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FETAL AND NEONATAL PULMONARY CIRCULATION

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During fetal life, gas exchange is carried out in the placenta. The lung does not have a physiological role, apart from possible metabolic functions which include secretion of hormones, enzymatic conversion of inactive substances to functional hormones, and degradation of active materials to inactive metabolites. Blood flow through the lungs is quite low during fetal life; most of the systemic and umbilical venous blood returning to the heart is shunted through the foramen ovale to the left atrium and left ventricle, or through the ductus arteriosus directly from the pulmonary trunk to the descending aorta. About 85–90% of the blood ejected by the right ventricle is diverted from the lungs through the ductus arteriosus (48). Because the right ventricle ejects about 66% of the combined ventricular output of the fetal heart, about 60% of the total output of the heart passes through the ductus arteriosus and thus does not enter the lungs. Should this volume of blood pass through the pulmonary circulation and return to the left ventricle, there would be an unnecessary increase in the volume of work placed on the heart.

The low fetal pulmonary blood flow has been explained on the basis of a high pulmonary vascular resistance. After birth, however, a marked increase in pulmonary blood flow is necessary to permit adequate gas exchange. This review considers: (*a*) pulmonary arterial pressures and flows in utero and changes during gestation; (*b*) patterns of fetal pulmonary blood flow; (*c*) factors that influence fetal pulmonary vascular responses; and (*d*) mechanisms responsible for the postnatal decrease in pulmonary vascular resistance.

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GESTATIONAL CHANGES

Until recently, measurements of fetal pulmonary arterial blood pressure and flow were obtained acutely in exteriorized fetal lambs or goats, after extensive surgical procedures and often under general anesthesia (3, 4). These measurements could not be considered to represent pressures and flows in undisturbed fetuses, particularly since the fetal pulmonary circulation is very labile. The authors reported that pulmonary arterial pressure was consistently higher than aortic pressure, with a systolic pressure difference of 10–15 mm Hg. In studies in chronically catheterized fetal lambs of 0.7–1.0 gestation, pulmonary arterial and aortic pressure levels were almost identical (40). It is reasonable to assume that these pressures are equal in younger fetal animals. Mean pulmonary arterial and aortic pressures increase progressively with gestational age; with amniotic cavity pressure as zero reference, pressures increased from approximately 30 mm Hg at 0.4 gestation to about 50 mm Hg at term (Figure 1) (40, 49). These pressures are considerably lower than those reported in acutely exteriorized fetal lambs (20).

Pulmonary blood flow has been measured by the radionuclide labeled microsphere technique (25, 50, 51) and by electromagnetic flowmeters in chronically instrumented fetal lambs (25, 40). Actual pulmonary blood flow increases from about 4 ml min^{-1} at 0.4 gestation to about 160 ml min^{-1} at

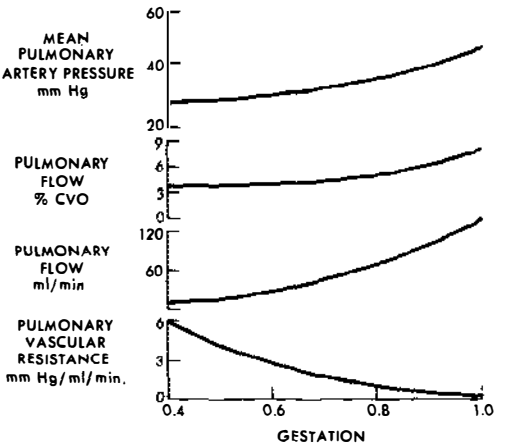

Figure 1 Diagrammatic representation of the changes in mean pulmonary arterial pressure, proportion of combined ventricular output (CVO) distributed to the lungs, actual pulmonary blood flow, and calculated pulmonary vascular resistance, in fetal lambs during gestational development from 0.4–1.0 gestation. [From (49)]

