

Early determinants of right and left ventricular output in ventilated preterm infants

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Abstract

One hundred and twenty ventilated preterm infants, birthweight <1500 g, were examined within the first 36 hours with colour Doppler echocardiography, to determine the cardiorespiratory influences on right (RVO) and left ventricular output (LVO). Forty nine of these infants had three further daily scans. Measurements included left ventricular (LV) ejection fraction, Doppler determination of RVO and LVO, and ductal and interatrial shunt direction, velocity and colour Doppler diameter. Infants were grouped by respiratory disease severity: mild, mean FIO₂ in first 24 hours <0.5; moderate/severe, mean FIO₂ <0.5; and fatal, death resulting directly from acute respiratory distress.

In the early studies ventricular outputs varied widely (RVO: 62–412 ml/kg/minute, LVO: 75–505 ml/kg/minute). The incidence of low ventricular outputs (<150 ml/kg/minute) increased with worsening respiratory disease. The incidence of low RVO in the mild group was 19%, in the moderate/severe group 42%, and in the fatal group 85%. More infants had a low RVO than a low LVO, reflecting the impact of ductal shunting. Ductal and atrial shunting was predominantly left to right except in those with fatal respiratory disease. In those studied longitudinally, RVO and LVO increased with age and low outputs were not seen after day 3.

Multilinear regression analyses, with RVO as the dependent variable, revealed increasing LVO and atrial shunt diameter as significant positive influences and increasing ductal shunt diameter and mean airway pressure as a significant negative influence. With LVO as the dependent variable, increasing RVO, ductal shunt diameter, and age were significant positive influences and increasing atrial shunt diameter was a significant negative influence.

Low ventricular outputs are more common with worsening respiratory disease. Mean airway pressure and ductal shunting are two negative influences on ventricular outputs over which there is some therapeutic control.

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stable systemic and pulmonary perfusion. The haemodynamics of the preterm cardiovascular system are complex with the problems of the transitional circulation and changing pulmonary vascular resistance being compounded by an immature myocardium¹ and shunting across the fetal channels of the ductus arteriosus and foremen ovale.^{2,3} Such shunting usually diverts blood left to right from the systemic back into the pulmonary circulation. For the ductus arteriosus, such shunting has been shown to 'steal' blood from the systemic circulation⁴; atrial shunting could have a similar effect. Occasionally these shunts are right to left and so divert blood from the pulmonary to the systemic circulation with resultant hypoxaemia. Positive pressure ventilation, often essential to maintain oxygenation, can also compromise cardiac output.⁵

The output from each ventricle will reflect many of these factors and will also depend intricately on the output from the other side; failure or overload at any point within the circuit will influence other parts of the circulation. Doppler echocardiographic study of cardiac output in preterm newborns has usually focused on one point in the circuit, the left ventricular output (LVO),^{6,7} and has not taken into account other influences, particularly that of atrial shunting and right ventricular output (RVO).

We have recently shown that reasonable estimates of ductal and atrial shunt size can be derived from their respective colour Doppler shunt diameters.^{2,3} In this Doppler echocardiographic study, these correlations are used to examine the cardiovascular and respiratory influences on both RVO and LVO in a group of ventilated preterm infants with the aim of improving our understanding of preterm cardiovascular haemodynamics and the main influences on cardiac output.

Methods

One hundred and twenty preterm infants, weighing less than 1500 g and with respiratory problems which required mechanical ventilation for more than 24 hours, were selected for echocardiographic study. The first 49 infants studied had a daily echocardiogram for each of the first four days, these infants were studied for 12 months from March 1992. The next 71 infants were studied once in the first 36 post-natal hours. These infants were studied for 12 months from June 1993. Twenty one eligible infants (14% of total eligible infants) were not studied as neither investigator was available to perform a scan when they were born. The infants who were studied had a mean

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A fundamental aim in intensive care of preterm infants is the maintenance of adequate and

gestational age of 27.3 weeks, ranging from 24 to 33 weeks, and had a mean birthweight of 993 g, ranging from 512 to 1490 g.

