0031-3998/91/2905-0449$03.00/0
PEDIATRIC RESEARCH

Vol. 29, No. 5, 1991
Printed in U.S.A.

Indomethacin Prevents Ventilation-Induced Decreases in Pulmonary Vascular Resistance of the Middle Region in Fetal Lambs

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ABSTRACT. Previously, we reported that the major site of pulmonary vascular resistance in fetal lambs occurred in the middle region defined by vascular occlusion, and that this region exhibited the greatest decrease upon ventilation with O_2. To assess the relative individual contributions of ventilation and oxygenation to this decrease, we determined the distribution of pressures across the pulmonary circulation in isolated perfused lungs from 20 fetal lambs (131–137 d gestation) by inflow and outflow vascular occlusions. A membrane oxygenator was included in the extracorporeal circuit to control the P_{O_2} at 4 kPa (30 torr) in the unventilated fetal lungs. Half of the fetal lungs were ventilated first without changing the initial gas tensions, and the others were oxygenated first by changing the initial gas tensions to a hyperoxic mixture [P_{O_2} = 26.6 kPa (200 torr)] without ventilation. Finally, both groups of lungs were ventilated and oxygenated. In addition, indomethacin was added to the perfusate (0.112 mM, or 40 μg/mL) in half of the preparations in each group to determine the effect of prostaglandins on the distribution of pressures during these conditions. The decrease in the total pulmonary vascular resistance with ventilation and/or oxygenation was primarily due to changes in the middle pressure gradient (ΔPm). In fetal lungs without indomethacin, ventilation without oxygenation reduced ΔPm from 6.1 ± 0.8 to 2.5 ± 1.0 kPa, or 74% of the total ventilation- and oxygenation-induced decrease in ΔPm (final value = 1.2 ± 0.6 kPa). In contrast, oxygenation without ventilation produced a decrease in ΔPm from 5.5 ± 0.7 to 3.8 ± 0.5 kPa, only 40% of the total decrease in ΔPm (1.2 ± 0.4 kPa). Furthermore, in fetal lungs with indomethacin, only oxygenation first caused a reduction in the resistance of the middle region, suggesting that dilator prostaglandins are not involved in the response to increased oxygen. We conclude that recruitment and/or distension of the small pulmonary vessels functionally located in the middle region by the mechanical effect of ventilation is dependent on dilator cyclooxygenase products, and that this mechanical effect is a major factor involved in the decrease in pulmonary vascular resistance occurring at birth. (*Pediatr Res* 29: 449–454, 1991)

Abbreviations

PVR, pulmonary vascular resistance
Ppa, pulmonary artery pressure
Ppa′, pulmonary artery pressure immediately after inflow occlusion
Pla′, left atrial pressure immediately after outflow occlusion
ΔPt, total pressure gradient
ΔPm, middle pressure gradient
U30, unventilated, hypoxic condition
V30, ventilated, hypoxic condition
V200, ventilated, hyperoxic condition

The dramatic fall in PVR that occurs at birth is due to a combination of factors, including: *1*) ventilation with a gas, resulting in establishment of an air-liquid interface; *2*) increasing arterial P_{O_2}; and *3*) decreasing arterial P_{CO_2} (1–3). Although these factors normally act in concert to result in the decrease in PVR, each has been found to exert independent effects on the transitional pulmonary vasculature. For example, ventilation with a gas mixture that does not change fetal arterial blood gas tensions results in pulmonary vasodilation, although this decrease in PVR is enhanced when O_2 is present in the ventilating gas mixture (2). Recent studies with unanesthetized, chronically instrumented fetal lambs have confirmed these earlier experiments, reporting that ventilation *in utero* with a fetal gas mixture significantly increases pulmonary blood flow (4), as does delivering hyperoxia to the pregnant ewe (5, 6). However, these latter studies did not evaluate the relative contributions of the effects of ventilation *versus* oxygenation in a direct comparison.

