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Characteristic Morphology of the Constricted Fetal Ductus Arteriosus following Maternal Administration of Indomethacin

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ABSTRACT. Indomethacin 10 mg/kg was administered to the maternal rat on the 21st day of pregnancy, and the fetal and neonatal ductus arteriosus were studied using the rapid whole-body freezing technique. The sagittal section of the frozen thorax disclosed characteristic localized constriction at the aortic end of the fetal ductus at 24 h after administration of indomethacin. Proximal dilatation of that fetal ductus persisted for more than 4 h after birth, and disappeared gradually. Shortening of the ductal length was associated with both intrauterine constriction by indomethacin in experimental rats and neonatal physiologic constriction of control rats, but significantly greater shortening was seen with intrauterine constriction. (*Pediatr Res* 19: 493–500, 1985)

Abbreviations

C, control
DA, ductus arteriosus
I, indomethacin
PPHN, persistent pulmonary hypertension of the newborn

The study of Sharpe *et al.* (1, 2) has shown that the fetal DA constricts following administration of indomethacin and sodium salicylate to pregnant rats. Their study (1, 2) using the whole-body freezing technique (3) has provided strong evidence for the hypothesis that intrinsic prostaglandins are essential for the fetal DA to remain widely open. At the same time, their study (1, 2) has presented an animal model of PPHN due to maternal ingestion of antiinflammatory drugs (4, 5). Further studies on pharmacologic manipulation of the fetal DA have been done with chronically instrumented fetal lambs (4, 6, 7), resulting in rapid advances in our knowledge of this problem and its clinical application in neonatal cardiology. However, morphology of the pharmacologically manipulated fetal and neonatal DA has not been well demonstrated. In this study we report the results of morphologic observation of the DA of the fetal and neonatal rat *in situ* following maternal administration of indomethacin.

MATERIALS AND METHODS

Wistar rats were raised in separate cages and fed with commercially obtained solid foods. Animals were mated overnight from 1600 h, and vaginal smears were checked at 900 h the next morning. Pregnancy 0 day was defined by the presence of sperm on vaginal smear.

Control studies were done on the 21st day of pregnancy. Pregnant animals were sacrificed by cervical dislocation, and fetuses were delivered quickly by cesarean section. Newborn rats were fixed by the rapid whole-body freezing technique using acetone cooled to −80° C by dry ice either immediately after birth or after survival of 30, 60, or 90 min in an incubator at 37° C. Another control group of 10 newborn rats were fixed and studied following spontaneous delivery without medication and after 48 h of nursing by the mother rat in a cage at 22° C. The thorax of the frozen newborn was trimmed and sectioned on the freezing microtome (Freezing Microtome, Komatsu Solidate Co., Tokyo, Japan) in one of three different planes as follows. The saggital plane was defined as the plane parallel to the long axis of DA, and in sections in this plane, anterior chest wall, the outflow tract of the right ventricle, the main and the left pulmonary arteries, the ductus arteriosus, and the descending aorta were seen. In neonatal rats the sagittal plane as defined was deviated to the left by some 20° from the anatomical sagittal plane. The frontal plane was defined as the plane that showed cross-sections of the main pulmonary artery and DA parallel to the spinal cord. The transverse plane was defined as that section of the thorax perpendicular to the thoracic long axis. The length and inner diameter of DA were measured with the binocular microscope (Nikon Binocular Stereoscopic Microscope, Nihon Kogaku Co., Tokyo, Japan) and micrometer (Nikon Ocular Micrometer, Nihon Kagaku Co., Tokyo, Japan) as was described in an earlier study (8–10). The length of DA was measured from the branching of the left pulmonary artery to the union of DA and aortic isthmus on sagittal sections. The inner diameter of the DA was measured every 50 μ on both sagittal and frontal sections. The smallest diameter and the morphologic pattern of each specimen were compared with that of the control. The morphologic pattern of the entire DA was most clearly recognized on sagittal sections. The numbers of newborn rats and litters in each experiment are shown in Table 1. In some specimens, only one or two of these three estimations (morphologic pattern, length, and inner diameter of DA) were possible because of inadequate angle of sectioning.

Intrauterine DA constriction was studied as follows. Pure indomethacin was supplied from Sumitomo Chemical Co., Osaka, Japan and diluted 40 times with lactose. Ten milligrams per kilogram of indomethacin were suspended in 2 ml water and administered through an orogastric tube to the pregnant rat on the 21st day of gestation. One, four, or eight hours later, fetuses were delivered by cesarean section and fixed immediately in the same way as the control rats. Tweny-four hours after administration of indomethacin, newborn rats which were delivered in the same way, were fixed, either immediately or following survival

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in an incubator at 37° C for 2 or 4 h, or in a cage at 22° C for 24 h without mother rats. These newborns were studied in the same way as control groups, and the numbers of newborn rats and numbers of litters in each experiment are listed in Table 1. Some of these sections were recorded photographically using a binocular stereoscopic microscope (Wild M 400 Photomakroskope, Wild Heerbrugg Ltd., CH-9435 Heerbrugg, Switzerland) and Kodak color film [Kodachrome 40 film 5070 (type A), Eastman Kodak Company, Rochester, NY].

Table 1. *Experimental groups and numbers of newborns*

Group	Drug and interval to delivery (h)	Survival time (h)	Sagittal section	Frontal section	Transverse section
C-0	None	0	26 (5)*	53 (6)	10 (1)
C-0.5	None	0.5	19 (4)	46 (4)	
C-1	None	1	7 (3)	14 (4)	
C-1.5	None	1.5	17 (3)	14 (4)	
C-48	None	48	10 (1)		
I-1	Indomethacin 1	0	17 (3)	22 (2)	
I-4	Indomethacin 4	0	30 (4)	43 (5)	
I-8	Indomethacin 8	0	40 (6)	6 (1)	
I-24-0	Indomethacin 24	0	35 (6)	16 (2)	7 (2)
I-24-2	Indomethacin 24	2	6 (4)		
I-24-4	Indomethacin 24	4	9 (4)		
I-24-24	Indomethacin 24	24	9 (2)		

* Parentheses indicate numbers of litters for morphologic studies.

