Danish Myo Technology). Isometric changes were digitized and recorded on-line (Myodaq, Danish Myo Technology). Tissues were bathed in Krebs-Henseleit buffer (115 mM NaCl, 25 mM NaHCO3, 1.38 mM NaHPO4, 2.51 mM KCl, 2.46 mM MgSO4·7H2O, 1.91 mM CaCl2, and 5.56 mM dextrose) bubbled with air-6% CO2 and maintained at 37°C.

After 1 h of equilibration, the optimal resting tension of the tissue was determined by repeated stimulation with 128 mM KCl until maximum active tension was reached. All subsequent force measurements were obtained at the optimal resting tension.

Pulmonary vascular muscle force generation was evaluated by stimulating with KCl and the thromboxane mimetic U-46619. Similarly, the bronchial muscle was stimulated with KCl, U-46619, and acetylcholine (ACh). Contractile responses were normalized to the tissue cross-sectional area as (width × diameter) × 2 and expressed in milli-Newtons per millimeter squared. For the acute hyperoxia studies, the pulmonary arteries were dissected, mounted, and studied on Krebs-Henseleit buffer bubbled with 94% O2-6% CO2 and maintained at 37°C.

The relaxant response to sodium nitroprusside (SNP), ACh (vascular), and adenosine triphosphate (bronchi) was determined by precontracting the pulmonary and bronchial muscle with U-46619 (10−6 M) and ACh (10−4 M), respectively. The antioxidant Trolox (10−4 M) and the endothelin-receptor antagonist SB-217242 (10−5 M) were used to evaluate the effect of ROS and endothelin, respectively, on the smooth muscle contraction and relaxation potential.

Drugs. Trolox was obtained from Hoffman-La Roche. SB-217242 was generously provided by Dr. Douglas Hay (Smith-Kline Beecham Pharmaceuticals, King of Prussia, PA). All other chemicals were obtained from Sigma Chemical (Oakville, ON) and dissolved in Krebs-Henseleit buffer.

Heart measurements. To assess for the presence of pulmonary hypertension in the experimental animals, we evaluated the degree of right ventricular hypertrophy by measuring the right ventricular weight-to-left ventricular + septum weight ratio (14).

Histology. Newborn lungs were removed immediately after death and immersed in 4% paraformaldehyde in a 0.2 M sodium phosphate buffer (pH 7.4). The tissue was postfixed at 4°C for 4–20 h, dehydrated in a graded series of ethanol, and cleared in xylene. The fixed tissue was embedded in molten paraffin in a heating incubator at 54°C for 2–3 days. After tissues were embedded, the paraffin block containing the tissue was trimmed and mounted on a rotary microtome (model 45, Lipshaw, Detroit, MI) equipped with a standard knife holder and a forward-moving block. The tissue was orientated to allow for the cutting of transverse sections (6-µm thickness) at midlung level to allow for visualization of bronchi and pulmonary artery of similar generation as used for the organ bath studies. Sections were mounted on gelatin-subbed microscope slides and immersed in xylene for 15 min to remove wax before staining. The dewaxed sections were dehydrated through a graded series of ethanol, stained with Gill’s hematoxylin for 2 min for nuclear staining, and rinsed with distilled water. The sections were then stained for 1 min with eosin for cytoplasmic staining.

Data analysis. Data were evaluated by the Student’s t-test or two-way ANOVA, with multiple comparisons obtained by the Newman-Keuls test when appropriate. Statistical significance was accepted if P < 0.05. Power analysis (α = 0.05) was performed for small-size samples (n = 4) to calculate the probability of rejecting a false null hypothesis. All statistical analyses were performed with the Number Cruncher Statistical System (NCSS, Kaysville, UT). Data are presented as means ± SE.

RESULTS

Hyperoxia induced pulmonary hypertension in the newborn and adult animals, as evidenced by the increased weight of the right ventricle (RV) relative to the weight of the left ventricle (LV) and septum [RV/LV + septum (Table 1)]. Figure 1 illustrates low- and high-power magnifications of the newborn’s bronchi and pulmonary artery of similar generations as those
utilized for functional studies. No obvious difference in the vascular and airway muscle layer thickness was noted between the control and oxygen-treated newborn animals.

After 2 wk of hyperoxia, pulmonary arterial smooth muscle force generation in response to KCl and U-466190 stimulation was significantly increased \( (P < 0.01) \) in the newborn and decreased \( (P < 0.01) \) in the adult (Fig. 2). Relaxation of previously constricted arteries was similar after endothelium-dependent stimulation with ACh (Fig. 3). In contrast, endothelium-independent relaxation in response to SNP was significantly reduced \( (P < 0.01) \) in the \( O_2 \)-exposed newborn but enhanced in the adult experimental animals (Fig. 6). Trolox or the endothelin-A and -B-receptor blocker abolished the \( O_2 \)-induced bronchial muscle force increase in the chronic \( O_2 \)-exposed newborn, but not adult, animals (Fig. 6).

