Archives of Disease in Childhood 1995; **72:** F156–F161

Longitudinal changes in the diameter of the ductus arteriosus in ventilated preterm infants: correlation with respiratory outcomes

Nick Evans, Parvathi Iyer

Abstract

This study aimed to examine the early natural history of ductal shunting in ventilated preterm infants (<1500 g) and to document the association between this shunting and respiratory outcomes. The size of the ductal shunt was assessed in 48 infants using serial echocardiographic measurement of colour Doppler internal ductal diameter and pulsed Doppler postductal aortic diastolic flow (PADF). At all postnatal ages, normal antegrade PADF was invariably seen when the ductal diameter was 1·5 mm or less, and was usually abnormal (absent or retrograde) when more than 1·5 mm. Longitudinal progress of ductal diameter fell into three groups: (i) asymptomatic spontaneous closure (n=31) – in 20 of these infants closure occurred within 48 hours; (ii) symptomatic PDA which enlarged after a postnatal constriction (n=9); and (iii) symptomatic PDA that showed minimal postnatal constriction (n=8). Infants in group 2 were significantly less mature and had PDAs which became symptomatic significantly later than those in group 3. Logistic regression showed that ductal shunting had a significant correlation with mean oxygenation index over the first five days but not with ventilator or oxygen days. Gestation had the most significant association with the latter two variables, with atrial shunting also being related to days in oxygen.

The preterm duct displays a wide spectrum of postnatal constrictive activity. Symptomatic PDAs usually showed slower early postnatal constriction. Ductal shunting independently related to short term but not long term respiratory outcomes.

(*Arch Dis Child* 1995; **72:** F156–F161)

Keywords: ductus arteriosus, ultrasonography, preterm infants, ventilation.

Department of Perinatal Medicine, King George V Hospital for Mothers and Babies, Part of Royal Prince Alfred Hospital, Camperdown, Sydney, NSW 2050, Australia
N Evans
P Iyer

Correspondence to:
Dr Nick Evans.

Accepted 2 February 1995

Studies of the natural history of the ductus arteriosus (PDA) in preterm infants have tended to look at whether the ductus was echocardiographically open or closed on a particular postnatal day,[1–3] not at the size of the ductal shunt. This reflects the lack of a validated non-invasive method to assess ductal shunt size. Traditionally the size of preterm ductal shunts in the early postnatal period was felt to be small. Increasing evidence shows that this is not the case and that this early shunting often has measurable haemodynamic implications.[4 5] An understanding of the natural history of ductal shunting in terms of shunt size is important for two reasons. Firstly, it may provide opportunities for early prediction of a symptomatic PDA, and, secondly, it will allow us to relate outcomes to the true haemodynamic relevance of a PDA. Symptomatic shunting through a PDA has been associated with worse respiratory outcomes.[1 6 7] This observation could have been confounded by several factors, most importantly gestation and respiratory disease. The ductus is also not the only site for left to right shunting within the preterm heart. Recently we showed that shunting at atrial level could be as important as that through a PDA,[8 9] and that this atrial shunting also seemed to be associated with a higher incidence of chronic lung disease.[8]

Using relative ventricular outputs to measure pulmonary to systemic flow ratios in patent ductus with minimal associated atrial shunting, we have shown that the closest correlation with shunt size was provided: firstly by the ductal colour Doppler shunt diameter; and secondly by the presence of absent or retrograde postductal aortic diastolic flow (PADF).[9] In this study we used these two echocardiographic parameters to describe, for the first time, individual longitudinal changes in estimated ductal diameter and so, by inference, changes in ductal shunting. And secondly, we used logistic regression to examine in a multivariant manner the correlation between ductal shunting and respiratory outcomes.

Methods

Fifty one preterm infants were examined with 465 serial colour Doppler echocardiograms from the first postnatal day. The infants were selected by two criteria: a birthweight of less than 1500 g; and respiratory problems which required mechanical ventilation for more than 24 hours. Forty three of these infants had hyaline membrane disease, eight were ventilated for prematurity and pulmonary immaturity. The study was conducted over 12 months from March 1992 at King George V Hospital, Sydney. The only eligible infants born during this time who were not included were born when the investigator with the echocardiographic skills (NE) was on leave. The infants had a mean gestation of 27·3 weeks (range 24–33 weeks) and had a mean birthweight of 993·5 g (range 512–1490 g).