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. The scan was recorded on videotape and the measurements then taken from the videotape. Structural normality of the heart was established on the initial scan.

M-mode measurements

LV ejection fraction was measured using a standardised method from M-mode echocardiograms taken from the parasternal long axis view.⁸

Pulmonary artery time to peak velocity to ejection time ratio (TPV:RVET)

This was measured in the main pulmonary artery as an index of pulmonary artery pressure. A standard measurement procedure was used and the ratio was averaged from three cardiac cycles.⁹

*Right ventricular output*¹⁰

Pulsed Doppler recordings of the flow at the level of the pulmonary valve were made from the parasternal long axis view, with care taken to minimise the angle of insonation. An average maximum velocity time integral was derived from the area under the curve of five consecutive cardiac cycles, using the incorporated Acuson cardiac software. The heart rate was measured from the peak to peak intervals of the Doppler velocity time signals. The diameter of the pulmonary valve insertion was measured at end systole from a frame by frame videotape analysis of the 2D parasternal long axis image and was averaged from three to five cardiac cycles.

Ductus arteriosus

This was imaged from the high left parasternal view. Colour Doppler was set for automatic preprocessing, lowest velocity variance setting, and filters set for maximum range for volume and velocity settings with 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. End systolic frames with the clearest discrete appearance to the shunt within the duct were used for measurement.³ A

mean was taken from three to five of the best quality cardiac cycles. 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. When left to right or bidirectional, the peak left to right velocity was measured. When bidirectional, the proportion of the cardiac cycle with right to left shunting was measured as the time of right to left shunting divided by the total length of the cardiac cycle.

Left ventricular output

The LV outflow tract was imaged from an apical view modified to incorporate the full length of the ascending aorta.¹¹ The pulsed Doppler range gate was placed distal to the aortic valve and the angle correction incorporated into the Acuson 128/XP10 was aligned along the long axis of the ascending aorta. If the angle was more than 20° the transducer was manoeuvred to further minimise the angle. The flow velocity time signal was recorded and the maximum velocity time integral averaged from five consecutive cardiac cycles. The heart rate was measured from the peak to peak intervals of the Doppler velocity time signals. The internal diameter of the ascending aorta at the site of flow analysis was measured at the end of systole using frame by frame analysis of the 2D image taken from a parasternal long axis view. This was averaged from three to five cardiac cycles.

Atrial shunting

The atrial septum was imaged from a subcostal four chamber view and colour flow Doppler mapping of any shunt across the septum was performed. The colour flow Doppler was set up as described in the section on ductal shunting. The peak frequency of the colour scale was usually set at 0.23 or 0.31 m/seconds, but sometimes higher for high velocity shunts. The gain was increased until the colour flow picture across the atrial septum was optimised and there was no peripheral colour interference. The diameter of the colour flow jet across the septum was measured at the level of the atrial septum. Frame by frame analysis of the videotape was performed until the clearest image of the left to right component of the interatrial shunt was achieved. The diameter was averaged from three to five of the clearest cardiac cycles.² The pulsed Doppler range gate was placed in the interatrial shunt at the level of the atrial septum with the angle correction adjusted along the long axis of the colour flow of the shunt. The velocity time signal of the interatrial flow was recorded. The pattern of flow was classified as left to right, bidirectional, or right to left. When left to right or bidirectional, the peak left to right velocity was measured. When bidirectional, the proportion of the cardiac cycle with right to left shunting was measured as the time of right to left shunting divided by the total length of the cardiac cycle, as described by Hiraishi *et al.*¹² When no

Table 1 Demographic and clinical parameters according to respiratory disease severity