The epithelium-independent (SNP) relaxation of the prestimulated airway smooth muscle was not altered by hyperoxia at either age (Fig. 7). In contrast, the epithelium-dependent (adenosine triphosphate) relaxation was reduced \( (P < 0.01) \) in the chronic \( O_2 \)-exposed adult, but not newborn, airway tissue (Fig. 7).

To evaluate the acute effect of \( O_2 \) exposure on the pulmonary vascular muscle, we compared the contraction and relaxation responses at two different muscle bath \( P_{O_2} \) values (air: \( P_{O_2} = 140 \) Torr and oxygen: \( P_{O_2} = 450 \) Torr). The higher muscle bath \( P_{O_2} \) increased \( (P < 0.01) \) KCl-induced force generation in the newborn and adult pulmonary arterial tissue (Fig. 8). The muscle bath \( P_{O_2} \) did not alter the endothelium-dependent relaxation.

### Table 1. Heart RV-to-LV + septum ratio for control and hyperoxia-treated animals

<table>
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<tr>
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<th>Control</th>
<th>Hyperoxia</th>
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<td>Newborn</td>
<td>0.26 ± 0.01</td>
<td>0.30 ± 0.01*</td>
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<tr>
<td>Adult</td>
<td>0.26 ± 0.00</td>
<td>0.29 ± 0.01*</td>
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Values are means ± SE. RV and LV, right and left ventricle, respectively. *\( P < 0.01 \) compared with control group measurements (Student’s *t*-test).

Fig. 1. Lung histology (hematoxylin and eosin) of a representative set of control (left) and chronic 60% \( O_2 \)-treated newborn animals (right). Pulmonary arteries (Art.) and bronchi (Bronc.) of a generation similar to the ones utilized for the functional studies are illustrated. The arrows point to the vascular and airway muscle layers. Top: \( 10 \)x magnification; bottom: \( 25 \)x magnification.
dose response. In contrast, the endothelium-independent SNP-induced response at higher O2 concentration was reduced \((P < 0.01)\) in the adult but not newborn (Fig. 9).

**DISCUSSION**

The factors leading to the development of pulmonary hypertension after chronic O2 exposure are not completely understood. In previous studies, our laboratory has shown that lung tissue ROS formation, thromboxane A2-receptor stimulation, possibly via local release of 8-isoprostane (19), and upregulation of endothelin-1 (20, 21) are involved in the process.

In this study, we evaluated 100-μm third- to fourth-generation pulmonary arteries and adjacent airways. On histology, the pulmonary arteries did not exhibit...
the increased muscularization that characterizes the more peripheral lung vessels of the chronic hyperoxic newborn animals (26). However, significant changes in their muscle mechanical properties were observed. This response was evident as early as 7 days after O₂ exposure (4), when no peripheral pulmonary vascular remodeling was present on lung histology.

Acutely, an increased P O₂ in the bath resulted in enhanced force generation in the newborn and adult, as well as reduced SNP-dependent relaxation in the adult pulmonary arterial muscle. In the bovine retina, SNP relaxation was also reported to be O₂ dependent (15). Although the bath P O₂ in air (145 Torr) was significantly higher than the pulmonary arterial P O₂, this does not necessarily result in tissue hyperoxia. In vivo, the vascular wall oxygenation is provided by the vasa vasorum, whereas, in the muscle bath, the oxygen has to diffuse across the tissue to reach the smooth muscle layer.

Fig. 4. Control and hyperoxia newborn (n = 4 for each group; A and B) and adult (n = 4 for each group; C and D) pulmonary arteries were studied after stimulation with U-46619 and relaxation with SNP in the presence of Trolox, a reactive oxygen species scavenger. A and C: force. B and D: relaxation. Values are means ± SE. **P < 0.01 compared with control group by two-way ANOVA.

Fig. 5. Control and hyperoxia newborn (n = 4 for each group; A and B) and adult (n = 4 for each group; C and D) pulmonary arteries were studied after stimulation with U-46619 and relaxation with SNP in the presence of SB-217242, an endothelin (ET) receptor-A and -B antagonist. A and C: force. B and D: relaxation. Values are means ± SE. **P < 0.01 compared with control group by two-way ANOVA.
Trolox abrogated the chronic hyperoxia-induced increase in force development and relaxation to SNP. Trolox is a water-soluble derivative of vitamin E that penetrates biomembranes, protects mammalian cells from oxidative damage, and scavenges superoxide anion formed by smooth muscle cells (27). This suggests that chronic O₂ exposure-induced changes in the lung smooth muscle properties are related to ROS formation.

