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PROSTAGLANDINS AND REGULATION OF THE PULMONARY CIRCULATION IN THE PERINATAL PERIOD

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Résumé

LES PROSTAGLANDINES ET LA REGULATION DE LA CIRCULATION PULMONAIRE DANS LA PERIODE PERINATALE. — Les effets de l'indométhacine sur la vasodilatation provoquée par une ventilation par l'air des poumons fœtaux ont été mesurés chez des fœtus de chevreaux anesthésiés et extériorisés, au moyen d'un système de poumon perfusé par une pompe, la cage thoracique étant ouverte. Lorsque les poumons fœtaux sont ventilés avec de l'air, la résistance vasculaire pulmonaire décroît en deux étapes : 1) une baisse rapide de la résistance vasculaire pulmonaire pendant les trente premières secondes de ventilation, et 2) une baisse plus lente qui continue pendant les 10 à 20 premières minutes ou plus, de ventilation. L'indométhacine a un effet minime sur la première composante. La seconde ne se produit pas après un traitement à l'indométhacine. Les effets observés avec l'indométhacine étaient plus prononcés chez les fœtus immatures (moins de 90 % de la gestation), que chez les fœtus matures. L'activité de la prostaglandine synthétase semble avoir un rôle dans la vasodilatation pulmonaire résultant de la ventilation par l'air des poumons fœtaux.

Introduction

At birth there is a rearrangement of the circulation in order that all blood returning

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to the heart from the systemic circulation will be pumped into the pulmonary circulation. The key step in transition from a fetal to a neonatal circulation is pulmonary vasodilation following ventilation of lungs with air. However, the basic mechanisms for the vasodilation have not been fully elucidated. Mediator(s) producing the decrease in pulmonary vascular resistance have not been determined. Several exogenous agents, for example histamine, bradykinin, and prostaglandins (E-series) may produce circulatory changes in the fetus which are in some ways similar to changes occurring at birth (1, 3, 5, 25). Bradykinin, which is released

by the lungs at birth, may be a mediator of neonatal circulatory changes (19).

In adult mammals distension of lungs causes prostaglandins to be released (8). Prostaglandins of the E-series are the major prostaglandins produced by the lungs (17). Prostaglandin E_1 is a potent vasodilator in pulmonary vascular beds of adult mammals (11, 12, 13). We have shown that prostaglandins of the E-series (3, 22) are also potent vasodilators of fetal and neonatal pulmonary circulations. Slow infusion of prostaglandin E_1 into the left pulmonary artery of unventilated fetal goats diminishes pulmonary vascular resistance almost as much as does ventilation (22). Additionally, inhibition of prostaglandin synthetase with indomethacin (9) increases pulmonary vascular resistance in newborn goats and newly ventilated fetuses (24). The increase in pulmonary vascular resistance produced by inhibition of prostaglandin synthetase is much greater in the ventilated fetus than in the newborn, several days old. One might expect these changes if large amounts of dilator prostaglandins were being released to establish and maintain decreased pulmonary vascular resistance of the newly ventilated lung. Thus, it seemed feasible to us that prostaglandins or other products of the prostaglandin synthetase system might be involved in the pulmonary vasodilation which accompanies ventilation of fetal lungs with air.

The following investigation was undertaken to evaluate the role of prostaglandin synthetase in the pulmonary vasodilation associated with ventilation of fetal goat lungs.

Methods

Thirty fetal goats (116-148 [term] days gestation) (1.2-3.2 kg) were delivered by cesarean section onto a warm table from goats anesthetized with chloralose (50 mg/kg i.v., supplemented hourly with 10 mg/kg). Umbilical circulation was left intact and a saline-filled rubber bag was placed over the fetal head to prevent breathing. The fetal abdomen was sutured to the uterus to protect the umbilicus. A polyethylene cannula filled with saline was placed in the trachea and the fetal head cover removed. Fetal colonic temperature was maintained at the temperature measured at delivery ($37.7 \pm$

