Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage

Martin Kluckow, MBBS, FRACP, and Nick Evans, DM, MRCP

Objective: To describe the relationship among ductal shunting, estimated pulmonary blood flow, and pulmonary hemorrhage in very preterm infants.

Study design: A total of 126 babies born before 30 weeks' gestation (median gestation 27 weeks, range 23 to 29 weeks) underwent echocardiography at 5, 12, 24, and 48 hours of age; measurements included right and left ventricular output, superior vena cava flow, and color Doppler diameter of any ductal shunt. Pulmonary blood flow was derived from the sum of right ventricular output and estimated ductal shunt flow.

Results: Twelve (9.5%) babies had a pulmonary hemorrhage at a mean age of 38 hours. Compared with the rest of the cohort, these 12 babies were less likely to have had antenatal steroids (59% vs 90%) and were less mature (26 weeks vs 27 weeks). At the echocardiogram closest to the pulmonary hemorrhage, 11 (92%) of the 12 babies had a significant patent ductus arteriosus >1.6 mm in diameter (median 2 mm, range 0.7 to 2.4 mm), and the median pulmonary blood flow was 326 mL/kg/min (range 210 to 598 mL/kg/min). These measurements were significantly higher than those found in the rest of the cohort in the same period (median duct diameter 0.5 mm [range 0 to 2.9 mm], median pulmonary blood flow 237 mL/kg/min [range 107 to 569 mL/kg/min]). At 5-hour echocardiography the babies with pulmonary hemorrhage had significantly larger diameter ducts but similar pulmonary blood flow.

Conclusions: Pulmonary hemorrhage in preterm babies is associated with significant ductal shunting and high estimated pulmonary blood flow. (J Pediatr 2000;137:68-72)

Pulmonary hemorrhage remains an uncommon but serious complication for the preterm infant. Since the work of Cole et al,[1] it has been recognized that what appears as blood is actually hemorrhagic pulmonary edema. In other clinical situations pulmonary hemorrhage probably results from high intracapillary pressure causing stress failure of the thin-walled pulmonary capillaries.[2] We have shown that hemodynamics in the early preterm infant are characterized by left to right shunts at the ductal and atrial levels, both of which serve to place a high volume load on the pulmonary capillary bed.[3,4] Although other studies have suggested an association between ductal shunting and pulmonary hemorrhage,[5] the hemodynamics close to the time of pulmonary hemorrhage have not been described.

Our hypothesis was that pulmonary hemorrhage is associated with high pulmonary blood flow resulting from significant left to right ductal shunting. The hemodynamics close to the time of pulmonary hemorrhage were observed in a cohort of babies as part of a prospective echocardiographic study of infants born before 30 weeks, which also aimed to explore the hemodynamics of intraventricular hemorrhage.[6] This article presents an analysis of the hemodynamic findings in these babies.

METHODS

Study Population

The entry criteria were preterm birth before 30 weeks' gestation and informed parental consent. The 126 babies enrolled during a 20-month period represented 85% of eligible babies. Parental consent was refused in 5 babies, and 19 eligible babies were not studied, because neither investigator was available when they were born. The 126 babies had a mean gestation of 27 weeks (range 23 to 29 weeks) and a mean birth weight of 991 g (range 420 to 1630 g); 52% were male, 87% had received some antenatal steroids, and 91% were born in Royal Prince Alfred Hospital; the rest were transferred after delivery. Seventy-six percent underwent ventilation for >1 day, and 79% of these babies were treated with early rescue surfactant (Survanta). High-frequency oscillatory ventilation was not used. The respiratory diagnosis was hyaline membrane disease in

From the Departments of Neonatal Medicine, Royal Prince Alfred Hospital, Royal North Shore Hospital, and the University of Sydney, Sydney, Australia.

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60%, pulmonary immaturity in 15%, pneumonia in 3%, and pulmonary hypoplasia in 0.8% (1 baby); 20% had normal lungs; 18% (n = 23) of the babies died in the neonatal period. The Royal Prince Alfred Hospital Ethics Committee approved the study, and babies were studied with informed written consent of their parents.

Ultrasound Studies

All infants had serial echocardiograms as close as possible to 5 hours, 12 hours, 24 hours, and 48 hours after birth. The first ultrasound study was performed after stabilization was complete and the first dose of surfactant had been given.