term (Figure 1). The combined ventricular output of the fetal lamb parallels changes in weight with intrauterine growth, and from 0.4–1.0 gestation, mean combined ventricular output is about 475 ml min^{-1} kg^{-1}. The proportion of cardiac output distributed to the lung is 3–4% from 0.4–0.7 gestation, but it increases progressively to 8–10% at term (51). Calculated pulmonary vascular resistance is extremely high at 6 mm Hg min^{-1} ml^{-1} at 0.4 gestation and falls progressively to 0.3–0.35 mm Hg min^{-1} ml^{-1} at term (Figure 1). This decrease in pulmonary vascular resistance represents a 17–20-fold increase in the cross-sectional area of the pulmonary vascular bed. It could result from a decrease in resting vascular constriction, or from an increase in individual vessel diameter, but probably is largely related to growth of new vessels, as discussed below.

PATTERNS OF PULMONARY FLOW

The velocity profiles of blood in the pulmonary trunk and pulmonary arteries have been recorded by chronically implanted cuff-type electromagnetic flow transducers (40, 53). The profile in the pulmonary trunk is similar to that seen in the main pulmonary artery after birth. Velocity rises rapidly in association with the rise of pulmonary arterial pressure, and, after reaching a peak, falls to reach zero coincident with the dicrotic notch; no flow is recorded during diastole. Flow in the pulmonary arteries commences with the rapid rise of pulmonary arterial pressure, reaches a peak early in systole, and then falls to zero in about the middle of systole. A pronounced reverse flow occurs in late systole and early diastole, after which there is zero flow to the onset of the next systole (Figure 2). The velocity pattern in the fetal pulmonary artery has been explained on the high (relative to systemic) pulmonary vascular resistance and the presence of the ductus arteriosus. During early systole, when blood is ejected at high velocity, blood flows through the large pulmonary arteries and through the peripheral pulmonary vessels. As velocity falls, blood flows preferentially through the ductus arteriosus to the descending aorta; since peripheral pulmonary vascular resistance is high, reverse flow is recorded as blood flows from the large pulmonary arteries through the ductus arteriosus in association with elastic recoil of these vessels (49). This concept is supported by observations of the effects of changing pulmonary vascular resistance (40). When pulmonary vascular resistance is increased by inducing fetal hypoxia by administering low-oxygen gas mixtures to the ewe, the forward flow phase decreases and the magnitude and duration of recorded backflow increases. Conversely, when pulmonary vascular resistance is reduced by infusion of acetylcholine, forward flow increases in magnitude and extends throughout systole, whereas backflow is greatly reduced.