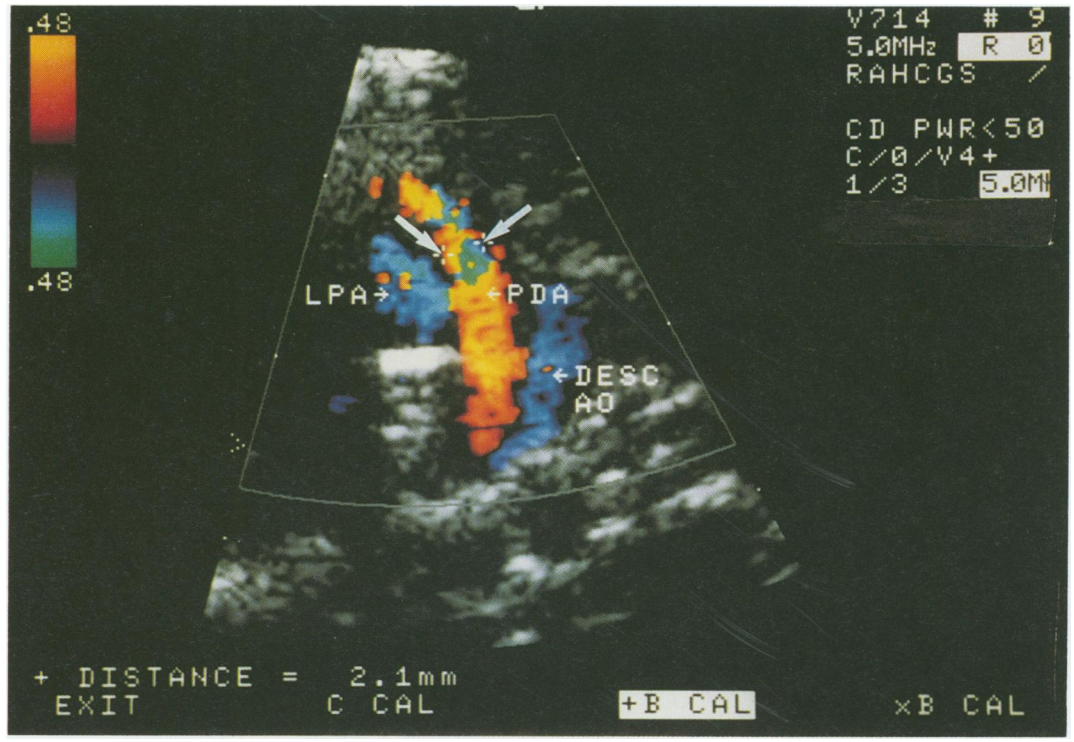

Figure 1 Measurement of colour flow Doppler of ductal shunt (orange). The calipers (marked by arrows) are positioned at the site of maximum constriction. In this case the minimum diameter was 2·1 mm near the pulmonary end of the ductus. Flow in the left pulmonary artery (LPA) and descending aorta (Desc Ao) is shown in blue.

ECHOCARDIOGRAPHIC DATA COLLECTION

This was performed with an Acuson 128/XP10 scanner with a 7 MHz transducer, incorporating colour flow, pulsed wave, and continuous wave Doppler. Scans were performed daily for the first seven days of life, twice in the second week, and then periodically as indicated until discharge home or to the referring hospital. The scans were recorded on to videotape and the measurements then taken from the videotape later. Structural normality of the heart was established on the initial scan; one infant with a ventricular septal defect was excluded.

DUCTUS ARTERIOSUS

This was imaged from the high left parasternal view. Colour Doppler was set for automatic preprocessing, lowest velocity variance setting, and filters were set for maximum range for volume and velocity settings with a medium degree of motion discrimination (Acuson 128/XP10 filter setting 3). The colour flow Doppler mapping scale was set to the maximum range of the automatic preprocessing, usually the maximum velocity was between 0·64 to 0·8 m/second. The gain was set to optimise the colour flow image within the course of the duct and eliminate any peripheral colour interference. When patent, the minimum diameter (the site of maximum constriction) of the colour flow jet within the course of the ductus was measured from a frame by frame analysis of the videotape (fig 1). End systolic frames with the clearest discrete appearance to the shunt within the duct were used for measurement. A mean was taken from three to five of the best quality cardiac cycles.[9] The shunt was assessed with pulsed and or continuous wave Doppler with the sample volume in the pulmonary end of the duct. The shunt pattern was classified as left to right, bidirectional, or right to left. Intra-observer variability for measurement of ductal diameter was tested by repeating the measurements from the videotape of 27 studies, blinded as to the original measurement. The coefficient of variation was 12%.