Recently, we observed that the major site of PVR in fetal lamb lungs was located in the middle region of the pulmonary circulation, as determined by inflow and outflow vascular occlusion (7). Furthermore, the pressure drop across this region was significantly decreased by ventilation with a gas mixture containing 28% O_2; however, the relative individual contributions of ventilation and oxygenation to this decrease were not assessed (7). The purpose of our present study was to determine the relative contributions of independently oxygenating and ventilating fetal lungs on the distribution of PVR. In addition, inasmuch as the effects of mechanical ventilation of fetal lungs are largely due to the release of dilator prostaglandins (8, 9), we also evaluated the effects of cyclooxygenase inhibition under these conditions.

MATERIALS AND METHODS

The isolated perfused lung preparation used for performing vascular occlusions has been described previously (7). All surgical procedures and experimental protocols were approved by the Institutional Animal Care and Use Committee of the University of Maryland School of Medicine and met the guidelines estab-

Received April 23, 1990; accepted December 6, 1990.
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lished by the American Physiological Society. Fetal lambs were delivered by cesarean section from chloralose-anesthetized ewes at 131–137 d of gestation (term = 148 d). Fetal lambs were exsanguinated rapidly via a femoral arterial catheter after administration of heparin (3000 U). A midsternal thoracotomy was performed, and the ductus arteriosus was ligated. After transection of the heart at the atrioventricular groove, large-bore, rigid cannulas were tied into the main pulmonary artery and the left atrium. With the lungs remaining in the thorax, the cannulas were connected to an extracorporeal perfusion circuit, which included a membrane oxygenator (model no. 0400-2A; Sci-Med Life Systems, Inc., Minneapolis, MN) to control blood gas tensions in the unventilated fetal lung (Fig. 1). The duration of pulmonary ischemia (from completion of exsanguination to initiation of perfusion) was 22–30 min (average, 25.4 ± 0.5 min), with one exception, which was 38 min; however, all baseline parameters were normal for this lamb. The lungs were perfused with a mixture of autologous blood, 3% dextran in lactated Ringer solution, and maternal blood, resulting in an average hematocrit of 25 ± 0.7%. Ppa, left atrial pressure (Pla), and tracheal pressures were measured with pressure transducers (P10EZ and P23ID; Spectramed, Oxnard, CA) referenced to the top of the lung and recorded continuously (model no. 7D; Grass Instrument Co., Quincy, MA). Blood flow was measured with an electromagnetic flowmeter and flow probe (model FM 501D and EP 300 A, ¼ inch, respectively; Carolina Medical Electronics, Inc., King, NC) and adjusted to a constant flow rate of 50 $mL \cdot kg^{-1} \cdot min^{-1}$. A hypoxic gas mixture containing 5.4% CO_2, 4.2% O_2, and 90.4% N_2 [P_{O_2} = 4kPa (30 torr)] was delivered to the membrane oxygenator, resulting in approximately normal fetal arterial values. Lungs were perfused for 20–30 min for stabilization of pressures and perfusate pH and gas tensions (model no. 170; Corning Medical, Medfield, MA).

After the stabilization period, left atrial pressure was set at 0.5–0.7 kPa (4–5 mm Hg) by adjusting the height of the reservoir. Determination of pressure gradients in the unventilated fetal lungs (U30) was performed in duplicate by vascular occlusion. Half of the preparations were then ventilated with the same gas mixture that was being delivered to the membrane oxygenator (V30), using the following ventilation parameters: tidal volume, 15 mL/kg; frequency, 10 breaths/min; and positive end-expiratory pressure, 0.3–0.4 kPa (2–3 mm Hg). When Ppa was stable after establishment of ventilation (approximately 15–20 min), determination of pressure gradients was performed. The gas mixture was then adjusted to a slightly hyperoxic mixture containing 5.4% CO_2, 28% O_2, and 66.6% N_2 [P_{O_2} = 26.6 kPa (200 torr)], with the ventilation maintained as before (V200), and determination of pressure gradients was repeated after achieving stable conditions (approximately 15–20 min). In the other half of the preparations, the gas mixture was adjusted to deliver the hyperoxic mixture (P_{O_2} = 26.6 kPa) to the oxygenator without ventilating the lungs (unventilated, hyperoxic condition), and vascular occlusions were performed after Ppa had stabilized (approximately 15–20 min). These lungs were then ventilated as above, using the O_2-enriched gas mixture (V200), and vascular occlusions were repeated during these conditions. In addition, half of the preparations in each of these two groups were treated with indomethacin (0.112 mM, or 40 μg/mL) before beginning perfusion. This dose of indomethacin has previously been shown to block production of prostaglandins in a similar preparation in newborn lambs (10). Thus, four groups were compared: ventilated first without oxygenation and oxygenated first without ventilation, both with and without indomethacin (n = 5 in each group).

