Persistent ductus arteriosus complicating the respiratory distress syndrome

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SUMMARY Persistent ductus arteriosus (PDA) complicated the clinical course in 45 (15%) of 299 babies with the respiratory distress syndrome (RDS) presenting over a 3-year period. The incidence of PDA complicating RDS rose with decreasing birthweight and was highest in babies with severe RDS as judged by the use of assisted ventilation. In babies with a birthweight of less than 1500 g, PDA occurred as a complication of RDS in 25% of cases. In babies who received intermittent positive pressure ventilation (IPPV) for management of RDS, the incidence of PDA was 35%.

Overall mortality for babies with RDS was 17%; when PDA occurred as a complication mortality was 31%. In survivors, spontaneous closure of the PDA occurred in all except one infant. The development of signs of PDA in 19 babies either necessitated a renewal of IPPV or prevented 'weaning' from IPPV or from continuous positive airways pressure. 9 (47%) of these babies died, 8 of them after the first week of life. The frequency of PDA complicating RDS and the relatively high mortality in this conservatively-treated group of babies is emphasized. The incidence reported here is likely to increase with the increased survival of very low birthweight infants with severe RDS. The high incidence of late deaths in babies who develop signs of PDA associated with an inability to wean from assisted ventilation suggests that early surgical ligation of the PDA in these babies should be considered. The results of a conservative approach to management of these infants are presented.

As the standard of perinatal care improves, particularly with recent techniques for artificial ventilation, a greater proportion of babies with the respiratory distress syndrome (RDS) survive. At the same time, persistent ductus arteriosus (PDA) has become more evident in association with RDS, especially among the smallest and sickest infants (Siassi *et al.*, 1969; Kitterman *et al.* 1972; Neal *et al.*, 1975).

Although much attention has recently been focused on this problem, there is no consistent agreement on management (Krovetz and Rowe, 1972; Lees, 1975). Most workers consider that heart failure should be managed medically at first, and that surgical ligation of the PDA should be performed when medical management is unsuccessful, and when heart failure results in an inability to wean from assisted ventilation (Gupta *et al.*, 1972; Kitterman *et al.*, 1972; Edmunds *et al.*, 1973; Thibeault *et al.*, 1975). Earlier ligation however has been suggested, since the presence of a left-to-right shunting PDA in the infant with RDS may

lead to a progressive deterioration in lung function and the possible development of bronchopulmonary dysplasia (Gupta *et al.*, 1972; Gay *et al.*, 1973; Neal *et al.*, 1975; Thibeault *et al.*, 1975). The latter complication has been one of the major factors responsible for the poor results of ductus ligation in most reported series (Edmunds *et al.*, 1973; Gay *et al.*, 1973).

Conversely, since the PDA frequently closes spontaneously in preterm infants, a more conservative approach has been recommended by several workers (Auld, 1966; Danilowicz *et al.*, 1966; Girling and Hallidie-Smith, 1971), and the prolonged application of continuous positive airways pressure (CPAP) to control heart failure and await spontaneous PDA closure has been reported in 2 cases from this hospital (Robertson, 1974). However, no large series of babies with PDA complicating RDS has previously been reported where surgical intervention has not been used. The present retrospective study was undertaken to assess the incidence of PDA complicating RDS at the John Radcliffe Hospital and to assess our experience with the

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conservative management of this problem over a 3-year period.

Patients and methods

From July 1972 to June 1975, 299 babies were diagnosed as suffering from RDS according to clinical and radiological criteria as described by Davies *et al.* (1972). Treatment of RDS in this unit has been outlined by these authors, and includes umbilical vessel catheterization, alteration of inspired oxygen concentration to maintain an arterial oxygen tension of 60–90 torr, and correction of metabolic acidosis with alkali. Hypotension or low haematocrit was treated with small fresh blood transfusions. CPAP was administered by a modification of the Bennett PR2 ventilator (Etches *et al.*, 1973) or by nasal prongs, the indication for CPAP being an arterial oxygen tension <60 torr in 60% inspired oxygen. Early in the study some babies received CPAP by head box, or continuous negative airways pressure via a body box. Intermittent positive pressure ventilation (IPPV) was administered by Bennett PR2 or Draeger Spiromat ventilator, the indications being apnoea or failure to maintain adequate oxygenation despite oxygen and CPAP.