	Mild respiratory distress (day 1 mean FIO ₂ <0.5, n=77)	Moderate to severe respiratory distress (day 1 mean FIO ₂ >0.5, n=36)	Fatal respiratory distress (n=7)
Gestation (weeks)	27 (24–34)	27 (24–30)	26 (24–30)
Age at scan (hours)	20 (7–31)	19.5 (7–27)	14 (5–25)
Mean FIO ₂ , first 24 hours	0.35 (0.21–0.49)*	0.6 (0.5–0.84)*	0.89 (0.69–0.98)*
Mean blood pressure (<36 hours)	32 (20–46)	30 (24–49)	31 (22–35)
% Given 5% albumin (ml/kg in first 24 hours)	26%*	59%*	72%
Inotropes, first 24 hours	14 (8–30)	10 (6–58)	18 (8–50)
MAP at scan	16%*	42%*	85%*
	7 (2–12)*†	9 (6–15)*	10 (7–19)†

Figures are medians (range) and incidence, * † significant difference between pairings: P<0.05.

clear interatrial shunt could be seen on colour flow Doppler mapping, this was classified as no significant atrial shunt.

Formulae

The following formulae were used in the cardiac calculation package incorporated into the software of the Accuson 128/XP10:

(1) Right and left ventricular stroke volume = Velocity time integral × (3.1416 × [Outflow diameter²/4])

(2) Right and left ventricular output = Stroke volume × Heart rate / Bodyweight (kg).

CLINICAL PARAMETERS

For each infant on each of the echocardiographic study days, hourly measures of fractional inspired oxygen concentration (FIO₂) and mean airway pressure (MAP) were recorded from the continuous display on the ventilator. MAP and FIO₂ were also recorded at the time of echocardiography.

Surfactant therapy was given as 2 doses of Exosurf, 12 hours apart, as rescue therapy when the alveolar to arterial oxygen ratio was less than 0.22. Blood pressure was supported if the mean blood pressure fell consistently below the infant's gestation in weeks. Human albumin 5% (10 ml/kg) was given initially, followed by dopamine (or occasionally dobutamine at the clinician's discretion) at 10 µg/kg/minute, increasing in steps to a maximum of 20 µg/kg/minute if blood pressure did not improve. Further boluses of 5% albumin were given, at the attending clinician's discretion, if hypotension persisted.

CLASSIFICATION OF RESPIRATORY DISEASE SEVERITY

The infants were divided up into groups on the basis of their early oxygen requirements along similar lines to that described by Walther *et al*¹³ except we used mean FIO₂ over the first 24 hours rather than maximum FIO₂. The infants were classified as mild (n=77) when the mean FIO₂ was less than 0.5, moderate to severe (n=36) when mean FIO₂ was more than 0.5, and fatal (n=7) when death resulted directly from the early acute phase of the respiratory disease. Median age at death of these seven infants was day 3 (range 1–9). The fatal group did not include nine infants who subsequently died from non-respiratory causes,

seven died from infection, and two from intraventricular haemorrhage. The respiratory diagnosis in the mild group was hyaline membrane disease in 46, immature lung in 27, and pneumonia in four; the moderate/severe group all had hyaline membrane disease; and in the fatal group, six had hyaline membrane disease and one had pulmonary hypoplasia.

The study was approved by the Royal Prince Alfred Hospital Ethics Committee and infants were studied with the consent of their parents unless there was a clinical indication for an echocardiogram.

Statistical analysis was done with a computer statistics package (SPSSPC, SPSS Inc, Chicago, Illinois) using stepwise multilinear regression analysis, Mann Whitney U test, χ² test, and Kruskal-Wallis analysis of variance for non-parametric data. P values of less than 0.05 were accepted as significant.

Results

INITIAL STUDIES (<36 HOURS)

The initial studies on all 120 infants were analysed, all of which had been carried out within the first 36 hours. Table 1 shows the clinical parameters for the three respiratory severity groups in these early scans. There were no differences in gestation, age at scan, or average mean blood pressure between the three groups, but the differences in mean FIO₂ were significant, P<0.0001. The mild group had significantly lower MAP at the time of the scan than the other two groups (P<0.001). Plasma volume expanders and inotropes were used more commonly with worse respiratory disease. Thirty one of the 33 infants in whom inotropes were used were receiving them at the time of echocardiography. Twenty eight were receiving dopamine and three dobutamine at a dose of at least 10 µg/kg/minute. In one infant in the moderate/severe group and one in the fatal group, inotropes were started after the initial echocardiogram.

