Doppler assessment of pulmonary artery pressure in neonates at risk of chronic lung disease

Bai-Horng Su, Toyoko Watanabe, Mitsumasa Shimizu, Masayoshi Yanagisawa

Abstract

Aim—To evaluate the pulmonary artery pressure (PAP) change in very low birth-weight (VLBW) infants at risk of chronic lung disease (CLD).

Methods—The time to peak velocity:right ventricular ejection time (TPV:RVET) ratio calculated from the pulmonary artery Doppler waveform, which is inversely related to PAP, was used. The TPV:RVET ratio was corrected for different heart rate (TPV:RVET(c)). Seventy three VLBW infants studied on days 1, 2, 3, 7, 14, 21 and 28 were enrolled for the analysis.

Results—Twenty two infants developed CLD with a characteristic chest radiograph at day 28. Fifty one did not, of whom 17 were oxygen dependent on account of apnoea rather than respiratory disease, and 34 were non-oxygen dependent. The TPV:RVET(c) ratio rose progressively in all three groups over the first three days of life, suggesting a fall in PAP. In the oxygen and non-oxygen dependent groups, the mean (SD) ratio rose to 0.53 (0.09) and 0.57 (0.09), respectively, on day 7, then remained relatively constant thereafter. The CLD group rose more slowly after day 3 and had a significantly lower mean ratio from day 7 onwards compared with the other two groups (day 7: $P<0.001$, days 14–28: $P<0.0001$), and fell significantly from 0.47 (0.11) on day 7 to 0.41 (0.07) on day 28 ($P=0.01$), suggesting a progressive rise in PAP. The mean (SD) ratios at day 28 of all infants were: CLD group 0.41 (0.07); oxygen dependent group 0.66 (0.15); and the non-oxygen group 0.67 (0.11). The CLD group had a significantly lower ratio than the oxygen dependent group and the non-oxygen group ($P<0.0001$). Using the TPV:RVET(c) ratio of <0.46 , infants at risk of developing CLD could be predicted on day 7 (predictive value 82.8%, sensitivity 54.5%, specificity 94.1%).

Conclusion—The non-invasive assessment of PAP using the TPV:RVET(c) ratio may be useful in the longitudinal monitoring of PAP change in VLBW infants, and for prediction of chronic lung disease.

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Keywords: Doppler echocardiography; pulmonary artery pressure; chronic lung disease

Improvements in intensive care for very low birthweight (VLBW) infants have achieved

remarkable survival rates, but the incidence of chronic lung disease (CLD) has also increased in recent years.^{1,2} The incidence of CLD differs from one institution to another³ and varies according to the definition, but a recent nationwide survey in Japan showed an incidence of 51.4% among neonatal survivors with a birthweight of less than 1000 g, and 12.3% among those weighing 1000–1499 g.¹ The oxygen dependence at 28 days of age does not exactly represent CLD, particularly in VLBW infants with a gestational age of less than 28 weeks.⁴ Therefore, CLD was defined as the presence of symptoms of persistent respiratory distress and characteristic chest x-ray, in addition to oxygen dependence at 28 days of age.¹

Infants with CLD accounted for half of all infants remaining in hospital for more than six months. The overall mortality of CLD infants was 6.2%.¹ Pulmonary hypertension and cor pulmonale have been demonstrated in infants with CLD as prognostic factors for subsequent morbidity and mortality.^{5–8}

Pulmonary artery pressure (PAP) may be assessed non-invasively using Doppler echocardiography with one of three methods. The detection of tricuspid regurgitation or ductal velocity pattern both permit quantitative estimation of PAP.^{9–14} Another method uses pulmonary systolic time intervals and ratios. By calculating the pulmonary artery Doppler waveform, the ratio of the time to peak velocity:right ventricular ejection time (TPV:RVET) can be measured. This ratio correlates inversely with PAP.^{15–20} The advantage of the tricuspid regurgitation technique and ductal velocity pattern is that a quantitative estimate of PAP can be obtained, but the disappearance of tricuspid regurgitation and ductal closure in most infants by day 10 precludes these methods from use in more long term studies.

This study aimed to evaluate the PAP change using the TPV:RVET ratio in VLBW infants at risk of CLD.