Echocardiographic data collection was performed with an Acuson 128/XP10 ultrasound scanner (Acuson Corp, Mountain View, Calif) with a 5-MHz or a 7-MHz transducer incorporating color flow, pulsed wave, and continuous-wave Doppler. The scan was recorded on videotape and later measured from the videotape. Structural normality of the heart was established on the initial scan. Some babies, including some of those who had pulmonary hemorrhage, had extra echocardiograms if clinically indicated. At each study the following measurements were taken with protocols that have been described in detail.[3-7]

1. Doppler volumetric measurement of right and left ventricular output
2. Color Doppler diameter of ductus arteriosus shunt (a semi-quantitative measure of shunt size[4]) and pulsed- or continuous-wave Doppler assessment of shunt direction and velocity
3. Color Doppler diameter of interatrial shunt (a semi-quantitative measure of shunt size[3]) and pulsed- or continuous-wave Doppler assessment of shunt direction and velocity
4. Superior vena cava flow[7]

Attending clinicians were blinded to the echocardiographic findings unless there was a defined concern such as clinical suspicion of a patent ductus arteriosus or hypotension unresponsive to treatment. Indomethacin was used to treat a clinically apparent patent ductus arteriosus confirmed to be hemodynamically significant on echocardiography. Thirty-five (27%) of the babies in the cohort received indomethacin, with the first dose given at a median time of 48 hours (range 12 to 365 hours). None of the babies who had pulmonary hemorrhage had received indomethacin before the pulmonary hemorrhage occurred. A standard first 24-hour fluid intake of 60 mL/kg/d was used in babies born after 26 weeks' gestation and 80 mL/kg/d in those born at <27 weeks' gestation. Human albumin solution (5%) to a maximum volume of 10 mL/kg was used to support low blood pressure.

Estimated pulmonary blood flow was taken as the measured right ventricular output when the duct was closed or tightly constricted (≤1 mm). When the duct was >1 mm, pulmonary blood flow was estimated as the sum of measured right ventricular output and the estimated volume of the shunt through the ductus arteriosus. The volume of the ductal shunt was derived as: Left ventricular output – Systemic blood flow. This is based on the fact that when the duct is patent, left ventricular output represents the sum of systemic blood flow and the ductal shunt. Because both ventricular outputs can be significantly confounded by shunts within the adapting heart,[3,4] we used superior vena cava flow as a measure of part of the systemic blood flow that is uncorrupted by these shunts.[7] Superior vena cava flow accounts for a mean of 37% (95% CI 35% to 39%) of total systemic blood flow[7,8]; therefore, superior vena cava flow was multiplied by 2.7 to derive an estimate of total systemic blood flow. This estimation of ductal shunt was necessary in 78% of babies at the 5-hour scan and in 40% of the babies at the averaged 24-hour and 48-hour scans.

Pulmonary hemorrhage was defined as blood or blood-stained fluid aspirated from the endotracheal tube in association with a respiratory deterioration and radiologic or autopsy evidence of pulmonary hemorrhage.

Cerebral ultrasonography was performed with a 7-MHz transducer, and any intraventricular hemorrhage was noted and classified according to the Papile grading. Further routine head ultrasonography was performed between days 4 and 7 and on day 28.

Statistics

Data were analyzed with a personal computer–based statistics package (SPSS for Windows; SPSS Inc, Chicago, Ill) with χ^2 test, multivariant analysis of variance, and Mann-Whitney *U* test. *P* values <.05 were accepted as significant.

RESULTS

Twelve (9.5%) of the 126 babies had a pulmonary hemorrhage at a mean age of 38 hours (range 14 to 55 hours). In 9 of these babies, the appearance of the aspirated fluid was of frank blood; in 3, it was of blood-stained fluid. The median increase in oxygenation index caused by the pulmonary hemorrhage was 8.9 (range 1 to 33), and the mean maximum P_{CO_2} during the acute respiratory deterioration was 60 mm Hg (range 35 to 86 mm Hg).