Fig. 6. Thromboxane mimetic (U-466619) induced airway muscle force generation for the newborn (control n = 21; hyperoxia n = 12; A) and adult (control n = 12; hyperoxia n = 8; B) control and 2-wk hyperoxia animals. Bronchi from chronic hyperoxia animals were also studied in the presence of SB-217242 (newborn and adult; n = 4 each) and Trolox (newborn and adult; n = 4 each). Values are means ± SE. **P < 0.01 vs. control by two-way ANOVA.

Fig. 7. Airway epithelium-dependent (ATP; A and B) and -independent (SNP; C and D) induced bronchi smooth muscle relaxation for the newborn (A and C) and adult (B and D) control and 2-wk hyperoxia animals. Values are means ± SE; n = 12 and 29 (A), 6 and 8 (B), 8 and 13 (C), and 4 and 8 (D) for control and hyperoxia, respectively. A, C, and D; P = NS. B; **P < 0.01 by two-way ANOVA.

Fig. 8. In vitro muscle bath O₂ concentration effect on the newborn (A) and adult (B) control pulmonary arterial muscle KCl-induced force generation. 94% O₂, 94% O₂-6% CO₂; Air, 94% air-6% CO₂. Values are means ± SE; n = 8 and 13 (A) and 4 and 9 (B) for 94% O₂ and Air, respectively. A; **P < 0.01, newborn 94% O₂ vs. Air. B; ***P = 0.01, adult 94% O₂ vs. Air (group comparison by two-way ANOVA).
ROS are required for vascular smooth muscle contraction and cell growth signaling. Inositol 1,4,5-trisphosphate-induced Ca$^{2+}$ release from vascular smooth muscle is selectively stimulated by ROS (45) and may enhance the degree of muscle contraction. ROS increase muscle force generation and/or contraction in rat aorta (43), and xanthine oxidase-derived O$_2$ ROS are involved in the pathogenesis of salt-induced hypertension (46, 49). Catalase, an H$_2$O$_2$ scavenger, abolishes the arterial smooth muscle contraction elicited by H$_2$O$_2$ in rats (39), suggesting that this phenomenon is directly dependent on the presence of ROS. Lastly, exposure to H$_2$O$_2$ causes smooth muscle contractions and dysfunction in isolated rat pulmonary arteries and activation of tyrosine kinases (24).

There is also mounting evidence that oxidative stress is responsible for systemic hypertension via a mechanism that involves the endothelin pathway (48). Our laboratory has previously reported that, in the chronic hyperoxia newborn rat model (21), lung endothelin-1 expression and content are increased. In this study, we demonstrated that SB-217242 abolished the newborn rat hyperoxia-induced altered response of pulmonary and airway smooth muscle contraction and relaxation. SB-217242 is an endothelin-A and -B-receptor antagonist that has been shown to be effective in human and animal pulmonary vascular tissue (28, 31).

This evidence strongly suggests that ROS and endothelin contribute to the enhanced force and reduced NO-induced relaxation of pulmonary vascular smooth muscle after chronic exposure of newborn rats to O$_2$.

Likely, these factors interact in a rather complex manner. Although endothelin-1 is produced by endothelial cells, recent evidence points to ROS having a stimulant effect on its release from endothelial, as well as pulmonary vascular (47), and other smooth muscle cells (25). Figure 10 illustrates a possible mechanism for the chronic O$_2$-induced changes in smooth muscle contraction and relaxation responses.

Our present data demonstrate that, developmentally, the newborn rat pulmonary vascular muscle has a lower potential for force generation compared with the adult. We have reported similar findings for the sheep pulmonary and systemic vascular smooth mus-

Fig. 9. In vitro muscle bath O$_2$ concentration effect on the endothelium-dependent (ACh; A and B) and -independent (SNP; C and D) relaxation properties of the newborn (A and C) and adult (B and D) control pulmonary arterial smooth muscle. Values are means ± SE; n = 6 and 15 (A), 20 and 13 (B), 6 and 11 (C), and 12 and 12 (D) for 94% O$_2$ and Air, respectively. A, B, and C: P = NS. D: ** P < 0.01, 94% O$_2$ vs. Air by two-way ANOVA.

