Responsiveness of the ductus arteriosus to prostaglandin E₁ assessed by combined cross sectional and pulsed Doppler echocardiography

SATOSHI HIRAISHI, NOBUYUKI FUJINO, KOICHI SAITO, KOHKI OGUCHI, NOBUAKI KADOI, YOUTARO AGATA, YASUNORI HORIGUCHI, HAJIME HOZUMI, KIMIO YASHIRO

From the Department of Paediatrics, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan

SUMMARY Cross sectional echocardiography combined with Doppler echocardiography was used to record either ductal morphology or the flow profile within the ductus arteriosus before and after infusion of prostaglandin E₁ in 25 newborn infants with cyanotic and acyanotic congenital heart disease with ductus dependent blood flow. The ultrasound results were compared with changes in arterial oxygen tension and the overall clinical response to prostaglandin E₁ seen during the same period in 24 of the 25 patients in whom the degree of ductal narrowing could be determined with the ultrasound method. At the time of the study, the ductus was widely patent or slightly narrowed in 12 patients and was closed in two patients. These patients did not respond to prostaglandin E₁. There was prominent localised narrowing of the ductus in seven patients and generalised narrowing in three. After the infusion of prostaglandin E₁ there was no ductal narrowing in these patients, except for one patient who had slight residual localised narrowing. There was also a considerable change in the ductal flow profiles in each patient. In these 10 patients infusion of prostaglandin E₁ resulted in an increase in arterial oxygen tension, clinical improvement, or both.

The present study indicates that prostaglandin E₁ is effective in patients with prominent narrowing of the ductus but is not in patients in whom the ductus is widely patent or closed. Cross sectional echocardiography combined with Doppler echocardiography was useful for predicting the responsiveness of the ductus arteriosus to the infusion.

Since 1975, prostaglandins E₁ and E₂ have been used to maintain the patency of the ductus arteriosus in newborn infants with cyanotic and acyanotic congenital heart disease with ductus dependent blood flow.¹⁻⁶ The clinical effects of prostaglandins are variable. The factors that determine an infant's responsiveness to the infusion are not clear.

Clyman *et al* showed that in newborn lambs the absence of ductus responsiveness to prostaglandin E₂ was directly related to reduced luminal blood flow.⁷ Recently, several investigators have shown that cross sectional echocardiography combined with Doppler echocardiography allows accurate assessment of both the shape of the ductus and the flow dynamics of the shunt in patients with the ductus arteriosus.⁸⁻¹³ We

therefore applied this technique to assess changes in the shape of the ductus arteriosus and the flow velocity profiles before and during prostaglandin E₁ infusion and to evaluate the difference between the group of patients who responded to the infusion and those who did not.

Patients and methods

Twenty five patients with congenital heart disease whose survival is dependent on ductal blood flow were evaluated prospectively between May 1985 and November 1987. All were treated with infusion of prostaglandin E₁ after cross sectional Doppler echocardiographic diagnosis before cardiac catheterisation. At the onset of infusion the infants were five hours to 35 days old (76% were <5 days old). Prostaglandin E₁ was infused at a dose of 0.05 to 0.1 µg/kg/min into a peripheral vein. The diagnosis was subsequently confirmed by angiography except for

Requests for reprints to Dr Satoshi Hiraishi, Department of Paediatrics, Kitasato University School of Medicine, 1-15-1 Kitasato, Sagamihara, Kanagawa, 228 Japan.

Accepted for publication 21 February 1989

Table Patient data

Patient No	Diagnosis	Age (days) at PGE ₁ infusion	Cross sectional echocardiogram	
			DA shape	DA appearance before PGE ₁
Group 1 (ductus dependent pulmonary blood flow):				
1	TA (Ia)	4	T	Narrow PA end
2	TA (Ia)	0	T	Wide
3	TA (Ib)	0	T	Wide
4	PA, VSD	1	T	Narrow PA end
5	PPA	2	T	Narrow PA end and middle
6	PPA	1	C	Wide
7	PPA	0	C	Narrow middle
8	PPA	1	T	Narrow middle
9	Ebstein, PS	1	T	Narrow whole length
10	d-TGA, VSD, PS	2	T	Narrow PA end
Group 2 (ductus dependent systemic venous mixing):				
11	d-TGA (IVS)	1	C	Wide
12	d-TGA (IVS)	0	C	Wide
13	d-TGA (IVS)	1	C	Narrow PA end and middle
14	d-TGA (IVS)	0	C	Wide
15	d-TGA (IVS)	3	C	Narrow PA end
16	d-TGA (IVS)	0	C	Wide
17	d-TGA (IVS)	1	C	Narrow PA end
Group 3 (ductus dependent systemic blood flow):				
18	Coarctation	8	C	Narrow whole length
19	Coarctation, UVH	35	C	Narrow whole length
20	HPLHS	2	C	Wide
21	HPLHS	1	C	Wide
22	Coarctation, UVH	12	C	Wide
23	Coarctation	8	C	Closed
24	Coarctation, VSD	10	C	Closed
Group 4				
25	TAPVC (infra), ASD	1	C	Narrow middle