Methods

An Aloka SSD-2000 echocardiographic machine with a 5 MHz real time Doppler transducer was used in this study. Pulmonary flow velocity was assessed by visualising the pulmonary artery from the left parasternal right ventricular outflow view. The pulsed Doppler range gate was placed just distal to the pulmonary valve in the centre of the pulmonary artery and the Doppler waveform recorded. The angle of insonation was always kept to below 20 degrees. Using the incorporated Doppler measurement system the time to

Department of Neonatology, Tokyo Metropolitan Tsukiji Maternity Hospital, Tokyo, Japan
B-H Su
T Watanabe
M Shimizu

Department of Paediatrics, Faculty of Medicine University of Tokyo
B-H Su
M Yanagisawa

Correspondence to:
Dr Bai-Horng Su,
Division of Neonatology,
Department of Paediatrics,
China Medical College
Hospital,
75 Yuh Der Road, Taichung,
Taiwan.

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Table 1 Demographic and clinical characteristics (values mean (SD) (range) or No (%))

	CLD (n=22)	OD (n=17)	N-OD (n=34)
Gestational age (weeks)	26.2 (0.5) (23-33) ^{a,b}	28.7 (0.3) (27-32) ^{a,c}	30.6 (0.3) (25-35) ^{b,c}
Birthweight (g)	867 (60) ^{d,e} (582-1498)	1067 (49) ^{d,f} (674-1316)	1268 (30) ^{e,f} (710-1487)
Gender (M/F)	11/11	10/7	13/19
Infants receiving artificial ventilation:			
Day 1	22 (100)	17 (100)	34 (100)
Day 2	22 (100)	15 (88.2)	22 (64.7)
Day 3	22 (100)	12 (70.6)	20 (58.8)
Day 7	21 (95.5)	8 (47.1)	8 (23.5)
Day 14	21 (95.5)	5 (29.4)	3 (8.8)
Day 21	21 (95.5)	2 (11.8)	2 (5.9)
Day 28	21 (95.5)	0	0

The CLD group had a significantly lower gestational age (^a: $P = 0.001$, ^b: $P < 0.0001$) and birthweight (^c: $P = 0.02$, ^d: $P < 0.0001$) and higher percentage receiving artificial ventilation on day 2 than the N-OD group ($P = 0.02$), on day 3 than the OD group ($P = 0.006$) and N-OD group ($P = 0.0005$), and from day 7 onwards than the OD and N-OD groups ($P < 0.0001$). There were also differences in gestational age (^e: $P = 0.02$) and birthweight (^f: $P = 0.01$) between the OD and N-OD groups, but no differences in numbers of infants receiving artificial ventilation. There were no differences in gender.

CLD = chronic lung disease; OD = oxygen dependent; N-OD = non-oxygen dependent.

peak velocity was measured from leaving the zero flow baseline to its peak velocity, the right ventricular ejection time was measured from leaving to returning to the zero baseline.¹⁵⁻²¹

Three to five clearly defined waveforms were measured and averaged. The TPV:RVET ratio was corrected for different heart rate (TPV:RVET(c)) by dividing by the square root of R-R interval in seconds on electrocardiography or peak-to-peak interval in seconds of the Doppler velocity time signals.¹⁹

Consecutive ventilated infants, including inborn and outborn, with birthweights of less than 1500 g and no congenital abnormalities were studied. All infants followed the unit's routine policy of management of VLBW infants under mechanical ventilation, including early treatment of a patent ductus arteriosus (PDA) with intravenous indomethacin if there were symptoms and signs of PDA in the presence of a predominant left to right shunt on an echocardiogram. All infants were studied at 1, 2, 3, 7, 14, 21 and 28 days of age. The fractional inspired oxygen (FIO₂) requirement at the time of scan was recorded. At the first echocardiographic examination normal cardiac anatomy was confirmed. All the Doppler examinations were made by one observer (BHS). Because the status of oxygen supplementation and ventilator dependence was obvious at the bedside, to avoid subjective bias in measurement the observer was blinded to the x-ray findings. Eighty echocardiograms were randomly sampled for independent measurement by other investigators, who were kept blind to the initial measurement and clinical condition. The correlation coefficient was 0.94, and the mean (SD) percentage of the differences between the paired measurements was -0.8 (7.0)%. At 28 days of age the infants were divided into CLD and non-CLD groups. The CLD group included infants with respiratory distress requiring oxygen and a characteristic chest radiograph,¹ and the non-CLD infants were further divided into oxygen dependent, which included infants with oxygen dependence and a normal chest radiograph, and non-oxygen dependent, which included infants who were not oxygen dependent and a normal chest radiograph.

