Effect of patency of the ductus arteriosus on blood pressure in very preterm infants

Nick Evans, James Moorcraft

Abstract

Forty one preterm infants (birth weight <1500 g) were studied by daily Doppler echocardiography for the first week of life to examine the effect of a haemodynamically significant ductus arteriosus (HSDA) on systemic blood pressure. Hourly records of blood pressure were averaged for each infant to produce a 24 hour mean value and the infants were then allocated to groups according to whether, by echocardiographic criteria, there was a HSDA on that day.

In infants from 1000 to 1500 g the differences in all parameters of blood pressure between those with and without a HSDA were not significant. In infants <1000 g the mean blood pressure was significantly less in the infants with a HSDA throughout the first week of life. Systolic blood pressure was reduced by as much as diastolic blood pressure and as a result the pulse pressure did not differ. Infants <1000 g with a HSDA were given more plasma and a greater number received inotropic support. Gestational age, respiratory disease severity, and complication rates did not differ between those with and without a HSDA.

The possibility of a clinically silent HSDA should be considered before large amounts of plasma volume expanders are given to treat hypotension in infants <1000 g.

(*Arch Dis Child* 1992; **67**:1169–73)

The classical description in many textbooks of neonatology of the effect of shunting through a haemodynamically significant ductus arteriosus (HSDA) on blood pressure is that it leads to a decrease in diastolic blood pressure causing a widened pulse pressure and hence bounding peripheral pulses.[1] Although this is true in older infants and children there is little published work to support this statement in preterm infants, particularly in the first week after birth when diagnosis is so important.

During a Doppler echocardiographic study of ductal shunting in preterm infants[2] we became aware that large, often clinically silent, ductal shunts seemed to be associated with a more global reduction in systemic blood pressure and that some of the smaller infants seemed to be requiring more medical support to maintain an acceptable blood pressure. These observations agreed with the findings of Ratner *et al* who showed that a HSDA was associated with a reduction in systolic and diastolic blood pressure.[3] Ratner *et al* used the left atrial aortic root ratio as an isolated measurement to assess ductal status and some indirect blood pressure measurements,[3] both of which could have limited the accuracy of their observations. We decided to re-examine this issue in preterm infants with a birth weight <1500 g using direct two dimensional and Doppler echocardiographic diagnosis and only measurements of blood pressure made through an intra-arterial catheter.

Subjects and methods

All subjects were studied with an ATL Ultramark 4 scanner with range gated pulsed Doppler. Cross sectional imaging was performed with a 7·5 MHz transducer incorporating a 5 MHz Doppler crystal. Infants, where possible, had daily echocardiographic examinations for the first week of life (first five days in infants, birth weight >1000 g) with the first study within 24 hours of birth. Occasional days were missed for technical or clinical reasons; blood pressure data from these days were not included in the analysis. Normal cardiac anatomy was confirmed then the ductus was imaged from the high left parasternal position, the Doppler sample volume was placed in the pulmonary end of the duct, and the flow pattern recorded. The duct was classified as 'closed' when patency could not be imaged and no flow could be detected on a pulsed Doppler search of the pulmonary end of the duct. It was classified as 'restricting' when local restriction or no patency could be imaged but a Doppler flow of variable signal intensity was recorded, and as 'widely patent' when unrestricting patency was imaged and a strong Doppler flow signal recorded. When ductal patency was established, the left atrial to aortic root ratio (LA:Ao) was measured according to previously reported criteria[4] as a quantitative measure of the degree of left to right shunt. A mean of three measurements was taken.

Hourly measurements of systolic blood pressure, diastolic blood pressure, and mean blood pressure were recorded from the time of insertion of the intra-arterial catheter. Umbilical lines were size 3·5 FG Argyle catheters; peripheral arterial catheters were 24GA Quik-Cath (R) cannulae. The catheter site was postductal (umbilical, left radial, or posterior tibial) in 17 of the 20 infants who developed a HSDA and in 19 of the 21

Neonatal Unit, University of Oxford, John Radcliffe Maternity Hospital, Oxford
Nick Evans
James Moorcraft

Correspondence to:
Dr Nick Evans, Department of Perinatal Medicine, King George V Hospital, Missenden Road, Camperdown, Sydney NSW 2050, Australia.