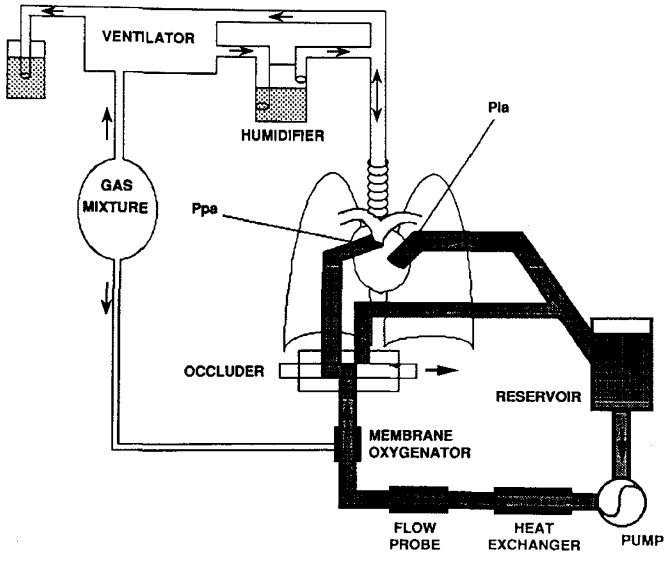

Fig. 1. The isolated perfused fetal lung preparation. Blood is pumped from a reservoir through a membrane oxygenator, which controls blood gas tensions in unventilated fetal lungs. An occluder is used to bypass the lungs for inflow occlusion. *Pla*, left atrial pressure.

Determination of pulmonary vascular pressure gradients was performed in duplicate by vascular occlusions as described previously (7). Briefly, inflow occlusion allowed the determination of the pressure (Ppa′) that existed at the distal end of the relatively noncompliant arterial region. Outflow occlusion allowed the determination of the pressure (Pla′) that existed at the proximal end of the relatively noncompliant venous region. The difference between Ppa′ and Pla′ is the pressure gradient across the relatively compliant middle region (ΔPm). Occlusions were performed after Ppa had stabilized (defined as no change for 5 min) in each of the conditions described above.

Results are presented as means ± SEM. Repeated measures analysis of variance was performed for each vascular pressure and pressure gradient to evaluate the effects of indomethacin and the ventilation/oxygenation condition (11). Comparison of the means was performed by least significant differences when significant F ratios were observed. Differences were considered significant when $p < 0.05$ (12).

RESULTS

There were no significant differences between the groups in arterial blood gas parameters, other than the expected differences due to the oxygen delivered to the preparation (Table 1). In addition, the average hematocrits were similar in all groups.

The effects of ventilation first without oxygenation on pulmonary vascular pressures and on the relative distribution of pressure gradients in fetal lamb lungs are shown in Figures 2 and 3, respectively. In the unventilated fetal lung (U30) without indomethacin, ΔPm accounted for the majority (78%) of ΔPt across the lungs. Although ventilation alone (V30) resulted in significant decreases in Ppa, Ppa′, and Pla′, as well as in all gradients in the absence of indomethacin (Table 2), the greatest decrease (60% reduction) occurred in the middle region. The addition of O_2 (V200) produced further decreases in Ppa, Ppa′, and ΔPm, with the final result of altering the relative distribution of pressure gradients (Fig. 3). When indomethacin was present in the perfusate, the initial pressures measured in the unventilated condition were significantly less than the corresponding values without indomethacin. In addition, the magnitude of the pressure gradients determined during the initial conditions was altered, with significantly smaller values for ΔPt, ΔPm, and venous pressure gradient; however, the distribution of these gradients was similar to those without indomethacin (Fig. 3), with 75% of ΔPt due to ΔPm. Ventilation alone had no effect on either the pressures or the gradients in the presence of indomethacin, and oxygenation also did not significantly reduce these pressures or gradients. Although it appeared that ΔPm was larger at V30 and V200 in the group with indomethacin compared with the group without indomethacin, these values were not significantly differ-

