Hypoxic Vasoconstriction Increases With Postnatal Age in Lungs From Newborn Rabbits

Candice D. Fike and Thomas N. Hansen

The pulmonary circulation undergoes dramatic structural and functional changes during the perinatal period. In particular, its response to the known pulmonary vasoconstrictor, hypoxia, appears to change with postnatal age. Since the response of the pulmonary circulation to hypoxia is key to the pathophysiology of many lung diseases of the newborn, including persistent pulmonary hypertension and hyaline membrane disease, the developmental aspects of this response are of considerable interest.

Most of the previous studies of the perinatal pulmonary circulation have used intact animals in which the responsiveness of the pulmonary vascular bed to local stimuli such as hypoxia may have been influenced by simultaneous changes in cardiac output or the presence of circulating mediators of vascular tone such as catecholamines. In studies of the pulmonary circulation of adult animals, these confounding variables have been overcome by using isolated, perfused lungs. In the only study where isolated, perfused lungs from newborn rabbits were studied, results suggested that the pressor response of pulmonary circulation to hypoxia was poorly developed at birth but improved with age. It was the purpose of the present study to develop a system for studying isolated, blood-perfused lungs from newborn rabbits to further assess the effects of postnatal age on hypoxia-induced pulmonary vasoconstriction.

Materials and Methods

This study consists of 2 sets of experiments. In Set 1, methods were developed for studying isolated, blood-perfused lungs from newborn rabbits, and a stimulus-response curve for hypoxic pulmonary vasoconstriction for 3-8-day-old New Zealand white rabbit pups was generated. In Set 2, the effects of postnatal age on the strength of the pressor response to hypoxia were studied.

Animals

Three- to five-day-old New Zealand white rabbit pups and their mothers were obtained from the Ray Nichols Rabbitry, Beaumont, Tex., and housed together until the pups reached the age for study. The mothers were subsequently used as blood donors for the perfusate.

Surgical preparation. The techniques for preparation and perfusion of the rabbit lungs were similar to those described by Owen-Thomas and Reeves, Olson et al., and Marshall and Marshall. First, the rabbit pups were anesthetized with pentobarbital (30-50 mg/kg i.p.) and a tracheostomy performed using a 5-mm length of Tygon tubing (1 mm i.d., 1.75 mm o.d.) (Norton Plastics, Akron, Ohio) as an endotracheal tube. Then the lungs were ventilated using a piston-type rodent respirator (Harvard Apparatus Inc., South Natick, Mass.) at a tidal volume of 3-3.5 ml, a rate of 60/min, and an end-expiratory pressure of 1 cm H2O maintained by exhausting the ventilator to an underwater seal. The inspired gases were mixed in Mylar bags so that the initial P O2 was 150 mm Hg and P CO2 was 38-42 mm Hg. The chest wall was then opened by midline sternotomy and 200 U of heparin was injected into the left ventricle. Without damaging the lung, the
anterior ribs, mediastinal tissues, and pericardium were dissected away and removed. The ductus arteriosus was ligated using a 3-0 silk suture. Then the right ventricle was incised, and a fluid-filled Tygon catheter (1 mm i.d., 1.75 mm o.d.) was placed in the pulmonary artery and secured by tightening a ligature around the artery. The tip of the left ventricle was incised and a catheter (1.25 mm i.d., 2.25 mm o.d.) manipulated through the mitral valve so that it fit snugly in the left atrium, without suturing. Finally, the entire thoracic cage was bluntly dissected from the rabbit by severing the clavicles and spinal column above and below the chest cavity. The chest cage was suspended from the endotracheal tube. The surgical procedure required 15–25 minutes and was performed with no apparent trauma to the lung tissue. Time between loss of the rabbit's own circulation and onset of perfusion was 5–10 minutes.

