Raised pulmonary artery pressure in very low birthweight infants requiring supplemental oxygen at 36 weeks after conception

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Abstract
This study aimed to investigate the changes in pulmonary artery pressure in infants with chronic lung disease who then developed prolonged oxygen dependency. The time to peak velocity:right ventricular ejection time (TPV:RVET) ratio calculated from the Doppler waveform, which correlates negatively with pulmonary artery pressure, was used.

Thirty four infants with chronic lung disease were studied. At 36 weeks after conception 19 infants still required supplemental oxygen (POD group) and 16 infants were in air (controls). Over the first three weeks, there was a significant rise in the ratio in both groups, indicating a fall in pulmonary arterial pressure. From the third week onwards the ratio was significantly lower in the POD group. There was a significant rise in the ratio from four to 36 weeks after conception in the control group; the POD group showed a tendency towards a fall over the same time period. The requirement for supplemental oxygen almost mirrored the changes in the ratio in both groups but was not significantly different until the fifth week after birth.

These data suggest that pulmonary arterial pressure has a significant role in the pathophysiology of prolonged oxygen dependency and may be important in the subsequent morbidity associated with this group of very low birthweight infants.

Keywords: pulmonary artery pressure, supplemental oxygen, very low birthweight.

Chronic lung disease was defined by Northway et al as oxygen dependence at 28 days. It is a major cause of short and long term morbidity and mortality, particularly in very low birthweight infants. Its incidence may be increasing and this cannot be fully accounted for by an increased survival rate for very low birthweight infants. The prognostic importance of oxygen dependency at 28 days is debated, particularly in infants with a gestational age of less than 26 weeks. Prolonged oxygen dependency (POD), defined as an oxygen requirement at the age of 36 weeks after conception (PCA), is likely to be a better predictor of subsequent respiratory morbidity and mortality.

The time to peak velocity:right ventricular ejection time (TPV:RVET) ratio correlates negatively with pulmonary artery pressure and has been used to study the changes in this in infants with hyaline membrane disease and in very low birthweight infants developing chronic lung disease. Raised pulmonary artery pressure was invariably found in those infants developing chronic lung disease compared with controls. Further evidence from a cross-sectional study design has suggested that pulmonary arterial pressure was raised in a significant proportion of infants who developed chronic lung disease during their neonatal course and who were examined between 2 and 4 years of age. Because the natural history of this increased pulmonary arterial pressure is not known, the aim of this study was to determine the TPV:RVET ratio in a group of infants developing POD who had previously fulfilled the diagnostic criteria for chronic lung disease.

Methods
All infants were studied using an ATL Ultramark 4 scanner with a 5 MHz range-gated, pulsed-wave Doppler probe. Two-dimensional imaging was performed using a 7.5 MHz probe. The pulmonary artery was visualised from the parasternal long axis view by rotating the probe and angling upwards until the right ventricular outflow tract, pulmonary valve, and main pulmonary artery were seen. The sample volume of the range-gated Doppler signal was placed distal to the pulmonary valve and the Doppler signal recorded. A sweep speed of 100 mm/second made it possible to identify individual Doppler waveforms. A minimum of five waveforms were recorded into the system's computer module for off-line analysis.

Using the Doppler measurement system incorporated into the machine, the time to peak velocity (TPV) and right ventricular ejection time (RVET) were measured as described before. The TPV:RVET ratio was corrected for heart rate (TPV:RVET (c)) by dividing by the square root of the R-R interval.

Thirty four very low birthweight infants fulfilled the diagnostic criteria for chronic lung disease, defined as those infants who were ventilated for hyaline membrane disease in the first 48 hours after birth and who were receiving supplemental oxygen at 28 days, with characteristic radiographic appearances of chronic lung disease. These infants were studied weekly from day 1 to 36 weeks after conception. Data for the first 28 days have...
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been reported before. The concentration of inspired oxygen (FiO2) at the time of each measurement was also recorded. No infant was sedated at the time of measurement and oxygen saturations were maintained between 90 and 96%. Right ventricular function was visually assessed during each study.

At 36 weeks after conception data from infants receiving supplemental oxygen (POD group) were compared with those in air (controls). Results were expressed as medians (interquartile range). Comparison of data between groups was performed using the Mann-Whitney U test. The Wilcoxon rank sum test was used for matched comparisons, within groups, from one week to another. Significance was taken at the 5% level.

The study was approved by the Liverpool Area Health Authority ethics committee, and informed consent was obtained from the parents of each infant studied.

Results

Nineteen infants developed POD; the 15 who were in air at 26 weeks after conception acted as controls. The groups were similar in respect of birth weight (780 g (POD) v 884 g (controls), p=0-12) and gestation (26 weeks (POD) v 27 weeks (controls), p=0-10). The figure shows the weekly changes in the TPV:RVET (c) ratio and FiO2 from day 1 to 36 weeks after conception. There was a significant rise in the ratio in both groups over the first two weeks (p<0.05). However, by week 3 after birth the ratio was significantly lower in the POD group compared with the controls (p=0-02). This difference remained significant for the remainder of the study period.