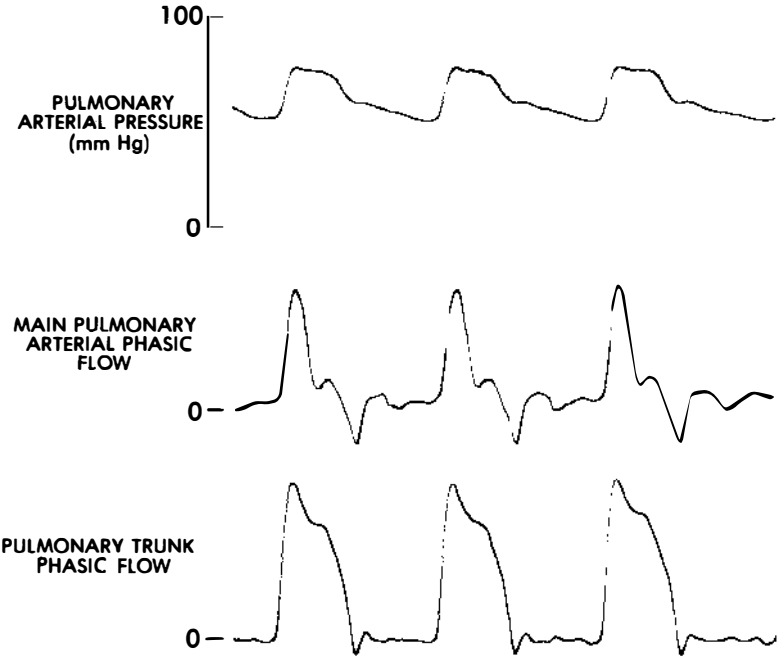

Figure 2 Recording of pulmonary arterial pressure, pulmonary arterial flow contour, and pulmonary trunk flow pattern in a fetal lamb with chronically implanted intravascular catheters and electromagnetic flow transducers. Forward flow occurs only in the early part of systole in the pulmonary artery, followed by rapid return to zero flow and then a pronounced backflow. In pulmonary trunk, representing right ventricular outflow, there is continuous forward flow throughout the whole of systole.

MORPHOLOGICAL FEATURES

The high pulmonary vascular resistance during fetal life and the greater vasomotor responsiveness in the lung as compared with adult animals have been explained by the greater muscularity of the arteries (16, 47). Earlier studies suggested that there was an extension of muscle into more distal pulmonary arteries as gestation advanced (47, 62) and that the area of muscle in the walls of vessels less than 50 μm diameter increased in the latter half of gestation (44). Recently, in fetal lungs in which the pulmonary circulation was distended to achieve pressures similar to those present during fetal life, it has been shown that there is no change in the thickness of the medial muscular layers in the small pulmonary arteries in human (28) or lamb (39). In the lamb lungs, there is a marked increase in the wall thickness as a percentage of vessel diameter at the fifth and sixth generation,

designating the left and right main branches as second generation vessels. The external diameter of these vessels ranges from 20–50 μm, and the medial layer is constituted almost entirely of smooth muscle; they appear to account for the major resistance to flow through the lungs. The thickness of the muscle layers in small fetal pulmonary arteries is increased by prolonged hypoxia of maternal rats (24). In fetal lambs, systemic arterial hypertension (resulting from either unilateral renal constriction or umbilical arterial constriction), and pulmonary arterial hypertension (produced by constriction of the ductus arteriosus) are also associated with increased thickness of smooth muscle in resistance vessels of the lung (38). Ingestion of prostaglandin synthetase inhibitors by pregnant women has been reported to be associated with the presence of increased pulmonary vascular smooth muscle development (37). It has been suggested that this may be due to constriction of the ductus arteriosus in the fetus, which results in pulmonary arterial hypertension (26), but a direct effect on pulmonary vessels cannot be excluded.

The pulmonary vessels rapidly lose the medial smooth muscle layer after birth (19, 61, 62). However, the muscle-layer thickness in the small vessels may increase again with pulmonary hypertension. Exposure of rats to a decreased oxygen environment for two weeks resulted in an increase in vessel-wall thickness (29). Furthermore, there is evidence that new muscle may develop in peripheral nonmuscular vessels as the result of differentiation of cells that are normally present in the vessel wall—the *pericytes* of nonmuscular arteries—and intermediate cells of partially muscular arteries (43). After return to normal oxygen levels, the vessel thickness decreased, but there was also a reduction in the total number of small vessels in the lung (30). It has been suggested that there may be a permanent reduction in the number of small vessels with a restricted cross-sectional area of the pulmonary vascular bed.

FACTORS AFFECTING FETAL PULMONARY CIRCULATION

Although the high pulmonary vascular resistance during fetal life has been ascribed to the muscularity of the small pulmonary arteries, the mechanisms that maintain vasoconstriction in utero and permit rapid vasodilatation after birth are not fully understood. The pulmonary vasoconstriction in the fetal lung has been related to the low P_{O_2} of blood perfusing the lungs, to autonomic nervous influences, and to circulating hormones.