Fig. 10. Mechanism of oxidant stress-induced changes in smooth muscle mechanical properties. IP-3, inositol 1,4,5-trisphosphate.
To our knowledge, there are no published studies comparing the mechanical properties of newborn and adult pulmonary vascular smooth muscle in animal models of pulmonary hypertension. However, there is evidence that the newborn is more susceptible to pulmonary hypertension than the adult. In the chronically hypoxic rat, the degree of pulmonary vascular remodeling and of pulmonary hypertension vary according to age (8, 32, 36). Newborn hypoxic animals exhibit greater residual elevated pressure and structural lung abnormalities after a return to normoxia, compared with adult rats (36).

We have shown that pulmonary arterial muscle force generation is decreased in two animal models of fetal pulmonary hypertension: the ductus-arterious ligature-induced sheep (3), and the nitrofen-induced congenital diaphragmatic hernia in rats (2). In the present study, we have documented that pulmonary arterial muscle force generation was also reduced in the chronically O2-exposed adult, but not newborn, rat. Others have also reported a reduced pulmonary vascular smooth muscle force in the pulmonary hypertensive adult rat (1, 8).

The endothelium-independent relaxation responses of the pulmonary, but not airway, muscle were found to be distinct for the newborn and adult experimental animals compared with control rats. Significant changes in relaxation properties have also been documented in the pulmonary hypertensive adult rat exposed to chronic hypoxia. In these, endothelium-dependent relaxation of pulmonary arterial smooth muscle was reported to increase in several (37, 38) studies and to decrease in at least one other study (9).

Our laboratory recently documented that the lungs of newborn rats exposed to 60% O2 for 14 days have an increased nitrotyrosine content (marker of peroxynitrite formation) but unaltered peroxynitrite-independent nitric oxide release (unpublished observations). Adult rat pulmonary arteries dilate in response to peroxynitrite (reaction product of NO and superoxide anions), and this compound potentiates the dilatory response of SNP (10). This is the most plausible explanation for the potentiation of the SNP-induced relaxation in the O2-treated pulmonary arteries obtained from the adult rats in this study.

We documented that the endothelium-independent, but not -dependent, relaxation was affected by chronic O2 treatment. Similar observations were made by other investigators. Endothelium-independent dilations of bovine pulmonary arteries induced by SNP are impaired by oxidized lipoprotein, whereas forskolin-induced dilator responses were unaffected (33). In fifth-generation pulmonary arteries isolated from lambs with persistent pulmonary hypertension of the newborn, pretreatment with superoxide dismutase significantly enhanced vascular relaxation in response to a NO donor (44). Thus this evidence suggests that, in our study, the relaxation potential of the pulmonary arterial smooth muscle is not affected by chronic O2 exposure, and the discrepancy between hyperoxia-induced changes in the ACh- and SNP-mediated relaxation is related to a direct effect of ROS and/or O2 on the latter response.

Alternatively, the altered SNP-induced relaxation of the chronic O2-exposed animals and the difference in response between the newborn (decreased) and adult (increased relaxation) are possibly related to the pulmonary arterial soluble guanylyl cyclase content. This enzyme responsible for cGMP production was found to be decreased (6, 30) or increased (7) in animal models of pulmonary hypertension.

In the present study, 60% O2 exposure for 14 days induced significant changes in airway smooth muscle mechanical properties in an age-dependent pattern that mimics that observed for the pulmonary arterial muscle. Similarly, to the vascular endothelium, the airway epithelium is capable of producing ROS (17). In the adult horse, H2O2 (one of the ROS products) alters the tracheal smooth muscle mechanical properties in a concentration-dependent manner (35). ROS products also appear to have distinct in vitro effects on airway smooth muscle. In the cat, H2O2 results in an increase in airway muscle tone and enhancement of contraction after supralecical stimulation, whereas superoxide inhibits muscle tone. The observed increase in the bronchial force generation in the O2-exposed newborn rat suggests that newborn airway muscle responds to O2 exposure and ROS formation in a unique way, compared with the adult.

Increased airway resistance is a common finding in neonates with bronchopulmonary dysplasia (29, 34) and is believed to be related to the supplemental O2 and ventilatory support required by these infants. Increased airway resistance has also been clinically reported in children with postoperative pulmonary hypertension (42). This suggests that cross talk between the vascular and airway compartments exists and may modulate the behavior of the airway when pulmonary hypertension is present.

In summary, we have demonstrated that 60% O2 treatment for 14 days results in vascular and airway smooth muscle property changes in an age-dependent manner. Oxygen toxicity in the newborn rat results in enhanced potential for vascular and airway smooth muscle contraction and reduced vascular endothelium-independent relaxation through a mechanism that involves ROS and the endothelin pathway. This uniquely distinct response of the newborn muscle to O2 exposure likely renders them more susceptible to pulmonary hypertension and increased airway hyperresponsiveness.

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