Wall thickness and wall cross-sectional area of DA were measured in six control fetal rats and 12 fetal rats 24 h after administration of indomethacin as follows. The frozen thorax of each fetus was sectioned in the frontal plane and wall thickness and inner diameter of DA were measured at each 10 μ over its entire length. At each cross-section of DA, the thinnest wall thickness was measured. The short diameter was measured if the cross-section of DA was elliptic. Wall cross area was calculated by the formula: $\pi \times$ (wall thickness) $\times$ (inner diameter + wall thickness).

Morphologic findings of DA were correlated with plasma indomethacin concentration in mothers and newborns. On the 21st day of gestation, 10 mg/kg of indomethacin was administered to the mother rat, and plasma indomethacin concentration was measured 1, 4, 8, or 24 h later using five mother rats in each study time group. Blood was drawn from the mother by cardiac puncture at the time of sacrifice. Three newborns of each litter were fixed immediately after delivery for morphologic study. Blood for measurement of indomethacin was collected as one sample from the remaining eight to 10 newborns of each litter by a deep cut in the neck. Serum concentration of indomethacin was measured with a gas-liquid chromatography method (11).

A two-tailed Student's t test was used for statistical analysis to determine significance of the difference of mean value.

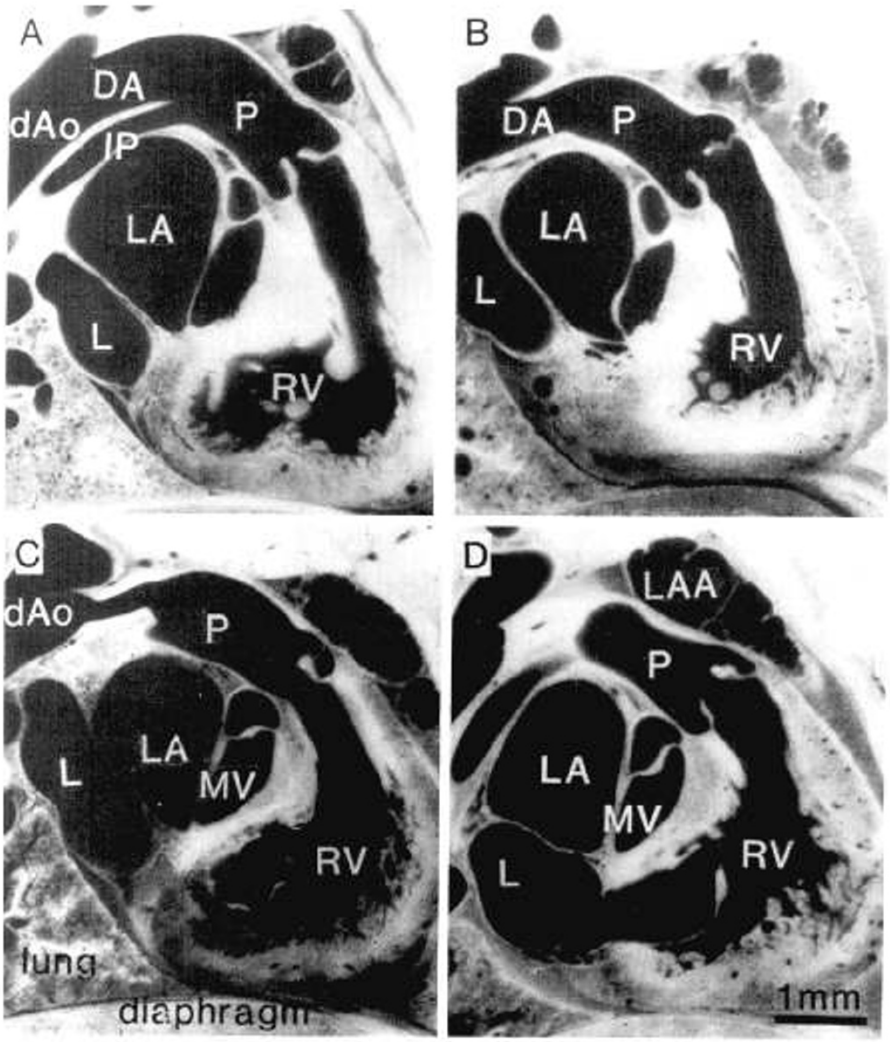

Fig. 1. Sagittal section of DA of control newborn rats. Note dilated fetal DA (*A*), uniform tubular constriction of DA at 30 min (*B*), severe uniform constriction at 60 min (*C*), and complete closure at 90 min (*D*) following incubation at 37° C. *dAo*, descending aorta; *L*, left superior vena cava; *LA*, left atrium; *LAA*, left atrial appendage; *lP*, left pulmonary artery; *MV*, mitral valve; *P*, pulmonary artery; *RV*, right ventricle.

RESULTS

On sagittal sections, the control of fetal DA of the C-0 group (Table 1) was a slightly curved, widely open tube with a uniform diameter which continued smoothly from the pulmonary trunk to the descending aorta (Fig. 1*A*). On frontal sections, DA and other vessels appeared round or ovoid with smooth thin wall (Figs. 2 and 3). The DA was recognized in all three different sections, but most clearly in sagittal section. Following survival of 30 min in an incubator, the DA constricted diffusely along its entire length (Fig. 1*B*). Sixty minutes after birth, the DA was constricted remarkably, and only a small lumen remained centrally along the entire length (Fig. 1*C*). The length and the smallest inner diameter of DA were measured and are shown in Figures 4 and 5. The inner diameter of DA in the C-0 group was 720 ± 20 μ (mean ± SEM) and decreased to 100 ± 30 μ 60 min after birth. The ductal length of the control fetuses (C-0 group) was 1170 ± 30 μ and decreased to 900 ± 50 μ at 60 min after birth. The shortening was 23% of the control fetal value and this change was highly significant ($p < 0.001$). The length remained the same 48 h after birth.

The intrauterine DA patterns following administration of indomethacin to the mother were quite different from the control groups. Sagittal sections of I-1 group revealed that DA was constricted mildly along its entire length, and the gross shape of DA was tubular (Fig. 6). Four hours after administration of indomethacin the DA contracted more and 55% of the 1–4 group showed an hourglass shape (Fig. 6), with the narrowest point at the distal half (Fig. 2*B*). At 8 h, the DA showed severe contraction at the distal half, and 52% of the I-8 group showed distal tubular constriction with a dilated proximal portion (Figs. 2*C* and 6). At 24 h, marked constriction of the distal DA persisted at the aortic end, but the proximal one-half or three-quarters of DA was dilated in 92% of all (Fig. 6). The gross pattern of DA was either distal membranous constriction (Fig. 2*D*) or distal tubular constriction. Membranous constriction was arbitrarily defined as localized constriction less than 150 μ in length. Thus defined, membranous constriction was present in 44%, and distal tubular constriction in 47% of the I-24 group (Fig. 6). Some distal tubular constrictions had additional localized membranous constriction at the aortic end. The remaining 9% of DA of the I-24 group showed uniform severe constriction along the entire length of DA (Fig. 6).