Table 1. *Blood gas data**

	(−) Indomethacin			(+) Indomethacin		
	pH	P_{CO_2}	P_{O_2}	pH	P_{CO_2}	P_{O_2}
Ventilated first						
U30	7.36 ± 0.02	5.67 ± 0.36	3.36 ± 0.09	7.34 ± 0.02	5.37 ± 0.20	3.75 ± 0.10
V30	7.35 ± 0.01	5.43 ± 0.29	4.22 ± 0.13	7.36 ± 0.01	5.14 ± 0.16	3.93 ± 0.39
V200	7.35 ± 0.02	5.31 ± 0.24	18.05 ± 1.84	7.36 ± 0.02	5.46 ± 0.12	19.34 ± 1.82
Oxygenated first						
U30	7.34 ± 0.01	5.54 ± 0.19	3.76 ± 0.21	7.38 ± 0.02	5.11 ± 0.25	3.79 ± 0.12
U200	7.40 ± 0.03	5.08 ± 0.45	14.90 ± 0.61	7.38 ± 0.01	5.12 ± 0.16	16.23 ± 0.89
V200	7.35 ± 0.01	5.49 ± 0.08	21.43 ± 0.76	7.38 ± 0.01	4.87 ± 0.13	21.72 ± 0.56

* There were no significant differences within or between groups in pH (units), P_{CO_2} (kPa), or P_{O_2} (kPa) other than differences due to the P_{O_2} in the gas mixtures for ventilation or oxygenation. U200, unventilated, hyperoxic condition.

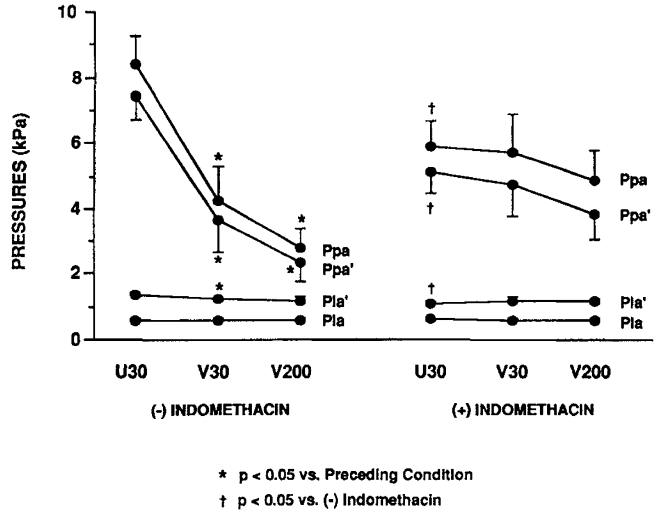

Fig. 2. The effects of ventilation first on pulmonary vascular pressures determined by vascular occlusion in fetal lamb lungs. Values shown are means ± SEM. *Pla*, left atrial pressure.

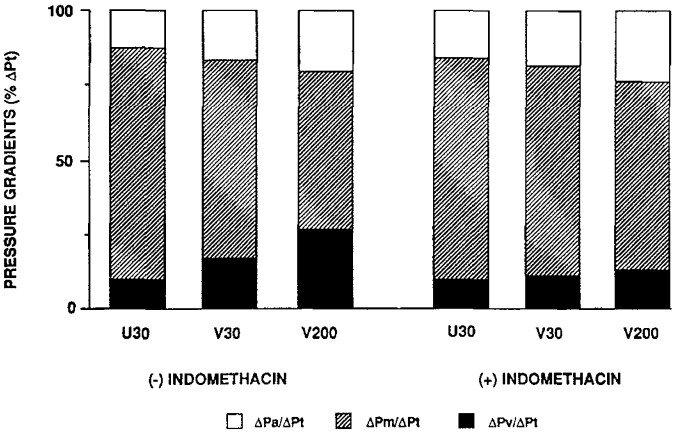

Fig. 3. The effects of ventilation first on the distribution of pressure gradients in fetal lamb lungs. Pressure gradients are normalized to ΔPt, which is set at 100% for each condition. Δ*Pa*, arterial pressure gradient; Δ*Pv*, venous pressure gradient.