Postductal aortic diastolic flow (PADF)

The descending aorta was imaged from the high left parasternal or suprasternal position. The insertion of the ductus arteriosus into the aorta was determined by colour flow Doppler mapping. The pulsed Doppler range gate was placed postductally in the aorta and the flow velocity time signal recorded. The PADF was classified into three groups: antegrade throughout diastole; no clear direction to diastolic flow; and retrograde throughout diastole (fig 2).[9]

Atrial shunting

Colour Doppler diameter of the atrial shunt was measured as described in previously published data.[8] Minimal atrial shunting was defined from these data as no shunt on colour Doppler or one with a diameter of less than 2 mm. Atrial shunt diameter has a significant correlation with atrial shunt size,[8] so atrial diameter was used to describe longitudinal patterns of atrial shunting into three groups: (1) no atrial shunt or a small shunt (<3 mm) which resolved in the early postnatal period (n=22); (2) a small atrial shunt (<3 mm) which remained for the period of follow up (n=11); and (3) a large atrial shunt (>3 mm) (n=15). In nine this resolved at an average of

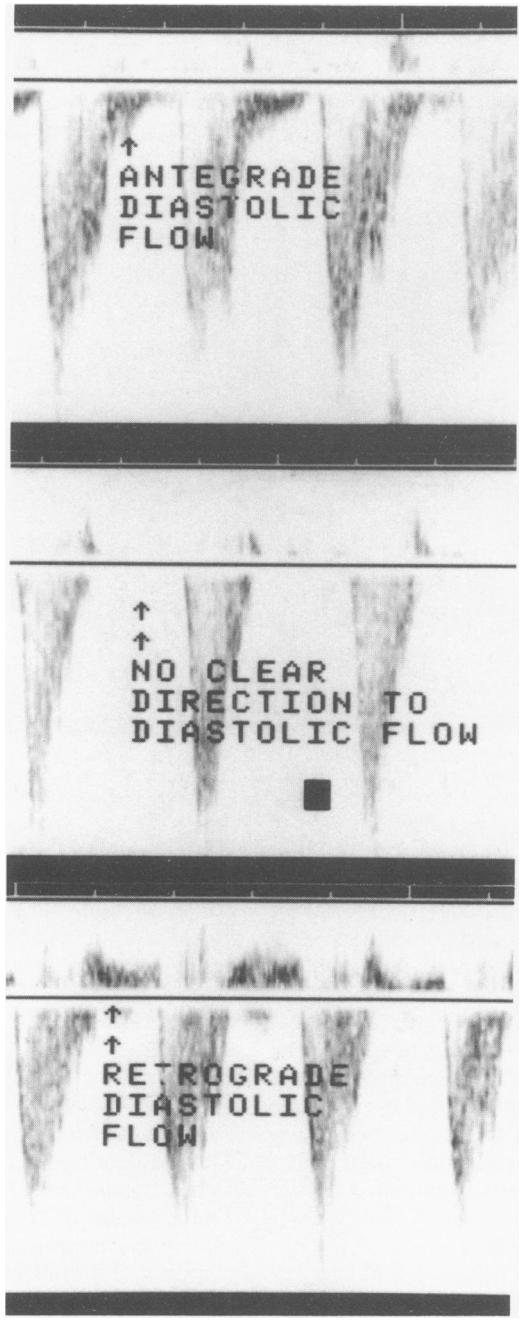

Figure 2 Post-ductal aortic Doppler. From a high right parasternal window the insertion of the ductus into the aorta is identified and the flow pattern beyond the insertion is recorded. The figure contrasts the normal antegrade diastolic flow seen with a closed or small PDA (top) with the absent diastolic flow seen with a moderate PDA (middle) and the retrograde diastolic flow seen with a large PDA. The ductus was patent in all examples shown here. The diameters were (from top to bottom) 1·1 mm, 1·7 mm, and 2·5 mm (reprinted with kind permission of Mosby Year Book Inc[9]).