0.2°C). Systemic arterial pressure (Statham P23DC transducer) and arterial pH, PO_2 , and PCO_2 (Radiometer Blood Gas and pH Analyzer) were monitored via a cannula in the descending aorta. A left thoracotomy was performed to give access to the left pulmonary artery. Following anticoagulation (Heparin, 2000 units/kg, i.v.), blood was withdrawn from the inferior vena cava (above the liver) via a cannula introduced through a femoral vein and pumped (Cole Parmer Master-flex Model 7016) into the cannulated left pulmonary artery. Left pulmonary arterial perfusion pressure, left atrial pressure, and left pulmonary arterial blood flow (Statham flowmeter with In Vivo Metric electromagnetic flow probe, Model FT2C) were recorded on a Brush polygraph. Left pulmonary arterial blood flow was set at a level that produced a left pulmonary arterial perfusion pressure approximately equal to the systemic blood pressure. The pulmonary arterial perfusion flow was kept constant for the remainder of the experiment. Left pulmonary vascular resistance was calculated as left pulmonary arterial perfusion pressure minus left atrial pressure divided by the flow per unit weight of animal (mmHg.kg.min/ml). Blood flow through the right pulmonary artery and the ductus arteriosus was left undisturbed.

In pregnant goats with twins or triplets the first fetuses served as controls while later fetuses received indomethacin² dissolved with equimolar Na_2CO_3 (3 mg/kg i.a.) to inhibit prostaglandin synthetase 30 minutes prior to ventilation. Control experiments (if mother had multiple fetuses) were always performed on fetuses delivered prior to those treated with indomethacin. Infusion of arachidonic acid (1000-5000 $\mu\text{g/kg.min}$) into the perfusion circuit of the untreated twins of indomethacin treated fetuses was without effect upon pulmonary vascular resistance or systemic arterial pressure. In fetuses which had not received prostaglandin synthetase inhibitors, intravenous infusion of a prostaglandin precursor, arachidonic acid, resulted in an increase in pulmonary arterial pressure and a decrease in systemic arterial pressure. These effects were abolished following treatment with indomethacin or meclofenamate (23). Thus, it appears that suf-

¹ Mean \pm SE.

² Kind gift of Dr. C.A. Stone, Merck, Sharp and Dohme.

ficient quantities of indomethacin crossed the placenta and reached the untreated twins to inhibit conversion of exogenous arachidonic acid into more vasoactive substances. This distribution of indomethacin prohibited the use of a second fetus as a control subsequent to treatment of a first fetus with indomethacin. Five sets of twins in which the first acted as control while the second received indomethacin, one set of triplets with two controls and the last indomethacin treated, two sets of triplets in which the first acted as control and the last two received indomethacin, and eight single fetuses (four control, four indomethacin treated) were used in these experiments. No differences were observed in responses to ventilation or treatment with indomethacin between single and multiple fetuses. Arachidonic acid was infused directly into the pulmonary arteries of six fetuses (four treated and two controls) to determine whether or not indomethacin had blocked prostaglandin synthetase. Both control animals showed marked increases in pulmonary vascular resistance during the infusion while arachidonic acid did not alter the pulmonary vascular resistance of the indomethacin treated animals.

Lung fluid was aspirated and ventilation initiated (25% O₂ in N₂, Palmer respirator) thirty minutes after the pulmonary arterial perfusion was begun. Fetuses were ventilated at volumes of 40 to 60 ml/breath and between 14 and 20 breaths/minute depending upon size. Twins and triplets (paired experiments) were ventilated at the same rate and volume. An end expiratory pressure of 2 mmHg was maintained. Lungs were examined visually at the end of each experiment and were found to be normal in appearance. Two minutes following the onset of ventilation the umbilical cord was tied.

In three fetal animals a polyethylene stand pipe was inserted between the carotid artery and the left pulmonary artery. The stand pipe was filled with carotid blood and pressure flow curves generated as described previously (2). Pressures and flows were recorded on the Brush polygraph as well as on a Houston X-Y recorder. This procedure allowed us to evaluate changes in pulmonary vascular resistance at a variety of pressures and flows. The volume of the stand pipe utilized was 50 ml. Each pressure flow curve required no more than 35 seconds for completion. The maximal rate of flow estab-

lished was 48 ml/min. Since weights of the three animals used varied only between 1.9 and 2.0 kg, flows are expressed simply as flow/minute and averaged. Pressure-flow curves were generated in the fetal state (prior to lung ventilation), and after ventilation as described above (with cord temporarily occluded with umbilical tape) with fetal gas (7% CO₂ and 3% O₂). Lungs were filled with O₂ and allowed to collapse while umbilical tape was removed. Fetal animals were then given indomethacin (3.0 mg/kg, i.a.). After a twenty minute wait a new control pressure flow curve was generated (no ventilation). This curve was followed by curves after ventilation with fetal gas and room air.

