Prostaglandin E₁ Opens the Ductus Venosus in the Newborn Lamb

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ABSTRACT. There is *in vitro* evidence that the ductus venosus of the fetal and newborn lamb relaxes to administration of E-series prostaglandins. We performed this study to determine whether the ductus venosus of the newborn lamb could be reopened by an infusion of prostaglandin E₁. Fifteen lambs between 4 and 28 h of life and six lambs between 42 and 96 h of life had portal angiograms to determine whether the ductus venosus was patent. Ten of the lambs between 4 and 28 h of age had a closed ductus venosus as did all of the lambs between 42 and 96 h of age. The lambs with a closed ductus venosus received an infusion of either prostaglandin E₁ or normal saline followed by repeat portal angiography. In the 4- to 28-h-old lambs, prostaglandin E₁ opened the ductus venosus in each of the five lambs who received it, while saline did not in any of the five who received it. In the 42- to 96-h-old lambs, neither prostaglandin E₁ in four lambs nor saline in two lambs opened the ductus venosus. Prostaglandin E₁, then, reopens the ductus venosus in the newborn lamb during the first day of life. We speculate that prostaglandin E₁ may be useful in reopening the ductus venosus in certain newborn infants such as those requiring catheterization of the right atrium and those with total anomalous pulmonary venous return below the diaphragm. (*Pediatr Res* 21: 225-228, 1987)

In the fetus, the ductus venosus provides a pathway by which umbilical venous return can bypass the liver and enter directly into the inferior vena cava (1-3). The ductus venosus could regulate hepatic blood flow and oxygenation by changing its diameter. It could also regulate umbilical venous return and, thereby, entry of well-oxygenated blood to the right and left atria. There is substantial evidence that the ductus venosus responds to autonomic and prostanoid stimulation (4-7). However, this responsiveness may not indicate an active role in fetal circulatory homeostasis (8-10).

The flow across the ductus venosus decreases substantially in the hours following birth and ceases within a few days (1, 2, 11). There are clinical situations in which it would be advantageous to maintain patency of the ductus venosus. Coceani *et al.* (6) and Adeagbo *et al.* (5) have found that the ductus venosus is constricted by indomethacin and dilated by E-series prostaglandins *in vitro*. There is also an abstract reporting that prostaglandin E₂ dilates the ductus venosus of the intact fetal lamb after it has been constricted with indomethacin. The current study extends this line of research to determine whether an infusion of prostaglandin E₁ can reopen the ductus venosus in the newborn lamb

and examines whether postnatal age modulates the effect of prostaglandin E₁.

METHODS

Of 22 lambs delivered vaginally at term, 15 were operated on 4-28 h later, six were operated on 42-96 h later, and one was operated on 36 h later. Under 1% halothane anesthesia a 2.5-cm incision was made just superior to the umbilical stump in each lamb. Both umbilical veins were exposed and a catheter inserted into each for injection of contrast dye and administration of prostaglandin E₁ or saline. The incision was closed and the lamb recovered from anesthesia. The lambs were, then, kept in a cage which allowed them to walk about.

After a 1-h recovery from surgery and anesthesia, each lamb had an initial angiography. If the lamb's ductus venosus was patent, no further experiments were performed on that lamb. If the lamb's ductus venosus was closed, the lamb was randomly assigned to receive an infusion of either normal saline or prostaglandin E₁ dissolved in normal saline. The infusion was begun 1 1/2 h after the initial angiography. After 2.4-4.8 h of infusion, angiography was repeated.

The prostaglandin E₁ was prepared immediately prior to administration. One 1 mg of desiccated prostaglandin E₁ was removed from storage at -20°C and dissolved in 0.06 ml of absolute ethyl alcohol. This solution was then diluted with sterile water to make 1 ml. This solution was diluted with normal saline to obtain the necessary concentration for each lamb's weight. The infusion rate of either normal saline or prostaglandin E₁ in saline was 5 ml/kg/h and the dose of prostaglandin E₁ was 1 µg/kg/min.

Each lamb was sedated with 10 mg/kg of Ketamine for each angiography. The lamb was placed slightly left anterior oblique from the true lateral position during the angiography. Four ml of 50% diatrizoate sodium radiographic contrast material were injected through each of the umbilical venous catheters. Two such injections were performed for each examination. During the first injection, the lamb was fluoroscoped for patency of the ductus venosus. During the second injection, a flat plate film of the upper abdomen and lower chest was obtained in order to document the status of the ductus venosus.