Sagittal sections of those DA with distal membranous or short tubular constriction revealed eccentric DA lumen deviated cranially at the constricted part (Fig. 1 *B*, *C*, and *D*). Transverse sections of those DA with distal membranous constriction revealed the location of the membranous constriction adjacent to the recurrent nerve (Fig. 4*C* and *D*) and an eccentric lumen deviated to the left (Fig. 4*C*). Morphometric results of DA of the I-1, 4, 8, and 24 groups are shown in Figure 7. The smallest inner diameter of each individual was collected and plotted. This showed progress of the ductal constriction along with the changing patterns shown in Figure 6. Total length of DA shortened progressively and was 750 ± 50 μ at 24 h after administration of indomethacin. This shortening was 36% of the control fetal value and highly significant ($p < 0.01$). This shortening was also statistically significantly greater ($p < 0.01$) than the closed DA of control 2-day-old rats (group C-48, 910 ± 40 μ).

Observations of groups I-24-2, 4, and 24 revealed postnatal progress of constriction of DA which had already constricted partially and characteristically in fetal life by transplacental indomethacin. Two hours after birth, the distal part of DA was closed completely without a lumen, and its length was 380 ± 60 μ ($n = 6$). The proximal part of DA remained dilated and formed a diverticulum or recess of 470 ± 64 μ in length and 630 ± 44 μ in diameter (Fig. 8). At 4 h of age the ductal diverticulum or recess became shallower and the distal closed part became longer.

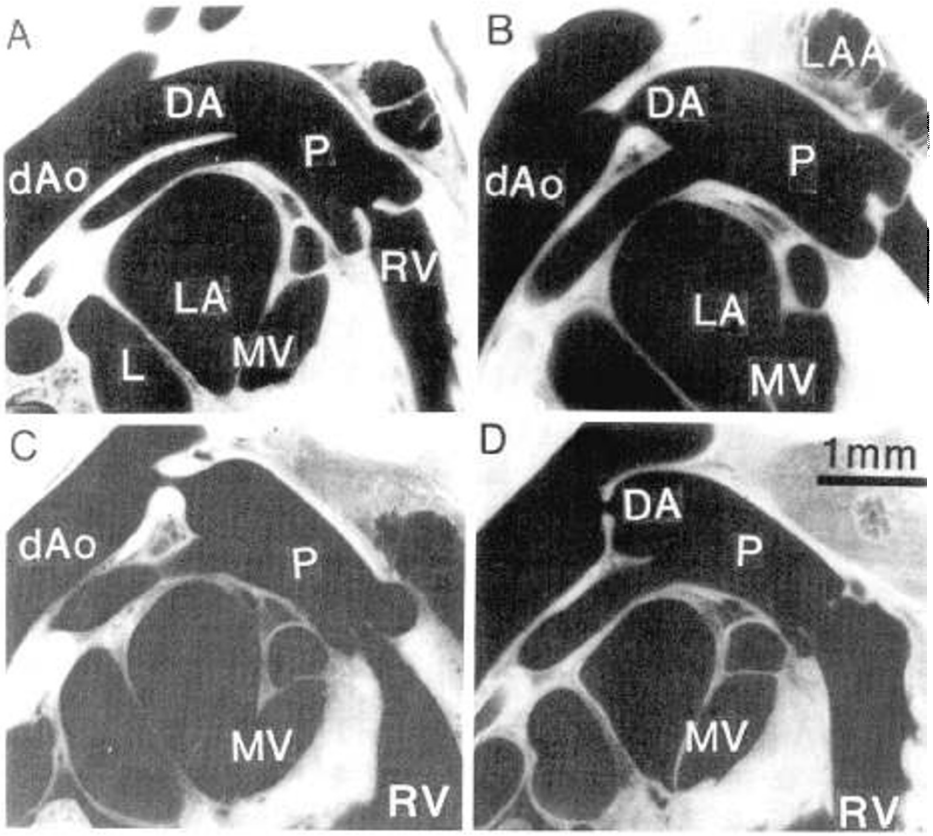

Fig. 2. Sagittal section of fetal DA following administration of 10 mg/kg indomethacin to pregnant rats. Note dilated DA in the control fetus (*A*), hourglass type, constricted DA at 4 h (*B*), distal tubular DA at 8 h (*C*), and distal membranous DA at 24 h (*D*). Abbreviations are the same as in Figure 1.