**Perfusion Circuit**

At the completion of surgery, the lungs were connected to the perfusion circuit shown in Figure 1 and the flow adjusted to 0.07 ml/g body wt/min. In this circuit, perfusate was pumped from a reservoir, using a rotary pump (Cole-Parmer Co., Chicago, Ill., Masterflex) through a bubble trap and blood filter (International Inc., San Antonio, Texas, Hemo-nate) into one limb of a t-connector attached to the pulmonary artery catheter, through the lungs into the left atrial catheter, and then allowed to drip back into the reservoir. The other end of the t-connector was used to measure pulmonary artery pressure. The tip of the left atrial catheter was exposed to atmospheric pressure at the base of the lungs. The perfusate was maintained at a constant temperature of 37.5°–39.0°C by suspending the reservoir in a water bath. The entire circuit, with the exception of the rotary pump, was enclosed in an air-filled isolette (Air Shields Inc., Hatboro, Penn.), with the temperature maintained at 37°–38°C. Humidification was provided by a steam generator.

**Perfusate**

The perfusate consisted of a mixture of equal parts of heparinized blood (10–20 U/ml), obtained fresh daily from adult female donor rabbits, and physiologic saline-albumin solution prepared by mixing 50 ml of a physiologic salt solution with 1.5 g bovine albumin and 0.5 g dextrose. The final hematocrit of the perfusate was 19–21%. A total volume of 30–40 ml of perfusate was required to prime the perfusion circuit and perform 1 experiment. The perfusate was added to the circuit and allowed to equilibrate for 20–30 minutes before being used to perfuse the lungs. At the end of the experiment, the perfusate was discarded, and the perfusion circuit meticulously cleaned.

**Measurements**

The pulmonary artery pressure was measured using a vascular pressure transducer (Gould Instruments, Hato Rey, PR, Model P23 Db) connected to the t-connector leading into the pulmonary artery. Airway pressure was measured using a differential pressure transducer (Gould Instruments, Hato Rey, PR, Model PM131 TC) connected to an 18-gauge needle inserted in the inspiratory limb of the ventilator circuit. Pressures were recorded on a 4-channel Grass polygraph recorder (Grass Instruments, Quincy, Mass., Model 5). Zero reference for the pulmonary artery was the level of the left atrium; zero reference for the airway pressure was atmospheric. Blood was collected anerobically from the left atrial catheter for measurement of blood gas tensions using a Radiometer Blood Gas Analyzer (Radiometer Inc., Copenhagen, Denmark, Model PHM 27).

Before beginning experiments, the perfusate pH was adjusted to 7.33–7.40, if necessary, by adding a small amount of NaHCO₃ to the perfusate, and the system was allowed to equilibrate for 30–45 minutes.

**Study 1 — Hypoxic Dose Response Curve**

**Stability of the Response.** To ensure that the response to hypoxia would remain stable, lungs from 9 newborn rabbit pups (postnatal ages 3–11 days) were exposed to repeated 6-minute periods of the same hypoxic mixture (P,O₂ = 0 mm Hg, P,CO₂ = 38–42 mm Hg) alternating with 6-minute recovery periods (P,O₂ = 150 mm Hg, P,CO₂ = 38–42 mm Hg). In this set of experiments, newborn rabbit pups (postnatal ages 3–11 days) were exposed to repeated 6-minute periods of the same hypoxic mixture (P,O₂ = 0 mm Hg, P,CO₂ = 38–42 mm Hg) alternating with 6-minute recovery periods (P,O₂ = 150 mm Hg, P,CO₂ = 38–42 mm Hg). The stability of the response to hypoxia was assessed by comparing the pulmonary artery pressure response to hypoxia with the response to the same hypoxic mixture in previous experiments. Pulmonary artery pressure was measured at other limb of the t-connector while tip of left atrial catheter is exposed to atmospheric pressure at base of lungs. Perfusion temperature is maintained at 37.5°–39.0°C by suspending reservoir in water bath, and entire circuit, with exception of rotary pump, in heated humidified Plexiglas chamber. Lungs are ventilated using rodent ventilator with mixtures of various inspired gases contained in mylar bags.

