Pulmonary hypertension in infants with chronic lung disease: non-invasive evaluation and short term effect of oxygen treatment

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Abstract

A total of 45 examinations on 30 premature infants with chronic lung disease (CLD) of prematurity were made using Doppler echocardiography. Pulmonary systolic time intervals and tricuspid regurgitant velocity were measured to assess the prevalence of pulmonary hypertension and short term responsiveness of the pulmonary circulation to oxygen. Twelve preterm infants matched for gestational age, served as controls. Tricuspid regurgitation (TR) was detected in 14 of the patients. Eleven of those with TR had pulmonary hypertension, of whom eight responded to oxygen treatment. Of the remaining three patients with 'fixed' pulmonary hypertension, one subsequently died. The detection of TR was the basis of the preferred method for measuring pulmonary artery pressure (Ppa) non-invasively, but the degree of correlation between the Ppa estimated from TR and pulmonary systolic time intervals was high ($r = -0.84$, $p < 0.001$).

In the absence of TR, systolic time intervals are an effective way to monitor pulmonary artery pressure in infants with CLD. Without these measurements, it would have been impossible to predict which subjects had pulmonary hypertension, and which might respond to oxygen treatment.

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Chronic lung disease (CLD) of prematurity is still a major problem in babies who survive neonatal intensive care. Its incidence in those infants who require ventilation for respiratory distress syndrome and who survive varies from 10% to 20%, according to gestational age¹ and definition. Infants with CLD are at risk of developing pulmonary hypertension, which is a predictor of subsequent morbidity and mortality.²⁻⁵ Heart failure associated with severe pulmonary hypertension used to be a common cause of death.⁵

There is a good deal of evidence that pulmonary hypertension in CLD is extremely sensitive to oxygen⁶ and that this may be responsible for the increased survival of infants with CLD given appropriate, longterm oxygen treatment. As there are major differences between individual infants in terms of the

relation between pulmonary artery pressure (Ppa) and arterial oxygen saturation (SaO_2),^{6,7} the level of longterm oxygen treatment may need to be determined not simply by an arbitrary target of SaO_2 , but by the degree of hypoxic pulmonary vascular responsiveness of individual infants. This would have the advantage that oxygen insensitive babies might be able to withdraw from oxygen treatment sooner than otherwise, while sensitive babies could be monitored more assiduously. However, a programme based on the control of pulmonary hypertension needs a safe and practical means of cardiovascular monitoring.

Cardiac catheterisation has been the gold standard for the measurement of pulmonary artery pressure.² This procedure carries significant risk in babies with CLD and is only available in paediatric cardiology units. Doppler echocardiography is proving to be a useful, non-invasive indirect way of assessing pulmonary artery pressure. Two principal methods are available. The first requires the presence of a tricuspid regurgitant jet from which the pressure gradient across the valve can be calculated from peak velocity. This allows the peak systolic right ventricular pressure and, with assumptions about the right atrial pressure, the absolute pulmonary artery systolic pressure to be calculated.⁸⁻¹² The second method uses pulmonary systolic time intervals and ratios. Although this method, technically, is much easier to perform, it cannot provide an absolute value for Ppa. In this method the Doppler wave form sampled from the pulmonary artery is analysed for the acceleration time (the time to peak velocity, AT) and the total right ventricular ejection time (ET) is also measured. Studies in children and adults have shown a close correlation between the dimensionless ratio AT:ET and Ppa measured directly at cardiac catheterisation.¹⁰⁻¹⁷ Both of these Doppler methods correlate with invasive measurements of Ppa.¹⁰⁻¹⁸

The aims of this study were to establish the prevalence of tricuspid regurgitation in infants with CLD; to estimate systolic right heart pressures from the tricuspid regurgitant jet velocity; to determine the correlation between calculated right heart pressures and Doppler pulmonary flow-velocity intervals; to compare values for pulmonary flow indices with preterm controls and with published reference data; and more importantly to assess the effects of oxygen on Doppler derived values of Ppa in infants with CLD and pulmonary hypertension.

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Methods

Group I comprised 30 patients (23 boys) with CLD who had been previously ventilated for hyaline membrane disease and were oxygen dependent beyond 35 weeks' gestation. Gestational age at birth ranged from 23 to 33 weeks and birth weight 600 to 1760 g (mean 1135 g). All were under 30 months of age at the time of study and were in sinus rhythm. Congenital heart disease and a patent ductus arteriosus were excluded by clinical examination, electrocardiography, and echocardiography. Forty five Doppler examinations were carried out. Seven patients were studied more than once, on separate occasions. Infants with CLD were sedated with chloral hydrate 100 mg/kg, 30 minutes before study.