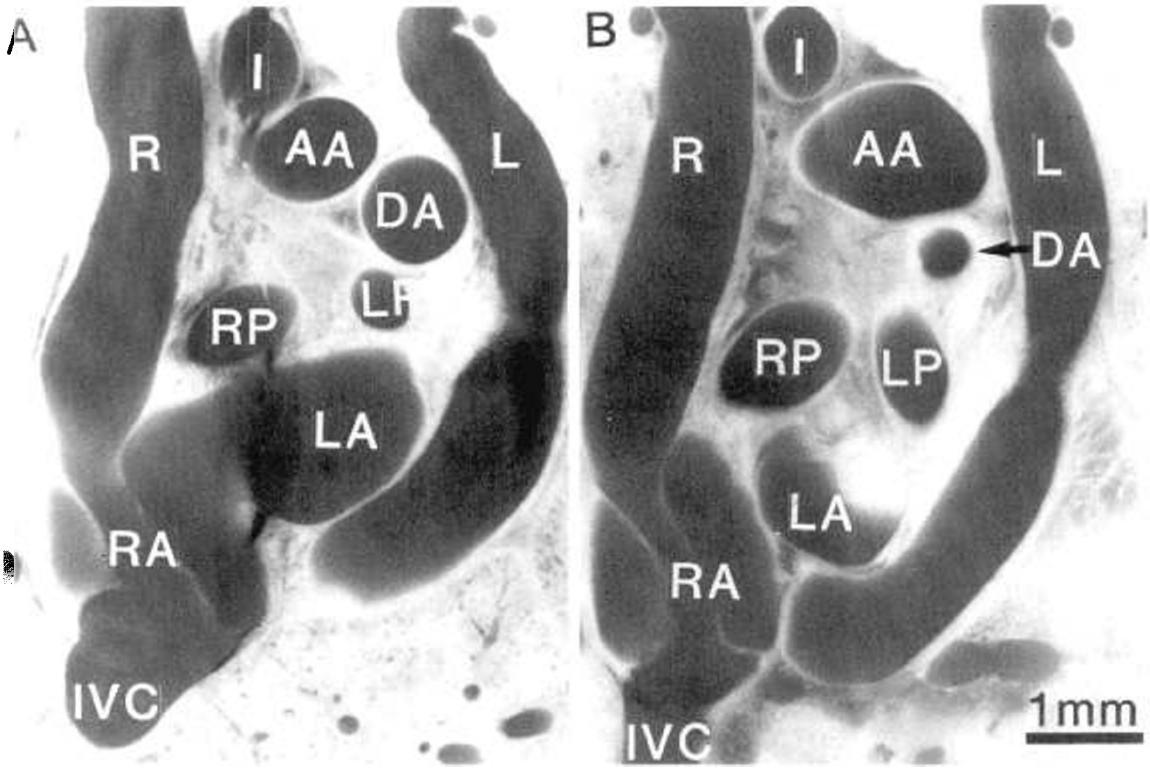

Fig. 3. Frontal section of DA of the fetal rats. Note round dilated DA with smooth thin wall of control fetal rat (*A*) and constricted DA with thick wall of fetal rat 24 h after administration of 10 mg/kg indomethacin (*B*). *AA*, aortic arch; *I*, innominate artery; *IVC*, inferior (posterior) vena cava; *LP*, left pulmonary artery; *R*, right superior vena cava; *RA*, right atrium; *RP*, right pulmonary artery. Other abbreviations are the same as in Figure 1.

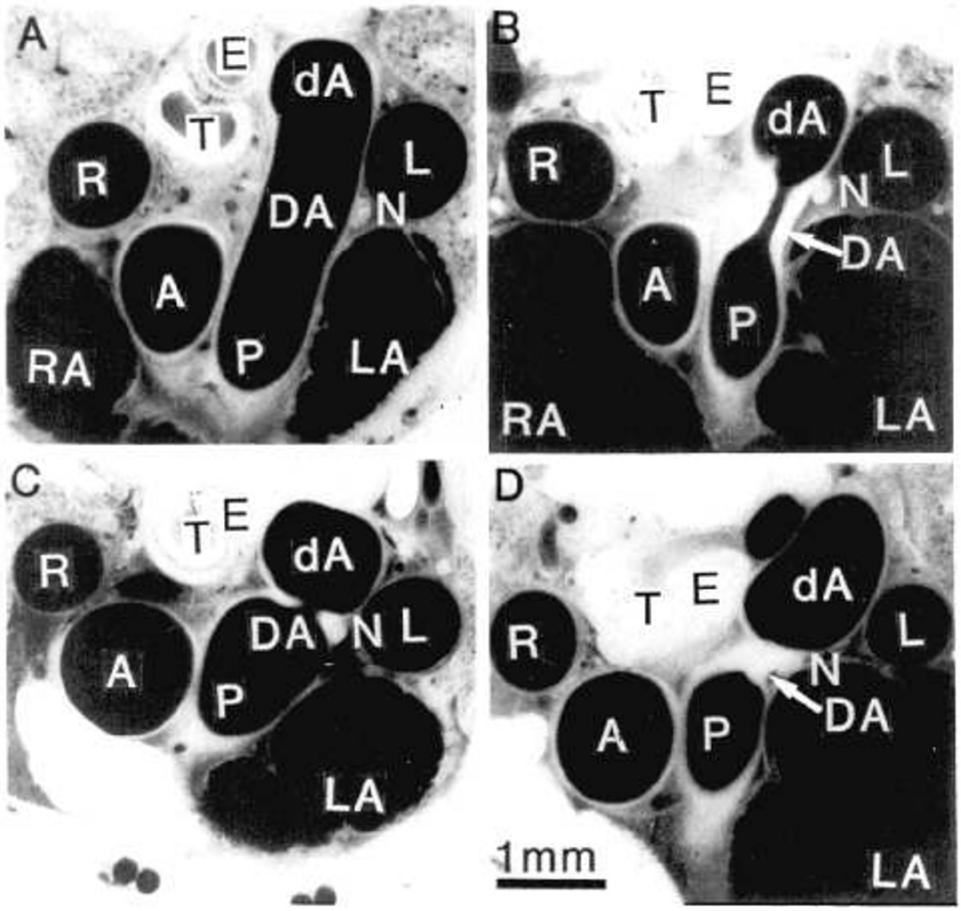

Fig. 4. Transverse section of DA of fetal rats. Note dilated DA of control fetus (*A*), diffusely constricted tubular DA of 1-h-old control newborn rat (*B*) and distal membranous (*C*) and tubular (*D*) constricted DA of fetal rats 24 h after administration of indomethacin (I-24-0). *A*, ascending aorta; *dA*, descending aorta; *E*, esophagus; *N*, recurrent nerve; *T*, trachea. Other abbreviations are the same as in Figures 1–3.

At 24 h after birth, DA was closed in its entire length, and no diverticulum was noticed at its proximal part (Fig. 8).

Wall thickness of the DA of C-0 group was 42 ± 2, 41 ± 1, and 36 ± 1 μ (mean ± SEM) at proximal, middle, and distal part. The distal wall thickness was significantly thinner than the other two ($p < 0.05$). Its inner diameter was uniform through the entire length and 790 ± 47 μ (mean ± SEM) at the middle part. The wall cross areas of the control fetus DA are shown in Figure 9.