Echocardiographic measurements are compared in table 2. Median RVO was significantly lower with increasing respiratory severity groups (P<0.02), and the proportion with RVO less than 150 ml/kg/minute increased significantly with increasing respiratory disease severity. Median LVO was also lower and the proportion with an LVO <150 ml/kg/minute increased with worsening respiratory disease. For LVO, the difference between the mild and moderate/severe groups was not significant but was significant for the fatal group (P<0.0001). While disparities between the ventricular outputs occurred in both directions as a result of shunts, the influence of ductal shunting tended to dominate, with LV output more likely to exceed RV output (fig 1). In 13 (11%) infants, as a result of ductal shunting, LV output was within the normal range while RV output was below the normal range. In seven (6%) babies, the reverse was the case due to atrial shunting (fig 1). Median LV ejection fraction and TPV:RVET did not differ across the groups.

The proportion of each group with a closed duct and the median diameter of the patent

Table 2 Cardiovascular parameters on early echocardiogram according to respiratory disease severity

	Mild respiratory distress (n=77)	Moderate to severe respiratory distress (n=36)	Fatal respiratory distress (n=7)
RVO ml/kg/minute	211 (69-412)*	169 (66-391)*	97 (62-151)*
Low RVO, <150 ml/kg/minute	19.5%	41%*	85%*
LVO ml/kg/minute	225 (82-505)*	195 (93-352)†	93 (75-209)*†
Low LVO, <150 ml/kg/minute	18%*	28%†	85%*†
LV ejection fraction	55 (14-95)	52 (28-95)	54 (26-62)
TPV:RVET	0.25 (0.16-0.49)	0.27 (0.15-0.37)	0.26 (0.14-0.29)
<i>Shunts:</i>			
Ductal diameter (mm)	35% closed 1.5 (0.6-3.4)	25% closed 1.6 (0.7-3.1)	28% closed 2.0 (1.1-3.3)
Ductal flow pattern	76% L to R 24% bidirectional 0% R to L*	63% L to R 33% bidirectional 4% R to L†	20% L to R 60% bidirectional 20% R to L*†
Ductal L to R Vmax (m/seconds)	1.4 (0.35-2.6)†	1.35 (0.6-2.1)*	0.37 (0.16-1.3)*†
Ductal R to L time (% cycle)	20 (9-37)	16.5 (8-100)*	38 (17-100)*
Atrial diameter (mm)	14% no shunt 3.1 (1.3-4.9)	19% no shunt 2.7 (1.4-7.5)	28% no shunt 3.0 (2.1-4.1)
Atrial flow pattern	21% L to R 74% bidirectional 5% R to L	13% L to R 83% bidirectional 3.5% R to L	100% bidirectional
Atrial R to L time (% cycle)	26 (10-100)†	26 (10-70)*	60 (37-81)*†

Figures are medians (range) and incidence. Vmax is maximum velocity, R to L is right to left and L to R is left to right.
* † significant difference between pairings: $P < 0.05$.

ducts did not differ significantly. The fatal group had significantly lower maximum left to right ductal shunt velocity and significantly more infants with bidirectional or right to left ductal shunting with significantly more of the cardiac cycle occupied by right to left shunting ($P < 0.05$). The differences between the mild and moderate/severe groups were again not significant. The proportion of each group with no atrial shunt and the colour Doppler diameter of the atrial shunt in those with foramen ovale incompetence did not differ significantly. The proportion of each group with bidirectional or right to left atrial shunting was also not significantly different, but the proportion of the cardiac cycle occupied by right to left shunt was significantly longer in the fatal group ($P < 0.002$).

The influences on RVO and LVO were examined in a stepwise multilinear regression analysis which included the initial study on all 120 infants.