Group II, the control subjects, consisted of 12 preterm infants (five boys), born consecutively over a seven month period, who either had no neonatal respiratory problems, or very mild respiratory distress (less than three days' ventilation and supplemental oxygen for less than seven days). Gestational age at birth was 27–32 weeks and birth weight 940–1780 g (mean 1346 g). They were examined between 3 and 17 weeks after birth, at a mean post-menstrual age of 40 weeks (range 35 to 49 weeks). Control patients were examined during natural sleep.

MONITORING

Oxygen was given via nasal cannula to those patients still oxygen dependent at the time of study (16 out of 45 examinations) to maintain SaO_2 above 94% (normoxia). The infants with CLD were monitored for oxygen saturation and heart rate using a pulse oximeter (Ohmeda Biox 3740, Louisville, USA) applied to the thumb or hand. Systemic blood pressure was not measured.

The study of control subjects was approved by the Hammersmith Hospital Ethics Committee and parental consent was given in all cases.

DOPPLER EXAMINATIONS

Tricuspid regurgitation velocity

Systolic right ventricular pressure was estimated from the tricuspid regurgitant jet detected by echoDoppler, as described before.^{10–12} A Toshiba SH 160 echocardiographic machine with a 3.75 MHz real time steerable Doppler transducer was used for continuous wave Doppler interrogation of tricuspid regurgitation. Doppler recordings were taken from the subcostal, apical, and parasternal positions. The search for the signal of tricuspid regurgitation was performed with the aid of colour flow mapping to achieve optimal recording. To derive a systolic trans-tricuspid gradient, the modified Bernoulli equation was used.^{19 20} In infancy the mean right atrial pressure is low (2–5 mm Hg, 0.267–0.667 kPa) and was assumed to be zero in this study.²¹ This method of right ventricular pressure estimation, validated previously only in older children and adults, has recently

been shown to be a reproducible and accurate technique in infants with tricuspid regurgitation.²²

Pulmonary flow indices

The same scanner equipped with a 5 or 3.75 MHz duplex transducer was utilised for the study of pulmonary flow velocities. The short axis and high parasternal views were used, with the Doppler sample volume positioned just distal to the valve in the centre of the pulmonary artery. The electrocardiogram was recorded simultaneously. Analysis of the pulmonary velocity contour provided the acceleration time and right ventricular ejection time, which were measured with the incorporated Doppler measurement calipers and software. The acceleration time was measured as the time interval between the systolic Doppler waveform leaving the zero flow baseline and reaching its peak velocity. The right ventricular ejection time (ET) is the interval between the systolic Doppler waveform leaving and returning to the zero flow baseline.²³ Five consecutive optimal beats with clearly defined envelopes were measured and averaged. For each beat, the R-R interval on the electrocardiogram and heart rate were measured with the incorporated calipers and software. Correction for different heart rates was performed by dividing the acceleration time by right ventricular ejection time (AT:ET), and dividing the acceleration time and AT:ET by the square root of the cycle length (that is, R-R interval in seconds) giving a corrected AT (ATc) and a corrected AT:ET (AT:ETc).¹⁷

OXYGEN CHALLENGE

Oxygen was given to assess its effect on pulmonary vascular resistance, and pulmonary systolic pressure and hence assess potential 'reactivity'. Thirteen patients (20 examinations) with baseline saturations of less than 95% and evidence of pulmonary hypertension from tricuspid regurgitation were given oxygen by funnel over the mouth and nose. The oxygen flow was adjusted so that the saturation rose to at least 95%. Reactivity to oxygen was defined as a drop of at least 5 mm Hg (0.667 kPa) peak systolic Ppa. Pulmonary flow velocity intervals were also recorded.

STATISTICAL ANALYSIS

The numerical variables are expressed as mean (standard deviation). A two tailed, unpaired *t* test was used for statistical comparison between patients and controls. The 95% confidence intervals for differences were calculated. Pulmonary arterial systolic pressures calculated from the tricuspid regurgitant velocity were correlated with pulmonary flow indices (AT:ET, AT:ETc and ATc) before and after oxygen challenge separately, using linear regression, and 95% confidence intervals were calculated. A paired *t* test combined with a Bonferroni correction was used to assess the

Figure 1 TR derived peak systolic pulmonary artery pressure (Ppa) plotted against AT:ET under basal conditions, with regression line (solid line).: confidence limits (95%) for the regression line; - - - - -: 95% limits for estimating AT:ET for a given TR value.