Wall thickness of DA diverticulum was 39 ± 2 μ ($n = 11$, mean ± SEM) and this was not statistically different from the control value. Wall cross-sectional area of the constricted fetal DA is show in Figure 9. In those fetal DA with diffuse tubular

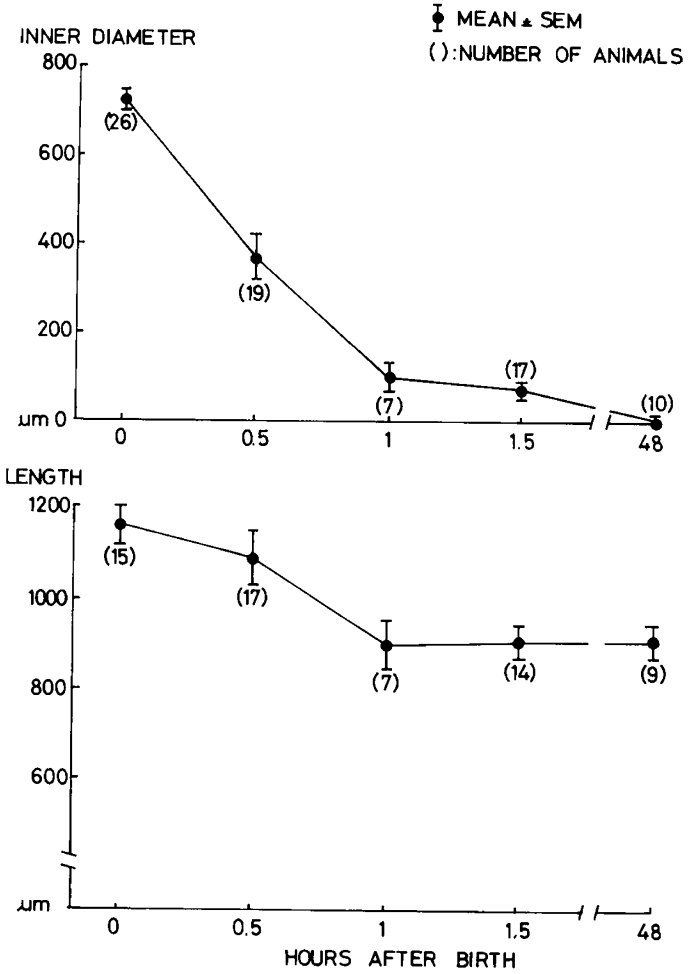

Fig. 5. Morphology of DA of control newborn rats incubated at 37° C. Note progressive constriction of DA in the 1st h after birth.

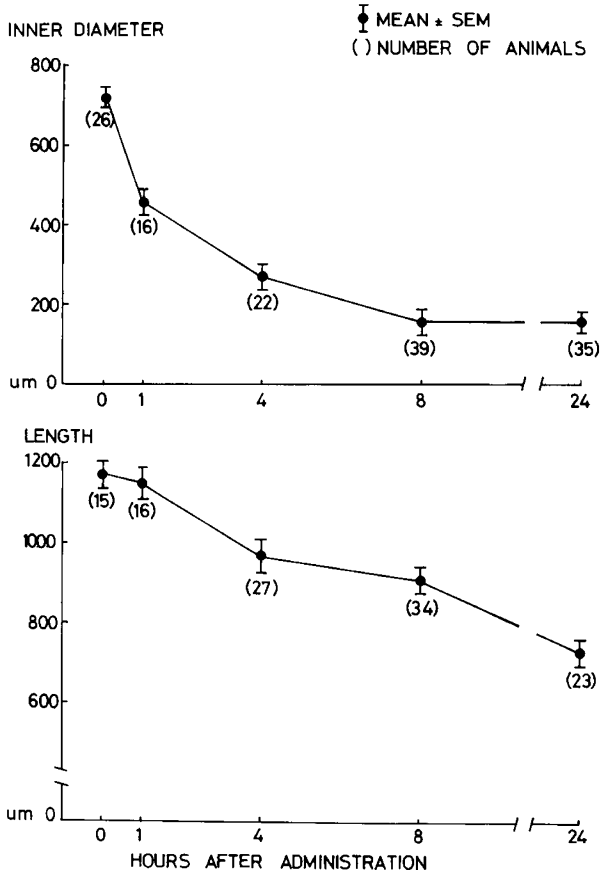

Fig. 7. Inner diameter and length of fetal constricted DA following administration of 10 mg/kg indomethacin to pregnant rats. Note progressive constriction associated with shortening of fetal DA.

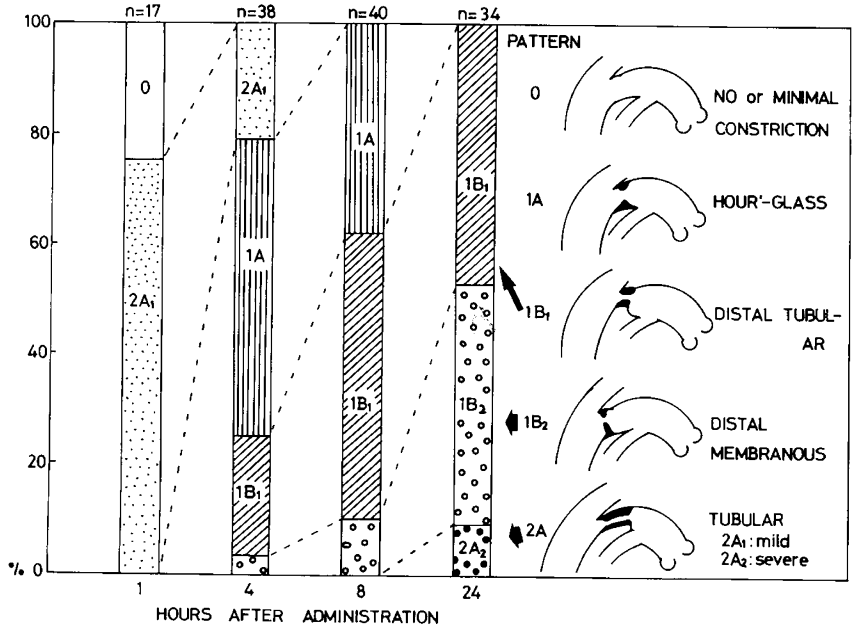

Fig. 6. Changing morphologic patterns of fetal DA at 1, 4, 8, and 24 h following administration of 10 mg/kg indomethacin to pregnant rats.