Effects of P_{O_2} and pH

The fetal pulmonary arterioles are exposed to the P_{O_2} of blood perfusing the lungs. Lung metabolism presumably results in some oxygen consump-

tion so that the Po_2 influencing the small pulmonary vessels may be somewhat lower than that in pulmonary arterial blood. In the normal fetal lamb, with the ewe breathing room air, pulmonary arterial Po_2 is 18–21 torr as compared with a descending aortic Po_2 of 21–24 torr (52). Earlier studies showed that fetal hypoxia induced by umbilical cord compression or maternal hypoxia resulted in pulmonary vasoconstriction (10, 11, 18, 21, 58). The lambs were exteriorized and anesthetized in most studies; the pulmonary vasculature responses thus may have been altered markedly in these experimental circumstances. In a study in fetal lambs in utero, pulmonary blood flow, measured by the radioactive microsphere technique, fell to 50% of resting levels when aortic Po_2 was reduced to 12–24 torr (17). Since pulmonary arterial pressure also rose, this reflected an increase in pulmonary vascular resistance.

A more detailed study of the effects of hypoxia was made in fetal lambs with chronically implanted flow transducers around the pulmonary artery, distal to the pulmonary trunk. Fetal arterial Po_2 was reduced progressively by lowering the oxygen concentration in gas inspired by the ewe (40). Pulmonary vascular resistance increased with reduction in Po_2, in a curvilinear fashion, with a progressively greater rise as Po_2 fell. Of great interest was the finding that the response to hypoxia increased in magnitude with advancing gestation; the curve became much steeper, so that small reductions of Po_2 resulted in more marked increases of pulmonary vascular resistance.

As mentioned above, there is no change in the morphology of the fifth and sixth generation resistance vessels over the latter half of gestation in fetal lambs. Since there was a greater percentage increase of pulmonary vascular resistance over control levels with hypoxia (40), it was suggested that the sensitivity of pulmonary vascular smooth muscle to hypoxia increases with advancing gestation.

PARASYMPATHETIC REGULATION Injection or infusion of acetylcholine into the fetal pulmonary circulation results in dramatic vasodilatation (21), as does electrical stimulation of the cut end of the vagus nerve (18). In perfused lungs of fetal lambs with gestational ages of about 120 days (0.8) and 75–90 days (0.5–0.6) similar responses of pulmonary vascular resistance were noted (13, 14). With increasing gestation of fetal lambs in utero, however, a progressively greater reduction of pulmonary vascular resistance occurs with comparable doses of acetylcholine [based on fetal body weight (40)]. Similarly, a progressively greater fall in pulmonary arterial pressure with increasing fetal age was observed after acetylcholine injection (1).

Although cholinergic stimulation of the pulmonary vasculature has a dramatic effect in the fetus, parasympathetic nerves do not exert a signifi-

cant effect on the fetus in utero. In exteriorized lambs, bilateral cervical vagotomy or atropine injection did not alter resting pulmonary vascular resistance (18), and atropine had no effect on the pulmonary circulation of fetal lambs in utero (40, 52).

SYMPATHETIC REGULATION Stimulation of both alpha- and beta-adrenergic receptor activity in fetal lambs results in pulmonary vascular responses. Methoxamine, an alpha stimulator, and norepinephrine, a predominantly alpha stimulator, increase pulmonary vascular resistance (5, 13, 14). Pulmonary vasoconstriction also results from electrical stimulation of the peripheral end of the cut thoracic sympathetic chain in fetal lambs (18). Isoproterenol, a beta stimulator, has a potent pulmonary vasodilator effect in exteriorized (13, 14, 57) as well as chronically instrumented fetal lambs (A. M. Rudolph, M. A. Heymann, unpublished observations). It does not appear, however, that the sympathetic nerves have a significant tonic effect on the resting fetal pulmonary circulation since administration of the beta-adrenergic blocker propranolol, or the alpha-adrenergic blockers phentolamine or dibenzyline, does not alter pulmonary vascular resistance (40).