PGE₁, prostaglandin E_1 ; DA, ductus arteriosus; TA (Ia), tricuspid atresia with intact ventricular septum and pulmonary atresia; TA (Ib), tricuspid atresia with small VSD (ventricular septal defect) and pulmonary stenosis; PA, pulmonary atresia; PPA, pulmonary atresia with intact ventricular septum; PS, pulmonary stenosis; d-TGA (IVS), d-transposition of the great arteries (intact ventricular septum); coarctation, coarctation of the aorta; UVH, univentricular heart; HPLHS, hypoplastic left heart syndrome; TAPVC (infra), total anomalous pulmonary venous connection (infracardiac type); ASD, atrial septal defect; T, tortuous; C, cylindrical.

two patients with hypoplastic left heart syndrome, which was diagnosed by cross sectional echocardiography alone. The patients were divided into four groups (table). Group 1 consisted of 10 patients with ductus dependent pulmonary blood flow (simple or complex pulmonary atresia and critical pulmonary stenosis). Group 2 consisted of seven patients with ductus dependent systemic venous mixing (complete transposition of the great arteries with intact ventricular septum and atrial septal defect or persistent foramen ovale). Group 3 consisted of seven patients with ductus dependent systemic blood flow (coarctation of aorta and hypoplastic left heart syndrome). The only patient in group 4 had total anomalous

pulmonary venous connection with venous obstruction in which the descending vein terminated in the hepatic vein, and with no other associated anomaly. In this patient, treatment with prostaglandin E_1 was started on the basis of Doppler determined ductal flow profiles and clinical deterioration. The efficacy of prostaglandin E_1 in the patients in groups 1 and 2 was assessed by changes in arterial oxygen tension. Arterial oxygen tension was usually measured immediately before and several times after the start of the infusion. When more than one value was obtained after the onset of the infusion, the value obtained closest to one hour after the start of the infusion was used for the analysis. The overall clinical effects of the infusion in the patients in groups 3 and 4 were evaluated by changes in blood pressure in the arms and legs, urine flow, and serial chest x ray films. In two infants with simple coarctation of the aorta, the systolic pressures in the femoral and radial arteries were monitored simultaneously throughout the period of infusion.

CROSS SECTIONAL AND DOPPLER ECHOCARDIOGRAPHIC STUDIES

All patients were studied with a pulsed Doppler echocardiographic system (Hewlett Packard, Model 77020 AC) with a 5 MHz shallow focus transducer immediately before and several times after the start of infusion of prostaglandin E_1 . The data obtained closest to one hour after the start of the infusion were used to compare arterial oxygen tension values in patients in groups 1 and 2. For a high parasternal approach, the transducer was positioned in the second or third left intercostal space, rotated counterclockwise, and directed inferiorly or slightly superiorly. In this plane the ductus arteriosus was imaged above the junction of the left pulmonary artery with the main pulmonary trunk as reported previously.¹³

If this standard parasternal approach failed to visualise the ductus along its entire length we used another plane. The transducer was placed just below the right or left clavicle. Then it was rotated to visualise the long axis of the aortic arch—clockwise when the arch was left sided and counterclockwise when the arch was right sided. Next the transducer was directed inferiorly to visualise the ductus, the main pulmonary artery, and the aortic arch in the same cut.