Figure 2 TR derived peak systolic pulmonary artery pressure (Ppa) plotted against AT:ET after an oxygen challenge.

significance of differences between variables before and after the administration of oxygen. The 95% confidence limits for estimating the AT:ET value corresponding to a given pulmonary systolic pressure by TR were also calculated before and after oxygen challenge.

Results

Forty five examinations were carried out in the 30 patients with CLD in group I. Good quality pulmonary pulsed Doppler proximal pulmonary artery flow velocity contours were obtained in all patients. No infant had pulmonary stenosis or right ventricular outflow obstruction. At the start of the study, when well sedated, measurable peak velocity signals of tricuspid regurgitation could be detected in 14 patients (20 of the 45 examinations, or 44%). Colour flow Doppler was helpful in steering the continuous wave beam. The detection of a transtricuspid regurgitant jet was unrelated to postnatal age, calculated systolic right ventricular pressures, or saturation. The detection of this jet was time consuming and required operator patience and use of several echocardiographic windows. In general, optimal flow velocity envelopes were obtained during the inspiratory phase of respiration. In each of six patients tricuspid regurgitation was detected on two separate examinations.

From TR calculation, two patients were found to have normal pulmonary systolic pressures (<29 mm Hg, 3.87 kPa), six had pressures between 30–39 mm Hg (4.00–5.20 kPa), five had pressures between 40–49 mm Hg (5.33–6.53 kPa), and in one patient the pressure was just less than 80 mm Hg (10.7 kPa). At the start of the study, supplemental oxygen via nasal cannula was being administered to one of the two patients with normal pressures (<30 mm Hg, 4.00 kPa), three with

pressures between 30–39 mm Hg (4.00–5.20 kPa), and two with pulmonary artery pressures above 40 mm Hg (5.33 kPa).

Pulmonary flow velocity ratios, AT:ET, AT:ETc and ATc, heart rate and oxygen saturations were plotted against the peak pulmonary artery systolic pressure from the TR jet. By linear regression analysis, AT:ET before and after oxygen challenge correlated better than other Doppler flow intervals with TR derived Ppa values. There was an inverse relation between AT:ET and calculated peak systolic Ppa before and during the oxygen challenge ($r = -0.72$ and -0.84 , respectively) (figs 1 and 2). The correlation was lower with the other variables.

Pulmonary Doppler flow velocities were obtained in all 12 control subjects. Two of these patients had measurable tricuspid regurgitation with normal calculated pulmonary systolic pressures. A significant difference between healthy infants and patients was found with all variables which was most striking for the 11 infants (15 examinations) with pulmonary artery pressures equal or greater than 35 mm Hg (4.67 kPa) (table 1).

Eleven of the patients given an oxygen challenge had measurable tricuspid regurgitation (table 2). In three examinations low flow oxygen was being administered at the start. Despite this, however, saturations were below 95% in two (cases 2 and 8), probably as a result of the sedation. Reactivity to oxygen was found in eight patients with TR (12 examinations) in association with a concomitant rise in oxygen saturation. Simultaneously, a substantial increase in AT:ET was measured in all these patients (figs 3 and 4). No significant change in AT:ETc or ATc was found after administration of oxygen. Three patients were unresponsive to oxygen despite an adequate rise in saturation. Case 11 (table 2) had very severe pulmonary hypertension and was exquisitely

Table 1 Mean (SD) pulmonary flow intervals in infants with CLD and in control infants

	AT:ET	AT:ETc	ATc	Heart rate per minute
All infants with CLD (n=45)	0.334 (0.049)**	0.485 (0.08)**	118.9 (18.2)*	126.6 (21)**
CI	-0.8, -0.02	-0.18, -0.09	-24.2, -3.3	-38, -21.6
CLD with Ppa of ≥ 35 mm Hg (n=15)	0.296 (0.029)**	0.416 (0.045)**	108.4 (12.3)**	118.4 (19.3)**
CI	-0.11, -0.06	-0.25, -0.16	-35.2, -13.1	-49.8, -26.3
Control infants (n=12)	0.385 (0.039)	0.624 (0.06)	132.6 (14.6)	156.5 (9.3)

AT:ET=acceleration time divided by ejection time; AT:ETc=AT:ET divided by the square root of the R-R interval on the electrocardiogram. ATc=acceleration time divided by the square root R-R interval on the simultaneous electrocardiogram; Ppa=pulmonary artery pressure in infants with tricuspid regurgitant jet; n=number of observations; CI=95% confidence interval of difference between mean CLD and control values. Difference from control group: * $p < 0.05$, ** $p < 0.01$.