30 days and in six the shunt remained for the period of follow up. This analysis has been described in detail before.[8]

Echocardiographic findings were not made available to the clinical staff unless there were clinical concerns about the presence of a PDA. Treatment was directed at their discretion on the basis of a clinically apparent PDA with characteristic physical signs and or symptoms which invariably related to respiratory instability, difficulty weaning from the ventilator or, in one case, hypotension. This was in line with established protocol on this unit. Indomethacin was given on a schedule of 0·1 mg/kg daily for six days unless contraindicated. Surgical ligation was used where a PDA remained symptomatic and haemodynamically important, despite a course of indomethacin. Infants with contraindications to indomethacin received conservative medical treatment which involved fluid intake reduction by 30 ml/kg/day.

Surfactant treatment comprised two doses of Exosurf, 12 hours apart, administered as rescue treatment when the alveolar to arterial oxygen ratio was less than 0·22.

For each of the first five postnatal days, a mean oxygenation index was calculated from averaged percentage inspired oxygen, mean airway pressure, and arterial partial pressure of oxygen. Using the formula (mean airway pressure×percentage inspired oxygen)/arterial partial pressure of oxygen, two measures were calculated: the mean oxygenation index for the first 24 postnatal hours as an index of initial disease severity; and the mean oxygenation index for all the first five postnatal days as an index of both initial severity and recovery. Total days requiring positive pressure ventilation and supplemental oxygen were recorded as long term respiratory outcomes.

The study was approved by the Royal Prince Alfred Hospital ethics committee and informed written parental consent was obtained in all cases studied.

Statistical analysis was done with a computer statistics package (SPSS/PC) using stepwise logistic regression analysis, the Mann Whitney U test, and χ^2 test. P values of less than 0·05 were regarded as significant.

Results

Ductal shunt flow patterns have been described before[9] and were mainly left to right (90%). Nine per cent showed bidirectional flow, but in these an average of 82% of the cardiac cycle was left to right. Just two (1%) studies showed right to left ductal shunting. After the first 48 hours all shunting was left to right.

In the 163 studies where the ductus was closed and the PADF was assessed, it was antegrade throughout diastole in all except one study where there was no clear direction to flow. When the PDA was less than 1·5 mm in diameter (n=61), PADF was antegrade in 58 (95%), with three showing no clear direction to flow. When the PDA was 1·5 to 1·7 mm (n=23), PADF was antegrade in 11, indeterminate direction in eight, and retrograde in four. And when the PDA was more than 1·7 mm (n=58), PADF was antegrade in one, indeterminate direction in seven, and retrograde in 50 (86%). Retrograde flow was always seen when the PDA diameter was greater than 2·1 mm (n=36).

The same association holds in studies done in the first 36 hours. All studies with a PDA of 1·5 mm or less had antegrade PADF (n=19), and all studies with a PDA of more than 1·5 mm had indeterminate or retrograde PADF (n=24). All PDAs of more than 2 mm

Clinical comparisons between ductal shunting groups (figures are presented as medians and range or percentage)*

	Asymptomatic spontaneous closure (n=31)	*Symptomatic PDA, constricted after birth (n=9)*	*Symptomatic PDA, minimal constriction (n=8)*
Gestation (weeks)	28 (24–33)*	26 (25–27)*†	27·5 (26–29)†
Birthweight (g)	1030 (512–1490)	906 (700–1030)	1047 (650–1340)
Antenatal steroids	90%	77%	75%
Surfactant	61%	66%	75%
Oxygenation index			
Day 1 mean	4·73 (1·1–10·7)	4·6 (2·9–19·1)	7·0 (3·1–12·1)
Mean of first 5 days	3·5 (1·0–7·9)*†	5·3 (2–21·9)*	5·6 (2·7–8·7)†
Ventilator days	7 (2–43)*	24 (9–58)*†	5 (5–29)†
Days in oxygen	29 (1–140)	44 (9–172)†	17 (6–39)†

*Indicate different pairings in same group of 3; †$p<0·05$.