The ductus venosus was scored as open or closed. In the lamb who was 36 h old there was questionable patency of the ductus venosus on the initial examination. This lamb was eliminated from the study. In the remaining lambs flow across the ductus venosus into the inferior vena cava was either absent or clearly present. Statistical analysis was performed by the two-tailed Fisher exact test.

RESULTS

The lamb has two veins in the umbilical cord which unite to form a single umbilical vein shortly after entering the abdomen (Fig. 1A). Injection of both veins was found to promote turbu-

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Fig. 1. *A*, portal angiogram of a 24-h-old lamb, posterior-anterior view. The ductus venosus is closed. *B*, portal angiogram of another 24-h-old lamb, left anterior oblique view. Note patent ductus venosus (*arrow*) and swirling of contrast material in the inferior vena cava and right atrium.

Fig. 2. *A*, portal angiogram of a 28-h-old lamb, left anterior oblique view. The ductus venosus is closed, *B*, portal angiogram of the same lamb seen in *A* after a 4.5-h infusion of PGE_1 . The ductus venosus is now open (*arrow*) and contrast swirls in the inferior vena cava. *C*, portal angiogram of a 48-h-old lamb, left anterior oblique position. The ductus venosus is closed. *D*, portal angiogram of the same lamb as in *C* after a 3.5-h infusion of PGE_1 . The ductus venosus remains closed.

lence in the umbilical vein and thus fill the umbilical and portal circulations better (Fig. 1*B*). The single umbilical vein courses along the underside of the liver, going posteriorly and to the left to connect with the portal sinus (Fig. 1*A*). If the ductus venosus is patent, part of the umbilical flow bypasses the liver and enters directly into the inferior vena cava (Fig. 1*B*). Because of this course, the umbilical vein and ductus venosus are best demonstrated in a slightly left anterior oblique projection. There appears

to be a sphincter at the junction of the umbilical vein and ductus venosus (Fig. 1*B*).

Two-thirds of the lambs between 4 and 28 h after birth had a closed ductus venosus on the initial angiogram (Fig. 2*A* and Table 1). In these lambs prostaglandin E_1 consistently opened the ductus venosus (Fig. 2*B* and Table 2) while saline did not (Table 2).

All of the lambs between 42 and 96 h after birth had a closed

Table 1. Status of ductus venosus on initial angiogram in 21 lambs

Status of ductus venosus	Age	
	4-28 h	42-96 h
Open	5	0
Closed	10	6
Total	15	6

Table 2. Response of ductus venosus in 4- to 28-hr-old lambs to an infusion of prostaglandin E₁ (PGE₁) versus an infusion of saline*

Status of ductus venosus	Infusion	
	PGE ₁	Saline
Open	5†	0
Closed	0	5

* PGE₁ infused at 1 µg/kg/min for 3.0 ± 0.4 h (mean ± SEM) and saline infused for 3.5 ± 0.3 h (mean ± SEM), both at volume of 5 ml/kg/h.

† Significantly greater than in the saline-infused lambs ($p \leq 0.01$).

Table 3. Response of ductus venosus in 42- to 96-h-old lambs to an infusion of prostaglandin E₁ (PGE₁) versus an infusion of saline*

Status of ductus venosus	Infusion	
	PGE ₁	Saline
Open	0†	0
Closed	4	2

† Significantly less than in the 4- to 28-h-old lambs ($p \leq 0.01$).

* PGE₁ infused at 1 µg/kg/min for 3.4 ± 0.5 h (mean ± SEM) and saline infused for 4.0 ± 0.5 h (mean ± SEM) both at a volume of 5 ml/kg/h.

ductus venosus on the initial angiogram (Fig. 2C and Table 1). In contrast to its effect in the 4- to 28-h-old lambs, prostaglandin E₁ did not open the ductus venosus in these lambs (Fig. 2D and Table 3).

The infusion of prostaglandin E₁ did not cause observable systemic effects. Following their sedation and initial angiography the lambs were quiet. However, during the infusion they stood and walked about. Some took bottle feedings. They did not have apnea, agitation, or muscle twitching.

DISCUSSION

We have found that an infusion of prostaglandin E₁ opens the ductus venosus in the newborn lamb. Cocceani *et al.* (6) and Adeagbo *et al.* (5) previously reported *in vitro* experiments in which rings cut from the sphincter region of the ductus venosus of fetal and newborn lambs constricted to administration of indomethacin and relaxed to administration of prostaglandin E₂. There is an abstract reporting that indomethacin constricts the ductus venosus and prostaglandin E₂ relaxes the ductus venosus, after such constriction, in the intact fetal lamb (12). There is also an abstract reporting the opening of the ductus venosus by infusions of catecholamines or acetylcholine (4). The current study is the first report of opening a previously closed neonatal ductus venosus with prostaglandins.