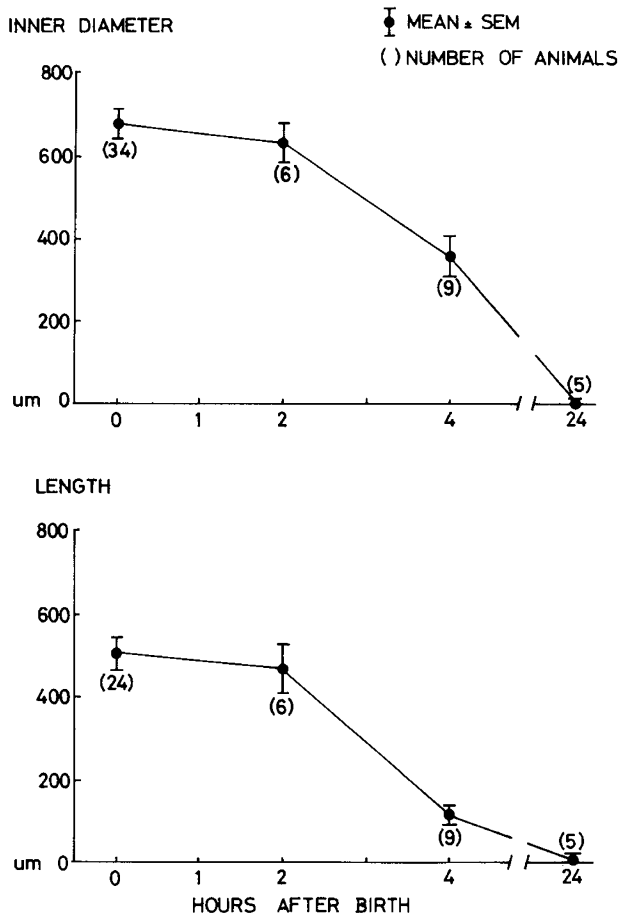

Fig. 8. Postnatal change of proximal DA diverticulum in newborn rats delivered 24 h after administration of 10 mg/kg indomethacin to the mothers, incubated at 37° C for 2 and 4 h, or after survival of 24 h at 22° C. Note persistence of proximal DA diverticulum for 4 h postnatally.

constriction, DA wall was thickened diffusely, but wall cross-sectional area was not increased. In those fetal DA with distal tubular constriction, DA wall was thickened at the constricted portion. Wall cross-sectional area was increased in four of eight at the distal part of DA in those with distal tubular constriction. These four were examples of distal tubular constriction with additional membranous stenosis. In those DA with distal membranous constriction, wall cross-sectional area was increased markedly at the aortic end.

Serum indomethacin concentrations of fetuses and mothers are shown in Figure 10. One hour after administration of 10 mg/kg indomethacin, fetal concentration was 3.7 ± 0.5 mg/ml (mean ± SEM). Mother's concentration reached maximum (63 ± 7 μg/ml) 4 h after administration. Fetal concentration reached maximum (19 ± 4 μg/ml) at 4 h after administration and remained at high level (13 ± 2 μg/ml) 24 h after administration.

DISCUSSION

The whole-body freezing technique was first applied to the study of DA by Hornblad and coworkers at Karolinska Institute (3, 12), and established as a reliable technique for the morphologic study of DA of fetal and newborn animals. They studied the rate of contraction of DA in newborn rats, and reported progressive uniform narrowing of the ductal lumen during the 1st h after birth (17). Sharpe *et al.* (1, 2) at the same Institute and with the same technique studied the effects of indomethacin and acetylsalicylic acid administered to the pregnant rat and rabbit, and reported constriction of the fetal DA at 6, 24, and 36 h after administration of the drug. They measured only the narrowest diameter of the ductus and did not describe the location of the maximum constriction. Olley and coworkers (18, 19) studied and proved transplacental fetal ductal constriction with indomethacin in pregnant sheep with the same freezing technique. In these early studies, frontal sections were used mainly to measure the diameter of DA. Sagittal sections are used extensively to assess the morphologic pattern of the DA for the first time in this study.

The presence of constrictive effects of indomethacin and salicylates on the fetal DA has been proved in chronically instru-

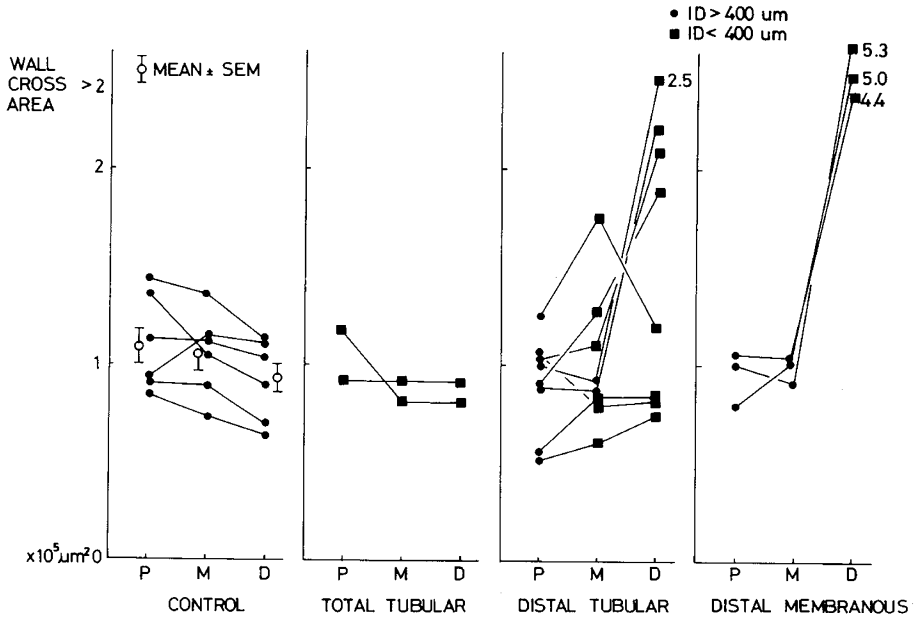

Fig. 9. Wall cross-sectional areas of proximal (*P*), middle (*M*), and distal (*D*) DA in control and I-24-0 fetuses. Constricted DA with inner diameters less than 400 μm are shown as *squares*. Note increased wall cross-sectional area at distal DA of I-24-0 fetuses with distal membranous constriction.