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**Figure 1.** Circuit for perfusing isolated lungs from newborn rabbits. Perfusion is pumped from reservoir using rotary pump through bubble trap and blood filter into one limb of t-connector attached to pulmonary artery catheter, through the lungs into left atrial catheter, then allowed to drip into reservoir. Pulmonary artery pressure is measured at other limb of the t-connector while tip of left atrial catheter is exposed to atmospheric pressure at base of lungs. Perfusion temperature is maintained at 37.5°–39.0°C by suspending reservoir in water bath, and entire circuit, with exception of rotary pump, in heated humidified Plexiglas chamber. Lungs are ventilated using rodent ventilator with mixtures of various inspired gases contained in mylar bags.
Hypoxic pulmonary vasoconstriction can be calculated as $P_{\text{VR}} = (P_{\text{pa}} - P_{\text{o}})/0$. Since $P_{\text{VR}}$, alveolar (P_{\text{av}}) and pulmonary arterial pressure (P_{\text{pa}}) are stable for up to 7 repetitions over 2.5-3 hours. In our experiments, changes in P_{\text{pa}} reflected changes in P_{\text{VR}}.

Changes in P_{\text{VR}} were assessed as the absolute change of P_{\text{pa}} in cm H_{2}O from baseline P_{\text{pa}} to maximum P_{\text{pa}} achieved during the hypoxic response, and percent change from baseline calculated by dividing the absolute change in pressure by the baseline pulmonary artery pressure. These measurements and calculations were made for each of the different gas mixtures.

Study 2 — Influence of Postnatal Age on Hypoxic Pulmonary Vasoconstriction

Two different age groups were used for this study: 3–8 postnatal days (young) and 10–14 postnatal days (old). A total of 21 young pups (mean wt = 107 ± 1 g) and 23 old pups (mean wt = 191 ± 2 g) were studied. All pups remained housed with their mothers until attaining the appropriate postnatal age. Of the total, 7 young pups and 11 old pups were from litters in which all pups were studied at the same age (5 random litters). To control for variability between litters, experiments were performed in which pups from the same litter were studied at each of the 2 postnatal ages (4 matched litters). There were 14 young pups and 12 old pups included in these experiments. In all, pups from 9 different litters were used.

After initial stabilization, the lungs were exposed repeatedly for 6-minute periods to the same hypoxic mixture ($P_{\text{o}_2} = 0$ mm Hg, $P_{\text{CO}_2} = 38–42$ mm Hg), alternating with 6-minute recovery periods ($P_{\text{o}_2} = 150$ mm Hg, $P_{\text{CO}_2} = 38–42$ mm Hg). The same pre-mixed hypoxic mixture was used for each stimulus for all the lungs. Blood gases were obtained during the hypoxic exposures and recovery periods. The hypoxic response was noted to increase with the first 2-4 challenges, so the maximal elicited response was used to calculate the absolute change in pulmonary artery pressure and the percent change for each lung. The lungs were carefully observed throughout the experiment, and the study was terminated if airway fluid was present or if airway pressure increased. The duration of perfusion for this set of experiments was 1.5–2.0 hours.

Statistical Analysis

All data are expressed as the mean ± 1 standard error of the mean. The data obtained for the dose-response curve was analyzed using analysis of variance and the Student-Newman-Keuls test. The absolute increase in pulmonary artery pressure and the percent change from baseline for the 2 age groups and the paired-litter mate subgroups were compared using a two-tailed unpaired Student’s $t$ test.

Results

Stability of the Response

Ventilation of the lungs with an hypoxic gas mixture resulted in a consistent increase in pulmonary artery pressure (Table 1, Figure 2) that after the first response was stable for up to 7 repetitions over 2.5–3 hours (Table 1, Figure 3). During ventilation with the hypoxic gas mixture, the P_{\text{o}_2} averaged 36 ± 2 mm Hg and varied little from exposure to exposure. In our system, after 3–4 hours of perfusion, the airway...
pressure tended to increase and fluid appeared in the airways, suggesting that the lungs had become edematous.  