Doppler interrogation was performed during simultaneous visualisation, with the sample volume placed in the middle of the ductus when it was widely patent and not tortuous, and at the pulmonary end, in the middle, and towards the aortic end when it was tortuous. Care was taken to place the sample volume at the same site in the ductus before and after the

Fig 1 (a and c) Long axis plane of the ductus showing localised narrowing in the middle (arrow). (b) Ductal flow profile indicating the left to right shunt flow of high velocity toward the transducer at a sampling site within the localised narrowing. (d) Non-phasic flow of low velocity upstream of the narrowing. Note the difference in flow velocity profile seen at two sampling sites within the ductus. A, anterior; P, posterior; S, superior; I, inferior; M-PA, main pulmonary artery; L-PA, left pulmonary artery; DA, ductus arteriosus; Des Ao, descending aorta.

infusion of prostaglandin E_1 . Previous reports of the closure process in normal newborn infants,¹⁴ suggest that narrowing of the entire length of the ductus should be regarded as prominent when the ductus is < 2 mm in diameter along its entire length. Similarly, we judged localised narrowing of the ductus to be prominent when the high velocity jet more than 2 m/s was directed superiorly from the localised narrowed portion of the ductus or if a characteristic non-phasic

continuous flow of low velocity was recorded upstream from the narrowed portion at an intercept angle of < 50° or both (fig 1). We regarded other degrees of localised intraluminal narrowing on imaging to be slight. When no lumen was visible and Doppler showed no left to right shunting, closure of the duct was diagnosed. The Doppler profile and electrocardiograms were recorded simultaneously at 100 mm/s and stored on video tape for later analysis.

Fig 2 (a) Cross sectional echocardiogram showing a tortuous ductus arteriosus (small arrows) in a patient with tricuspid atresia and pulmonary atresia with intact ventricular septum (type Ia). The window was obtained with a transducer just below the right clavicle. The widely patent ductus supplied the pulmonary arteries and formed an acute angle with the descending aorta. (b) The angiocardigram for the same patient. See legend to fig 1 for abbreviations.

Flow toward the transducer was displayed above the baseline, whereas flow away from the transducer was displayed below it.

STATISTICAL ANALYSIS

A two tailed Student's t test was used for statistical analysis of the difference of mean values between the two groups.

Results

DUCTAL MORPHOLOGY AND FLOW PROFILES BEFORE PROSTAGLANDIN E_1 INFUSION

The ductus could be clearly visualised along its entire length from a high parasternal approach in two planes in all patients except for two with a closed ductus, seven with a tortuous ductus in whom it was not possible to obtain an adequate imaging by the standard parasternal plane (fig 2), and two patients who had a cylindrical ductus. Ten patients had a ductus widely patent along its entire length, ranging from 3 to 7.5 mm (mean 5.3 mm) in the widest inner diameter. Of the remaining 13 patients with patent ducts, ductal narrowing was seen in the localised portion in 10 and along its entire length in three patients (table).

The Doppler method showed continuous left to right shunt flow within the ductus in all patients with ductus dependent pulmonary blood flow (group 1). A change in direction in the continuous velocity pattern was noted within tortuous ducts. In the other groups of patients with a patent ductus, ductal shunt flow profiles ranged from continuous left to right shunting to right to left shunting. In 14 of the 15 patients with a cylindrical ductus, the angle of intercept was $< 30^\circ$ within the ductus. In eight patients with a tortuous ductus the angle varied considerably with the sampling site in the ductus, but in seven patients it was $< 50^\circ$ at the aortic end, the pulmonary end, or both. This cross sectional and Doppler echocardiographic method showed that the degree of the ductal narrowing in a localised portion or along its entire length was prominent in 10 and mild in two; another patient had a localised narrowing and the ductus was almost vertically aligned with the Doppler cursor.

CLINICAL AND DUCTAL RESPONSIVENESS TO PROSTAGLANDIN E_1

In 16 of the 17 patients in groups 1 and 2 arterial oxygen tension was studied after prostaglandin E_1 infusion. A good clinical response, that is an increase in arterial oxygen tension of ≥ 10 mm Hg, was noted

Fig 3 Arterial oxygen tension (PaO_2) (mean (SD)) before and during infusion of prostaglandin E_1 in patients in groups 1 and 2. Note the difference in the response to prostaglandin E_1 between 7 patients with prominent narrowing of the ductus (a) and nine patients with slight narrowing of the ductus or a widely patent ductus (b).

in only the seven patients in groups 1 and 2 who had prominent localised narrowing or narrowing along the whole length of the ductus before the infusion ($p < 0.001$) (fig 3a).