Diagnosis of PDA was made clinically by the neonatal resident staff by auscultation (Rowe and Lowe, 1964) together with palpation of the femoral or brachial pulses. Essential features were (1) a continuous murmur or (2) a systolic murmur maximal at the left sternal edge or below the left clavicle, associated with bounding pulses. When an umbilical arterial catheter was *in situ*, intra-aortic measurement of a wide pulse pressure provided confirmation of the clinical impression of bounding pulses. One infant (Case 40, Table 2) underwent cardiac catheterization.

Babies in whom there was doubt about the diagnosis of PDA have been omitted. This includes 5 in whom transient murmurs were heard during recovery from RDS, 2 in whom documentation was inadequate, and one with a widely conducted continuous murmur thought to be due to peripheral pulmonary artery stenosis (Dunkle and Rowe, 1972).

During the 3 years of the study this unit lacked easy access to cardiological and surgical facilities and a conservative approach to the management of PDA complicating RDS was made in all cases.

Results

PDA was diagnosed in 45 (15%) of 299 babies with RDS presenting over the 3-year period. The main clinical features of these babies are shown for survivors in Table 1 and for deaths in Table 2. There

were 26 males and 19 females; 10 babies were from multiple pregnancies.

Birthweight. The incidence of RDS and RDS plus PDA is shown in Table 3. Mean birthweight was 1890 g (range 850–3870 g) for survivors and 1369 g (range 880–1850 g) for deaths. The incidence of PDA complicating RDS increases with decrease in birthweight. The lower incidence in babies with a birthweight of less than 1000 g may be explained by the large number in this group who died early in the course of their respiratory illness. Of 17 babies of less than 1000 g with RDS, only 7 survived for more than 48 hours and of these, 3 (43%) developed signs of PDA.

Gestational age. Mean gestational age in this group of 45 babies was 31.7 weeks (range 27–40). 5 babies had birthweights below the 10th centile for gestational age (Milner and Richards, 1974).

Birth asphyxia. Intubation was performed and IPPV started at birth in 26 (58%) of the 45 babies with RDS plus PDA and in 112 (44%) of the 254 babies with RDS who did not develop PDA. This difference is not significant ($\chi^2=2.88$, $P>0.05$).

Assisted ventilation for RDS. PDA occurred predominantly in babies who received assisted ventilation for management of their RDS (Table 4). Of 95 who received IPPV, 33 (35%) developed PDA, whereas the incidence in babies on CPAP alone was 6 (12%) out of 50 babies. Taken together, in those babies receiving either IPPV or CPAP PDA developed in 39 (22%) out of 145 babies. Only 6 (4%) of 154 babies who received no assisted ventilation for management of RDS developed signs of PDA. There were 38 early deaths (<1 week) in the 95 babies with RDS receiving IPPV (Table 4). If these are excluded, PDA developed in 30 (53%) of the remaining 57 babies who survived the first week of life.