Table 2 Mean values of oxygen challenge (and during administration of oxygen) in those infants with pulmonary hypertension and TR

Case No	Age (months)	O ₂	Saturation (%)	Ppa (mm Hg)	AT:ET	AT:ETc	ATc	Heart rate per minute
1	12	—	85 (96)	35 (30)	0.31 (0.35)	0.41 (0.49)	113 (120)	110 (100)
	13	—	91 (95)	35 (27)	0.34 (0.36)	0.48 (0.51)	126 (130)	119 (115)
2	5.5	+	93 (96)	44 (44)	0.28 (0.28)	0.44 (0.44)	99 (100)	147 (146)
3	9	—	95 (96)	44 (44)	0.29 (0.30)	0.40 (0.41)	112 (114)	110 (108)
	14	+	96 (97)	42 (42)	0.33 (0.34)	0.47 (0.48)	120 (119)	120 (128)
4	21	—	86 (95)	43 (30)	0.31 (0.41)	0.42 (0.51)	107 (124)	89 (83)
5	23	—	87 (95)	48 (35)	0.32 (0.33)	0.46 (0.48)	119 (124)	125 (115)
	25	—	92 (95)	44 (35)	0.29 (0.33)	0.39 (0.46)	114 (120)	112 (108)
6	17	—	88 (95)	45 (42)	0.27 (0.28)	0.39 (0.40)	111 (111)	127 (115)
7	21	—	96 (97)	41 (33)	0.29 (0.38)	0.37 (0.53)	112 (129)	95 (90)
	25	—	94 (97)	42 (32)	0.31 (0.39)	0.39 (0.54)	113 (126)	97 (95)
8	12	+	90 (96)	38 (30)	0.28 (0.35)	0.38 (0.55)	92 (120)	114 (100)
9	29	—	90 (97)	38 (25)	0.28 (0.38)	0.39 (0.55)	102 (118)	115 (109)
10	3	—	94 (97)	42 (35)	0.28 (0.32)	0.44 (0.47)	102 (108)	157 (145)
11	5.5	—	86 (97)	78 (30)	0.23 (0.33)	0.34 (0.53)	83 (126)	132 (115)

O₂=maintenance oxygen treatment before study; *arterial saturations by oximeter; Ppa=pulmonary artery pressure calculated from TR.

sensitive to oxygen, with a dramatic drop in Ppa to normal values. Towards the end of the study, when sedation wore off, he awoke abruptly and dislodged the oxygen nasal cannula. The SaO₂ dropped below 90%, and a TR calculated pressure of above 60 mm Hg (8.00 kPa) was again recorded.

Discussion

Survival of very low birthweight infants has improved with advances in neonatal intensive care, but with a concomitant increase in the incidence of CLD.^{25–27} Pulmonary hypertension with its sequelae may be an important complicating factor in infants discharged home on supplemental oxygen. Pulmonary hypertension and cor pulmonale have been clearly demonstrated in infants with CLD by direct measurement,^{2,4,5} and by histological studies.^{27–29} The mechanisms responsible for the development and resolution of pulmonary hypertension in patients with CLD are unknown. Controversy exists as to whether the increased pulmonary vascular resistance is 'fixed' or can decrease in response to increasing concentrations of oxygen ('reactive').^{2,6} One of the main aims of longterm domiciliary oxygen treatment⁷ is to reduce pulmonary hypertension, but the amount of oxygen needed for optimal treatment is not clearly defined and may vary widely between patients.⁶

In this study we found Doppler evidence of TR in 44% of infants with CLD in the absence of clinical signs of TR. In most instances, the detection of TR was time consuming, taking up to 45 minutes. Colour flow mapping was very useful in directing the continuous wave Doppler beam. In many patients the best TR envelopes were obtained during inspiration. We suggest that this is due to the increased venous return to the right side of the heart which normally occurs during inspiration. In this small study the presence of a tricuspid regurgitant jet was unrelated to gestational age, duration of disease, or calculated right ventricular systolic pressure. Measurement of this echoDoppler velocity is the method of choice in the non-invasive assessment of pulmonary systolic pressure^{10,22} and has been validated during cardiac catheterisation in infants.²² The major disadvantages of this method are the

occurrence of TR in less than half of patients, the need for sedation, and the time taken to detect it.

Pulmonary systolic time intervals, on the other hand, are easier to obtain and were measurable in all patients. They are influenced by numerous variables, such as heart rate, ventricular function, and the Doppler sampling site within the pulmonary artery.¹⁶ Great care was taken to use a constant site in the centre of the pulmonary artery distal to the valve. Using two-dimensional imaging and M mode echocardiography, right ventricular function was normal in all patients.