Demographic and clinical characteristics of these 12 babies were compared with those of the 114 babies in the rest of the cohort. The 12 babies with pulmonary hemorrhage were of lower mean gestation (25.9 ± 1.9 weeks [1 SD] vs 27.1 ± 1.6 weeks, *P* = .03); fewer had received antenatal steroids (59% vs 90%, *P* = .0008), more received human albumin solution (83% vs 44%, *P* = .02), more received indomethacin for a patent ductus arteriosus (92% vs 23%, *P* = .0001), more had grade 3 or 4 intraventricular hemorrhage (42% vs 6%, *P* = .0002), and more died (50% vs 15%, *P* = .008). Although more of the babies with pul-

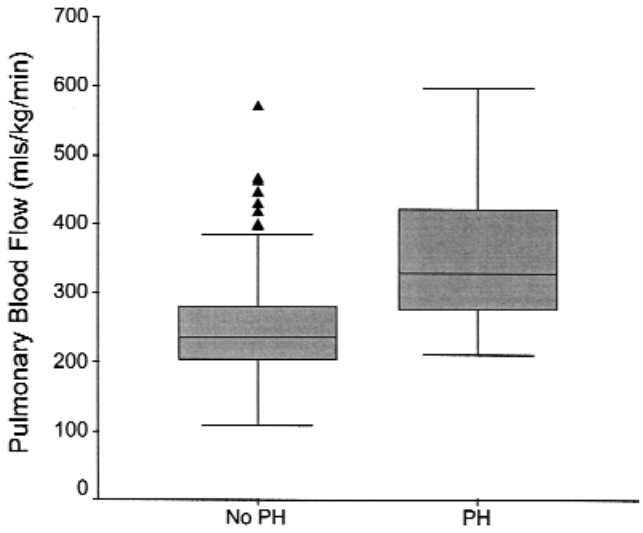

Fig 1. Boxplot comparing estimated pulmonary blood flow closest to pulmonary hemorrhage *(PH)* with averaged 24- and 48-hour pulmonary blood flow in rest of cohort *(No PH)*.

Table I. Comparison, at the scan closest to the pulmonary hemorrhage, of intracardiac shunts and estimated pulmonary blood flow between babies who did and did not have pulmonary hemorrhage

	Pulmonary hemorrhage (n = 12)	No pulmonary hemorrhage (n = 109)	*P* value
Ductal diameter (mm)	2.0 (0.7-2.4)	0.5 (0-2.95)	<.0001
Maximum left to right ductal shunt velocity (m/s)	1.2 (0.7-2.7)	1.6 (0.3-3.1)	.06
Atrial shunt diameter (mm) [n = 9]	2.8 (1.75-3.63)	2.13 (0-3.75)	.02
Maximal left to right atrial shunt velocity (m/s)	0.63 (0.3-1.3)	0.45 (0.1-1.2)	.015
Right ventricular output (mL/kg/min)	257 (158-407)	223 (91-465)	.08
Estimated ductal shunt (mL/kg/min)	85 (0-216)	0 (0-216)	.0001
Estimated pulmonary blood flow (mL/kg/min)	328 (210-598)	236 (107-569)	.001

The values for the babies without pulmonary hemorrhage represent an average of the 24- and 48-hour measurements. Values are given as medians with ranges in parentheses.

monary hemorrhage had been treated with surfactant, this did not reach statistical significance (83% vs 59%, P = .08). There were no significant differences in birth weight percentile, sex, type of delivery, maternal hypertensive disease, 5-minute Apgar score, or mean oxygenation index during the first 12 hours.

Echocardiographic Findings Close to the Pulmonary Hemorrhage

Seven of the 12 babies with pulmonary hemorrhage underwent scanning within 3 hours of the pulmonary hemorrhage (4 before the pulmonary hemorrhage, 3 just after). In 4 babies this was as an additional scan to the protocol. In the other 5 babies the scan preceded the pulmonary hemorrhage by 6, 9, 13, 17, and 20 hours, respectively. The mean postnatal age at the time of the scan nearest the pulmonary hemorrhage was 34 hours (range 15 to 48 hours). For comparison with the rest of the cohort, the findings in these scans near to the pulmonary hemorrhage have been compared with the average of the 24- and 48-hour findings in the other 104 babies.