We have also noted that the terminal end of the umbilical vein and the ductus venosus course slightly from the right to left when viewed in the anterior-posterior view. This is somewhat different from the anterior-posterior view often presented (3, 13). Our angiography also reveals a constriction consistent with a sphincter at the take off of the ductus venosus from the junction of the umbilical vein and the portal sinus. There is general agreement

that there is a ridge of tissue which contains smooth muscle cells and is responsive to prostaglandins and catecholamines at this junction (2, 5-7); whether it acts as a sphincter is not clear (2).

We found the ductus venosus was open in one-third of our lambs during the 1st day of life but was closed in all of our lambs after the 2nd day. Previous studies have examined the patency of the ductus venosus in neonatal lambs using umbilical angiography. Peltonen and Hirvonen (1) found the ductus venosus was usually open during the first 2 days of life and was closed thereafter (1). Their lambs were more deeply anesthetized and their angiograms were performed with mechanical injectors. These conditions may have increased the likelihood of their having or producing a patent ductus venosus. Using the radioactive microsphere technique, Zink and Petten (11) and Botti *et al.* (13) found the ductus venosus conducts 15-20% of portal venous flow during the first 2 days of life. Thereafter, the portion of portal venous blood flow passing through the ductus venosus averaged $\leq 10\%$. There are several possible explanations for the difference between the measurement of flow across the ductus venosus after the 2nd day of life in these studies and the current study: 1) the difference in site of injection from the portal vein in these studies to the umbilical vein in the current study affected the result; 2) the angiographic technique did not detect a flow of $\leq 10\%$ of portal venous return; or 3) the measurement of ductus venosus flow in these studies was elevated by passage of a small proportion of the injected microspheres through the sinusoids of the liver. In any case, the results of the current study regarding closure of the ductus venosus in the newborn lamb are not substantially different from those of previous authors.

There are, then, both *in vitro* and *in vivo* data that the diameter of the ductus venosus in the fetal and newborn lamb can be manipulated with indomethacin and prostaglandins (5, 6, 12). This story is symmetric with the effects of indomethacin and E-series prostaglandins on the ductus arteriosus (6, 14, 15). Whether this ability to pharmacologically manipulate the diameter of the ductus venosus indicates an active regulatory role in fetal, newborn, or transitional circulatory homeostasis remains a question (8-10, 16, 17).

In any case, we may have the ability to pharmacologically manipulate the ductus venosus. We can speculate that narrowing or closure of the ductus venosus would be an additional reason for avoiding prostaglandin synthetase inhibitors in pregnant women (6, 18). In addition, opening the ductus venosus in the newborn with an infusion of prostaglandin E₁ might allow placement of a central venous line or catheterization of the heart through the umbilical vein (6). Such an infusion might also be helpful in decreasing the degree of pulmonary venous obstruction in newborns with total anomalous pulmonary venous return below the diaphragm (19).

The dose of prostaglandin E₁ used in the current study was similar to that used to produce pulmonary vascular effects in newborn laboratory animals (20-22). It was, however, 10 times the dose of E-series prostaglandins used to open the ductus arteriosus in newborn infants with congenital heart diseases causing right to left shunting of blood (23-25). Perhaps no untoward systemic effects were noted in the current study because the lambs had no right to left shunting and all of the infused prostaglandin E₁ passed through the lungs where it was largely cleared before reaching the systemic circulation (26). However, further studies at lower doses, known to be tolerated clinically, need to be performed before clinical trials can be advocated.

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REFERENCES

1. Peltonen T, Hirvonen L 1965 Experimental studies on fetal and neonatal circulation. *Acta paediatr Scand [Suppl]* 161:1-55