Accepted 14 May 1992

No reprints available.

infants who did not; the other catheters were preductal in the right radial artery. All catheters were connected for continuous arterial pressure monitoring to a Viggo-Spectramed (R) Quartz transducer placed at mid-thoracic level, which was in turn connected to a Hewlett-Packard HP78834A multichannel monitor. All systems were routinely recalibrated according to the manufacturers' recommended protocol at least once every 24 hours. Pulse pressure was calculated from the difference between the systolic blood pressure and the diastolic blood pressure. The signal was regarded as damped when the pulse pressure was less than 12 mm Hg; only the mean blood pressure was used from these recordings. For each infant the hourly measurements of systolic blood pressure, diastolic blood pressure, and mean blood pressure were averaged over each day to produce 24 hour means for each parameter. For the purpose of this study we defined HSDA as a widely patent duct from which a strong Doppler signal could be recorded where the LA:Ao ratio was greater than or equal to 1·5. The 24 hour means for blood pressure parameters were allocated to groups according to whether the duct fulfilled these criteria within that 24 hour period.

Forty one preterm infants were studied over two six month periods which ended in February 1990 and August 1991 respectively. All infants <1500 g who had satisfactory intra-arterial blood pressure monitoring were recruited during these periods. The only infants not included were born when the investigator with the echocardiographic skills (NE) was on leave. The results were analysed in two different weight groups: <1000 g (n=16) and 1000–1500 g (n=25). Eight of the <1000 g and 12 of the >1000 g infants developed a HSDA during this study. In the two weight groups the mean gestation and birth weight did not differ significantly between those that did and did not develop a HSDA (table 1).

Before the beginning of this study, the diagnosis of a HSDA in this unit was made from the development of clinical signs and then confirmed by echocardiography. In order that prospective echocardiography did not change clinical practice with regard to support of blood pressure, it was agreed with the doctors in charge of the infants that they would be blind to the echocardiographic findings unless there were specific clinical concerns, in which instance the findings would be made known to them. The current clinical practice on this unit with respect to blood pressure in very low birthweight infants is to try to maintain the mean blood pressure at or above 30 mm Hg. Initially plasma or blood are used as volume expanders, with 10 ml/kg given over 30 minutes and repeated if necessary. If the response is not maintained dopamine is started at a dose of 5 μg/kg/min and increased if necessary to a maximum of 20 μg/kg/min.

The study was approved by the central Oxford regional ethics committee. Statistical analysis was by unpaired Student's t test, Wilcoxon rank sum test, and the χ^2 test. Significance was accepted at p values of less than 0·05.

Table 1 Gestation and birth weight of infants with and without a HSDA

	Infants with HSDA (LA:Ao >1·5)	*Infants without HSDA (LA:Ao <1·5)*
Infants 1000–1500 g		
Mean (range) gestation (weeks)	28·8 (27–31)*	29·2 (27–31)†
Mean (range) birth weight (g)	1200 (1005–1500)*	1250 (1009–1500)†
Infants <1000 g		
Mean (range) gestation (weeks)	25·8 (24–29)‡	26·6 (24–30)‡
Mean (range) birth weight (g)	710 (500–950)‡	780 (620–940)‡

*n=12; †n=13; ‡n=8.

Results

WEIGHT GROUP 1000–1500 g

Blood pressure

Over the first five days of life the average mean blood pressure was slightly lower in the group with a HSDA (fig 1). The differences were small and not statistically significant. Mean systolic blood pressure and mean diastolic blood pressure were lower by similar amounts in the group with a HSDA with no disproportionate reduction in diastolic blood pressure (fig 2). Again the differences were small and not significant. As a result of the mean pulse pressure did not differ between the two groups. Table 2 gives the number of studies for each group on each day.

Further subdividing the infants with a HSDA into weight groups 1000–1200 g and

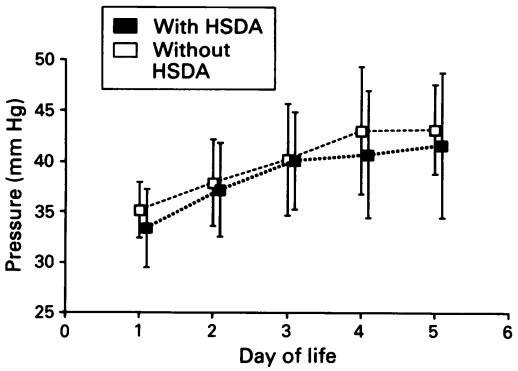

Figure 1 Mean (SD) mean blood pressure in infants 1000-1500 g comparing those with a HSDA with those without.