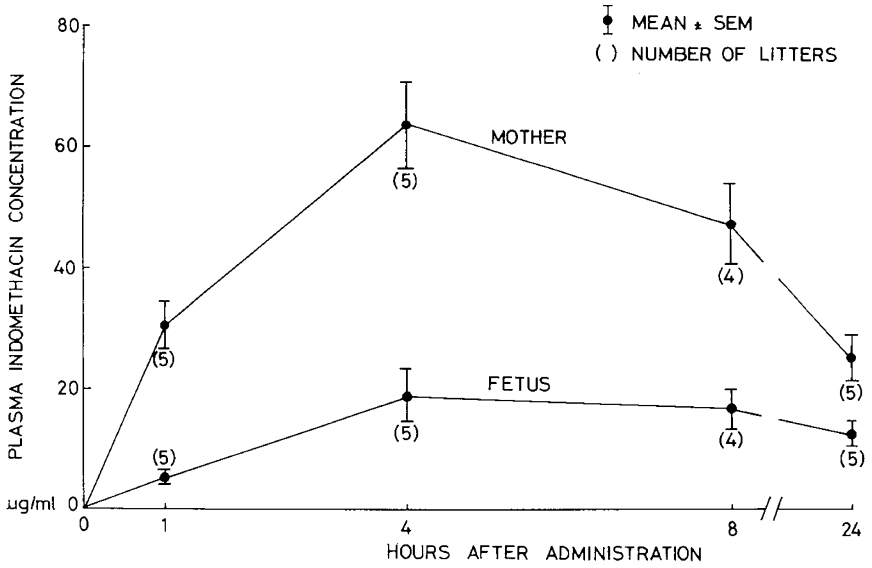

Fig. 10. Plasma indomethacin concentrations of mother and fetal rats following orogastric administration of 10 mg/kg indomethacin to the mother.

mented animals (4–7, 15). Levin *et al.* (4) studied the transplacental effects of indomethacin injected intravenously in the pregnant sheep, and noticed fetal ductal constriction starting 30 min after injection and lasting 1–4 days. Heymann and Rudolph (7) studied the hemodynamic effects of acetylsalicylic acid administered directly into the stomach of instrumented fetal lambs and noticed maximum fetal ductal constriction 40–80 min after drug administration. In parallel to these observations in laboratory animals, several clinical observations presented examples of PPHN following ingestion of indomethacin or other nonsteroidal antiinflammatory drugs (5). Therefore the animal study of these effects became important as an animal model of PPHN.

The time course of transplacental constrictive effects of indomethacin and salicylates to fetal DA was studied, although incompletely, in these early animal studies. Sharpe and coworkers (1, 2) reported persistence of effects from 6–36 h after administration of these drugs to pregnant rats. The earlier onset of these effects were subsequently confirmed by Levin *et al.* (4) who showed fetal ductal constriction starting at 30 min and lasting more than 6 h following intravenous administration of indomethacin in the pregnant sheep. In chronically instrumented fetal lambs, maximum DA constriction occurred in 40–80 min after acetylsalicylic acid was administered into the fetal stomach (7) or at 44 min after indomethacin was injected into the fetal vessel (6). Our present study shows the total time course of these effects in rats and correlation with fetal indomethacin concentration.

In early studies, morphology of constricted fetal ductus induced by antiinflammatory drugs was difficult to study and only limited descriptions were made. Olley *et al.* (13) noticed a sphincter-like constriction of either, or both, ends of the ductus near its junction with the main arteries in some fetuses following administration of indomethacin to the pregnant sheep. In another report, Olley and Coceani (14) reported the results of reconstruction of serially sectioned constricted fetal DA and noticed maximum constriction of DA at the middle and aortic end of the DA following 3 days of indomethacin administration to the mother sheep. Friedman *et al.* (6) showed by angiography of the fetal ductus 3–10% shortening and more prominent constriction at the aortic end of the ductus following administration of indomethacin. These angiographic findings were further confirmed and extended in this study. Our present study clarifies changing morphologic patterns of the fetal DA following administration of indomethacin in fetal rats for the first time, and shows the time course of the changing morphologic pattern of constricted fetal ductus following administration of indomethacin to the mother rat.

In clinical and pathologic materials, the mode of constriction of physiologic and pathologic DA was variable. Pathologic study of DA at all ages by Jager and Wollenman (16) revealed that 66 of 71 DA were cylindrical, three were window-type, and the other two were of the cylindrical type closed only at the pulmonic end. Three window-type DA apparently represented pathologic patent ductus arteriosus, but most others were presumed to show physiologic process of closure. No case in their series showed partial patency of proximal DA with a closed aortic end. Isolated small or moderate-sized pathologic patent ductus arteriosus is usually either cylindrical or funnel-shaped with a narrow pulmonary end and wide aortic end (17). In both patients and dogs, ductus diverticulum develops usually at the aortic end of DA (18, 19). In contrast, partial proximal persistence of DA is not rarely associated with congenital heart disease with decreased pulmonary blood flow (20). However, isolated proximal ductus diverticulum has been only rarely reported (21).

The characteristic constriction of fetal DA at the aortic end was remarkable at 8 and 24 h after administration of indomethacin in this study. Because DA constricted fairly uniformly following birth in control newborn rats, uneven localized constriction of DA at the aortic end was difficult to explain on the basis of uneven distribution of medial muscle mass. Another possible mechanism of this uneven constriction might be uneven sensitivity of the DA muscle to prostaglandins, assuming that the distal DA was more sensitive and dependent on prostaglandins. This hypothesis remains to be proved.

An alternative explanation of the characteristic CA constriction at the aortic end might be persistent strong constriction at the distal part and dilatation of the proximal part by increased pulmonary arterial pressure. In lamb experiments, fetal DA constriction is consistently associated with increase in pulmonary arterial pressure (4, 6, 7). Our study showed increased wall cross-sectional area at the site of distal membranous constriction, and this suggests localized strong constriction of longitudinally or spirally oriented medial smooth muscle at this locus.

Another finding in this study was quantitative estimation of shortening of DA associated with both physiologic postnatal and pharmacologic intrauterine constriction by indomethacin. Interestingly, pharmacologic intrauterine constriction of DA was associated with significantly greater shortening than postnatal physiologic constriction. The reason for this difference is not clear at first glance. However, some difference in DA length is to be

expected because of grossly different morphologic patterns of fetal and postnatal constriction. Early histological studies showed the presence of longitudinally or spirally oriented smooth muscle in DA media (17, 22). The increased shortening and localized constriction of fetal distal DA suggest marked contraction of longitudinally or spirally oriented medial smooth muscle at the distal DA at 8 and 24 h following administration of indomethacin. Further histologic study on these constricted DA would clarify differences of microscopic architecture of pharmacologically constricted fetal DA and postnatal constricted DA.