In all of these patients ductal narrowing on cross sectional and Doppler echocardiography disappeared after the infusion (fig 4). In contrast, the remaining nine patients who had a slightly narrowed or widely patent ductus did not show any significant change in arterial oxygen tension after the infusion (fig 3b). None of the 10 patients who had a widely patent ductus before and during the infusion showed a significant change in the widest ductal diameter. In two group 3 patients (cases 18 and 19) with coarctation of the aorta, the femoral artery pulse and urine flow improved during the infusion. In one patient the systolic pressure difference between radial and femoral arteries decreased from 55 to 30 mm Hg. In both patients the ductus was widely patent and the

ductal flow profile changed from a right to left shunt to a bidirectional shunt after the infusion. In the other five group 3 patients, who had a widely patent or closed ductus, we saw no major changes in overall clinical findings after the infusion. In the two patients with a closed ductus, the ductus remained closed even when a high dose of prostaglandin E_1 ($0.1 \mu\text{g/kg/min}$) was given. In one patient (group 4) who had obstructive total anomalous pulmonary venous connection, the infusion resulted in an apparent improvement in pulmonary oedema on serial chest x ray films obtained 10 hours later and an increase in urine flow. This coincided with ductal dilatation and an increase in ductal right to left shunting (fig 5).

Discussion

In patients who did not respond to prostaglandin E_1 , echocardiography combined with Doppler echocardiography showed that the ductus was widely patent or only slightly narrowed before prostaglandin E_1 infusion. Furthermore, the infusion had no effect on ductal diameter in any patient with a widely patent ductus. These data confirm the hypothesis that the diameter to which prostaglandin E_1 will dilate the ductus is limited.⁵ In such patients, the infusion will not produce a further increase in oxygenation or clinical improvement, though it can be administered prophylactically to prevent ductal narrowing. Nor was prostaglandin E_1 effective in patients in whom the ductus was fully closed. But the infusion was very effective in patients in whom the ductus was patent with prominent localised or generalised narrowing. The ductus may remain responsive to prostaglandin E_1 as long as the ductus is not allowed to close fully before the infusion. The number of patients that we studied was too small to conclude that this outcome will always be achieved in such cases. Further study is needed to clarify this point.

In most of the patients with ductal narrowing, intraluminal changes were noted at a localised portion before the infusion. This localised narrowing was shown to be early evidence of ductal changes leading to spontaneous closure.¹⁴ Cross sectional echocardiographic imaging alone provides important information of changes within the ductal lumen.^{10 11 14} However, when the degree of localised narrowing is assessed by direct imaging the dimension of the narrowing in one plane cannot be used to assess the absolute size of the narrow portion and if the narrowed portion is < 2 mm in diameter it may fall outside the range of lateral resolution of the equipment being used. In the present study, the Doppler method could be used to confirm the ductal patency in patients with narrowing along the entire length of

Fig 4 Cross sectional echocardiograms and Doppler echocardiograms in a patient with pulmonary atresia and ventricular septal defect. (a) Localised narrowing (arrow) is indicated near the pulmonary end of the ductus before infusion of prostaglandin E_1 . (b) The localised narrowing disappeared during the infusion. (c) Characteristic low velocity flow near aortic end of the ductus before the infusion. (d) A high velocity continuous flow away from the transducer at the same site as (c). The intercept angle was 30° in both panels. See legend to fig 1 for abbreviations.

the ductus. This technique also provided additional information on the degree of the localised narrowing within the ductus. A high velocity jet was detected within and downstream from the narrowed portion. The flow velocity seen upstream of a localised narrowing was low and was usually non-phasic. Smallhorn and Freedom found that in patients with obstructive total anomalous venous connection the Doppler determined flow was non-phasic with a low

velocity and turbulent with a high velocity, respectively, in the areas proximal and distal to the site of obstruction.¹⁵ Thus the characteristic flow profiles seen in patients with prominent localised narrowing seem to reflect the actual narrowing within the ductus. But this Doppler approach is not accurate in patients in whom the ductus is imaged in a near vertical position to the Doppler cursor.

In two patients in group 3 with coarctation of the

Fig 5 Cross sectional echocardiograms and Doppler echocardiograms in a patient with obstructive total anomalous pulmonary venous connection. (a) Localised narrowing in the ductus (arrow) in its middle portion before infusion of prostaglandin E₁. (b) Ductus was widely patent during the infusion (c and d) Right to left ductal shunt flow away from the transducer was predominant before and during the infusion. Ductal dilatation resulted in laminar right to left ductal shunt flow. R-PA, right pulmonary artery; L-PA, left pulmonary artery; Ao, aorta; see legend to fig 1 for other abbreviations.

aorta, a right to left ductal shunt became bidirectional after the infusion. This raises the possibility that the additional left to right shunt and diminished radiofemoral gradient are a consequence of diminished coarctation in such cases.