All differences cited are significant at $P < 0.05$ (t-test) (7).

Results

Table 1 contains the arterial blood gases and pHs of all fetuses immediately prior to ventilation and 10 minutes after ventilation was begun. Differences between control animals and animals treated with indomethacin were not significantly different. Gas exchange in ventilated older fetuses seemed better than in the younger animals. Thus, mean arterial PCO₂ of ventilated fetuses less than 135 days gestation (41.1 ± 2.3 mmHg) was greater than that of ventilated fetuses greater than 135 days gestation (31.3 ± 1.9 mmHg). In addition, the mean arterial PO₂ of younger ventilated fetuses (54.3 ± 6.4 mmHg) was less than that of older ventilated fetuses (102.7 ± 9.5 mmHg).

Treatment with indomethacin did not affect significantly, the pulmonary vascular resistance of pump perfused unventilated fetuses during the thirty minutes prior to ventilation. During the 30 minutes following administration of indomethacin systemic arterial pressure increased slightly.

Table 2 provides mean systemic arterial pressures of the animals before and after ventilation. While the mean systemic arterial pressures of the two groups are not significantly different at the moment ventilation is initiated, goats treated with indomethacin maintained this pressure after ventilation while systemic arterial pressures of control animals fell after ventilation.

Table 1: Arterial blood gases of fetuses before and after ventilation (gaz pressures in mm Hg).

Treatment	Age of foetus (days)	Before ventilation			After ventilation (10 min)		
		pH	PCO ₂	PO ₂	pH	PCO ₂	PO ₂
Control	< 135	7.32	44	23	7.31	37	42
		7.28	60	14	7.32	45	39
		7.24	54	21	7.26	51	35
		7.30	51	21	7.28	45	53
		7.35	46	27	7.24	47	93
		7.31	55	18	7.33	47	80
		7.30	51	21	7.31	46	60
	> 135	7.35	34	23	7.37	33	135
		7.40	44	20	7.56	21	93
		7.25	52	16	7.38	42	68
		7.37	44	15	7.37	33	43
		7.26	34	25	7.29	31	136
		7.35	34	25	7.34	34	95
		Indomethacin	< 135	7.28	40	24	7.23
7.33	51			26	7.38	42	113
7.30	48			31	7.43	26	26
7.38	44			22	7.53	27	53
7.47	45			25	7.47	28	26
7.06	85			15	7.28	56	56
7.20	61			25	7.30	35	43
7.27	37		29	7.20	38	32	
> 135	7.29		42	23	7.31	33	116
	7.26		47	24	7.33	38	128
	7.31	47	24	7.48	20	86	
	7.32	49	16	7.37	36	130	
	7.34	42	27	7.37	26	62	
	7.21	35	29	7.22	29	140	

The effect of ventilation upon the pulmonary arterial perfusion pressure at a constant flow of a control fetus and a fetus treated with indomethacin is seen in Figure 1. Left atrial pressure did not change more than 1 mmHg_i in either fetus. An initial sharp decline in pulmonary arterial perfusion pressure is noted in both animals during the first 30 seconds following the onset of ventilation. This was followed by a temporary increase in pressure during the next 30 seconds. In the control animal, there was a slower but continuous drop in pulmonary arterial perfusion pressure from 1 to 9 minutes, (continuing through 15 minutes). The pulmonary arterial perfusion pressure of the indomethacin treated fetus did not decline further after the initial fall in the first minute but actually increased slightly.

Indomethacin treatment has a greater effect upon the decrease in pulmonary

arterial perfusion pressure that follows ventilation in younger fetuses (Figure 2a) than it has upon that of fetuses nearer term (Figure 2b). The mean pulmonary arterial perfusion pressure of fetuses less than 135 days gestation treated with indomethacin did not continue to decline beyond the first 30 seconds of ventilation but, instead, increased during the next 30 minutes. Thus, 30 minutes after the onset of ventilation the mean pulmonary arterial perfusion pressure of indomethacin treated fetuses less than 135 days gestation was only 7% less than before ventilation. In older fetuses (greater than 135 days gestation) the difference between indomethacin and control groups is less dramatic (Figure 2b). In the more mature control animals there is, just as in younger controls, a progressive decrease in pulmonary arterial perfusion pressure beyond the first-post ventilation minute. Thirty minutes following the onset of ventila-

Table 2: Mean systemic arterial pressures in mm Hg of control and indomethacin treated fetuses before and after ventilation.