ent by least significant difference for comparisons between groups (2.18). Furthermore, the additional significant decreases in ΔPt and ΔPm observed with oxygenation after ventilation (V200) in the untreated lungs were not present in the group treated with indomethacin. The net effect in the indomethacin-treated lungs was a minor shift in the relative distribution of pressure gradients (Fig. 3).

The effects of oxygenation first without ventilation on pulmonary vascular pressures and on the relative distribution of pressure gradients in fetal lamb lungs are shown in Figures 4 and 5, respectively. The baseline pulmonary vascular pressures and distribution of pressure gradients in the unventilated fetal lung (U30) without indomethacin were similar to those of the lungs that were ventilated first for the same condition, with ΔPm contributing 75% to the total. In contrast to the lungs that were ventilated first, however, lungs that were oxygenated first exhibited smaller decreases in Ppa and Ppa′, with corresponding smaller decreases in ΔPt and ΔPm (29 and 32% reductions, respectively). Ventilation of lungs that were oxygenated first produced a further reduction in ΔPm (Table 2), such that the final distribution of pressure gradients was similar in the two groups without indomethacin (Figs. 3 and 5). When indomethacin was present in the perfusate of lungs that were to be oxygenated first, the baseline pulmonary vascular pressures, as well as the magnitude and distribution of pressure gradients, were similar during initial conditions (U30; Figs. 4 and 5, Table 2). In these lungs, indomethacin did not prevent the decrease in ΔPm due to oxygenation, but did prevent the decrease in arterial pressure gradient from occurring. Ventilation of these lungs resulted in no additional changes in pressures or the distribution of pressure gradients.

DISCUSSION

The decrease in PVR that occurs at the time of birth upon ventilation of the lungs with an oxygen-containing gas mixture is well described. Much of the original research in this area was performed in acutely prepared, exteriorized fetal lambs under anesthesia by Dawes and colleagues (1, 2, 13) and others (3, 14, 15). These early investigations established that expansion of fetal lungs with a gas of any composition, including a mixture that did not change the fetal arterial P_{O_2} or P_{CO_2}, resulted in an increase in pulmonary blood flow (1–3, 15). Expansion of the lungs with fluid that was deoxygenated did not produce this pulmonary vasodilation, but the addition of O_2 to the fluid expanding the lungs caused a significant fall in PVR (3, 15). These observations caused Enhorning *et al.* (3) to propose that the establishment of an air-liquid interface in previously fluid-filled lungs leads to dilation of the pulmonary capillaries due to the effects of surface tension in the gas-filled alveoli and an increase in pulmonary blood flow. The addition of O_2 to the gas mixture used to ventilate the lungs caused a further reduction in PVR (2, 14). Increasing the O_2 tension of the blood perfusing the fetal lung, without inflating the lungs, also resulted in a significant decrease in PVR (2, 13). Recently, observations made in chronically instrumented, unanesthetized fetal lambs have supported the findings in acute, exteriorized preparations. Ventilation of fetal lambs *in utero* with a gas that did not alter fetal blood gas tensions significantly increased pulmonary perfusion by more than 400%, with a further increase in blood flow occurring after changing the ventilating gas to 100% O_2 (4). Alternatively, increasing fetal P_{O_2} by delivering 100% O_2 to the pregnant ewe, either at normobaric (5) or hyperbaric pressures