Right ventricular output

This was analysed as a dependent variable against gestation, postnatal age at scan, inotrope use and volume of plasma expander given on the day of the scan, MAP at the time of the scan, FIO_2 at the time of the scan, left ventricular ejection fraction, TPV:RVET, diameter of the ductus arteriosus (a measure of ductal shunt size), diameter of the atrial shunt (a measure of atrial shunt size), and LVO. The three factors incorporated into the equation as

significant were, in step number order, increasing LVO as a positive influence ($P < 0.0001$), increasing ductal diameter as a negative influence ($P < 0.0001$), and increasing atrial shunt diameter as a positive influence ($P < 0.003$); multiple $r = 0.79$.

Left ventricular output

This was analysed against the same variables including RVO. The three factors incorporated as significant were increasing RVO as a positive influence ($P < 0.0001$), increasing ductal diameter as a positive influence ($P < 0.0001$), increasing atrial shunt diameter as a negative influence ($P < 0.0001$); multiple $r = 0.81$.

LONGITUDINAL STUDIES

Forty nine of the infants were studied daily for each of the first four days. Only one of the infants in the fatal RDS group survived longer than 48 hours so numbers were insufficient to describe longitudinal changes for this group. The longitudinal changes in the parameters described above are shown for the mild group (table 3) and the moderate/severe group (table 4). Median MAP at the time of the scan fell over the first four days, significantly so in the moderate/severe group. In both groups median RVO increased significantly with time and by day 4 no infant had an RVO of <150 ml/kg/minute. The increase in LVO seen with time did not reach significance for either group. Outputs below 150 ml/kg/minute were not seen after day 1 in the mild group.

Ductal closure occurred at a similar rate in the two groups and for both groups the diameter of the patent ducts trended smaller. Four infants in each group received indomethacin to close a patent ductus arteriosus during the first four days. Only one infant had a pure right to left shunt on day 1. Bidirectional shunting occurred in a minority of both groups, the right to left component of this pattern usually occupied only a small proportion of the cardiac cycle. Bidirectional shunting was not seen after day 2. The predominant pattern of atrial shunting was

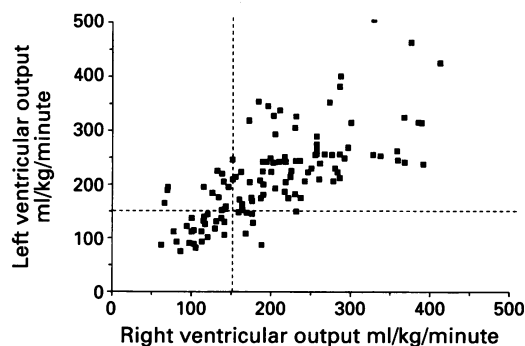


Figure 1 This graph plots LVO against RVO in the initial studies done within the first 36 postnatal hours on all 120 infants. The dotted lines mark the lower limit of normal for each ventricular output.