Murmur. A continuous murmur was heard in 22 babies, and a systolic murmur associated with bounding pulses was found in the remaining 23 babies. In the former group, the murmur was frequently systolic initially, but later became continuous. The murmur was usually first heard when the infant was in the early recovery stage of RDS, frequently when IPPV was being changed to CPAP, or when CPAP was being discontinued. The murmur was first detected at a mean age of 6.7 days (range 1–25 days) and disappeared at a mean postnatal age of 50 days (range 4–192 days). Expressed as postconceptional age, the mean time of disappearance of the murmur

Table 1 RDS plus PDA: survivors

Case no.	Birthweight (g)	Sex	Gestational age (w)	Intubated at birth	Assisted ventilation for RDS	Age off assisted ventilation (d)
1	850	M	27	+	CPAP + IPPV	19
2	990*	F	29	+	CPAP + IPPV	7
3	1020*	F	30	—	CPAP + IPPV	10
4	1030*	F	30	+	CPAP + IPPV	19
5	1120	M	28	—	CPAP + IPPV	84
6†	1150	M	29	+	CPAP	2
7‡*	1190	F	28	+	CPAP + IPPV	42
8	1290	F	28	+	CPAP + IPPV	11
9†	1420	M	30	+	CPAP + IPPV	21
10	1610	M	29	—	CPAP	5
11	1620	M	33	—	CPAP + IPPV	7
12	1700	F	32	—	—	—
13†	1710	M	32	+	—	—
14	1710	M	33	+	CPAP + IPPV	20
15	1760	F	32	—	CPAP + IPPV	11
16	1800	M	33	+	CPAP	3
17	2030	M	34	—	CPAP + IPPV	5
18†	2040	F	34	+	CPAP + IPPV	6
19	2070	F	33	—	—	—
20	2200	F	34	+	CPAP	4
21	2250	M	33	—	CPAP	4
22	2260	F	35	+	CPAP + IPPV	7
23	2270	F	34	+	CPAP + IPPV	7
24	2420	F	37	+	—	—
25	2441	M	32	+	CPAP + IPPV	10
26	2470	M	37	+	CPAP + IPPV	8
27	2505	M	35	—	CPAP + IPPV	14
28†	2550	F	36	—	—	—
29	2615	F	37	+	CPAP + IPPV	6
30	3060	M	40	—	—	—
31	3870	F	37	+	CPAP + IPPV	3

*Birthweight below 10th centile. †Multiple pregnancy. ‡Previously reported by Robertson (1974).

Table 2 RDS plus PDA: deaths

Case no.	Birthweight (g)	Sex	Gestational age (w)	Intubated at birth	Age off assisted ventilation (d)	Murmur
32	880	M	28	—	Never	Continuous
33†	1035	F	30	+	21	„
34†	1050	M	28	—	Never	„
35†	1070	M	28	—	„	„
36	1270*	M	32	+	„	„
37†	1290	M	29	+	„	Systolic
38	1310	M	28	+	77	Continuous
39	1330	F	31	—	4	Systolic
40	1400	M	28	+	17	Continuous
41†	1620	M	29	—	Never	„
42‡	1650	M	29	—	26	Systolic
43	1700*	M	35	+	Never	„
44	1710	M	32	—	„	Continuous
45	1850	F	30	+	10	„

All babies received IPPV and CPAP for management of RDS except Case 39 who received CPAP only.

*Birthweight below 10th centile. †Multiple pregnancy. ‡Previously reported by Robertson (1974). §Lung biopsy; necropsy not performed. PDA closed at cardiac catheterization shortly before death.

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<i>Murmur</i>	<i>First detected (d)</i>	<i>Ceased (d)</i>	<i>Failure to wean from assisted ventilation</i>	<i>Digoxin and diuretics</i>	<i>Chest x-ray</i>
Systolic	1	28	+	+	Pulmonary oedema
"	7	150	—	+	" "
Continuous	8	11	—	—	—
Systolic	4	35	—	+	—
Continuous	4	84	+	+	Cardiomegaly
Systolic	7	84	—	+	"
Continuous	2	192	+	+	Pulmonary oedema
Systolic	10	20	+	+	" "
"	5	22	—	—	—
"	12	84	—	—	—
Continuous	9	14	—	+	Pulmonary oedema
Systolic	25	84	—	—	—
"	21	56	—	—	—
Continuous	8	22	+	+	Pulmonary oedema
"	5	35	—	—	—
Systolic	14	—	—	—	Cardiomegaly
"	5	11	—	—	"
Continuous	7	??	—	+	—
"	14	84	—	—	—
Systolic	2	84	+	—	—
Continuous	10	84	—	—	—
Systolic	2	28	—	—	Cardiomegaly
Continuous	2	42	+	+	Pulmonary oedema
Systolic	7	21	—	—	—
Continuous	7	42	+	—	—
Systolic	4	16	+	+	—
Continuous	4	17	+	+	—
Systolic	9	56	—	—	—
"	6	8	—	—	—
"	1	4	—	+	Cardiomegaly
"	1	5	—	—	—