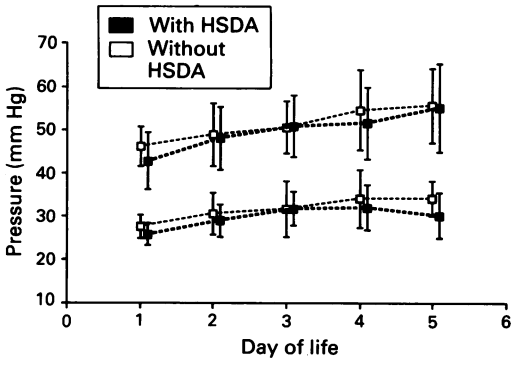

Figure 2 Mean (SD) systolic blood pressure (upper two lines) and mean diastolic blood pressure (lower two lines) in infants 1000-1500 g comparing those with a HSDA with those without.

Table 2 Number of studies on each day after birth for each weight group

Day of life	Infants 1000–1500 g		Infants <1000 g	
	HSDA	No HSDA	HSDA	No HSDA
1	5	18	7	6
2	9	15	7	8
3	11	13	6	9
4	8	13	8	7
5	7	10	7	8
6	—	—	7	9
7	—	—	7	8

1201–1500 g did not change this analysis. The five day cumulative mean mean blood pressure values were 39 and 37·4 mm Hg respectively.

Respiratory disease

Criteria of acute respiratory disease severity are compared in table 3 for those with and without a HSDA in this weight group. Mean maximum fractional inspired oxygen (FIO_2) and time spent in FIO_2 >0·5 did not differ; however, the mean maximum mean airway pressure (MAP) was significantly higher in those infants with a HSDA.

Complications

The incidence of complications which might also be associated with low blood pressure are compared in table 4. None of the differences is significant.

WEIGHT GROUP <1000 g

Blood pressure

Over the first seven days the average mean blood pressure was significantly lower in the group with a HSDA (fig 3). The mean systolic blood pressure was not consistently significantly lower until day 4, the difference just reaching significance on day 1 (p=0·03) but not on days 2 and 3 (fig. 4). Mean diastolic blood pressure was significantly lower in those with a HSDA throughout the week, with all the infants' diastolic blood pressure falling into a narrow band between 20 and 24 mm Hg by day 7 (fig 4). Mean pulse pressure did not differ significantly between the two groups. The number of studies on each day for each group are shown in table 2.

Respiratory disease

Parameters of respiratory disease severity are compared for this group in table 3. There are no significant differences between those with and without a HSDA.

Table 3 Parameters of acute respiratory disease in infants studied

	Infants with HSDA (LA:Ao >1·5)	Infants without HSDA (LA:Ao <1·5)
Infants 1000–1500 g		
Mean (SD) maximum FIO_2	0·71 (0·25)*	0·6 (0·21)†
Mean (SD) maximum MAP (cm H_2O)	11·5 (3·5)*	7·9** (3·1)†
Mean (SD) time FIO_2 >0·05 (hours)	61·25 (38·9)*	59 (36)†
Infants <1000 g		
Mean (SD) maximum FIO_2	0·57 (0·3)‡	0·57 (0·3)‡
Mean (SD) maximum MAP (cm H_2O)	9·9 (2·8)‡	4·6 (4·6)‡
Mean (SD) time FIO_2 >0·05 (hours)	41·4 (54)‡	41·9 (46)‡

*n=12; †n=13; ‡n=8. **p<0·05.

Table 4 Complication rates in infants studied. Results given as No (%) of infants

	Infants with HSDA (LA:Ao >1·5)	Infants without HSDA (LA:Ao <1·5)
Infants 1000–1500 g		
IVH (grade 2 or more)	7 (58)*	3 (23)†
Pneumothorax	2 (16)*	4 (131)†
Infection	1 (7·5)*	0
Infants <1000 g		
IVH (grade 2 or more)	3 (37)‡	2 (25)‡
Pneumothorax	1 (12)‡	2 (25)‡
Infection	1 (12·5)‡	1 (12·5)‡

IVH, intraventricular haemorrahge. *n=12; †n=13; ‡n=8.

Complications

The incidences of complications associated with low blood pressure are compared in table 4. None of the differences is significant.