Table 3 Longitudinal cardiovascular changes in mild respiratory distress*

	Day 1 (n=20)	Day 2 (n=22)	Day 3 (n=25)	Day 4 (n=20)	P value
Age at scan (hours)	18.5 (7-24)	38 (25-47)	62 (49-72)	83 (73-95)	
MAP at scan	7 (2-11)	7.5 (4-12)	6 (0-13)	6 (0-12)	0.2
<i>Ventricular outputs:</i>					
RVO ml/kg/minute	202 (102-376)	239 (160-300)	240 (187-375)	287 (166-385)	0.008
RVO <150 ml/kg/minute	15%	0%	0%	0%	
LVO ml/kg/minute	233 (144-463)	241 (150-400)	239 (154-446)	282 (170-489)	0.26
LVO <150 ml/kg/minute	5%	0%	0%	0%	
LV ejection fraction	58 (31-71)	56 (32-95)	58 (25-79)	56 (37-79)	0.88
TPV:RVET	0.25 (0.19-0.32)	0.25 (0.16-0.33)	0.32 (0.2-0.33)	0.27 (0.21-0.35)	0.03
<i>Shunts:</i>					
Ductal diameter (mm)	35% closed 2.0 (1.1-3.2)	50% closed 1.5 (1.1-3.5)	68% closed 1.85 (1.1-2.5)	65% closed 1.5 (1.3-3.3)	0.85
Ductal shunt patterns	85% L to R 15% bidirectional	81% L to R 19% bidirectional	100% L to R	100% L to R	
L to R ductal Vmax (m/second)	1.37 (0.8-2.1)	1.38 (0.8-1.8)	1.66 (0.95-2.8)	1.61 (0.38-2.1)	0.38
Ductal R to L time % of cycle	24 (24)	15 (8-22)			
Atrial diameter (mm)	20% no shunt 3.25 (1.3-4.6)	14% no shunt 2.56 (1.3-4.2)	16% no shunt 2.8 (1.6-4.5)	10% no shunt 2.56 (0.6-4.6)	0.12
Atrial flow pattern	20% L to R 66% bidirectional 13% R to L	26% L to R 74% bidirectional	21% L to R 79% bidirectional	25% L to R 75% bidirectional	
Atrial R to L time % cardiac cycle	26 (14-100)	24 (16-33)	24 (14-41)	27 (6-46)	0.8

*Figures are medians (range) and incidence. Statistics achieved with Kruskal-Wallis analysis of variance.

bidirectional throughout the first four days, though pure left to right shunting was slightly more common in the mild/moderate group. Pure right to left atrial shunt was seen in two infants with mild respiratory distress on day 1 and one severe infant on day 2. The median right to left proportion of this atrial shunting did not differ with time or between the two groups.

MULTILINEAR REGRESSION ANALYSIS ON THE LONGITUDINAL STUDIES

The influences on RVO and LVO were examined in a stepwise multilinear regression analysis, including the 174 studies done on the 49 infants who were studied longitudinally.

Right ventricular output

This was analysed as a dependent variable against gestation, postnatal age at scan, inotrope use and volume of plasma expander given on the day of the scan, MAP at the time of the scan, FIO₂ at the time of the scan, left ventricular ejection fraction, TPV:RVET, diameter of the ductus arteriosus (a measure of

ductal shunt size), diameter of the atrial shunt (a measure of atrial shunt size), and LVO. The four factors incorporated into the equation as significant were, in step number order, increasing LVO as a positive influence (P<0.0001), increasing ductal diameter as a negative influence (P<0.0001), increasing atrial shunt diameter as a positive influence (P<0.0002), and increasing MAP as a negative influence (P<0.001); multiple r=0.78.

Left ventricular output

This was analysed against the same variables including RVO. The three factors incorporated as significant were increasing RVO as a positive influence (P<0.0001), increasing ductal diameter as a positive influence (P<0.0001), and increasing atrial shunt diameter as a negative influence (P<0.0004); multiple r=0.76.

Discussion

Few studies have examined LVO serially in a cohort of sick preterm infants and none, to our knowledge, have examined this together with RVO. Doppler echocardiographic means of

Table 4 Longitudinal cardiovascular changes in moderate/severe respiratory distress*

