Histopathology of the ductus arteriosus after prostaglandin E₁ administration in ductus dependent cardiac anomalies

A. C. GITTENBERGER-DE GROOT, A. J. MOULAERT, E. HARINCK, AND A. E. BECKER

From the Anatomical and Embryological Laboratory of the University of Leiden; the Department of Paediatric Cardiology, University Children's Hospital, Wilhelmina Kinderziekenhuis, Utrecht; and the Department of Pathology, University of Amsterdam, Wilhelmina Gasthuis, Amsterdam, The Netherlands

SUMMARY The histology of the ductus arteriosus was studied after prostaglandin E₁ (PGE₁) administration in 4 infants with ductus dependent cardiac malformations. Pronounced pathological changes were found in each instance. The changes consisted of oedema of the media with separation of medial components by clear spaces, pathological interruptions of the internal elastic lamina, and intimal lacerations, some of which extended into the media.

The findings suggest that PGE₁ administration has a profound weakening effect on the structure of the wall of the ductus arteriosus, rendering the vessel prone to laceration.

Prostaglandin E₁ (PGE₁) is presently used with increasing frequency as an emergency treatment in infants with ductus dependent cardiac malformations (Christensen and Fabricus, 1975; Elliott *et al.*, 1975; Olley *et al.*, 1976; Schöber and Lorenz, 1976; Moulaert *et al.*, 1977b; Neutze *et al.*, 1977; Rudolph and Heymann, 1977), because it reverses ductus constriction by abolishing the vascular tone (Cocceani and Olley, 1973; Elliott *et al.*, 1975; Sharpe and Larsson, 1975; Moulaert *et al.*, 1977b; Neutze *et al.*, 1977; Rudolph and Heymann, 1977). Several reports deal with the clinical aspects of PGE₁ administration but little is known of its influence on the morphology of the ductus. In the present paper the histological findings concerning the wall of the ductus in 4 infants treated with PGE₁ are presented.

Patients and methods

The clinical data of each of the 4 infants are summarised in Table 1. The dose of PGE₁ used was 0.1 µg/kg per min over periods ranging from 10 hours to 3 days.

In 3 of the 4 cases the ductus with the pulmonary trunk and the aorta were obtained at necropsy. The ductal width and length were measured and

compared with ductus arteriosi from similar cardiac malformations which had not been treated with PGE₁. In the fourth case the distal part of the ductus was removed during surgery, together with a segment of the adjoining distal aorta. Since ductal tissue extended into the aorta this specimen could also be used for this study and will be included in our total group of four ductus.

The material was fixed in an alcohol-glycerin mixture and routinely processed. Complete serial sectioning of each ductus was carried out and the sections were stained alternately with haematoxylin and eosin, azan, and van Gieson elastic tissue stain.

The histology of the ductus arteriosus in the 4 cases treated with PGE₁ was compared with that of the ductus in cases of congenital heart disease. This group contained both ductus dependent and independent cardiac abnormalities. The details of the type of anomalies in both these groups have been reported previously (Gittenberger-de Groot, 1977). Moreover, further comparisons were made with ductus obtained from cases without any cardiovascular malformation.

NORMAL DUCTAL HISTOLOGY

For a proper understanding of the histology of the ductus in the prostaglandin treated group of infants it is necessary to know the normal histology

Table 1 Clinical data

Case	Diagnosis	Age at start of PGE ₁ admin (d)	Duration of infusion PGE ₁	Place catheter HC	IC	Improvement Clinical	Angio	Maximum rise in O ₂ PaO ₂ O ₂ % mmHg	Side effects	Remarks
1*	Pulmonary atresia, complex anomaly, polysplenia syndrome	1	3 days	Ao	Ao	+	+	35 50	Pyrexia flush right arm and chest	Surgery: valvulotomy, complex cardiac anomaly, infusion stopped, died 4 days later
2	Pulmonary atresia, VSD	1	10 hours	Ao	Ao	+		12 28	Apnoeic spells, flush right arm and right chest, shock kidneys?	Surgery: Waterston shunt, died 18 hours later of intractable hypotension and metabolic acidosis despite PaO ₂ 73 mmHg
3	Hypoplastic left heart	4	34 hours	PV	PV	+	diuresis	NI BG	Pyrexia	After diagnosis hypoplastic left heart infusion stopped, died 10 days later
4	Aortic arch interruption, aorto-pulmonary defect	10	32 hours	P	PV	+	diuresis	NI BG	Pyrexia, friable ductus extension in aorta	Surgery: anastomosis, rupture ductal suture resulted in fatal haemorrhagia

Abbreviations: VSD, ventricular septal defect; HC, heart catheterisation room; IC, neonatal care unit; Ao, aortic arch; PV, peripheral vein; P, pulmonary trunk; PaO₂, arterial oxygen pressure in mmHg; O₂%, oxygen saturation %; NI BG, normalisation of blood gases.