The present study shows persistence of ductal diverticulum (dilated proximal DA with closed aortic end) for the several postnatal hours in newborn rats delivered 24 h after administration of indomethacin to the mother. Similar ductal diverticulum was reported by Arcilla *et al.* (21) in a 4-h-old baby with PPHN. This baby was born to a mother who had received salicylate for 2 wk preceding delivery. The baby developed typical signs and symptoms of PPHN. Dilated proximal DA with closed aortic end was clearly shown by angiography at 4 h of age, but had disappeared 3½ months later. Becker *et al.* (23) reported two autopsied newborn infants with fetal ductal constriction and noticed most prominent constriction at the aortic end of DA. Kohler (24) reported three autopsy cases of stillborn infants with an almost completely closed DA. The attached figure showed closed aortic end and open pulmonary end of DA in case 1 of his report. In these two papers, no mention was made of maternal drug ingestion. These clinical and pathologic observations suggest that stronger or localized constriction at the aortic end is the rule in fetal ductal constriction. Certainly antiinflammatory drugs administered to pregnant women might be one cause of fetal DA constriction (5). At the present time other causes of fetal ductal constriction are not clarified. It is speculated that proximal ductal persistence or diverticulum in the fetus or newborn baby without other congenital heart disease may be diagnostic of fetal ductal constriction by nonsteroidal antiinflammatory drugs administered to the mother.

CONCLUSION

Morphology of fetal ductus arteriosus showed characteristic changes during the 24 h following administration of indomethacin to the full-term rat. The initial hourglass-type constriction became more localized at the distal end of DA, and the proximal part was dilated forming a recess or diverticulum at the end of this period. The diverticulum persisted for 2–4 h after birth, and may be a diagnostic sign of persistent pulmonary hypertension in the newborn infant or fetus following administration of antiinflammatory drugs to the pregnant woman.

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REFERENCES

1. Sharpe GE, Thalme B, Larsson KS 1974 Studies on closure of the ductus arteriosus. XI. Ductus closure in utero by a prostaglandin synthetase inhibitor. Prostaglandins 8:363–368
2. Sharpe GE, Larsson KS, Thalme BN 1975 Studies on closure of the ductus arteriosus. XII. In utero effect of indomethacin and sorium salicylate in rats and rabbits. Prostaglandins 9:585–596
3. Hornblad PY, Larsson KS 1967 Studies on closure of the ductus arteriosus. I. Whole-body freezing as improvement of fixation procedures. Cardiologia 51:231–241
4. Levin DL, Mills LJ, Parkey M, Gariott J, Campbell W 1979 Constriction of the fetal ductus arteriosus after administration of indomethacin to the pregnant ewe. J Pediatr 94:647–650
5. Levin DL 1980 Effects of inhibition of prostaglandin synthesis on fetal development, oxygenation, and the fetal circulation. In: Heymann MA (ed) Prostaglandins in the Perinatal Period. Their Physiologic and Clinical Importance. Grune & Stratton, New York, pp 35–44
6. Friedman WF, Printz MP, Kirkpatrick SE, Hoskins ED 1983 The vasoactivity of the fetal lamb ductus arteriosus studied in utero. Pediatr Res 17:331–337
7. Heymann MA, Rudolph AM 1976 Effects of acetylsalicylic acid on the ductus arteriosus and circulation in fetal lambs in utero. Circ Res 38:418–422
8. Momma K, Uemura S, Nishihara S, Ota Y 1980 Dilatation of the ductus arteriosus by prostaglandins and prostaglandin's precursors. Pediatr Res 14:1074–1077
9. Momma K, Nishihara S, Ota Y 1981 Constriction of the fetal ductus arteriosus by glucocorticoid hormones. Pediatr Res 15:19–21
10. Momma K, Takeuchi H 1983 Constriction of fetal ductus arteriosus by nonsteroidal anti-inflammatory drugs. Prostaglandins 26:631–643
11. Helleberg A 1976 Determination of indomethacin in serum and urine by electrocapture gas-liquid chromatography. J Chromatogr 117:167
12. Hornblad PY 1967 Studies on closure of the ductus arteriosus. III. Species differences in closure rate and morphology. Cardiologia 51:262–282
13. Olley PM, Bodach E, Heaton J, Coceani F 1975 Further evidence implicating E-type prostaglandins in the patency of the lamb ductus arteriosus. Eur J Pharmacol 34:247–250
14. Olley PM, Coceani F 1979 Mechanism of closure of the ductus arteriosus. In: Godman MJ, Marquis RM (eds) Pediatric Cardiology, Vol 2. Churchill Livingstone, Edinburgh, pp 15–24
15. Kirkpatrick SE, Printz MF, Friedmann WF 1977 Prostaglandins (PGs) and the fetal ductus arteriosus (PDA). Pediatr Res 11:395
16. Jager BY, Wollenman OJ Jr 1942 An anatomical study of the ductus arteriosus. Am J Pathol 48:595–613
17. Cassels DE 1973 The Ductus Arteriosus. Charles C Thomas, Springfield IL, pp 37–50
18. Falcone MW, Perloff JK, Roberts WC 1972 Aneurysm of the nonpatent ductus arteriosus. Am J Cardiol 29:422–426
19. Patterson DF 1979 Genetic factors in persistence of the ductus arteriosus. In: Godman MJ, Marquis RM (eds) Pediatric Cardiology, Vol 2. Churchill Livingstone, Edinbrugh, pp 45–64
20. Quiroga C 1961 Partial persistence of the ductus arteriosus. Acta Radiol 55:103–108
21. Arcilla RA, Thilenius OG, Ranniger K 1969 Congestive heart failure from suspected ductal closure in utero. J Pediatr 75:74–78
22. Walsh SZ, Meyer WW, Lind J 1974 The Human Fetal and Neonatal Circulation. Function and Structure. Charles C Thomas, Springfield, IL, pp 115–128
23. Becker AE, Becker MJ, Wagenvoort CC 1977 Premature contraction of the ductus arteriosus: a cause of fetal death. J Pathol 121:187–191
24. Kohler HG 1978 Premature closure of the ductus arteriosus (P.C.D.A.): a possible cause of intrauterine circulatory failure. Early Hum Dev 2:15–23