Treatment for hypotension

Over the first five days the infants with a HSDA received a mean of 15·7 ml/kg of plasma compared with 8·2 ml/kg in those with no HSDA. Four of the eight in this group with a HSDA required a dopamine infusion to maintain an acceptable blood pressure compared with one of eight in those with no

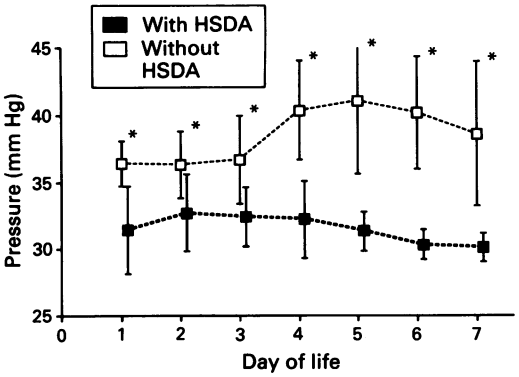

*Figure 3 Mean (SD) mean blood pressure in infants <1000 g comparing those with a HSDA with those without; *p<0·05.*

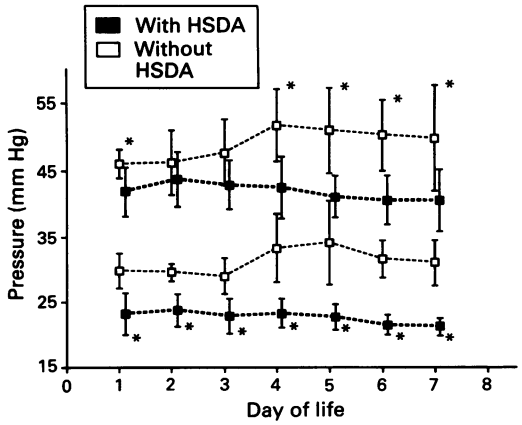

*Figure 4 Mean (SD) systolic blood pressure and mean diastolic blood pressure in infants <1000 g comparing those with a HSDA with those without; *p<0·05.*

HSDA. Neither of these differences reach statistical significance.

Discussion

This study has shown that a HSDA in very preterm infants over the first week of life is associated with a reduction in both systolic blood pressure and diastolic blood pressure and as a result the pulse pressure is not significantly affected. This is in keeping with the findings of Ratner *et al.*[3] In contrast to Ratner's study, however, we have shown the most dramatic reductions in blood pressure in those infants of <1000 g. Ratner did not look separately at this group of infants, analysing data on all infants of <1200 g. In our analysis the mean blood pressure in those with a HSDA did not differ significantly between infants of 1000–1200 g and those of 1201–1500 g.

In basic physiological terms blood pressure is a product of cardiac output and systemic vascular resistance. Although systolic blood pressure and diastolic blood pressure are affected by both these factors, systolic pressure is more affected by changes in cardiac output, particularly in stroke volume and ejection velocity, and diastolic pressure is more affected by changes in systemic vascular resistance.[5] In subjects with normal myocardial function and reserve, the left ventricle will respond to the increased volume load produced by a left to right ductal shunt by increasing stroke volume and consequently peak ejection velocity. As a result systolic pressure will be relatively protected whereas diastolic pressure will decrease due to the effect of the patent duct on systemic vascular resistance.

The immature myocardium of the very preterm infant has incomplete sympathetic innervation and less contractile tissue mass[6] and so will have less reserve to cope with the volume load which results from a large ductal shunt. There is, however, evidence from studies on preterm animals[7] and humans[8] that, particularly in the first few days of life, the immature heart is capable of producing fairly significant increases in cardiac output in response to ductal shunting. Baylen *et al* pointed out that in preterm lambs cardiac output was maintained at the expense of increasing left ventricular end diastolic volume and speculated that the immature myocardium might be unable to sustain this response over a period of time.[7] Rudolf *et al* described two patterns of haemodynamic response to large artificial aortopulmonary communication in dogs: one in which arterial pressure was maintained with increased cardiac output as already described and the other, seen in older dogs, where output and arterial pressure decreased.[9] They speculated that the latter response reflected less myocardial reserve. In our study the infants >1000 g with a HSDA had slightly but not significantly lower systolic pressures, suggesting that on the whole these infants can increase output to protect pressures in line with the first response described by Rudolf *et al.*[9] In contrast the infants <1000 g with a HSDA had markedly lower systolic pressures. Systolic pressure in this group was not consistently significantly lower until after day three, suggesting that some of these infants may have produced an initial compensatory increase in cardiac output which then failed in line with the second response described by Rudolf *et al.*[9]