(n=11) had retrograde PADF. Retrograde PADF was seen as early as 7 hours of age.

Three infants were excluded from analysis of longitudinal changes in ductal shunt, two because of late initial echocardiogram, and one due to early death. The patterns of ductal closure and patency in the other 48 infants fell into three groups.

GROUP 1: ASYMPTOMATIC SPONTANEOUS CLOSURE n=31 (65%)

In 20 infants the ductus closed within the first 48 hours. Fourteen had a closed ductus at the time of the first scan (mean 25 hours); of these, 12 remained closed and two temporarily reopened at the end of week 2, but both remained clinically important and asymptomatic. Eleven closed after 48 hours, four between days 2 and 3, three between days 3 and 4, one between days 4 and 5 and one between days 5 and 7. Two others were not seen to close due to back transfer to referring unit, but neither developed clinical signs or symptoms of a PDA. Their last scans were, respectively, on days 4 and 30.

Fourteen infants had a closed ductus at the time of the first scan. In the 17 infants with a PDA on the first scan the median colour Doppler diameter was 1·3 mm (range 0·8–2·5 mm) at an average postnatal age of 15 hours (8–24 hours). Five of these had a diameter greater than or equal to 1·5 mm. Three of these retained a clinically silent but significant PDA greater than 1·8 mm in diameter with absent or retrograde PADF for at least 33 hours before spontaneously restricting or closing on day 3. Ductal diameters remained less than 1·5 mm in the other 12 until spontaneous closure.

GROUP 2: SYMPTOMATIC PDA, DUCTUS ENLARGED AFTER CONSTRICTING n=9 (19%)

The PDA diameters were moderate in size at the time of the first scan, median 1·8 mm (0–2·5 mm) at a mean of 13·5 hours. Only two were less than 1·5 mm. There followed a period of variable duration, during which the duct was constricted to diameters of less than 1·51 mm. This was associated with normal antegrade PADF, and in two cases the ductus closed. The ductus then enlarged and became clinically apparent. Median diameter at clinical diagnosis was 2·5 mm (1·5–3·0 mm).

The median time of the scan performed to confirm the clinical diagnosis was 175 hours (98–354 hours). Eight of these infants were successfully treated with indomethacin with closure occurring during the treatment course; one then reopened and was treated surgically. The other infant was successfully treated conservatively due to contraindications to indomethacin.

GROUP 3: SYMPTOMATIC PDA, MINIMAL POSTNATAL CONSTRICTION n=8 (16%)

PDA diameters were large at the time of the first scan, median 2·65 mm (1·8–3·2 mm) at a mean time of 22·5 hours. The ducts in this group remained large, or increased in size, with continuing abnormal retrograde PADF until clinical diagnosis. The median diameter at clinical diagnosis was 3·25 mm (2·2–3·8 mm).

Median time of scan to confirm clinical diagnosis was 59 hours (22–144 hours) which was significantly earlier than group 2 ($p=0·004$). All but one infant were successfully treated with indomethacin: this infant had contraindications to indomethacin and was successfully treated conservatively.

The clinical associations of ductal shunting groups are shown in the table. Group 2 infants were of significantly lower gestation than the other groups ($p<0·003$). Averaged oxygenation index over the first five days was significantly higher in groups 2 and 3 than group 1 ($p<0·03$). Group 2 were ventilated significantly longer than the other two groups ($p<0·007$) and spent significantly longer in oxygen than group 3 ($p<0·01$). All other differences were insignificant.

MULTIVARIANT ANALYSIS OF CORRELATIONS WITH RESPIRATORY OUTCOMES

In these stepwise logistic regression analyses, ductal and atrial shunting were analysed as categorical variables. The ductal shunting groups above 1 to 3 were respectively allocated to categories 0 to 2, and the three atrial shunting groups described in the methods section were respectively allocated to categories 0 to 2. In both categories, those with minimal atrial or ductal shunting (category 0) were compared with the other groups.

Day 1 oxygenation index

Gestation, birthweight, antenatal steroids, five minute Apgar score, maternal hypertensive disease, atrial shunting group and ductal shunting group were analysed against day 1 mean oxygenation index as a dichotomous dependent variable of more or less than 7·5 (75th centile). None of the factors reached significance, only the presence of maternal hypertensive disease came close ($p=0·08$).