Table 2. *Pulmonary vascular pressure gradients**

	(−) Indomethacin			(+) Indomethacin		
	ΔPa	ΔPm	ΔPv	ΔPa	ΔPm	ΔPv
Ventilated first						
U30	0.97 ± 0.10	6.11 ± 0.78	0.75 ± 0.05	0.84 ± 0.13	4.00 ± 0.61†	0.51 ± 0.05†
V30	0.59 ± 0.18‡	2.45 ± 0.99‡	0.61 ± 0.03‡	0.95 ± 0.17†	3.59 ± 0.95	0.59 ± 0.08
V200	0.45 ± 0.08	1.15 ± 0.58‡	0.59 ± 0.09	1.01 ± 0.12†	2.70 ± 0.75	0.57 ± 0.09
Oxygenated first						
U30	1.11 ± 0.13	5.51 ± 0.66	0.70 ± 0.12	1.24 ± 0.12	5.80 ± 0.33	0.61 ± 0.04
U200	0.73 ± 0.12‡	3.76 ± 0.51‡	0.74 ± 0.13	1.19 ± 0.13†	3.99 ± 0.36‡	0.58 ± 0.04
V200	0.47 ± 0.10	1.16 ± 0.88‡	0.72 ± 0.10	1.28 ± 0.11†	4.03 ± 0.68†	0.52 ± 0.04

* ΔPa, arterial pressure gradient; ΔPv, venous pressure gradient; U200, unventilated, hyperoxic condition.
† $p < 0.05$ *vs* (−) indomethacin.
‡ $p < 0.05$ *vs* preceding condition.

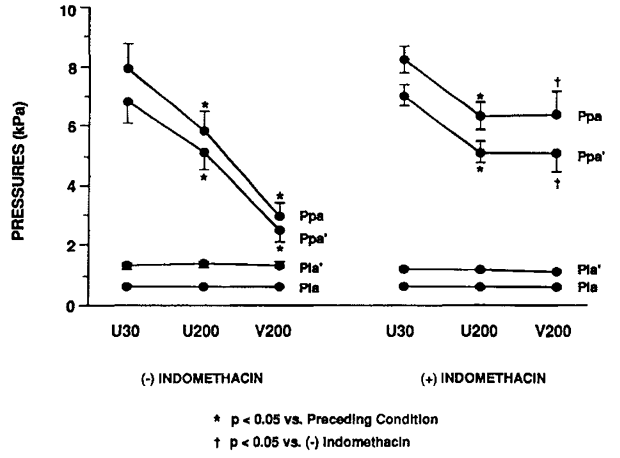

Fig. 4. The effects of oxygenation first on pulmonary vascular pressures determined by vascular occlusion in fetal lamb lungs. *Pla*, left atrial pressure; *U200*, unventilated, hyperoxic condition.

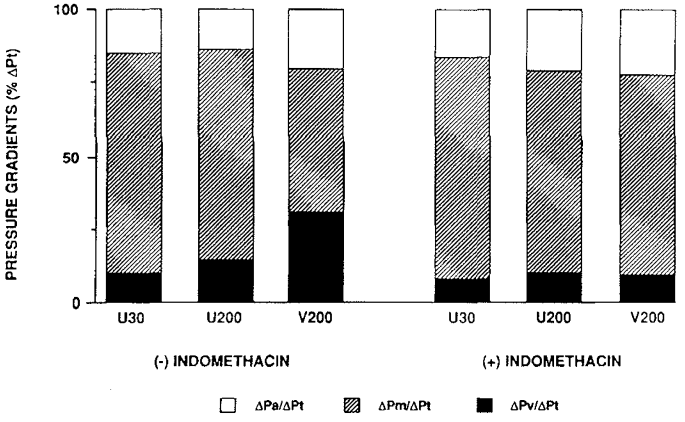

Fig. 5. The effects of oxygenation first on the distribution of pressure gradients in fetal lamb lungs. Δ*Pa*, arterial pressure gradient, Δ*Pv*, venous pressure gradient; *U200*, unventilated, hyperoxic condition.

(6), also caused a several-fold increase in pulmonary blood flow. Thus, these various investigations into the mechanisms responsible for the increase in pulmonary blood flow at the time of birth have established that both ventilation and oxygenation contribute significantly to the fall in PVR.