**Stimulus Response Curve to Hypoxia in 3-8-Day-Old Newborn Rabbit Pups**

During the baseline period, the peak airway pressure was 8.3 ± 0.2 cm H₂O, the mean Pco₂ of the effluent blood was 40 ± 1 mm Hg, and the perfusion rate was 0.07 ml/g body wt/min. None of these variables changed during the remainder of the experiment. Ventilation of the lungs with progressively increasing hypoxic gas mixtures resulted in a progressive increase in pulmonary artery pressure and progressive decrease in the Po₂ of the effluent blood (Table 2, Figure 4). The pH of the effluent blood decreased slightly throughout the experiments from 7.38 ± 0.03 to a final pH = 7.35 ± 0.01, while the baseline pulmonary artery pressure increased by 0.7 ± 0.1 cm H₂O.

**Influence of Postnatal Age on Hypoxic Pulmonary Vasoconstriction**

During the baseline period, values for pH, Po₂, and Pco₂ of effluent blood and peak airway pressures were identical for both age groups of rabbit pups (Table 3). The perfusion rate of 0.07 ml/g body wt/min resulted in flow rates of 7.5 ± 0.4 ml/min (range 5-11 ml/min) in the younger animals and 13 ± 0.6 ml/min (range 9-16 ml/min) in the older animals. In addition, the baseline pulmonary artery pressure in the old rabbits was significantly higher than in the young rabbits (older vs. younger: 11.9 ± 0.4 vs. 8.6 ± 0.5 cm H₂O for rabbits from random litters and 12.2 ± 0.7 vs. 9.0 ± 0.5 cm H₂O for pups from matched litters).

The increase in pulmonary artery pressure in response to the hypoxic stimulus (Pco₂ = 0 mm Hg, Pco₂ = 38-42 mm Hg) was significantly greater (p <0.05) in the old pups than in the young pups for rabbits from random litters (6.7 ± 0.7 vs. 3.0 ± 0.4 cm H₂O) and for pups from matched litters (7.3 ± 0.7 vs. 3.2 ± 0.6 cm H₂O) (Figure 5). Because there was a wide range of weights at each postnatal age, there was some overlap in flow rates and baseline pulmonary artery pressures between the 2 groups, making it possible to compare subsets of rabbits from each group that had similar baseline pulmonary artery pressures and blood flows (Figure 6). When rabbits were matched for similar baseline pulmonary artery pressures (10.1 ± 0.2 cm H₂O in 6 old pups vs. 9.8 ± 0.3 cm H₂O in 5 young pups), the pressor response to the hypoxic stimulus was still greater in the old pups (p <0.05). Similarly, when matched for similar rates of blood flow (9.5 ± 0.3 vs. 9.9 ± 0.2 ml/g body wt/min in 8 old vs. 8 young pups, respectively), the pressor response to hypoxia was still greater in the old pups (p <0.05). The Po₂ of the effluent blood during alveolar hypoxia was similar for young and old pups (32.4 ± 1.2 and 33 ± 1.1, respectively). There was no change in pH, Pco₂, airway pressure, and perfusion rate during the hypoxic challenges.