The patent duct also causes a decrease in diastolic pressure by reducing systemic vascular resistance. In the infants >1000 g the diastolic pressure was not significantly lower in those with a HSDA. The effect the patent duct has on systemic vascular resistance will in turn be dependent on the pulmonary vascular resistance. Most of these infants had hyaline membrane disease and so pulmonary vascular resistance is likely to have been high.[2] This would reduce the effect of the duct on systemic vascular resistance. Despite this the usual direction of shunting was left to right and by the LA:Ao ratio criteria most became significant within three days of birth. This is in line with the observations of other workers[8 10] and is not inconsistent with the presence of increased pulmonary vascular resistance. The diameter of the defect, as well as the pressure differential, will be an important determinant of shunt size. We have observed anecdotally that the diameter of the ductus arteriosus is greatest in the first few days of life with a tendency to decrease in size with age.

In contrast the infants <1000 g with a HSDA had consistently and significantly lower diastolic pressures. This may have reflected the cumulative effect of myocardial failure and reduced systemic vascular resistance; on the whole this group had less severe acute respiratory problems.

In all infants with a HSDA the consequence of similiar reductions in systolic blood pressure and diastolic blood pressure is that the pulse pressure was not significantly affected. This implies that a widened pulse pressure is not a useful physical sign in the first week of life. Despite this many of the infants with a HSDA did develop full pulses. This suggests that other factors may also be important in the perception of full pulses, such as increased left ventricular stroke volume and ejection velocity. This study was made during the first week after birth; we limited it to this period firstly because this is the important period diagnostically and secondly because this is the time that blood pressure is most consistently monitored for clinical reasons. With increasing age it might be expected that the more classical picture would emerge, firstly because pulmonary vascular resistance will fall and secondly because hypertrophy will start to compensate for the lack of myocardial reserve.

The significant hypotension seen in several of the infants <1000 g with HSDA is reflected in the higher use of volume expanders and inotropes. If a HSDA is the cause of hypotension in these infants then neither of these treatments are appropriate. Plasma and blood products will increase the volume load on an

already volume overloaded heart. In addition, although dopamine will have an inotropic effect, it will also increase systemic vascular resistance which could theoretically increase the left to right shunt. The most appropriate treatment would be medical or surgical closure of the ductus arteriosus.

This study has shown that the haemodynamic effects of HSDA can be demonstrated well before it becomes clinically apparent and that in extremely low birthweight infants the possibility of a clinically silent HSDA should be considered before large volumes of plasma expanders are given to treat hypotension.

We thank Drs Andrew Wilkinson, Peter Hope, and Kevin Ives for their help and advice and for allowing us to study the infants under their care.

1 Wilkinson J, Cooke RWI. Cardiovascular problems of the newborn. In: Roberton NRC, ed. *Textbook of neonatology*. London: Churchill Livingstone, 1986:342.
2 Evans NJ, 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.
3 Ratner I, Perelmuter B, Toews W, Whitfield J. Association of low systolic and diastolic blood pressure with significant patent ductus arteriosus in very low birth weight infants. *Crit Care Med* 1985;**13**:497-500.
4 Johnson GL, Breart GL, Gewitz MH, *et al.* Echocardiographic characteristics of premature infants with patent ductus arteriosus. *Pediatrics* 1983;**72**:864-71.
5 Bray JJ, Cragg PA, Macknight ADC, Mills RG, Taylor DW, eds. Blood pressure. *Lecture notes on human physiology*. Oxford: Blackwell, 1989:427-8.
6 Freidman WF. Intrinsic physiological properties of the developing heart. *Prog Cardiovasc Dis* 1972;**15**:87–111.
7 Baylen BG, Ogata H, Oguchi K, *et al.* The contractility and performance of the preterm left ventricle before and after early patent ductus arteriosus occlusion in surfactant treated lambs. *Pediatr Res* 1985;**19**:1053-8.
8 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.
9 Rudolf AM, Scarpelli EM, Golinko RJ, Gootman NL. The haemodynamic basis for the clinical manifestations of patent ductus arteriosus. *Am Heart J* 1964;**68**: 447–58.
10 Mellander M, Larson LE, Ekstrom-Jodel B, Sabel KG. Prediction of symptomatic patent ductus arteriosus in preterm infants using Doppler and M-mode echocardiography. *Acta Paediatr Scand* 1987;**76**:553-9.