The 12 babies with pulmonary hemorrhage had significantly larger diameter ducts than the rest of the cohort (Table I); 11 of the 12 had ducts that fulfilled criteria of hemodynamic significance; that is, they were >1.5 mm in diameter with predominantly left to right shunts and had absent or retrograde diastolic flow in the postductal descending aorta.[4] In 9 babies with pulmonary hemorrhage for whom study of atrial shunting was complete, both the atrial shunt diameter and the maximum left to right velocity of that shunt were significantly higher than those of the rest of the cohort (Table I). These 12 babies had significantly higher estimated pulmonary blood flow than the rest of the cohort (Fig 1). All 7 babies who underwent scanning closest to the pulmonary hemorrhage had estimated pulmonary blood flow >300 mL/kg/min. Although the mean pulmonary blood flow was significantly lower in the babies without pulmonary hemorrhage, it should be noted that 20% of these babies also had a mean pulmonary blood flow >300 mL/kg/min in the second 24 hours after birth. When these univariant differences were controlled for gestation, antenatal steroids, and albumin use with multivariant analysis of variance, the differences in duct diameter, estimated pulmonary blood flow, and atrial shunt velocity remained significant (P < .002). The difference in atrial shunt diameter ceased to be significant (P = .12).

The one baby who never had a significant patent ductus arteriosus was born to a mother who had received high doses of antihypertensive agents

just before delivery. This baby had been in a high output state from birth and had an estimated pulmonary blood flow of 309 mL/kg/min recorded 2 hours after the pulmonary hemorrhage.

Prediction of Pulmonary Hemorrhage From Early Echocardiographic Findings

At the first postnatal scan at 5 hours of age, the 12 babies who had a pulmonary hemorrhage had significantly larger diameter ducts than the rest of the cohort (Table II). The ductal shunts were of lower maximum left to right velocity, reflecting more babies with a bidirectional pattern. However, the predominant direction of ductal shunting was left to right even in those with bidirectional shunting. The 61 babies with a ductal diameter above the median for the whole group (>1.6 mm) at the 5-hour scan included 11 of the 12 babies who had pulmonary hemorrhage (the same 11 who had a significant duct close to the pulmonary hemorrhage) (Fig 2). These 61 babies with ducts >1.6 mm also included 33 of the 37 babies who had a subsequent symptomatic patent ductus arteriosus. Early ductal diameter >1.6 mm predicted pulmonary hemorrhage with a sensitivity of 92% and a specificity of 55% and predicted symptomatic patent ductus arteriosus with a sensitivity of 89% and a specificity of 67%. At this time there were no significant differences in the diameter or flow patterns of the atrial shunts or in the estimated pulmonary blood flow (Table II).

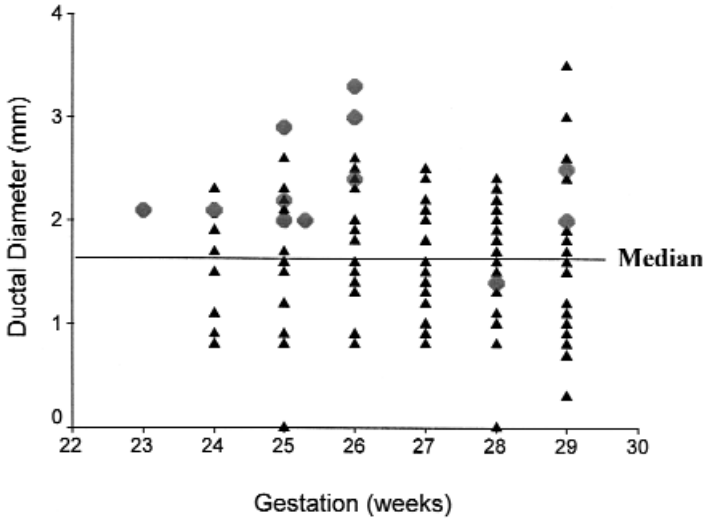

Fig 2. Range of ductal diameter at 5 hours of age plotted against gestation. *Grey circles* indicate 12 babies who had pulmonary hemorrhage. *Line* indicates median for whole cohort.