<i>First detected (d)</i>	<i>Ceased (d)</i>	<i>Failure to wean from assisted ventilation</i>	<i>Digoxin and diuretics</i>	<i>Chest x-ray</i>	<i>Age at death (d)</i>	<i>Post-mortem findings</i>
4	—	+	+	—	8	Enterocolitis congested lungs
11	19	—	—	—	28	Enterocolitis, emphysema
1	—	—	—	—	1	Intraventricular haemorrhage, PDA
1	—	—	—	—	2	Intraventricular haemorrhage, PDA
3	46	+	+	Pulmonary oedema	77	Enterocolitis; duct closed
12	—	+	+	"	42	Aspiration
7	126	+	+	"	196	Bronchopulmonary dysplasia, tracheal stenosis, PDA small VSD
3	—	—	+	—	6	Intraventricular haemorrhage
3	—	+	+	Pulmonary oedema	126	Bronchopulmonary dysplasia §
3	13	+	+	"	14	Bowel obstruction
2	42	+	+	"	50	Hydrocephalus congested lungs, duct closed
3	—	+	+	—	9	Bronchopulmonary dysplasia, PDA
2	—	+	+	Pulmonary oedema	6	Bronchopulmonary dysplasia, kernicterus
23	—	—	+	"	35	Bronchopulmonary dysplasia, sepsis, PDA

Table 3 Incidence and mortality for babies with RDS, and with PDA plus RDS

Birthweight (g)	RDS—all cases		RDS plus PDA	
	No. of babies	Died (%)	No. of babies (%)	Died (%)
<1000	17	12 (70)	3 (18)	1 (33)
1001–1500	56	26 (46)	15 (27)	8 (53)
1501–2000	52	11 (21)	12 (23)	5 (42)
2001–2500	72	2 (3)	10 (14)	—
2501–3000	102	1 (1)	5 (5)	—
Total	299	52 (17)	45 (15)	14 (31)

Table 4 Assisted ventilation for RDS, incidence of PDA, and mortality

Total	Assisted ventilation	Incidence of PDA	Deaths	<div> <div>Early (<1 week)</div> <div>Late (>1 week)</div> </div>
299 babies	IPPV in 95	33 (35%) with PDA	13 (40%)	3 early 10 late
		62 without PDA	38 (61%)	35 early 3 late
	CPAP in 50	6 (12%) with PDA	1	early
		44 without PDA	—	nil
	IPPV or CPAP in 145	39 (22%) with PDA	14 (36%)	4 early 10 late
		106 without PDA	38 (36%)	35 early 3 late
	no assisted ventilation in 154	6 (4%) with PDA	—	nil
		148 without PDA	—	nil

was 39.2 weeks (range 31–55 weeks). One baby still had a murmur when seen at the age of 6 months (Case 16) and one was lost to follow-up (Case 18).

Heart failure. 25 of the 45 babies with PDA received digoxin and diuretics. Radiological cardiomegaly, or the appearances of pulmonary oedema, were noted in 21 babies.

