NON-INVASIVE DETERMINATION OF PULMONARY ARTERIAL PRESSURE IN THE NEWBORN

M.D. thesis

Jonathan Robert Skinner

1993
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Acknowledgements

Turning the wide-eyed optimism of a young researcher into practical and worth-while research can be a most difficult job, and I am exceedingly grateful to my two supervisors for keeping me (more-or-less) on the straight and narrow. Stewart Hunter introduced me to the exciting world of echo-Doppler, and in particular Doppler techniques for the estimation of pulmonary arterial pressure. He was (and still is) always available to give advice, and was the main driving force in getting financial backing, which was a considerable headache and worry on several occasions. He also introduced me to Edmund Hey, who, after saying that he had been waiting for somebody to come along and look seriously at neonatal haemodynamics for years, fuelled my enthusiasm tremendously and directed me to the most relevant previous research from more than twenty years ago. Edmunds' attention to detail in the writing up phase has been invaluable; he has an uncanny knack of spotting the dot on a graph which was not in the table! My thanks to David Milligan for his kind and enthusiastic support and in particular for his practical help and advice with the study of central venous pressure, and for being instrumental in obtaining the Doppler upgrade for the ultrasound machine at the General Hospital.

I am grateful to Alison Heads for her excellent and patient teaching of the practical aspects of echocardiography, and her help in the variability studies. My thanks also to Richard Boys who has given advice and practical help with the statistical analyses, and to Bernie McKenna for her secretarial help with the bibliography.

Financial support came firstly from the local scientific and research committee of Newcastle upon Tyne, and latterly from the National Heart Research Fund, who stayed with me loyally despite financial difficulties of their own. I am most thankful for their generous support, and I hope that they are pleased with the outcome of the project. I am indebted to Hewlett-Packard for the loan of the Sonos 100 ultrasound machine at the start of the study, and to "Children in Need" who spent twenty thousand pounds on the Doppler upgrade of the ultrasound machine at the General Hospital.

My thanks also to Professor Aynsley Green, and to the many members of the Newcastle university department of child health, for the kind support and excellent facilities made available to me.

The neonatal nursing staff at both the Princess Mary Maternity Hospital and the General Hospital have shown patience and good humour beyond the call of duty. I hope the few occasions that I was of practical help made up for the many days when I was a pain in the neck. The same goes for all the babies and their parents.
The project would have been unbearable without Lisa, who has had to live with the MD almost as much as I have. She has given advice, encouragement and support and kept me from losing my sanity (at least that's what the voices tell me...). I now hope to see more of her and less of this.

Finally, my thanks to anyone who gives this thesis the ultimate accolade, by taking the trouble to read it.

The thesis is dedicated to my family and in particular to Thomas Skinner, my beloved grandad, who died in January 1992 aged ninety years. It was his unfulfilled ambition to have a book published, and was looking forward to seeing this thesis. I hope he finds it to be a "proper job".
"Non-invasive determination of pulmonary arterial pressure in the newborn"

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Abstract

In the newborn preterm baby with respiratory failure, pulmonary arterial pressure can fluctuate dramatically, yet invasive monitoring is not usually practical in this population. This thesis studies the use of Doppler echocardiography in the non-invasive assessment of pulmonary arterial (PA) pressure in the newborn, concentrating on measuring peak velocity of tricuspid regurgitation and applying the modified Bernoulli equation (the "TR method"), but also assessing the alternatives; analysis of ductal flow and two right ventricular systolic time interval ratios.

The TR method was found to be reasonably accurate when compared to direct cardiac catheter measurement (95% confidence limits -12 mmHg to +8 mmHg) and repeatable (repeatability index <10%) but feasibility of measurement was limited, particularly in babies with bronchopulmonary dysplasia. Ductal flow and right ventricular systolic time intervals (TPV/RVET ratio (time to peak velocity at the pulmonary valve/right ventricular ejection time) and PEP/RVET ratio (right ventricular pre-ejection period/RVET) were assessed as alternative techniques by comparing values with those obtained simultaneously using the TR method. 741 Doppler echocardiograms from 203 babies in the first month of life were analysed.