The contribution of vasodilator prostaglandins to this event was initially evaluated by cyclooxygenase inhibition, and later corroborated by measurements of pulmonary prostaglandin synthesis. Leffler *et al.* (16) reported that the ventilation-induced decrease in PVR was attenuated by pretreatment with indomethacin, and that this effect of indomethacin was more pronounced in premature fetal goats (<135 d) than in mature fetuses (>135 d). In addition, spontaneous onset of breathing by unanesthetized fetuses at delivery was associated with a net production of prostacyclin by the newly ventilated lungs (8, 17). Moreover, indomethacin pretreatment of mature fetal lambs prevented the birth-related production of prostacyclin and attenuated, but did not completely prevent, the decrease in PVR (17). Leffler *et al.* (9) further determined that mechanical ventilation of fetal lungs, and not oxygenation, resulted in pulmonary prostacyclin production, which was concluded to be due to tissue distortion as a consequence of establishing rhythmic ventilation and gaseous expansion of the lungs. Additional support for this conclusion was provided by the finding that indomethacin pretreatment did not alter the increased pulmonary blood flow due to increased fetal P_{O_2} (18). Our results of the effects of indomethacin on ventilation- and oxygenation-induced decreases in PVR are in agreement with these previous studies. We found that ΔPt was decreased significantly by either ventilation or oxygenation, but indomethacin prevented the decrease due to ventilation alone without affecting the decrease due to oxygenation alone.

Our study also characterized the distribution of pressure gradients in fetal lungs, and demonstrated that the pressure drop across vessels in the middle region of the pulmonary vasculature was significantly influenced by ventilation and by oxygenation. Previously, we reported that this region accounted for greater than 75% of the total fetal PVR, and was the site of greatest decrease upon ventilation with 28% O_2 (7). Our present study confirms these observations, and extends them by demonstrating (in the absence of indomethacin) that, of the total decrease in ΔPm produced by the combination of ventilation and oxygenation, ventilation is responsible for up to 75% of this effect, whereas oxygenation alone can account for 40%. In addition, we found that indomethacin prevented the decrease in ΔPm due to ventilation, but had no effect on that due to oxygenation first. Although the addition of oxygenation after ventilation did not result in a significant decrease in ΔPt or ΔPm in indomethacin-treated lungs (Table 2), this lack of effect of oxygenation may have been related to the lower initial pressures in this group compared with the other groups. For example, the final pressures and gradients achieved in this group (at V200) were not different from those in the other indomethacin-treated lungs. Furthermore, there were no obvious differences in duration of pulmonary ischemia, initial arterial blood gases, or hematocrits among the four groups of lungs that might explain the differences observed in baseline pressures. It is possible that in the indomethacin-treated group that was to be ventilated first there was a greater release of a vasodilator into the blood during exsanguination. Taken together, the factors involved in reducing the resistance to blood flow in the middle region by mechanical ventilation, whether by unfolding of partially compressed alveolar vessels (19) or by negative interstitial pressures due to establishing an air-liquid interface (3), appear to be related to the production of vasodilator prostaglandins and/or related compounds. In contrast, the effect of O_2 on pulmonary vessels in the

middle region is completely independent of prostaglandin production.

Our present study only evaluated two levels of O_2 tension; the effects of more physiologic levels that are obtained at the time of birth on the distribution of pulmonary vascular pressures are unknown. These P_{O_2} levels were chosen to allow comparisons with our previous study in fetal lambs (7). Clarke *et al.* (20) have reported that fetal PVR has an inversely linear relationship with log P_{O_2} over a 50-fold range of perfusate O_2 tensions. Although we have no direct observations, it is possible that the magnitude of the decrease in pressure with oxygenation may have been less if a lower P_{O_2} had been used in this preparation.