Return to assisted ventilation. In 19 of the 45 babies with PDA, the appearance of a murmur was associated with either the need to return to IPPV or an inability to wean from IPPV or CPAP. Apnoeic attacks were encountered frequently in this group of babies, and were commonly the acute event necessitating a return to assisted ventilation. Further assisted ventilation was required for a mean of 26 days (range 1–80 days). Tracheal secretions, sepsis, and recurrent apnoea were additional problems preventing weaning. Several babies required frequent re-intubation and one (Case 38) developed tracheal

stenosis as a result. 2 babies whose heart failure was successfully treated with CPAP via endotracheal tube over prolonged periods (Case 7, 40 days; Case 42, 24 days) have previously been described by Robertson (1974).

Mortality. This is shown for babies with RDS and for those with RDS plus PDA in Table 3. The overall mortality for RDS was 17% and was significantly increased (31%, $\chi^2=4.75$, $P<0.05$) when PDA occurred as a complication. Since this high mortality in the PDA group probably reflects the severity of RDS at lower birthweights rather than the effects of a PDA, the mortality in babies with severe RDS (receiving IPPV) with and without PDA has also been compared (Table 4). Mortality is higher in the non-PDA group (61%) compared to the PDA group (40%, $\chi^2=4.15$, $P<0.05$). However, 35 of the 38 deaths in the non-PDA group were early deaths (<1 week) whereas most deaths in the PDA group occurred much later (Fig.), 10 of the 13

Fig. Comparison of age at death in babies with RDS plus PDA and in babies with RDS uncomplicated by PDA

deaths being after the first week. Thus, in babies with severe RDS who survive the first week of life, mortality is significantly higher in those who develop PDA (33%) than in those who do not (11%, $\chi^2=3.99$, $P<0.05$).

In babies with PDA complicating RDS, a significantly increased mortality was found in those with a continuous rather than a systolic murmur ($\chi^2=4.13$, $P<0.05$). Babies in whom the appearance of the murmur was associated with a return to IPPV or delay in weaning from IPPV or CPAP had a significantly higher mortality (47%) than babies whose PDA either required no treatment, or digoxin and diuretics only for heart failure (19%, $\chi^2=4.06$, $P<0.05$).

The main post-mortem findings in the 14 babies with PDA who died are shown in Table 2. Bronchopulmonary dysplasia (Northway *et al.*, 1967) was the main finding in 5 babies. Necrotizing enterocolitis was the cause of death in 3 babies, and intraventricular haemorrhage in 3. One baby had hydrocephalus due to old intraventricular haemorrhage (Case 42). The ductus arteriosus was stated to be 'open' in 5 babies, 'closed' in 2, and was not commented on in the remainder.

Discussion

The ductus arteriosus normally attains functional closure in the first 15 hours of life (Moss *et al.*, 1963), but frequently remains latent for longer periods in preterm infants (Burnard, 1959; Powell, 1963; Clarkson and Orgill, 1974). Patency of the ductus in infants with RDS has been recognized for many years

(Rudolph *et al.*, 1961), but only more recently has heart failure due to a left-to-right shunting PDA been increasingly recognized as a complication in babies recovering from RDS (Auld, 1966; Siassi *et al.*, 1969; Kitterman *et al.*, 1972; Krovetz and Rowe, 1972; Neal *et al.*, 1975; Lees, 1975).

The 15% incidence of PDA complicating RDS reported here is similar to those in previous series (Kitterman *et al.*, 1972; Neal *et al.*, 1975). The present study is retrospective, and based on the findings noted on repeated clinical examination by the resident medical staff. PDA has been diagnosed only in the presence of a murmur as described by Rowe and Lowe (1964) who have pointed out that, even in infancy, a clinical diagnosis without resort to cardiac catheterization is nearly always possible. However, Thibeault *et al.* (1975) have suggested that large left-to-right ductal shunts might contribute to early mortality in RDS even in the absence of a murmur. The incidence of PDA complicating RDS in our series may therefore be an underestimate. This incidence may be expected to increase with the increased survival of low birthweight infants with severe RDS. The importance of temporarily turning off the ventilator to allow accurate auscultation for murmurs in infants with RDS has been stressed by Siassi *et al.* (1969) and Kitterman *et al.* (1972).