*This case has briefly been reported previously (Moulaert *et al.*, 1977a).

of the ductus arteriosus in the same age group when the anatomical closure is not completed (Gittenberger-de Groot, 1977). Hence a brief review seems warranted.

The ductus arteriosus resembles a muscular artery with an intact, wavy internal elastic lamina, interrupted only underneath the intimal cushions. At those sites the elastic lamina is fragmented and is sometimes split up into several layers. The media is mainly composed of circularly arranged smooth muscle cells, with only minimal elastin fibres in between. The medial components may be widely separated, predominantly along the line of junction with intimal cushions, thereby creating large pools filled with a mucoid, slightly eosinophilic substance, the so-called mucoid lakes. In more advanced stages of anatomical closure, necrosis of cellular components of the media and a diffuse fibrous proliferation of the intima begin to appear.

Results

The length of the ductus arteriosus in the first 3 cases was 14, 10, and 10 mm and the maximal external diameter 8, 5, and 7 mm, respectively (Fig. 1).

The wall structure of the ductus arteriosi in the non-treated group all disclosed a basically normal architecture (Gittenberger-de Groot, 1977). Indeed there were no noticeable differences between the ductus in the groups with congenital heart disease, whether cyanotic or not, and the ductus obtained

Fig. 1 A comparison of the postmortem ductal width ($\emptyset$) and length, after alcohol/glycerine fixation, between cases treated with PGE₁ (indicated by x) and 'controls'. (A) 26 cases of left hypoplastic heart; (B) 23 cases of pulmonary atresia. (Note the greater width of the ductus in A.)

from cases without any cardiovascular malformation (Fig. 2). The ductus arteriosi in the 4 cases with PGE₁ administration, on the other hand, all showed distinct abnormalities (Fig. 2). These affected primarily the intima, the internal elastic lamina, and the media. The internal elastic lamina showed many interruptions at inappropriate sites, that is at locations not covered by intimal cushions (cases 1, 2, and 4) (Fig. 3, 4, and 5). In one instance (case 3) the intimal cushions completely covered the luminal aspects of the media; therefore, this feature could not be evaluated. In the remaining 3

Fig. 2 Schematic ductal wall, normal and after PGE₁. Abbreviations: cn, cytolytic necrosis; ery, erythrocytes; ic, intimal cushions; iel, internal elastic lamina; int, interruptions; la, laceration; leu, leucocytes; m, media; med, medial oedema; ml, mucoid lakes; pip, postnatal intimal proliferation; thr, thrombus.

cases the interruptions of the internal elastic lamina were sometimes accompanied by intimal lacerations (Fig. 3, 4, and 6-8), some of which extended into the media (Fig. 3, 4, 6, and 8). Thrombosis was often present at these sites (Fig. 3, 4, 6, and 7), in one case accompanied by a polymorphonuclear infiltrate (case 4) (Fig. 8).

The media of the PGE₁ ductus showed distinct oedema which accounted for the diffuse presence of clear spaces, variable in size, separating the medial components. These spaces differed from the normally occurring mucoid lakes in their staining capacities, in showing no eosinophilia. In cases 1 and 2 the general architecture of the media was largely preserved, despite the oedematous changes (Fig. 4 and 5). However, in case 3, the presence of large lacunae distorted the regular medial wall structure, whereas in case 4 the changes were so profound that the wall had changed into a sponge-like structure (Fig. 3 and 6). In one instance (case 1) a sudden interruption of the media was seen, albeit without interruption of wall continuity, in which it appeared as if the fibres of the media had been torn apart to either side, the 'gap' being filled by an oedematous connective tissue.

Table 2 shows the incidence of the abnormalities, predominantly encountered at the aortic end of the ductus. No malformations of the adjacent elastic arteries, that is the aorta and the pulmonary trunk, could be detected.

Discussion

The ductus arteriosi in the 4 patients treated with

Fig. 3 Transverse section of ductal tissue extending into the aorta (a) in case 4. There is laceration (la) of ductal tissue with thrombus formation (thr) protruding into the lumen. The intima shows small lesions with thrombosis and interruptions (int) of the internal elastic lamina. (Elastic van Gieson $\times 19$.)