Pulmonary artery pressure from TR correlated inversely with the Doppler derived pulmonary time intervals AT:ET, AT:ETc, and ATc. Of the three pulmonary Doppler time ratios, AT:ET gave the best correlation; AT:ETc and ATc correlated poorly. We have concerns with regard to the accuracy of these dimensionless time ratios and intervals. Their major disadvantage is their approximate correlation with Ppa (systolic, mean, or diastolic).³⁰ Figures 1 and 2 show that the wide 95% confidence intervals make the prediction of Ppa inaccurate. Nevertheless, we found that the change in AT:ET accurately reflected the change in Ppa brought about by oxygen challenge (fig 3). As an empirical guide to pulmonary vascular reactivity, it could therefore be valuable.

Reactivity to oxygen was found in eight of 11 patients with TR, with a drop in tricuspid valve

Figure 3 Values of TR and AT:ET before and after oxygen challenge in individual patients. Solid lines join values before and after an oxygen challenge.

Figure 4 Effect of oxygen on TR derived peak systolic pulmonary artery pressure and measured oxygen saturation, SaO_2 . Solid lines join values before and after an oxygen challenge.

gradient measured pulmonary hypertension of at least 5 mm Hg (0.667 kPa). Three patients were unreactive to oxygen (fig 4) and one of these finally died from severe respiratory failure and cor pulmonale. One patient with severe pulmonary hypertension was exquisitely oxygen sensitive. 'Reactivity' or 'non-reactivity' was unrelated to the age of the patient or duration of disease.

Previous studies have shown that the lower limit of the AT:ET in preterm infants is 0.34^{23 24} and for AT:ETc it is 0.54.¹⁷ Values measured in all our control subjects were comparable with these published ranges.

Cardiac catheter data show that hypoxia is a potent pulmonary vasoconstrictor, and persistent hypoxia may have a deleterious effect on the pulmonary vasculature.³¹ Abman *et al* have shown that oxygen treatment can significantly reduce pulmonary hypertension in older patients with CLD (mean age 25 months).⁶ They suggested that the pronounced reactivity of the pulmonary vascular bed indicated that pulmonary hypertension was probably not just the result of a greatly diminished vascular bed. However, they found that mean Ppa values remained abnormal despite oxygen exposure, and postulated a second fixed component of pulmonary hypertension in these patients. This oxygen unresponsive element is likely to be structural, perhaps due to muscularisation of

the pulmonary arterioles or a reduction in the number of channels. Beyond 4 weeks of age, infants with CLD and pulmonary hypertension have substantial muscularisation of the pulmonary arterioles which progressively increases the longer the CLD is present.^{27 29} Goodman *et al* found that in infants with CLD complicated by pulmonary hypertension, maximum dilatation of the pulmonary vascular bed with oxygen was achieved when arterial oxygen saturations rose to or exceed 95%. They also found that persistence of the pulmonary hypertension when supplemental oxygen was used carried a poor prognosis.

It is important to provide optimal oxygen treatment. Too little may be associated with the complications of chronic hypoxaemia; too much will lead to unnecessarily prolonged treatment and may be a factor in systemic hypertension.³¹ It is apparent from this study that normoxia (saturations equal to or above 95%) may not necessarily abolish pre-existing pulmonary hypertension. Moreover, some patients with CLD were insensitive to oxygen treatment. Whether continuous administration of additive oxygen could afford protection to babies with pulmonary hypertension who are normoxic in ambient air was not determined in the present study.

Other factors, which may have an influence on the 'vascular tone' of the pulmonary vascular bed, such as pH, PCO_2 , sedatives, and intercurrent 'viral' infections, need to be taken into account when assessing pulmonary hypertension. All infants with CLD ought to be regularly evaluated for pulmonary artery pressure and if indicated given an oxygen challenge to determine 'reactivity', as the symptoms and signs of pulmonary hypertension cannot be relied on and are apt to be obscured by the underlying respiratory disease.

Oxygen, a very potent pulmonary vasodilator, remains the mainstay of treatment for infants with CLD to prevent pulmonary hypertension and its consequences. The variability in Ppa in relation to oxygen saturation, seen in patients with CLD, necessitates individual adjustment, and echoDoppler evaluation of Ppa, particularly in the presence of TR, is an important non-invasive tool in its assessment. The role of echocardiography in the management of oxygen treatment in CLD should now be subject to evaluation by appropriate clinical trials.

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