Oxygenation index averaged for first five days

The same factors were analysed against oxygenation index averaged over the first five days as a dichotomous dependent variable of more or less than 5 (75th centile). The only factor incorporated as significant was ductal shunting group, with groups 2 and 3 having a significant

influence on this outcome (p values, respectively, 0·007 and 0·016).

Days ventilated

Gestation, birthweight, day 1 and five day oxygenation index, antenatal steroids, five minute Apgar score, maternal hypertensive disease, atrial and ductal shunting groups were analysed against days ventilated as a dichotomous dependent variable of more or less than 14 days. Gestation was the only significant factor (p=0·004).

Days in oxygen

The same factors were analysed against days in oxygen as a dichotomous dependent variable of more or less than 28 days. The two factors incorporated as significant were gestation (p=0·003) and atrial shunt group (p=0·043).

Discussion

The normal postnatal course for the ductus arteriosus is constriction and functional closure. In babies born at term and in preterm babies without respiratory problems this process is usually completed within the first 48 postnatal hours.[10 11] This is not the case in very preterm infants with respiratory problems, where about 35% of babies will have symptoms resulting from persisting PDA. Previous studies of the natural history of the preterm PDA have looked either at whether the duct was open or closed – without taking into account the size of the ductal shunt[1 2] – or have serially plotted indirect measures which have only a loose association with ductal shunt size.[12 13] The closest association with ductal shunt size is provided by the diameter of the duct, as assessed by colour Doppler and the presence of retrograde PADF.[9] These data have confirmed that, regardless of postnatal age, there is also a close correlation between these two assessments. When the PDA is less than 1·5 mm, the PADF was almost always normal antegrade; when more than this, the PADF was usually absent or retrograde. This was also true in studies performed within the first 36 hours with retrograde PADF seen as early as 7 hours of age, confirming that early shunting through large PDAs is usually haemodynamically important. Plotting the longitudinal change in colour flow Doppler ductal diameter therefore provides useful information about changes in the haemodynamics of a duct. Measurement of defect size with colour Doppler mapping is reasonably accurate[14] but there are limitations. For example, other machines with different colour Doppler settings could give different results. To minimise error, we used a standardised colour Doppler setup and took averaged measurements from only the clearest videotape frames.

Although functional immaturity of the duct is important in the pathophysiology of PDA, it may not be the only factor. First, PDA is rare in preterm babies without respiratory problems[10 11] and secondly, 65% of very preterm babies with respiratory problems do not develop PDA. In 20 (42%) of the babies in this study the duct was closed within 48 hours of birth, much the same time frame as might be seen in a term baby.[11] This group of babies were of comparable gestation to the other groups, though they tended to have less severe acute lung disease. The others display a wide spectrum of failure of constriction of the ductus arteriosus. In a further 11 (23%) infants the duct closed spontaneously after 48 hours without causing symptoms. In seven (15%) spontaneous closure occurred after day 3. This is in contrast to previous studies which have suggested that if the duct was patent on day 3 or 4 then it was unlikely to close spontaneously.[1 2]

The other 17 infants developed symptomatic PDA. The factors determining PDA in the preterm are likely to represent an interplay between immaturity of the ductal constrictive mechanisms and exogenous factors relating to the respiratory disease, and possibly circulating prostaglandins.[15] In eight babies in group 3 the absence of any evidence of constriction would suggest that factors such as high circulating prostaglandins were maintaining ductal patency. In nine babies in group 2 ductal closure failed after initially constricting. These babies were of significantly lower gestation, and functional immaturity may have had a more important role here. In most of the babies with asymptomatic spontaneous closure the duct was always small, but five of these babies had large ducts (>1·5 mm) during the first 48 hours. These five babies had a higher average gestation that the group as a whole – 29 weeks (range 28–30) – and a more mature duct may have been able to overcome the initial dilating stimulus from the respiratory distress. Some babies do have large PDAs early on which then close spontaneously, and some have small PDAs early on which then reopen, but in most infants where the duct became symptomatic, the duct was more than 1·5 mm on the first scan. Thus the rate of early postnatal constriction of the duct seems to relate to the likelihood of persisting PDA. This observation may provide a means for early prediction of symptomatic PDA, thus allowing targeted prophylaxis. We are currently testing this hypothesis prospectively.