Treatment	Before ventilation	After ventilation			
		2 min	5 min	30 min	
Control	48 ± 3*	39 ± 2	Umbilical	40 ± 2	38 ± 2
Indomethacin	51 ± 4		cord		
*Mean ± SE		46 ± 4	tied	50 ± 5	51 ± 4

ation the mean pulmonary arterial perfusion pressure of these animals is 67% less than before ventilation. In mature fetuses treated with indomethacin, there is minimal change after the first post-ventilation minute. As a result the pulmonary arterial perfusion pressure thirty minutes following the onset of ventilation is only 36% less than before ventilation. It had been 28% less by 30 seconds post-ventilation. Left atrial pressure differences between groups are not significantly different.

Average changes in pulmonary pressure and flow in three fetal kids (133-135 days gestational age) are plotted in Figure 3 (left atrial pressure did not change significantly). Ventilation of fetal lungs with a gas mixture (fetal gas) designed not to change fetal blood gases (7% CO₂ and 3% O₂) resulted in a shift in the pressure flow curve to the left indicating a decrease in pulmonary vascular resistance. Following collapse of the lungs with oxygen and administration of indomethacin, the slope of the pressure flow curve decreased and the curve shifted

to the right indicating an increase in pulmonary vascular resistance. Ventilation with fetal gas thirty minutes subsequent to administration of indomethacin, not only did not result in a vasodilation, but gave evidence of further vasoconstriction. (Blood gases and pH were not significantly different from those obtained after ventilation with fetal gas prior to treatment with indomethacin.) Ventilation with air did in fact increase arterial PO₂, decrease arterial PCO₂ and shift the curve to the left of the control curve for the unventilated lungs.

Discussion

Ventilation of the fetal goat lungs with air results in a decrease in pulmonary vascular resistance which consists of two phases: (a) a rapid fall in resistance in the first 30 seconds, and (b) a slower decline in pulmonary vascular resistance over the next 10 to 20 minutes or more.

Indomethacin, which blocks prostaglandin synthetase activity (9), has no effect upon the initial rapid decline in pulmonary vascular resistance which occurs at the onset of ventilation of the fetal goat. However, indomethacin attenuates the slower decline. Therefore, it appears to us that prostaglandin synthetase activity plays an important role in this slower, prolonged decline in pulmonary vascular resistance that follows ventilation. These results are not unexpected when one considers the variety of stimuli including lung distension, anaphylaxis, embolization, serotonin, and phospholipase which cause prostaglandins to be synthesized and released into pulmonary blood (8, 15, 21). Lungs (guinea pig) produce mostly prostaglandins of the E-series normally and during anaphylactic shock (17).

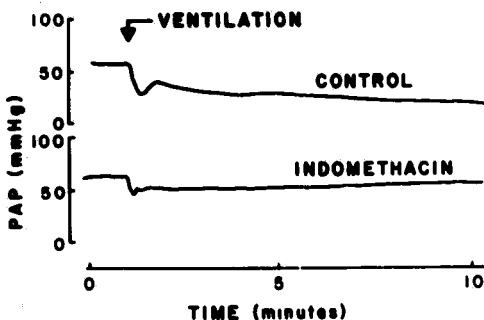


Figure 1. Effect of ventilation upon the pulmonary arterial perfusion pressure (PAP) at constant flow and left atrial pressure of an untreated fetus (top) and a fetus treated with indomethacin (bottom).