Freedom *et al* reported that prostaglandin E₁ infusion resulted in severe pulmonary oedema with considerable respiratory distress in one patient who had visceral heterotaxia, asplenia, and complex congenital heart disease including pulmonary atresia and

an obstructive total anomalous pulmonary venous connection.¹⁶ In the patient with obstructive total anomalous pulmonary venous connection and uncomplicated pulmonary outflow tract obstruction included in this study, the pulmonary oedema and urine flow improved within 10 hours of the infusion. The major change here may be that from a turbulent jet to a more laminar jet suggesting that a larger volume is passing through the ductus from the pulmonary artery to the aorta. Therefore, the

Responsiveness of the ductus arteriosus to prostaglandin E₁

difference in the clinical response to prostaglandin E₁ between Freedom's case¹⁶ and ours seems to relate to the direction of shunt flow across the ductus and its flow volume, consequent on the presence or absence of pulmonary valve atresia.

We thank Miki Sakakibara, Harumi Kawai, and Masahiro Ohe for technical assistance.

References

- 1 Elliott RB, Starling MB, Neutze JM. Medical manipulation of the ductus arteriosus. *Lancet* 1975;i: 140-2.
- 2 Olley PM, Coceani F, Bodach E. E type prostaglandins. A new emergency therapy for certain cyanotic congenital heart malformations. *Circulation* 1976;53: 728-31.
- 3 Heymann MA, Berman W Jr, Rudolph AM, Whitman V. Dilatation of the ductus arteriosus by prostaglandin E₁ in aortic arch abnormalities. *Circulation* 1979;59:169-73.
- 4 Benson LN, Olley PM, Patel RG, Coceani F, Rowe RD. Role of prostaglandin E₁ infusion in the management of transposition of the great arteries. *Am J Cardiol* 1979;44:691-6.
- 5 Freed MD, Heymann MA, Lewis AB, Roehl SL, Kensey RC. Prostaglandin E₁ in infants with ductus arteriosus-dependent congenital heart disease. *Circulation* 1981;64:899-905.
- 6 Beitzke A, Suppan CH. Use of prostaglandin E₂ in management of transposition of great arteries before balloon atrial septostomy. *Br Heart J* 1983;49:341-4.
- 7 Clyman RI, Mauray F, Roman C, Heymann MA, Payne B. Factors determining the loss of ductus arteriosus responsiveness to prostaglandin E. *Circulation* 1983;68:433-6.
- 8 Sahn DJ, Allen HD. Real-time cross-sectional echocardiographic imaging and measurement of the patent ductus arteriosus in infants and children. *Circulation* 1978;58:343-54.
- 9 Smallhorn JF, Huhta JC, Anderson RH, Macartney FJ. Suprasternal cross-sectional echocardiography in assessment of patent ductus arteriosus. *Br Heart J* 1982;48:321-30.
- 10 Huhta JC, Cohen M, Gutgesell HP. Patency of the ductus arteriosus in normal neonates: two-dimensional echocardiography versus Doppler assessment. *J Am Coll Cardiol* 1984;4:561-4.
- 11 Smallhorn JF, Gow R, Olley PM, et al. Combined noninvasive assessment of the patent ductus arteriosus in the preterm infants before and after indomethacin treatment. *Am J Cardiol* 1984;54: 1300-4.
- 12 Cloez JL, Isaaz K, Pernot C. Pulsed Doppler flow characteristics of the ductus arteriosus in infants with associated congenital anomalies of the heart or great arteries. *Am J Cardiol* 1986;57:845-51.
- 13 Hiraishi S, Horiguchi Y, Misawa H, et al. Noninvasive Doppler echocardiographic evaluation of shunt flow dynamics of the ductus arteriosus. *Circulation* 1987;75:1146-53.
- 14 Hiraishi S, Misawa H, Oguchi K, et al. Two-dimensional Doppler echocardiographic assessment of closure of the ductus arteriosus in normal newborn infants. *J Pediatr* 1987;111:755-60.
- 15 Smallhorn JF, Freedom RM. Pulsed Doppler echocardiography in the preoperative evaluation of total anomalous pulmonary venous connection. *J Am Coll Cardiol* 1986;8:1413-20.
- 16 Freedom RM, Olley PM, Coceani F, Rowe RD. The prostaglandin challenge. Test to unmask obstructed total anomalous pulmonary venous connections in asplenia syndrome. *Br Heart J* 1978;40:91-4.