	Day 1 (n=19)	Day 2 (n=22)	Day 3 (n=19)	Day 4 (n=20)	P value
Age at scan (hours)	16 (7-24)	37 (25-48)	60 (49-72)	83 (73-96)	
MAP at scan	9 (6-13)	9 (6-12)	8 (3-11)	6 (0-9)	0.0001
<i>Ventricular outputs:</i>					
RV output ml/kg/minute	189 (66-300)	197 (70-359)	218 (97-385)	248 (172-347)	0.03
RVO <150 ml/kg/minute	37%	27%	16%	0%	
LV output ml/kg/minute	214 (93-352)	232 (112-404)	224 (97-398)	237 (172-332)	0.88
LVO <150 ml/kg/minute	10%	20%	5%	0%	
LV ejection fraction	47 (30-95)	55 (26-80)	50 (18-79)	48 (18-77)	0.8
TPV:RVET	0.25 (0.16-0.37)	0.24 (0.13-0.34)	0.25 (0.18-0.4)	0.27 (0.18-0.38)	0.33
<i>Shunting:</i>					
Ductal diameter (mm)	10% closed 1.8 (0.8-3.1)	41% closed 1.8 (1-3.3)	53% closed 1.4 (0.5-3.2)	70% closed 1.1 (0.8-2.1)	0.18
Ductal shunt patterns	59% L to R 35% bidirectional 6% R to L	77% L to R 23% bidirectional	100% L to R	100% L to R	
L to R ductal Vmax (m/second)	1.28 (0.63-2.06)	1.46 (0.54-2.3)	1.72 (0.68-2.32)	1.89 (1.35-2.55)	0.066
Ductal R to L % cardiac cycle	18 (8-100)	24 (13-24)			
Atrial diameter (mm)	26% no shunt 2.5 (1.4-2)	23% no shunt 2.45 (1.4-3)	32% no shunt 3.1 (1.5-4.7)	25% no shunt 2.9 (1.1-5.5)	0.35
Atrial flow pattern	14% L to R 86% bidirectional	6% L to R 88% bidirectional 6% R to L	100% bidirectional	7% L to R 93% bidirectional	
Atrial R to L time % cardiac cycle	26 (17-70)	30 (20-46)	25 (13-33)	23 (14-50)	0.17

*Figures are medians (range) and incidence. Statistics with Kruskal-Wallis analysis of variance.

assessing LVO have been validated over a wide age range and have shown a consistently close correlation with invasive methods of assessing cardiac output.^{14 15} While concerns have been raised about the interpretation of Doppler derived cardiac output in individual critically ill infants,¹⁶ it remains the best validated and most applicable methodology for the study of preterm newborns. The use of Doppler echocardiography to measure RVO is less well validated in infants, but close correlations have been found in older subjects and animals,^{17 18} and we have shown a close correlation between Doppler measures of RVO and LVO in infants in whom there were no shunts.^{2 3}

An important finding in this study is the wide range of cardiac outputs found in these infants. The extent of low cardiac output in these early stages has not, to our knowledge, been documented before. Different methodologies for measuring aortic diameter confound the definition of a low ventricular output in newborns, but term babies usually have an LVO between 200 and 300 ml/kg/minute.¹⁹⁻²² We chose 150 ml/kg/minute as our lower limit of normal, as measurements below this were unusual in two previous studies of well preterm infants, which used the same methodology as this study.^{6 22}

The primary aim in measuring cardiac output is to derive an index of systemic perfusion. In reality, neither ventricular output does this accurately in all cases. LVO will be the sum of systemic flow and any left to right flow at ductal level and RVO is the sum of the systemic venous return and any left to right atrial shunt. In the few instances where there is right to left shunting, the situation is even more complex. Atrial shunts, while they can be large, tend to be smaller than ductal shunts,^{2 3} thus RVO showed low systemic blood flow more often than LVO. RVO fell significantly with worsening respiratory disease severity while LVO was only significantly lower in the fatal group. Thus these data would suggest a proportion of ventilated preterm infants have sub-optimal early systemic blood flows which would not be detected if LVO alone was measured. The incidence of low outputs increased with worse respiratory disease and decreased with age, outputs below 150 ml/kg/minute were not seen after day 3.

The other finding of this study is that the determinants of cardiac output are multifactorial. Poor preterm cardiac output has been seen primarily as a product of an immature myocardium.²³ LV ejection fraction, admittedly a broad measure of myocardial function in the preterm infant,²⁴ was not significantly associated with either ventricular output. The significant negative influences on RVO were increasing ductal diameter and higher MAP, and negative influences on LVO were increasing atrial shunt diameter and earlier postnatal age. The predominantly left to right pattern of ductal shunting will reduce RVO and atrial shunting will reduce LVO by shunting blood from the systemic back to the pulmonary circulations.⁴ This effect is apparent even at this early postnatal time.