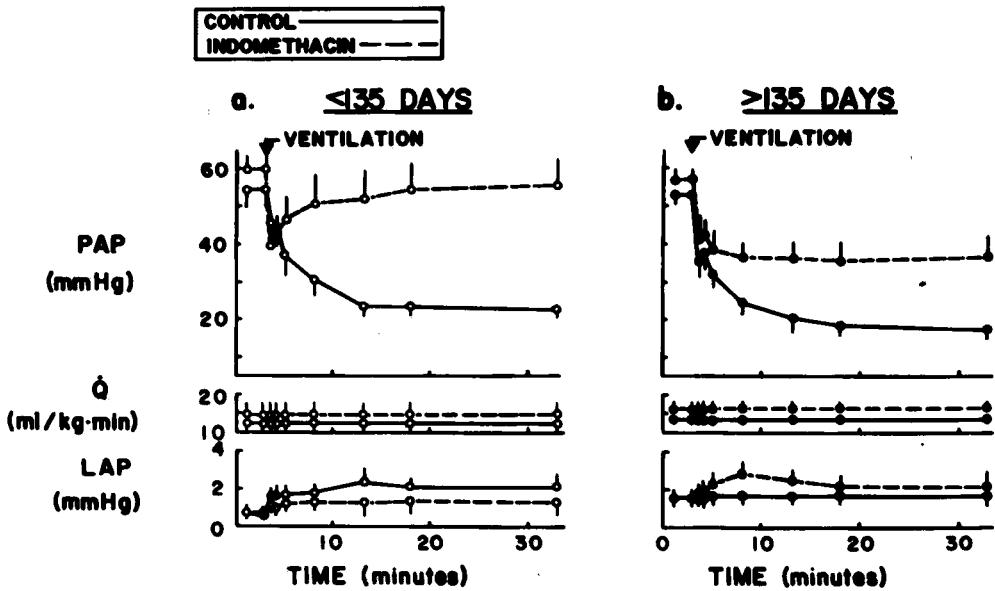


Figure 2. Effect of ventilation upon the left pulmonary arterial perfusion pressures (PAP) at constant left pulmonary arterial blood flows (Q) and left atrial pressures (LAP) of: (a) untreated fetuses (n=7) and indomethacin treated fetuses (n=8) less than 135 days gestation (130 ± 0.5 days) and (b) untreated fetuses (n=6) and indomethacin treated fetuses (n=6) greater than 135 days gestation (140.5 ± 0.5 days). (Vertical ranges are SE.)

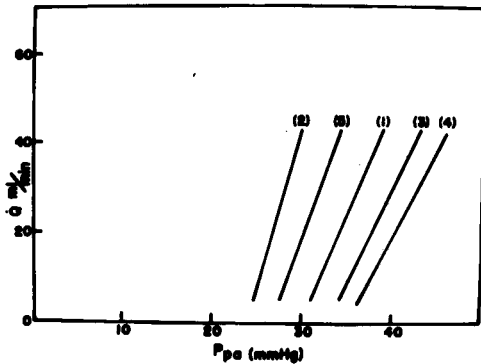


Figure 3. Effects of ventilation upon pulmonary arterial pressure and flow curves of three fetal goats (133-135 days gestational age). (1) control prior to ventilation; (2) after expansion with fetal gas; (3) control after indomethacin; (4) ventilation 20 minutes after indomethacin; (5) ventilation with air after treatment with indomethacin. Slopes and intercepts are averages of three sets of curves. Left atrial pressure did not change significantly and was not used in calculations.

These prostaglandins are potent vasodilators in the pulmonary circulation of fetal goats (3).

Indomethacin might be expected to have a greater effect upon the newly ventilated lung than upon the unventilated lung if, with ventilation, prostaglandin synthetase activity normally produced dilator substances. Indomethacin does have a pronounced effect upon the pulmonary vasculature of newly ventilated fetuses, increasing the pulmonary vascular resistance 82% (24). Indomethacin treatment has less effect (26% increase) upon the pulmonary vascular resistance of newborn goats several days old (24). In contrast to its effect upon the newly ventilated lung, indomethacin treatment had minimal effect on the pulmonary vascular resistance of the unventilated pump perfused fetal goat lung during the time course of this study. These results might be expected if dilators were produced by prostaglandin synthetase activity in the newly ventilated lung and continued to be produced during the early neonatal period.

Prostaglandin synthetase inhibition with indomethacin has a greater effect upon pulmonary vasodilation, due to ventilation of lungs of less mature fetuses (less than 135 days gestation) than upon more mature

ones (greater than 135 days gestation). The reason for this age dependence is not known. Gas exchange in older ventilated fetuses is better than in younger ones (Table 1). Treatment with indomethacin augments hypoxic pulmonary vasoconstriction in newborn goats (24). Thus, it is possible that the lower PO_2 of the younger animals, if it existed in pulmonary resistance vessels as well as arterial blood, could result in the higher pulmonary vascular resistance following indomethacin and ventilation in these fetuses. It is also possible that more than one system is operating during the slow decline phase of the pulmonary vasodilation. Prostaglandin synthetase activity appears to be important as the decline in resistance from 30 seconds to 30 minutes is either missing (less than 135 days gestation) or markedly reduced (greater than 135 days gestation). Other dilator substances may also be acting during this period. For example, bradykinin is released when fetal lungs are ventilated with O_2 (10). It is possible that kallikrein or other enzymes mature later than does the prostaglandin synthetase system. Continuous release of dilator substances may be necessary in the early neonatal period not only to establish a low pulmonary vascular resistance, but also to maintain it. It may be that fewer dilators not dependent upon prostaglandin synthetase are released in immature fetuses than in mature ones. After treatment with indomethacin, sufficient dilator influence does not exist in immature fetuses to maintain the decrease in pulmonary vascular resistance.