PGE₁ all showed pronounced changes in the histology of the wall, which were not seen to this extent in the non-treated cases. This is of particular significance since the latter group also contained cases which suffered from severe hypoxia and acidosis, factors which themselves could have been held responsible for the histological changes observed in the PGE₁ treated group.

In each instance of the PGE₁ treated cases, the wall of the ductus showed oedema and wall lacerations. These observations lead to the conclusion that the ductus in the PGE₁ treated patients had weakened, rendering it prone to laceration. We can only speculate about the pathogenesis of the alterations.

It is well known that PGE₁ increases vessel wall permeability (Solomon *et al.*, 1968; Persaud, 1973). This process may lead to oedema causing a succulent wall, which is prone to laceration by mechanical

Fig. 4 Transverse section of the ductus of case 1. The internal elastic lamina (iel) bordering the lumen is interrupted (int) in several places. There is a laceration (la) into the media containing a thrombus (thr). (Elastic van Gieson $\times 22$.)

forces such as luminal dilatation and augmented flow. Moreover, increased pressures may also play a role. The finding of medial oedema has its parallel in systemic arteries under increased pressures, such as the early phase of malignant hypertension and experimentally induced hypertension (Gardner and Matthews, 1969; Heptinstall, 1974). In those circumstances the mechanisms underlying the phenomenon of wall oedema are considered to be related to the increased filtration pressures. With PGE₁ the vascular tone itself is much affected and this phenomenon may well contribute in facilitating filtration through the vessel wall.

It is debatable whether the action of the infused PGE₁ is solely reversing postnatal ductal constriction or whether it even induces a ductal width exceeding that at birth (Solomon *et al.*, 1968; Sharpe and Larsson, 1975; Starling *et al.*, 1976; Moulaert *et al.*, 1977b). The measurements obtained from 2 of our cases showed a relatively large diameter as

compared with the ductus arteriosus in non-treated patients. In one instance (case 1) there was a distinct increase in both diameter and length of the ductus (Fig. 1). However, the number of cases is too small to permit a conclusive statement.

The effects of wall weakening are dramatically shown in one of our patients (case 4), when the surgeon was hampered in restoring vascular continuity by the extreme weakness of the aortic wall. In this particular instance ductal tissue extended into the wall of the aorta, a situation that may occur in interrupted aortic arch (Gittenberger-de Groot, unpublished data).

As the catheter used to infuse the PGE₁ had not been manoeuvred through the ductus, the intimal laceration could not be the result of direct trauma by the catheter. Therefore, it seems that the lacerations occurred 'spontaneously', within a succulent and friable wall.

The influence of the PGE₁ on vessels other than

Fig. 5 Detail of the wall of the ductus of case 2, with many interruptions (int) of the internal elastic lamina (iel) bordering the lumen. The fibres of the inner third of the media are separated by oedema (med). (Elastic van Gieson $\times 57$.)

Fig. 6 Detail of the ductal tissue in the aortic wall in case 4, with laceration (la) and thrombosis (thr). The media has lost its normal structure being succulent by oedema (med). (Haematoxylin and eosin $\times 57$.)

Fig. 8 Laceration (la) of ductal wall of case 4 at another site than pictured in Fig 3 and 6. A polymorphonuclear leucocyte infiltrate (leu) is present in the tear (la) which nearly crosses the complete media (m). (Haematoxylin and eosin $\times 57$.)

Fig. 7 Detail of an intimal lesion with thrombosis (thr) in the ductal wall of case 2. The internal elastic lamina is interrupted. (Haematoxylin and eosin $\times 105$.)

the ductus arteriosus is not well known (Strong and Bohr, 1967). In guinea-pigs and dogs the lungs contain a high degree of degrading enzymes, eliminating 90 per cent of the circulating prostaglandins in one lung passage (Ferreira and Vane, 1967). Effects on systemic blood vessels will, therefore, largely depend on the route of admission. It is of interest in this respect that of our series of 8 patients thus far treated with PGE₁, 3 showed a dramatic flush of the perfused subclavian area, which disappeared after the catheter tip was

Table 2 Incidence of abnormalities

Case	1	2	3	4
Medial oedema	+	+	+	+
Interruption i.e.l.	+	+	-	+
Intimal damage	+	+	+	+
Laceration intima + media	+	+	-	+
Thrombus formation	+	+	-	+
Polymorphonuclear infiltrate	-	-	-	+

repositioned. It seems advisable, therefore, to study more vessels in patients treated with PGE₁.