The negative impact of worse respiratory disease was significantly related to MAP. The negative impact of positive pressure ventilation on cardiac output has been consistently demonstrated in older people and animals.²⁵⁻²⁷ At low pressures, it is felt that this negative influence is mediated primarily through reduced systemic venous return but that, at very high pressures, direct effects on pulmonary vascular resistance, and myocardial function become important.²⁷ In the sickest infants all these factors were probably important. MAP was often very high, hypoxia and acidosis were common, and high pulmonary artery pressure was suggested by lower ductal shunt velocities. But when comparing the mild and moderate/severe groups of infants, there was no significant difference in pulmonary artery pressure between the two groups, measured by either TPV:RVET or ductal shunt velocity, nor was there any difference in LV ejection fraction to account for the difference in incidence of low outputs. By exclusion, this might point to reduced systemic venous return as an important limiting factor. Both ventricles also show an ability to increase substantially their outputs when the preload of a ventricle is increased by a ductal or atrial shunt, confirming a degree of myocardial reserve. We speculate that the effect of positive pressure ventilation in reducing systemic venous return, and so cardiac output, may be as important in preterm infants as it has been recognised to be in adults.^{25 27} There are few studies on the effect of ventilation on cardiac output in preterm infants. Hausdorf and Hellwege⁵ demonstrated a 25% to 30% reduction in ventricular stroke and minute volumes, with no effect on blood pressure, by increasing PEEP from zero to 8 cm H₂O in a group of preterm infants. The clinical importance of this is that if by improving arterial oxygenation we reduce perfusion, tissue oxygenation will be compromised. Trang *et al*²⁸ suggested that this occurs at PEEP levels above 6 cm H₂O in preterm infants.

Therapeutic efforts to improve systemic perfusion usually involve intravascular volume expansion and/or inotropes. Volume expansion does not improve blood pressure in many preterm infants and has inconsistent effects on LVO.^{29 30} But there is some evidence from adults²⁵ and one study in the preterm newborn³¹ to suggest that volume expansion can correct some of the preload deficit which results from positive pressure ventilation and improve cardiac output in the short term. Inotropes, while improving blood pressure, have not been shown to consistently improve LVO in non-asphyxiated preterm infants.^{29 32} Roze *et al*³² actually demonstrated a reduction in LVO in response to dopamine which was most pronounced in those with the worst lung disease. If systemic venous return rather than myocardial dysfunction were the main problem, inotropes might be expected to have little effect on ventricular outputs. In this study low outputs were more common with worse respiratory disease, despite the increased use of inotropes. Almost all the babies given

inotropes were receiving them at the time of the scan and averaged mean blood pressure was not significantly different across the groups. This would be in line with the observation of Roze,³² that dopamine is better at improving blood pressure than LVO. Our data suggest that the two negative influences on ventricular outputs over which we have some therapeutic control are MAP and ductal shunting.

The outputs from each ventricle relate closely to the other, although the correlation between the two is not that strong ($r=0.68$), reflecting shunting. These data highlight that each point of the circulation can have an influence on the other parts and that in the complex flux of the preterm heart, ventricular output measures will often not be representative of systemic flow. Single site measures of flow will be subject to misinterpretation. Walther *et al*¹³ suggested that low flow in the left pulmonary artery in infants with severe HMD was due to right to left ductal shunting. The present data have shown that often this finding would be due to low total right heart output, not just ductal shunting. Although right to left ductal shunting, usually as part of a bidirectional pattern, does occur in the early postnatal period, it was common, as was right to left atrial shunting, only in those with fatal respiratory disease. For other infants, right to left intracardiac shunting is uncommon and transient.

In conclusion, both ventricular outputs are very variable in the early postnatal period. Low outputs are common and are significantly associated with worse lung disease and large left to right intracardiac shunts. A clearer understanding of this complex haemodynamic situation is important to permit appropriate interpretation of studies of blood flow to various organs, particularly the brain, and to enable clinicians to rationalise interventions designed to support systemic blood flow in sick preterm infants.

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