The results are expressed as mean and standard deviation (SD) or standard error (SE), as appropriate, and range. Statistical comparison between groups used the two tailed *t* test for categorical data, the Wilcoxon rank sum test for sequential data within groups, and the χ^2 test for the comparison of numbers receiving mechanical ventilation and those with PDA. A *P* value below 0.05 was considered significant.

The study was approved by the Institutional Review Board of Tokyo Metropolitan Tsukiji Maternity Hospital and parental permission was obtained for all infants.

Results

From March 1995 through March 1996, 80 infants were enrolled into the study. Of the 80 infants enrolled, seven were excluded from further analysis because they died, and a total of 73 infants completed the study. At 28 days of age, 22 infants were identified as belonging to the CLD group, 17 infants as oxygen dependent, and 34 infants as non-oxygen dependent. Table 1 gives the demographic and clinical data for the three groups. Infants with CLD were of significantly lower birthweight and gestational age when compared with the other two groups. There was no significant difference in gender among the groups. The number of infants in the oxygen and non-oxygen dependent groups receiving artificial ventilation decreased from day 2 until none was being ventilated by day 28. Only one of the CLD infants could be taken off artificial ventilation by this time. Table 2 shows the FIO₂ on each day of the study. The pulse oximetry saturation (Ohmeda, Biox 3700 or 3740) was maintained between 92 and 96%. The FIO₂ from day 1 was significantly lower in the oxygen and non-oxygen dependent groups than the CLD group ($P < 0.001$ - 0.0001). There was no difference in the oxygen and non-oxygen dependent groups. There was a rise in the FIO₂ in the CLD group from day 14 to day 28, but this was not significant. Table 3 shows the ductal patency in three groups. There were no significant differences in the duration of ductal patency in the three groups.

Figure 1 shows the change in the TPV:RVET(c) ratio on days 1, 2, 3, 7, 14, 21 and 28. There was a progressive rise in

Figure 1 Mean (SD) TPV:RVET(c) ratio in the three groups according to day of study. Broken line represents lower limit of normal range for TPV:RVET(c) = 0.46; CLD, chronic lung disease; OD oxygen dependent; N-OD non-oxygen dependent. * $P < 0.001$; ** $P < 0.0001$ (differences between CLD and other two groups).

Table 2 FIO_2 on the day of study in three groups

Day of study	CLD (n=22)	OD (n=17)	N-OD (n=34)
1	67 (3)	47 (4)	44 (1)
2	54 (3)	37 (1)	33 (1)
3	43 (3)	34 (2)	29 (1)
7	37 (2)	28 (2)	26 (1)
14	36 (2)	28 (1)	23 (1)
21	38 (3)	26 (2)	22 (1)
28	40 (3)	25 (1)	21 (2)

Values are mean (SE) FIO_2 (%). The FIO_2 from day 1 was significantly lower in the OD and N-OD groups than the CLD group ($P < 0.001$ – 0.0001). There was no difference in the OD and N-OD groups.

Table 3 Number of infants with patent ductus arteriosus

Day of study	CLD (n=22)	OD (n=17)	N-OD (n=34)
1	21 (95.5)	14 (82.4)	29 (85.3)
2	19 (86.4)	14 (82.4)	24 (70.6)
3	11 (50)	7 (41.2)	12 (35.3)
7	2 (9.1)	1 (5.9)	0
14	2 (9.1)	0	0
21	1 (4.5)	0	0
28	1 (4.5)	0	0

Values are number (per cent). There were no significant differences among the three groups.

TPV:RVET(c) ratio in all three groups over the first three days of life, suggesting a progressive fall in PAP. In oxygen and non-oxygen dependent groups, the mean (SD) ratio rose to 0.53 (0.09) and 0.57 (0.09), respectively, on day 7, then continued to rise and remained relatively constant thereafter. However, in the CLD group the TPV:RVET(c) ratio rose more slowly after day 3 and there was a significantly lower mean ratio from day 7 onwards compared with the other two groups (day 7: $P < 0.001$, days 14–28: $P < 0.0001$), and fell significantly from 0.47 (0.11) on day 7 to 0.41 (0.07) on day 28 ($P = 0.01$), suggesting a progressive rise in PAP.

Figure 2 shows the distribution of the TPV:RVET(c) ratio on day 28 for all the infants; the mean (SD) TPV:RVET(c) ratio for the CLD group was 0.41 (0.07), which was significantly lower than the mean for the oxygen dependent group (0.66 (0.15) $P < 0.0001$) and the mean for the non-oxygen dependent group (0.67 (0.11) $P < 0.0001$). There was no difference between the oxygen and non-oxygen dependent groups.