In the POD group the TPV:RVET (c) ratio declined from week 3 to 36 weeks after conception but this did not reach significance (0.48 (week 3) v 0.46 (36 weeks); p=0.096). By contrast, there was a significant rise in the ratio over the same period in the control group (0.51 v 0.55; p=0.014).

The FiO2 fell sharply in both groups over the first two weeks but was not significantly different until the fifth week after birth (0.26 (controls) v 0.35 (POD); p=0.007). This significant difference persisted for the remainder of the study period. All infants in the control group were in air by the age of 34 weeks after conception.

Discussion

The improved survival of the more preterm infant has arguably diminished the usefulness of oxygen dependency at 28 days as a marker for subsequent prognosis. Shennan et al examined subsequent respiratory morbidity over the first two years after birth and found that oxygen dependency at 36 weeks after conception had the highest sensitivity, specificity, and positive predictive value, particularly for infants of less than 30 weeks’ gestation. It seems hardly surprising that infants, especially those of less than 26 weeks’ gestation, still require supplemental oxygen 28 days after birth, and this has detracted from the clinical usefulness of outcome measures described by Northway et al in their original cohort. Better prognostic indicators are required.

The correlation between the TPV:RVET (c) ratio and pulmonary artery pressure and the factors influencing the ratio have been discussed in detail both by ourselves and others, and in the interests of brevity, we refer the reader to these papers.

The results of this study confirmed the sharp fall in pulmonary artery pressure over the first week after birth even in those infants who subsequently developed POD, as described before. This seems to be part of the pulmonary vascular adaptation to extra-uterine life, but more importantly it suggests that pulmonary vasculature resistance has the potential for reversibility even in those who go on to develop POD. The fact that the fall in pulmonary artery pressure is not sustained in some infants, in whom it then rises, suggests that treatment aimed at improving pulmonary function by decreasing pulmonary hypertension needs to be started early in the postnatal course. Recent evidence by Evans on the use of dexamethasone in chronic lung disease showed a transient but unsustainable rise in the TPV:RVET (c) during treatment. Some of this may be explained by the wide range of postnatal ages at which dexamethasone was started as pathology studies have shown that the severity of the pulmonary vascular changes in infants with chronic lung disease, suggestive of pulmonary hypertension, increased with increasing postnatal age.

Our data suggest that in some infants pulmonary artery pressure remains persistently increased while those infants are receiving supplemental FiO2. In a cross-sectional study design Fitzgerald et al suggested that infants who developed chronic lung disease in the neonatal period seemed to have raised pulmonary arterial pressure when examined between 2 and 4 years of age, despite no longer requiring supplemental oxygen. Evidence is appearing which suggests that persistent
respiratory problems are a consistent finding in children who had chronic lung disease in the newborn period.\(^5\) \(^7\) \(^8\) \(^20\) Further study is required to determine if pulmonary vascular disease is a feature in these children.

It may be important that the median value for the TPV:RVT (c) ratio in the control group lay only at the lower limit of the normal range and seemed to lag behind the fall in FIO\(_2\) as it could suggest that there is an important underlying problem. Evidence suggests that respiratory compromise, requiring hospital admission, is more common in preterm infants, even those who did not have prolonged oxygen dependency or chronic lung disease.\(^21\)

In a study of infants admitted with respiratory syncytial virus bronchiolitis (without underlying lung disease) Sreram \textit{et al} invariably found an increase in pulmonary artery pressure during the acute phase of the illness.\(^22\) The level seemed to correlate with disease severity. If the resting pulmonary artery pressure is at the upper limit of normal then respiratory infection may lead to a further increase in pulmonary artery pressure and, combined with a deterioration in respiratory function, could lead to sustained respiratory compromise, requiring hospital admission.

The changes in supplemental FIO\(_2\) seemed to mirror the changes in the TPV:RVT (c). This is not surprising given the interrelation between arterial oxygen tension and pulmonary arterial pressure, and the effect that improvements in pulmonary function will have on a perceived need for supplemental FIO\(_2\). In the control group the slow decline in FIO\(_2\) was matched by the slow rise in the TPV:RVT (c). In contrast, in the POD group there was a decrease in the ratio without a rise in FIO\(_2\) over the same time period. Data on cardiac catheters in children with chronic lung disease\(^23\) \(^24\) showed that increased pulmonary arterial pressure correlated with outcome and, more importantly, that infants who failed to show changes in pulmonary pressure while receiving 100% FIO\(_2\) had a uniformly poor prognosis. This suggested that chronic irreversible pulmonary vascular changes may be important in contributing to long term respiratory morbidity.

In summary, this study has shown that increased pulmonary artery pressure was a feature in infants developing prolonged oxygen dependency. The potential for a fall in pulmonary artery pressure seemed to diminish after the third week, suggesting that any therapeutic manoeuvre should begin before this time. The increased pulmonary artery pressure may well contribute to the significant morbidity found in these infants and further study is required to determine the natural history of this increased pulmonary artery pressure as it may be an important determinant of long term outcome in these children.

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