**Discussion**

Isolated, perfused lungs have been used by numerous investigators to study the pulmonary circulation of adult animals. These studies have shown that the reactivity of the pulmonary vessels to hypoxia can be affected by alterations in temperature, 24 pH and composition of perfusate, 7,13,14 inspired Pco₂, 15 mixed venous Po₂, 6,15 and length of time between death of the animal and onset of perfusion. 16 These factors were all considered in establishing the perfusion system for this study. The environment was maintained at 37-38°C and was well humidified. The perfusate, a mixture of 50% blood and 50% physiologic saline albumin solution, was maintained at a temperature of 37.5-39.0°C and a pH of 7.38 ± 0.08. The lungs were continuously ventilated at a constant inspired Pco₂, surgical time was limited to 15-25 minutes, and time between loss of the rabbit's own circulation and onset of perfusion was 5-10 minutes. Under these conditions, the lungs from the rabbit pups consistently developed a pressor response to alveolar hypoxia. The response to hypoxia elicited in these experiments was similar to that described by other investigators using lungs obtained from adult animals. 7,13,14-16
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the first hypoxic challenge and then remained relatively constant until the final 2.5–3.0 hours of perfusion. Examination of the stimulus response curve constructed for the 3–8-day-old pups showed that the magnitude of the pressor response was inversely proportional to the inspired PO2 so that the maximum increase in pulmonary artery pressure occurred at an inspired PO2 = 0 mm Hg. It should be pointed out that short (6-minute) exposures to hypoxia were used to generate this stimulus response curve. Sylvester et al. 17 have shown that the shape of the stimulus-response curve is dependent on the duration of the hypoxic challenge. Using lungs from adult pigs, they showed that prolonged exposures (50–60 minutes) to very low levels of inspired oxygen actually resulted in pulmonary vasodilatation, hence, a biphasic stimulus-response curve, while shorter exposures (10-minute) resulted in a monophasic curve similar to the one in the present experiments.

Other investigators have also noted that the response of the pulmonary circulation to hypoxia varies at different prenatal and postnatal ages. In studies using chronically instrumented fetal lambs, Lewis et al. 18 found that the ability of the pulmonary vascular bed to constrict in response to hypoxia increased with increasing gestational age. Similarly, in experiments where the left lung was isolated and perfused in situ, Tyler et al. 19 showed that the pulmonary vessels in the lungs of term, newborn goats constricted more in response to alveolar hypoxia than those from preterm goats. Newborn calves, on the other hand, demonstrated a decrease in the pulmonary vascular reactivity to alveolar hypoxia with increasing postnatal age from < 12 hours to 4 weeks, 1 while piglets showed an increase with advancing postnatal age. 4 In studies using isolated perfused lungs from newborn rabbits, Owen-Thomas and Reeves 3 found that pulmonary vascular reactivity to alveolar hypoxia increased with advancing postnatal age (no change at 1 day, 6% increase at 2–3 days, 14% at 4–7 days, and 16% at 9–11 days). The magnitude of the pressor response to hypoxia in their study was small, however, and the evidence for maturation of the response between 4 and 11 days was not strong. The magnitude of the pressor response in the current study was considerably greater and strongly supports the hypothesis that the pressor response to hypoxia in the newborn rabbit increases with advancing postnatal age.

It is unlikely that the difference between the 2 age groups in our study was related to perfusion technique, since the only difference between the 2 groups was the absolute rate of flow of the perfusate. Flow was based on body weight (0.07 ml/g body wt/min), so the older group had a higher mean perfusion rate and higher pulmonary artery pressure. However, when subsets from the 2 groups that had comparable flow rates and pulmonary artery pressures were compared, the older group still had a greater pressor response to hypoxia. In addition, most evidence in the literature suggests that vessels exposed to higher pressures and flows have