While prostaglandin synthetase activity appears to be important in causing and maintaining pulmonary vasodilation after 30 seconds of ventilation, it appears to play a minimal role in the rapid fall in pulmonary vascular resistance during the first 30 seconds. The initial drop could be entirely mechanical resulting from the reduction of transmural pressure by establishment of an air-liquid interface in the alveoli. Conversely, gaseous ventilation might cause a transient release of other dilators that causes the initial sharp decline in pulmonary vascular resistance. Clearly, gaseous ventilation alone, without corresponding blood gas changes, causes pulmonary vasodilation although not as great in magnitude as that caused by ventilation with air (2). It is not

known whether the reduction in pulmonary vascular resistance which occurs when fetal lungs are ventilated with fetal gas (a gas mixture which does not change blood gases) is confined to the rapid initial decline in pulmonary vascular resistance or has a rapid and a slower component.

Although there are only three animals in the series, pressure flow curves generated over a range of flows and pressures clearly indicate that inhibition of prostaglandin synthetase activity increases the pulmonary vascular resistance of newly ventilated fetal goats. The decrease in pulmonary vascular resistance normally observed with initiation of respiration is depressed. Even after ventilation with room air, the decrease in pulmonary vascular resistance after indomethacin is less than that seen with fetal gas before indomethacin.

Ventilation with O_2 but not with N_2 causes bradykinin to be released (10). The role of O_2 -dependent bradykinin release in the fast pulmonary vascular resistance decrease and/or the slow decline is also not clear. Bradykinin has been shown to cause the synthesis of E-series prostaglandins in canine and rabbit kidneys (4,18) and rat skeletal muscle (20). These prostaglandins mediate, in part, the dilator responses to bradykinin. If bradykinin also causes release of dilator prostaglandin synthetase products in the fetal lung, the dilator effect of O_2 dependent bradykinin release would be augmented by products of prostaglandin synthetase activity.

Blocking the prostaglandin synthetase system with indomethacin results in a reduction of the pulmonary vasodilation which occurs when fetal goat lungs are ventilated with air. Therefore, a substance or substances dependent upon prostaglandin synthetase activity for production must be important in the pulmonary vasodilation caused by ventilation. This substance (substances) could be produced and released in response to mechanical stimuli or changes in O_2 or CO_2 tension or in response to all these stimuli. The overall effect of prostaglandin synthetase activity is to produce a slow decline in pulmonary vascular resistance from the first minute of ventilation through the first 30 minutes or more.

Therefore, inhibition of fetal prostaglandin synthetase could be expected to predispose the neonate to continued high pulmonary

vascular resistance following ventilation. Prostaglandin synthetase inhibitors, most notably aspirin, are among the most widely used of all drugs. In addition to use as analgesics, antipyretics, and anti-inflammatory agents, these agents are used to prolong gestation and prevent premature labor (16). If prostaglandins are major mediators of the decrease in pulmonary vascular resistance at birth, use of their inhibitors by pre-

gnant women may be highly disadvantageous to newly born infants.

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Summary

Effects of indomethacin on pulmonary vasodilation caused by ventilation of the fetal lungs with air were evaluated in anesthetized, exteriorized fetal goats by means of an open-chest, pump perfused lung preparation. When fetal lungs are ventilated with air, pulmonary vascular resistance decreases in two steps: 1) a rapid decrease in pulmonary vascular resistance during the first 30 seconds of ventilation, and 2) a slower decline which continues through the first 10-20 minutes of more of ventilation. Indomethacin has minimal effect upon the first component. The second component is absent following treatment with indomethacin. Effects observed with indomethacin were more pronounced in immature fetuses (less than 90% gestation), than in mature fetuses. Prostaglandin synthetase activity appears to have a role in the pulmonary vasodilation resulting from ventilation of the fetal lungs with air.

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