The vessels that compose the middle region include, but are not limited to, capillaries. In addition, small muscular pulmonary arteries and veins probably are included in this region (21, 22). Thus, it is not surprising that oxygen would affect the resistance of these vessels. For example, hypoxia causes an increase in the pressure gradient of the middle region in adult dog (23) and pig lungs (24), as well as in neonatal lamb lungs (7, 25). We (7) and others (25) have observed that hypoxic pulmonary vasoconstriction of the middle region increases with increasing neonatal age; Gordon *et al.* (25) recently demonstrated that this age-related effect was reversed by pretreatment with indomethacin. In those studies, indomethacin enhanced the vasoconstriction occurring in ΔPm at all ages, suggesting that dilator prostaglandins modulate the response of this region to hypoxia. It is of interest that we did not observe an increase in ΔPm in the unventilated (*i.e.* hypoxic) fetal lungs with the addition of indomethacin, suggesting that perhaps the level of dilator products of the cyclooxygenase pathway was not elevated in the isolated, perfused fetal lung before ventilation. A similar observation was reported in unventilated fetal goats (16). However, as discussed above, we did find an unexplained decrease in all pressures and pressure gradients in one of the indomethacin-treated groups during the initial unventilated fetal conditions.

It is possible that the presence of fluid in the potential air spaces of fetal lungs may have contributed to the large ΔPm observed before ventilation. Although the impact of interstitial fluid and vascular compression may increase vascular resistance by a different mechanism, severe pulmonary edema has also been shown to cause an increase in ΔPm in canine lobes (26) and newborn lamb lungs (27). The introduction of a ventilating gas mixture forces the fetal lung fluid to be reabsorbed into the pulmonary circulation or drained from the interstitium by the lymphatics (28). The increase in alveolar surface tension resulting from the establishment of an air-liquid interface in newly ventilated alveoli may have reduced the interstitial fluid pressure surrounding the pulmonary capillaries, leading to distension of these vessels due to an increase in their transmural pressure (29). The net effect of these multiple factors would be an increased ΔPm in the unventilated, fluid-filled lung and a decrease in ΔPm with the expansion of the lungs with a gas. Indomethacin significantly reduces the rate of fluid formation in fetal lamb lungs (30); this may explain, in part, the initial decrease in ΔPm observed in the presence of indomethacin in the lungs that were ventilated first (Table 2). However, if the removal of fluid were responsible for the ventilation-induced distension of the alveolar vessels (29), then a decrease in fluid formation by indomethacin would not prevent the ventilation-induced fall in PVR and ΔPm. Furthermore, indomethacin-treated lungs from the group to be oxygenated first had no change in ΔPm initially as compared with untreated lungs. Although we have no assessment of fluid balance in our present study, the total duration of these experiments was substantially less than 180 min, which we have previously reported in neonatal lamb lungs undergoing similar vascular occlusion protocols to be associated with minimal disturbance of lung fluid balance (31).

In summary, we observed that both ventilation and oxygenation independently contribute to the reduction in PVR of fetal lungs. The majority of this decrease is due to ventilation alone, and the major site of this effect is the vessels of the middle region. Indomethacin prevents this effect of ventilation, but does not inhibit the lesser effect of oxygenation alone. Thus, it appears that the effect of ventilation on the small pulmonary vessels is dependent on the formation of dilator products of the cyclooxygenase pathway.

Acknowledgments. The authors thank Kristi Pier for technical assistance.

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Erratum

An error in the publication "Energy expenditure and deposition of breast-fed and formula-fed infants during early infancy" (Pediatr Res 28:631–640, 1990) has been brought to the attention of the authors by the manufacturer of Similac. It was incorrectly stated that the estimate of the gross energy content of formula (0.67 kcal/g) determined by bomb calorimetry was inconsistent with the manufacturer's stated value for metabolizable energy (0.67–0.68 kcal/g). The formula manufacturer, however, expresses the metabolizable content as kcal/mL. Adjusting the manufacturer's stated value of 20 kcal/oz or 68 kcal/mL for the density of formula (1.0295 g/mL), the metabolizable energy content of formula expressed as kcal/g is 0.657. Proximate analysis provided by the manufacturer indicates a gross energy content for formula of 0.689 kcal/g. This value is 3% higher than the directly measured value obtained by the authors. This level of agreement is likely within the errors of proximate analyses, bomb calorimetry, and assumptions made by the application of Atwater factors. The authors wish to thank Ross Laboratories for bringing this error to their attention.