Role of Hormones

The renin-angiotensin system is well developed in the fetus at an early period of gestation (56). Administration of angiotensin II results in general vasoconstriction, including the umbilical vessels (8), the peripheral circulation, and the pulmonary circulation (31). It had been demonstrated in isolated perfused rodent lungs that the presence of angiotensin II was necessary to elicit a vasoconstrictor response to hypoxia (7). This suggested the possibility that the high pulmonary vascular resistance in the fetus might result from potentiation of the response to the low pulmonary arterial P_{O_2} by local conversion of renin to angiotensin II in the lung. However, infusion of Saralasin, a competitive blocker of angiotensin II, in amounts that prevent the effects of infused angiotensin II, does not affect the pulmonary vascular resistance of fetal lambs in utero (31). Furthermore, it does not influence the pulmonary vasoconstrictor response to hypoxia.

Mechanisms of Pulmonary Vascular Response to Changes of P_{O_2}

Although it had been shown that fetal hypoxia results in pulmonary vasoconstriction, it was not clear whether this occurred exclusively as the direct effect of the low P_{O_2} in the lung or whether a reflex response resulting from chemoreceptor stimulation was also involved, or an hormonal response from circulating catecholamines. Vagotomy and thoracic sympathectomy did not inhibit hypoxic pulmonary vasoconstriction (18). Studies in twin

lamb fetuses with cross-perfusion of the lung, however, suggested that the role of the sympathetic nervous system is related to gestational age (10, 11). When hypoxia was induced in the fetus whose lung was being infused from its twin, pulmonary vasoconstriction was not elicited in immature lambs (0.6 gestation) but did occur in mature lambs; the effect was abolished by section of the sympathetic nerves to the lung or by administering hexamethonium. These studies were performed acutely in anesthetized, exteriorized fetuses and are not borne out by observations in lambs in utero. Administration of phenoxybenzamine or phentolamine in doses that produce complete alpha-adrenergic blockade does not have any effect on the pulmonary vascular response to hypoxia (40). Similarly, the hypoxic response was not affected by beta-adrenergic blockade with propranolol or by parasympathetic blockade with atropine. It was also concluded that the sympathetic nervous system is not involved in hypoxic pulmonary vasoconstriction in newborn calves since pretreatment with reserpine did not affect the response (55).

MECHANISMS RESPONSIBLE FOR POSTNATAL PULMONARY VASODILATATION

Several studies have demonstrated conclusively that ventilation of the lungs with air results in a dramatic decrease in pulmonary vascular resistance. This work has been reviewed extensively (20, 54). In summary, it was shown that physical expansion of the lungs with gas produces a small drop in vascular resistance, but the main effect is related to the increased P_{O_2}. An increase in P_{O_2} without the associated lung expansion was produced in two studies by placing the ewe in a hyperbaric oxygen environment. In one study pulmonary blood flow, as measured by electromagnetic flowmeter in acutely exteriorized lambs, increased (2); in the other, flows were measured in lambs in utero with the microsphere method and a marked drop in pulmonary vascular resistance was noted (27).

It is not known whether oxygen produces its dilator effect directly on the pulmonary vascular smooth muscle, or if it stimulates the release of a chemical mediator. Because kinin levels are high in the fetal circulation after birth, the possibility that kinins may be involved in the decrease in pulmonary vascular resistance after birth has been investigated in lambs (27). These studies were stimulated by the finding that bradykinin is a potent pulmonary vasodilator in the fetal lamb (12). When P_{O_2} was increased by ventilating the lungs of mature fetal lambs with oxygen, levels of kininogen, a bradykinin precursor, decreased and levels of bradykinin increased in blood that had passed through the lungs. The release of bradykinin in the lungs was not the result of physical expansion of the lungs

alone, as ventilation of the lungs with nitrogen did not influence kininogen or kinin levels. A similar increase in kinin levels in fetal blood was noted when ewes were exposed to hyperbaric oxygen. Although kinins may be involved in the immediate pulmonary vasodilatation after birth, they do not appear to be important in maintaining the lowered pulmonary vascular resistance since blood kinin levels rapidly fall within the first hour after ventilation of fetal lambs. Kinin release may be a supplementary mechanism, in addition to direct vascular effects of oxygen or other mediators, in establishing pulmonary circulation in the immediate neonatal period.