Despite its damaging effects, PGE₁ administration may have its place as an emergency treatment in paediatric cardiology, in order to improve the condition of both the neonate awaiting catheterisation for diagnostic purposes and the infant with a ductus dependent anomaly awaiting operation. However, prolonged treatment with PGE₁ or a long-term PG-analogue may have a hazardous effect on the ductus arteriosus. In view of these observations it is advisable to administer the drug only in a low dose and for as short a time as possible.

We thank Dr D. ter Haar, Upjohn Co., The Netherlands, for the supply of prostaglandins.

References

- Christensen, N. C., and Fabricus, A. (1975). Medical manipulation of the ductus arteriosus. *Lancet*, **2**, 406-407.
- Cocceani, F., and Olley, P. M. (1973). The response of the ductus arteriosus to prostaglandins. *Canadian Journal of Physiology and Pharmacology*, **51**, 220-225.
- Elliott, R. B., Starling, M. B., and Neutze, J. M. (1975). Medical manipulation of the ductus arteriosus. *Lancet*, **1**, 140-143.
- Ferreira, S. H., and Vane, J. R. (1967). Prostaglandins: their disappearance from and release into the circulation. *Nature*, **216**, 868-873.
- Gardner, D. L., and Matthews, M. A. (1969). Ultrastructure of the wall of small arteries in early experimental rat hypertension. *Journal of Pathology*, **97**, 51-62.
- Gittenberger-de Groot, A. C. (1977). Persistent ductus arteriosus: most probably a primary congenital malformation. *British Heart Journal*, **39**, 610-618.
- Heptinstall, R. H. (1974). *Pathology of the Kidney*, 2nd ed., Vol. I, p. 142. Little, Brown, Boston.
- Moulaert, A., Gittenberger, A., and Harinck, E. (1977a). Prostaglandin and damage to ductus arteriosus. *Lancet*, **1**, 703-704.
- Moulaert, A., Senders, R., van Erbruggen, I., Huysmans, H., and Harinck, E. (1977b). Effect of E₁ type prostaglandins on hypoxemia in a cyanotic congenital cardiac malformation. *European Journal of Cardiology*, **5**, 321-325.
- Neutze, J. M., Starling, M. B., Elliott, R. B., and Barratt-Boyes, B. G. (1977). Palliation of cyanotic congenital heart disease in infancy with E-type prostaglandins. *Circulation*, **55**, 238-241.
- Olley, P. M., Cocceani, F., and Bodach, E. (1976). E-type prostaglandins. A new emergency therapy for certain cyanotic congenital heart malformations. *Circulation*, **53**, 728-731.
- Persaud, T. V. N. (1973). Pregnancy and progeny in rats treated with prostaglandin E₂. *Prostaglandins*, **3**, 299-305.
- Rudolph, A. M., and Heymann, M. A. (1977). Medical treatment of the ductus arteriosus. *Hospital Practice*, **57**, 57-65.
- Schöber, J. G., and Lorenz, H. P. (1976). Verbesserung der arteriellen O₂-Sättigung bei zyanotischen Neugeborenen mit Prostaglandin E₁ (in German). *Herz Kreislauf*, **1**, 198-200.
- Sharpe, G. L., and Larsson, K. S. (1975). Studies on closure of the ductus arteriosus. X. In vivo effect of prostaglandin. *Prostaglandins*, **9**, 703-719.
- Solomon, L. M., Juhlin, L., and Kirschenbaum, M. B. (1968). Prostaglandin on cutaneous vasculature. *Journal of Investigative Dermatology*, **51**, 280-282.
- Starling, B. M., Neutze, J. M., Elliott, R. L., and Elliott, R. B. (1976). Studies on the effects of prostaglandins E₁, E₂, A₁ and A₂ on the ductus arteriosus of swine in vivo using cineangiography. *Prostaglandins*, **12**, 355-367.
- Strong, C. G., and Bohr, D. F. (1967). Effects of prostaglandins E₁, E₂, A₁ and F_{1α} on isolated vascular smooth muscle. *American Journal of Physiology*, **213**, 725-733.

Requests for reprints to Dr A. C. Gittenberger-de Groot, Department of Anatomy and Embryology, Rijksuniversiteit Leiden, Wassenaarseweg 62, Leiden, The Netherlands.