What are the clinical effects of ductal patency on respiratory outcomes? An increase in pulmonary blood flow from a ductal shunt has been shown to reduce lung compliance,[16] increase capillary protein leakage,[17 18] and possibly inhibit responsiveness to endogenous and exogenous surfactant.[19] The suggested clinical impact of this has been prolongation of the requirement for ventilation and subsequent oxygen therapy.[1 6 7] In this study none of the factors examined seemed to influence the mean day 1 oxygenation index, suggesting that a PDA was neither the cause, nor simply the result of, the initial severity of the respiratory disease. Ductal shunting was, however, significantly related to the mean oxygenation index over the first five days. This would fit in with

the clinical observation that a PDA often presents with respiratory instability and failure to wean from ventilation during recovery. We were unable, using multivariant analysis, to demonstrate an independent association of ductal shunting to ventilator time or days in oxygen. Gestation has the most significant correlation with both these outcomes and probably accounts for the univariant differences in these outcomes for group 2 (table). When oxygen requirement beyond 28 days was the dependent variable, the only other factor incorporated into the equation as significant was atrial shunting group. While gestation is clearly the most important factor, these data support our previous observation that the prolonged nature of atrial shunting may have more influence on long term respiratory outcomes than ductal shunting.[8]

Why is this so, when other studies have linked PDA to time on the ventilator and days in oxygen? These studies all analysed this association in a univariant manner and did not control for confounding variables which will influence the incidence of PDA – most importantly, gestation and respiratory disease.[1 6 7 20] In the study by Reller *et al*[20] most of the babies without PDA did not need ventilation for their initial respiratory distress: this is likely to have been an important factor in their reduced time on ventilators and in oxygen. By controlling for these factors in a multivariant manner and excluding infants without significant respiratory problems, our study has shown that gestation, independent of ductal status, is the dominant influence on these respiratory outcomes. Progress in perinatal and neonatal care may have blunted the effect of a PDA on respiratory outcomes. Eighty five per cent of our infants were treated with antenatal steroids and exogenous surfactant was routinely used as rescue treatment. The former intervention probably reduces the incidence of PDA,[21] the latter reduces the incidence of chronic lung disease.[22] The other important difference between this and previous studies is the timing of treatment. In the studies by Dudell and Gersony[1] and Reller *et al*,[20] where gestation was controlled for in a univariant manner, most PDAs were not treated until the second week or later. Most babies in our study were treated well within the first week. Duration is probably as important as degree of left to right shunt in determining long term respiratory effects. This observation may explain why randomised trials of early prophylactic indomethacin have not shown any beneficial effects on long term respiratory outcomes. In these trials infants in the placebo control arms had symptomatic PDAs treated with indomethacin well within the first week,[23] often within the first three days.[24 25]

In conclusion, the preterm duct displays a wide spectrum of postnatal constrictive activity, and to classify the ductus arteriosus as simply open or closed is to ignore the breadth of this spectrum. The range of haemodynamic effects needs to be taken into account when examining outcomes in relation to the ductus arteriosus. Ducts which eventually become symptomatic usually display slower early postnatal constriction, which may permit early prediction of a symptomatic PDA. Ductal shunting in this study group was significantly related to short term respiratory outcomes only.