2. Meyer WW, Lind J 1966 The ductus venosus and the mechanism of its closure. *Arch Dis Child* 41:597-605
3. Rudolph AM 1983 Hepatic and ductus venosus blood flows during fetal life. *Hepatology* 3:254-258
4. Peltonen T, Hirvonen L 1963 The ductus venosus. *Acta Paediatr Scand* 52:202(abstr)
5. Adeagbo ASO, Coceani F, Olley PM 1982 The response of the lamb ductus venosus to prostaglandins and inhibitors of prostaglandin and thromboxane synthesis. *Circ Res* 51:580-586
6. Coceani F, Adeagbo A, Bishai I, Hamilton F, Huhtanen D, Jhamandas V, Labuc J, Olley PM 1983 Involvement of prostaglandins in the ductus arteriosus and the ductus venosus of the lamb. *Adv Prostaglandin Thromboxane Leukotriene Res* 12:471-475
7. Coceani F, Adeagbo ASO, Cutz E, Olley PM 1984 Autonomic mechanisms in the ductus venosus of the lamb. *Am J Physiol* 247:H17-H24
8. Edelstone DI, Rudolph AM, Heymann MA 1978 Liver and ductus venosus blood flows in fetal lambs *in utero*. *Circ Res* 42:426-433
9. Edelstone DI, Merick RE, Caritis SN, Mueller-Heubach E 1980 Umbilical venous blood flow and its distribution before and during autonomic blockade in fetal lambs. *Am J Obstet Gynecol* 138:703-707
10. Edelstone DI, Rudolph AM, Heymann MA 1980 Effects of hypoxemia and decreasing umbilical flow on liver and ductus venosus blood flows in fetal lambs. *Am J Physiol* H656-663
11. Zink J, Van Petten GR 1980 Time course of closure of the ductus venosus in the newborn lamb. *Pediatr Res* 14:1-3
12. Sideris EB, Yokochi K, Vanhelder T, Coceani F, Olley PM 1982 Effects of indomethacin and prostaglandin E₂ (PGE₂) on the lamb fetal ductus venosus. *Circulation* 66(suppl II):112(abstr)
13. Botti JJ, Edelstone DI, Caritis SN, Mueller-Heubach E 1982 Portal venous blood flow distribution to liver and ductus venosus in newborn lambs. *Am J Obstet Gynecol* 144:303-308
14. Clyman RI, Wong L, Heymann MA, Rudolph AM 1978 Responsiveness of the lamb ductus arteriosus to prostaglandins and their metabolites. *Prostaglandins* 15:325-331
15. Friedman WF, Printz MP, Kirkpatrick SE, Hoskins EJ 1983 The vasoactivity of the fetal lamb ductus arteriosus studied *in utero*. *Pediatr Res* 17:331-337
16. Zink J, Van Petten GR 1980 The effect of norepinephrine on blood flow through the fetal liver and ductus venosus. *Am J Obstet Gynecol* 138:71-77
17. Itskovitz J, Goetzman BW, Rudolph AM 1982 Effects of hemorrhage on umbilical venous return and oxygen delivery in fetal lambs. *Am J Physiol* 242:H543-H548
18. Levin DL, Mills LJ, Weinberg AG 1979 Hemodynamic, pulmonary vascular, and myocardial abnormalities secondary to pharmacologic constriction of the fetal ductus arteriosus: a possible mechanism for persistent pulmonary hypertension and transient tricuspid insufficiency in the newborn infant. *Circulation* 60:360-364
19. Bullaboy CA, Johnson DH, Azar H, Jennings RB Jr 1984 Total anomalous pulmonary venous connection to portal system: a new therapeutic role for prostaglandin E₁? *Pediatr Cardiol* 5:115-116
20. Cassin S, Tyler T, Leffler C, Wallis R 1979 Pulmonary and systemic vascular responses of perinatal goats to prostaglandins E₁ and E₂. *Am J Physiol* 236:H828-H832
21. Tyler T, Leffler C, Wallis R, Cassin S 1975 Effects of prostaglandins of the E-series on pulmonary and systemic circulations of newborn goats during normoxia and hypoxia. *Prostaglandins* 10:963-970
22. Tripp ME, Drummond WH, Hymann MA, Rudolph AM 1980 Hemodynamic effects of pulmonary arterial infusion of vasodilators in newborn lambs. *Pediatr Res* 14:1311-1315
23. Elliott RB, Starling MB, Neutze JM 1975 Medical manipulation of the ductus arteriosus. *Lancet* i:140-142
24. Olley PM, Coceani F, Bodach E 1976 E-type prostaglandins: a new emergency therapy for certain cyanotic congenital heart malformations. *Circulation* 53:728-731
25. Heymann MA, Rudolph AM 1977 Ductus arteriosus dilatation by prostaglandin E₁ in infants with pulmonary atresia. *Pediatrics* 59:325-329
26. Olley PM, Coceani F, Kent G 1974 Inactivation of Prostaglandin E₁ by lungs of the foetal lamb. *Experientia* 30:58-59