PROSTAGLANDINS AND PERINATAL PULMONARY CIRCULATION

Prostaglandins of the E and F series have been shown to produce marked cardiovascular responses when injected into the circulation of animals or humans. E-series prostaglandins generally produce vasodilatation, whereas F-series prostaglandins tend to be vasoconstrictors (6, 9, 32–35). In the pulmonary circulation PGE_1 consistently results in a small decrease in pulmonary vascular resistance (32, 33), but PGE_2 has produced conflicting effects (35, 41, 45).

In acutely exteriorized fetal goats, infusion of PGE_1 consistently produced a marked decrease in pulmonary vascular resistance of the perfused left lower lobe by about 50% (15). In a similar experimental preparation in which the lungs were ventilated, PGE_1 produced a lesser effect on the pulmonary circulation of the ventilated newborn goat breathing room air, but when pulmonary vasoconstriction was induced by ventilation with an hypoxia-producing gas mixture, PGE_1 resulted in a marked fall in vascular resistance (60). When PGE_1 was infused before hypoxia was induced, the rise in pulmonary vascular resistance was almost completely prevented.

PGE_2 produced similar but considerably less dramatic effects (59, 60). In these studies, systemic vasodilatation was observed only when large amounts of PGE_1 were infused into the pulmonary artery. It was suggested that this was due to the degradation of the PGE_1 in its passage through the lung. In adults, almost all prostaglandins are metabolized as blood passes through the lung (23), and the fetal lung also has a high capacity to degrade prostaglandins (46). Infusion of PGE_1 into a peripheral pulmonary artery in fetal lambs in utero resulted in a 50% reduction of pulmonary vascular resistance but, as infusion rates were increased, the PGE_1 passed through the lungs and resulted in umbilical vasoconstriction. In newborn lambs in which the ductus had been ligated, PGE_1 had insignificant effects on the pulmonary vascular resistance during normoxia but produced pulmonary vasodilatation during hypoxia. The dose of PGE_1 required to produce this

effect, however, consistently resulted in systemic vasodilatation (M. E. Tripp and associates, unpublished observations). The differences in these results could be explained by the type of experimental preparation, but it is possible that the fetal and neonatal lung does not have the degrading capability of the adult lung.

$PGF_{2\alpha}$ is a vasoconstrictor in the perfused lung of the fetal and neonatal goat (59). Infusion of the prostaglandin precursors arachidonic and dihomo-γ-linolenic acid also produces pulmonary vasoconstriction, and this effect is blocked by prostaglandin synthetase inhibitors. The authors suggest that the pulmonary vascular response could not be explained by singular formation of E or F series prostaglandins because the pulmonary vasoconstriction is associated with systemic vasodilatation.

Distension of the lungs of adult animals results in release of prostaglandins (22), and the lungs produce E-series prostaglandins predominantly (42). The possibility that PGE_1 may be involved in the fall in pulmonary vascular resistance after birth has been examined in fetal and neonatal goats. In the acutely exteriorized fetal goat in which the left lower lobe pulmonary artery was perfused, administration of indomethacin, a prostaglandin synthetase inhibitor, resulted in no change in pulmonary vascular resistance (36). The decrease in pulmonary vascular resistance following ventilation, however, was influenced. Two phases of pulmonary arterial pressure reduction were noted following ventilation. The initial rapid fall in pulmonary vascular resistance occurred within 30 seconds, and this result was not affected by indomethacin. The slower decline over the next 10–20 minutes was impaired by indomethacin; this effect was only slight in mature animals, but it was more pronounced in immature animals of less than 0.9 gestation. It was suggested that prostaglandin release was important in the pulmonary vasodilatation associated with ventilation of the fetal lungs with air.

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