1 Dudell GG, Gersony WM. Patent ductus arteriosus in severe respiratory disease. *J Pediatr* 1984; **104:** 915–20.
2 Reller MD, Colasurdo MA, Rice MJ, McDonald RW. The timing of spontaneous closure of the ductus arteriosus in infants with respiratory distress syndrome. *Am J Cardiol* 1990; **66:** 75–8.
3 Evans N, Archer LNJ. Doppler assessment of pulmonary artery pressure and extrapulmonary shunting in the acute phase of hyaline membrane disease. *Arch Dis Child* 1991; **66:** 6–11.
4 Knight DB. Patent ductus arteriosus: how important to which babies? *Early Hum Dev* 1992; **29:** 287–92.
5 Evans N, Moorcraft J. Effect of patency of the ductus arteriosus on blood pressure in very preterm infants. *Arch Dis Child* 1992; **67:** 1169–73.
6 Jacob J, Gluck L, Disessa T, Edwards D, Kulovich M, Kurlinski J, *et al*. The contribution of PDA in the neonate with severe RDS. *J Pediatr* 1980; **96:** 79–87.
7 Brown ER. Increase risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. *J Pediatr* 1979; **95:** 865–6.
8 Evans N, Iyer P. Incompetence of the foramen ovale in preterm infants supported by mechanical ventilation. *J Pediatr* 1994; **125:** 786–92.
9 Evans N, Iyer P. Assessment of ductus arteriosus shunt in preterm infants supported by mechanical ventilation: Effect of interatrial shunt. *J Pediatr* 1994; **125:** 778–85.
10 Reller MD, Zeigler ML, Rice MJ, Solin RC, McDonald RW. Duration of ductal shunting in healthy preterm infants; an echocardiographic color flow Doppler study. *J Pediatr* 1988; **112:** 441–6.
11 Evans N, Archer LNJ. Postnatal circulatory adaptation in healthy term and preterm neonates. *Arch Dis Child* 1990; **65:** 24–6.
12 Walther FJ, Kim DH, Ebrahimi M, Siassi B. Pulsed Doppler measurement of left ventricular output as an early predictor of symptomatic patent ductus arteriosus in very preterm infants. *Biol Neonate* 1989; **56:** 121–8.
13 Mellander M, Larsson LE, Ekström-Jodal B, Sabel KG. Prediction of symptomatic patent ductus arteriosus in preterm infants using Doppler and M-mode echocardiography. *Acta Paediatrica Scandinavica* 1987; **76:** 553–9.
14 Hornberger LK, Sahn DJ, Krabill KA, Sherman FS, Swensson RE, Pesonen E, *et al*. Elucidation of the natural history of ventricular septal defects by serial Doppler color flow mapping studies. *J Am Coll Cardiol* 1989; **13:** 1111–8.
15 Hammerman C, Strates E, Valaitis S. The silent ductus: its precursers and aftermath. *Pediatr Cardiol* 1986; **7:** 121–7.
16 Gerhardt T, Bancalari E. Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation. *Biol Neonate* 1980; **38:** 96–105.
17 Jobe AH, Ikegami M, Jacobs HC, Berry D. Increased lung protein permeability of prematurely delivered and ventilated lambs. *Pediatr Res* 1984; **18:** 394A.
18 Jefferies AL, Coates G, O'Brodorich. Pulmonary epithelial permeability in hyaline membrane disease. *N Engl J Med* 1984; **311:** 1075–80.
19 Ikegami M, Jacobs H, Jobe A. Surfactant function in respiratory distress syndrome. *J Pediatr* 1983; **102:** 443–7.
20 Reller MD, Lorenz JM, Kotagal UR, Meyer RA, Kaplan S. Hemodynamically significant PDA: an echocardiographic and clinical assessment of incidence, natural history and outcome in very low birth weight infants maintained in negative fluid balance. *Pediatr Cardiol* 1985; **6:** 17–24.
21 Clyman RI, Ballard PL, Sniderman S, Ballard RA, Roth R, Heymann MA, *et al*. Prenatal administration of betamethasone for prevention of patent ductus arteriosus. *J Pediatr* 1981; **98:** 123–6.
22 Soll RF, McQueen MC. Respiratory distress syndrome. In: Sinclair JC, Bracken MB, eds. *Effective care of the newborn.* Oxford: Oxford University Press, 1992: 325–52.
23 Bandstra ES, Montalvo BM, Goldberg RN, Pachecho I, Ferrer PL, Flynn J, *et al*. Prophylactic indomethacin for prevention of intraventricular haemorrhage in premature infants. *Pediatrics* 1988; **82:** 533–42.
24 Krueger E, Mellander M, Bratton D, Cotton R. Prevention of symptomatic patent ductus arteriosus with a single dose of indomethacin. *J Pediatr* 1987; **111:** 749–54.
25 Ment LR, Oh W, Ehrenkranz RA, Phillips AGS, Vohr B, Allen V, *et al*. Low dose indomethacin and prevention of intraventricular haemorrhage: A multicenter randomized control trial. *Pediatrics* 1994; **93:** 543–50.