Table II. Comparison, at 5 hours of age, of intracardiac shunts and estimated pulmonary blood flow between babies who did and did not have pulmonary hemorrhage

	Pulmonary hemorrhage (n = 12)	No pulmonary hemorrhage (n = 112)	*P* value
Ductal diameter (mm)	2.1 (1.4-3.3)	1.6 (0-3.5)	.0002
Maximum left to right ductal shunt velocity (m/s)	0.88 (0.2-1.2)	1.2 (0.2-2.5)	.015
Some right to left ductal shunt	66%	42%	.89
Proportion cardiac cycle with right to left shunt	19% (10%-38%)	21% (5%-100%)	.54
Atrial shunt diameter (mm)	2.25 (0-4.4)	2.5 (0-3.9)	.97
Maximum left to right atrial shunt velocity (m/s)	0.46 (0.25-0.74)	0.33 (0.04-1.16)	.06
Estimated pulmonary blood flow (mL/kg/min)	218 (137-434)	197 (52-503)	.15

Values are given as medians with ranges in parentheses.

DISCUSSION

These data have confirmed an association between pulmonary hemorrhage and significant left to right ductal shunting with resultant high estimated pulmonary blood flow. This study has 2 limitations. First, because pulmonary hemorrhage is an unpredictable acute event, we were unable to perform echocardiograms at a consistent time in relation to the pulmonary hemorrhage. Despite this, these data still represent the closest hemodynamic data in relation to a pulmonary hemorrhage currently available in the literature. Second, the method by which we have estimated systemic blood flow with superior vena cava flow is vulnerable to a degree of error. This indirect method was necessary because the turbulent flow through the ductus does not lend itself to direct volumetric measurement. All ultrasound measurements have a degree of error, and combining measures in this way will cause a cumulative increase in error. This cumulative error should be random with the large numbers of babies we have studied and will apply equally to both babies with and without pulmonary hemorrhage, and we would argue that this is a valid, if approximate, estimate for comparative purposes.[9]

These findings are compatible with the concept that pulmonary hemor-

rhage results from stress failure of the fragile pulmonary capillaries.[2] At an empirical level, the pulmonary capillaries of preterm babies are developed for fetal pulmonary blood flow, which would be approximately 10 to 20 mL/kg/min. In preterm babies with left to right shunts at ductal and atrial level, this can increase pulmonary blood flow to 2 or 3 times systemic blood flow.[3,4] Pulmonary blood flows of >500 mL/kg/min were present in some babies. At the scan closest to the pulmonary hemorrhage, the pulmonary blood flows were significantly higher than for the rest of the cohort, a difference that was most marked in those who underwent scanning close to the pulmonary hemorrhage. This may point to a surge in pulmonary blood flow as cardiac output increases during the second 24 hours of life.[10]

Left to right shunts in the heart increase pulmonary blood flow. All except one of the babies with a pulmonary hemorrhage had a hemodynamically significant patent ductus arteriosus at the scan closest to the pulmonary hemorrhage. This result supports previous observations about a relationship between patent ductus arteriosus and pulmonary hemorrhage.[5] However, left to right shunting at the atrial level will also increase pulmonary blood flow, and, although less marked than for the ductus, babies with pulmonary hemorrhage had both larger diameter and higher velocity atrial shunts. The suggested relationship between pulmonary hemorrhage and surfactant therapy[11] may be related to this in that surfactant has been shown to augment the postnatal fall in pulmonary vascular resistance.[12]

There were also babies who had large ducts and high estimated pulmonary blood flow who did not have a pulmonary hemorrhage, so these factors are not the only problem in babies who have pulmonary hemorrhage. Analysis of other differences between the group revealed only gestation as being significantly lower in the pulmonary hemorrhage group. Although immaturity will increase vulnerability, pathologic studies show that some pulmonary hemorrhage is asymptomatic.[13] Studies in immature animals[14] suggest that the combination of high pulmonary blood flow and increased left atrial pressure consistently causes capillary stress failure.

These data would support early closure of the ductus to prevent pulmonary hemorrhage. Covert et al[15] showed a significant reduction in pulmonary hemorrhage after the administration of prophylactic indomethacin. However, it may be possible to target this prevention more specifically. By treating the 48% of babies who had a duct diameter >1.6 mm at the 5-hour echocardiogram, we would have selected 92% of the babies who had a pulmonary hemorrhage, and also 89% of those who later had a symptomatic patent ductus arteriosus.

In conclusion, these data show a significant association among ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage in preterm infants. Medical closure of ducts that fail to constrict spontaneously within the first few postnatal hours may reduce the risk of pulmonary hemorrhage.

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