From the time course of the change of PAP, it seems that days 3 to 7 were a watershed for the CLD and non-CLD groups. Therefore, the normal range for TPV:RVET(c) in VLBW infants was derived from the postnatal stable state on day 7 achieved in the non-oxygen dependent group (0.46 to 0.77). Using CLD at day 28 as the end point, a TPV:RVET(c) ratio of < 0.46 on day 7 had a positive predictive value of 80% (12/15) and a negative predictive value of 82.8% (48/58), with a sensitivity of 54.5% (12/22) and specificity of 94.1% (48/51).

Discussion

CLD is mainly confined to VLBW infants. In this study there was a 30.1% (22/73) incidence of CLD. The remaining 69.9% (51/73) of non-CLD infants were further divided into oxygen dependent (23.3%, 17/73) and non-oxygen dependent groups (46.6%, 34/73) (table 1). The infants with CLD had a significantly lower

birthweight and gestational age than the other two groups. There was also a significant difference between the oxygen dependent and non-oxygen dependent groups. This implied that CLD develops easily in extremely low birthweight (ELBW) infants with a birthweight of less than 1000 g, and that the VLBW infants, even though without CLD, were often given supplementary oxygen for apnoea. The data support the belief that oxygen dependence at 28 days of age was not CLD, particularly in VLBW infants with a gestational age of less than 28 weeks.⁴

The confounding variables for interpretation of the TPV:RVET ratio are heart rate, Doppler sample position for measuring the ratio, right ventricular dysfunction, and the presence of large left to right shunts.^{17–22–24} As the TPV:RVET ratio may fall with increasing heart rate, we corrected the TPV:RVET ratio by the square root of R-R interval on electrocardiography or peak-to-peak intervals of the Doppler velocity time signals.¹⁹ There was no evidence of right ventricular dysfunction at each echocardiographic study. The incidence of PDA requiring indomethacin treatment in three groups revealed no significant differences.

We found that there was a progressive fall in pulmonary artery pressure in all three groups over the first three days of life, reflected by a rise in TPV:RVET(c) ratio. However, the rate of rise in TPV:RVET(c) ratio after day 3 was slower in the CLD group, and therefore had a significantly lower ratio on day 7. This is probably attributable to the fact that these infants had more premature lungs, reflected by the significantly higher FIO_2 during the first three days. The mean TPV:RVET(c) ratio in the CLD group never reached the same level as that in the non-CLD group and fell significantly from day 7 to 28, suggesting a

Figure 2 TPV:RVET (c) ratio for each group at day 28. Broken line represents lower limit of normal range for TPV:RVET(c) = 0.46. Mean ratio for each group is shown by horizontal black line. The mean of the CLD groups is significantly different from that of the OD and N-OD groups ($P < 0.001$). The means of these latter groups were not significantly different.

progressive rise in pulmonary artery pressure. Evans and Archer²⁰ showed the TPV:RVET ratio rose after birth in all healthy infants, but it rose more slowly in the premature infants, and by 73 to 96 hours was not significantly different. They also showed the mean ratio was significantly lower during the acute phase of respiratory distress syndrome (RDS) than in those without RDS,²¹ and during the recovery phase the group of significantly lower gestation still had a below normal range ratio.²⁵ In another longitudinal study Gill and Weindling²⁶ showed during the first 14 days that the TPV:RVET(c) ratio rose progressively in both CLD and non-CLD groups; from day 14 to day 28 a significant fall in the ratio in the CLD group was noted. We found that all infants had a progressive rise in the ratio over the first three days of life; in the non-CLD group the ratio continued to rise through day 7 and then remained constant. In contrast, in the CLD group the ratio rose slowly after day 3 and then had a lower mean ratio from day 3 onwards. Our results show that there was a significant difference in the TPV:RVET(c) ratio between CLD and non-CLD groups from the second week, and not until the third week, as Gill and Weindling showed.²⁶ Our results suggest that the cardiovascular adaptation to extrauterine life occurs over the first seven days, even in VLBW infants with severe RDS, although at a slower rate. However, persistent impairment in lung function and parenchymal damage due to barotrauma and oxygen toxicity during the course of mechanical ventilation seem to reverse these changes, leading to a rise in PAP. Previous studies in vitro and in vivo have suggested that oxygen toxic effects and barotrauma occur very early in the course of RDS,²⁷⁻²⁹ during which the underlying pathogenesis of bronchopulmonary dysplasia was probably already established. The reason for the rise in PAP in CLD is unclear, but is supposed to be due to significant musculation of the small pulmonary arterioles which progressively increased the longer the CLD was present.^{6, 30} Our CLD group had more infants receiving artificial ventilation for longer (95% from day 7 through day 28) compared with those of Gill and Weindling (79% at day 7 and 38% at day 28).