Table 2. Stimulus Response Data for 3–8-Day-Old Rabbit Pups

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<tr>
<th>Borrowed PO2 (mm Hg)</th>
<th>150</th>
<th>100–80</th>
<th>50–40</th>
<th>30–20</th>
<th>20–10</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial PO2 (mm Hg)</td>
<td>152 ± 2</td>
<td>114 ± 4</td>
<td>77 ± 4</td>
<td>51 ± 2</td>
<td>43 ± 1</td>
<td>35 ± 2</td>
</tr>
<tr>
<td>Baseline pulmonary artery pressure (cm H2O)</td>
<td>8.5 ± 0.5</td>
<td>9.0 ± 0.9</td>
<td>9.2 ± 0.7</td>
<td>9.0 ± 0.8</td>
<td>8.7 ± 0.5</td>
<td>8.8 ± 0.6</td>
</tr>
<tr>
<td>Increase in pulmonary artery pressure (cm H2O)</td>
<td>0</td>
<td>0.10 ± 0.12</td>
<td>0.62 ± 0.21</td>
<td>1.20 ± 0.23</td>
<td>1.80 ± 0.25†</td>
<td>2.60 ± 0.41</td>
</tr>
<tr>
<td>% increase in pulmonary artery pressure from baseline</td>
<td>0</td>
<td>1.1 ± 1.0</td>
<td>6.7 ± 2.0</td>
<td>13.3 ± 2.5</td>
<td>21.0 ± 3.0†</td>
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<td>Total number</td>
<td>19</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>10</td>
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Mean ± one standard error.†Greater than the response at 20–30 mm Hg, p < 0.05.
*Greater than the response at 40–50 mm Hg, p < 0.05.

Table 3. Baseline Measurements of Effluent Blood Gas Tensions and Airway Pressure in 3–8 and 10–14-Day-Old Rabbit Pups

<table>
<thead>
<tr>
<th>Postnatal age (days)</th>
<th>pH</th>
<th>PO2 (mm Hg)</th>
<th>Pco2 (mm Hg)</th>
<th>Peak airway pressure (mm Hg)</th>
</tr>
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<tr>
<td>3–8 day</td>
<td>7.38 ± 0.01</td>
<td>155 ± 2</td>
<td>40 ± 1</td>
<td>8.3 ± 0.3</td>
</tr>
<tr>
<td>10–14 day</td>
<td>7.38 ± 0.01</td>
<td>155 ± 1</td>
<td>40 ± 1</td>
<td>7.7 ± 0.2</td>
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Mean ± one standard error.
We conclude that isolated perfused lungs from newborn rabbits exhibit a consistent and highly reproducible pressor response to alveolar hypoxia. The strength of this response is inversely related to the inspired Po2, and is greater in 10–14-day-old pups than in 3–8-day-old pups. The reason for the difference in responsiveness at different postnatal ages is unknown but may relate to morphologic or metabolic changes in the pulmonary circulation that occur with postnatal development.

Acknowledgments

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References

4. Rendas A, Branhwaite M, Lennox S, Reid L: Response of the pulmonary vessels in response to alveolar hypoxia (P,O2 = 0 mm Hg, PCO2 = 38–42 mm Hg) was greater in older pups (n = 23) than young pups (n = 21) (unpaired t test, p < 0.05) for pups from random litters (n = 18) and for pups from matched litters (n = 26).

![Figure 5](image-url) Influence of postnatal age on hypoxic pulmonary vasoconstriction. Data are given as mean ± SEM. Increase in pulmonary artery pressure in response to alveolar hypoxia (P,F2 = 0 mm Hg, Pco2 = 38–42 mm Hg) was greater in older pups (n = 23) than young pups (n = 21) (unpaired t test, p < 0.05) for pups from random litters (n = 18) and for pups from matched litters (n = 26).

![Figure 6](image-url) Influence of postnatal age on hypoxic pulmonary vasoconstriction in subsets of rabbit pups matched for baseline pulmonary artery pressures and rates of blood flow. Data are given as mean ± SEM. Increase in pulmonary artery pressure in response to alveolar hypoxia (P,F2 = 0 mm Hg, Pco2 = 38–42 mm Hg) was greater in older pups than young pups (unpaired t test, p < 0.05) for pups with similar baseline pulmonary artery pressure (10.1 ± 0.2 cm H2O in 6 old pups vs. 9.8 ± 0.3 cm H2O in 5 young pups) and similar rates of blood flow (9.5 ± 0.3 vs. 9.9 ± 0.2 ml/kg body wt/min in 8 old vs. 8 young pups, respectively).


KEY WORDS • hypoxic pulmonary vasoconstriction • isolated perfused lungs • persistent pulmonary hypertension
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