Prolonged patency of the ductus arteriosus in preterm infants, and the increased incidence with decreasing birthweight in the present series (Table 3) may be explained on the basis of a decreased constrictor response of the ductus to oxygen and other vasoactive agents with shorter gestation (McMurphy *et al.*, 1972), though in some other series (Girling and Hallidie-Smith, 1971; Clarkson and Orgill, 1974) no similar increase with decreasing gestational age was found. Since a rise in arterial oxygen tension after birth is probably the main factor initiating normal duct closure (Heymann and Rudolph, 1975), more prolonged patency might be expected in infants with prolonged hypoxaemia after birth. The higher incidence of PDA in infants with severe RDS (Table 4) is therefore not unexpected, though, perhaps surprisingly, no increased incidence of PDA in infants asphyxiated at birth was found, either in the present series or in that of Girling and Hallidie-Smith (1971). That prolonged patency of the ductus in infants with RDS might be due to the effects of artificial ventilation rather than be secondary to the lung disease has been suggested by Krovetz and Rowe (1972). The appearance of the murmur of PDA during the recovery stage of RDS may be explained on the basis of a fall in pulmonary vascular resistance at this time, with a resultant increase in left-to-right shunting. That the murmur is frequently systolic initially and later becomes

continuous is also consistent with this hypothesis.

In the present series progressive hepatomegaly and lung crepitations in the infant with a murmur, bounding pulses, and a hyperactive praecordium were the usual indications for digoxin and diuretics. The clinical assessment of liver size in the infant receiving IPPV, however, can be misleading. In this situation radiological assessment of heart size and pulmonary vascularity may similarly be difficult, and electrocardiography is frequently unhelpful (Kitterman *et al.*, 1972). Increased oxygen requirements, hypercapnia, and the need for increased inflation pressures were frequently seen in infants on assisted ventilation who developed heart failure due to PDA. In other infants apnoea necessitated a return to IPPV shortly after the appearance of a PDA murmur, a finding similar to that of Kitterman *et al.* (1972).

Infants in whom the appearance of a PDA murmur was associated with a return to IPPV, or inability to wean from IPPV or CPAP, frequently required further assisted ventilation for prolonged periods. Although this may provide effective treatment for heart failure due to PDA in some cases (Robertson, 1974), the mortality in this group of infants was high (47%). Bronchopulmonary dysplasia and tracheal stenosis might have been prevented by PDA ligation at an early stage. In addition, the duration of the need for intensive care with its attendant physical and emotional complications in this ill group of infants might have been shortened by early operation. The results of PDA ligation in most reported series, however, are poor (Edmunds *et al.*, 1973; Gay *et al.*, 1973). Bronchopulmonary dysplasia and intracranial haemorrhage have been a major cause of mortality. Operation, however, has frequently been performed several days after the development of heart failure, and perhaps much earlier ligation of the PDA would prevent the development of bronchopulmonary dysplasia and improve the results of surgically treated cases (Gupta *et al.*, 1972; Edmunds *et al.*, 1973; Gay *et al.*, 1973; Neal *et al.*, 1975). Assessment of the size of a left-to-right ductal shunt by single injection aortography via the umbilical arterial catheter (Thibeault *et al.*, 1975) and noninvasive measurement of left atrial and left ventricular size by echocardiography (Silvermann *et al.*, 1974; Baylen *et al.*, 1975) may help to select those cases requiring surgery. Our results suggest that in conjunction with these specialized investigations an inability to wean from assisted ventilation may define that group of infants with PDA complicating RDS who are most likely to benefit from early PDA ligation.

The recent observation that the ductus arteriosus may constrict or close after administration of

prostaglandin inhibitors such as indomethacin (Friedman *et al.*, 1976; Heyman *et al.*, 1976), suggests that medical rather than surgical closure of the PDA may in future become the treatment of choice in these infants.

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