Kitabatake *et al*¹⁵ and Akiba *et al*¹⁹ have shown a close negative correlation between the TPV:RVET ratio and pulmonary artery pressure in older infants and adults. The results of Evans and Archer²⁰ show that the normal range of the TPV:RVET ratio in premature infants (0.34 to 0.41) was derived from a group of 19 healthy premature infants with a gestational age of 31.8 weeks (range 28–34) and birthweight 1610 g (range 950–2050), of whom seven were between 28 and 31 weeks. Our infants were significantly smaller than those. In the longitudinal study of Gill and Weindling²⁶ they adopted 0.34 as the lower limit for TPV:RVET ratio, and 155/minute as the average heart rate²¹ to achieve a TPV:RVET(c) of 0.54 as a lower limit of PAP in the premature infants, even though they had a control group of significantly smaller infants than those of

Evans and Archer. Fitzgerald and Evans,³¹ in another study on older infants and children of survivors of CLD, even though they enrolled a control group of 12 premature and nine term infants, and two of these premature infants had a TPV:RVET ratio of 0.31 and 0.34, still used 0.35 as the lower limit and defined those two premature infants into “possibly low” TPV:RVET. Indirect methods of assessing PAP are subject to a certain degree of error. We cannot know if the actual PAP is high in clinically healthy infants with Doppler echocardiographic evidence of possibly raised PAP. A recent study showed a considerable intraobserver variation in Doppler assessment of PAP.³² An interobserver variation would also be greater. Therefore, in this study we tried to use our own control group of smaller infants, providing a normal range. From the time course of the PAP change it seems that days 3 through to 7 were a watershed for further progress in the CLD and non-CLD groups. Therefore, the normal range for the TPV:RVET(c) ratio in VLBW infants was derived from the postnatal stable state at day 7, achieved in the non-oxygen dependent group (0.46 to 0.77). The reason for this at day 7 was that it might be the most stable postnatal state with the mean FIO₂ of 26%, only 23.5% of infants still on the ventilator, and no infants with persistent PDA. Using CLD at day 28 as the end point, a TPV:RVET(c) ratio of < 0.46 on day 7 had a positive predictive value of 80% and a negative predictive value of 82.8%, with a sensitivity of 54.5% and specificity of 94.1%. Using the TPV:RVET(c) ratio of < 0.54²⁶ on day 7, would give a positive predictive value of 46.2% and a negative predictive value of 88.2%, with a sensitivity 81.8% and specificity 58.8%. Using different indices produced remarkably different results.

Our results show the low TPV:RVET(c) group had a significantly lower gestational age and birthweight than the normal range group, which is compatible with the results of Evans and Archer.²⁵ Although the low ratio might reflect the presence of raised PAP in the CLD group, it might also mean that normal values of the TPV:RVET(c) ratio for smaller infants are lower. Using the TPV:RVET(c) ratio as an indirect method for assessing PAP, all such results need to be interpreted with caution.

We also found a progressive increase in the correlation between the TPV:RVET(c) ratio and FIO₂ from days 1 to 28. This agrees with the results of Gill and Weindling, which show an association between PAP and the severity of CLD. Benatar *et al*³³ found that PAP using the tricuspid regurgitation technique correlated inversely with the Doppler derived time interval TPV:RVET and TPV:RVET(c), but the wide 95% confidence intervals from linear regression analysis make the prediction of PAP using the ratios inaccurate. However, the change in TPV:RVET(c) accurately reflected the change in PAP brought about by oxygen challenge.

In conclusion, while less accurate than the tricuspid regurgitation technique, in the infants without detectable tricuspid regurgitation, the

TPV:RVET(c) ratio may be useful for longitudinal monitoring of PAP change. Our results show significant difference in the ratio between CLD and non-CLD groups which can be detected by the second week. This provides an early prediction of infants at risk of developing CLD and the opportunity for appropriate management to prevent the progressive rise in PAP and to decrease the severity of CLD.

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