The pattern of ductal flow during the cardiac cycle was shown to reflect both the pulmonary : systemic arterial pressure ratio, and the quantity of left-to-right shunting. Measurement of the velocity of flow across the duct was useful in studying serial haemodynamic change within a baby, particularly in persistent transitional circulation, but application of the modified Bernoulli equation to the velocity, to determine pressure drop across the duct, was unreliable. Systolic time intervals and ratios were subject to considerable error in measurement, and the relationship to pulmonary arterial pressure was not consistent between babies of different gestation and was influenced by other factors such as ductal patency.

Using a combination of the TR method and analysis of ductal flow, longitudinal studies of
systolic PA pressure in healthy newborns and babies ventilated for HMD were performed in the first days of life. The rate of fall in the pulmonary : systemic (PA:Ao) arterial pressure ratio was similar in healthy term and preterm babies. In the babies with HMD, PA pressure fell more slowly, Ao pressure rose more slowly and ductal closure was delayed. PA pressure did not correlate with disease severity. Babies of lower gestation had lower PA pressure values, and, in general, a more rapid fall in the PA:Ao arterial pressure ratio than more mature babies.

The haemodynamic effects of altering inspired oxygen levels was investigated using all four methods of PA pressure estimation. This was done by expressing the haemodynamic changes in terms of multiples of confidence limits of repeatability of each technique (termed "confidence steps") a technique which shows considerable promise for further study.

Amongst babies with persistent fetal circulation, ductal flow velocities were particularly sensitive in detecting haemodynamic change, but none of the initial measurements of PA pressure correlated with eventual outcome.

Doppler echocardiography now permits reasonably accurate and clinically useful non-invasive determination of pulmonary arterial pressure in most newborn babies with cardiorespiratory distress. Four techniques were evaluated in this thesis, and while each was found to have advantages and disadvantages, the TR method, limited by feasibility in some patients, was found to be the most reliable.
Summary of the thesis

In chapter 1, the thesis begins with a review of the fetal and transitional circulation, and identifies the fall in pulmonary vascular resistance and pulmonary arterial pressure as the central event in the transitional circulation. The few studies in the human fetus and neonate are discussed in some depth, and the pulmonary : systemic arterial pressure ratio is identified as particularly useful in monitoring postnatal circulatory adaptation, although longitudinal data are scarce. Some of the many factors influencing post-natal circulatory adaptation are discussed, based mostly on studies in animals. Studies on the pulmonary circulation in the human neonate are reviewed, and reveal that there is remarkably little information about the effect of prematurity on the transition that occurs after birth although publications from the early 1970's suggest low pulmonary blood flow or "pulmonary ischaemia" as the primary underlying cause of hyaline membrane disease (chapter 2). After surfactant deficiency was accepted as the primary underlying cause, there is little data on the pulmonary circulation, during the era of modern neonatal intensive care.

Non-invasive methods of haemodynamic assessment, concentrating on determination of pulmonary arterial pressure using Doppler echocardiography, are then reviewed in detail in chapter 3. Previous studies in the adult and older child reveal that measurement of pulmonary arterial pressure by measuring peak velocity of tricuspid regurgitation (TR) and application of the modified Bernoulli equation is the most repeatable and accurate technique. However, the method had not previously been validated in the newborn, and the incidence of tricuspid regurgitation was not known. Another method of some potential was assessment of flow across the arterial duct, although authors differed as to the accuracy of determining pressure drop across the duct by applying the modified Bernoulli equation. Most of the few previous echocardiographic studies of pulmonary arterial pressure in the neonate (reviewed in chapter 4) had used right ventricular systolic time intervals, techniques which did not appear to reliably reflect pulmonary arterial pressure when compared with direct pressure measurements.

This thesis studies the use of Doppler echocardiography in the non-invasive assessment of pulmonary arterial pressure in the newborn, concentrating on measuring peak velocity of tricuspid regurgitation and applying the modified Bernoulli equation (the "TR method"), but also assessing the alternatives. The aims and methods are outlined in chapters 5 and 6.

In chapter 7, twenty eight direct measurements of right ventricle to right atrial (RV-RA) pressure drop were compared with the RV-RA pressure drop derived from applying the modified Bernoulli equation (p=4v^2) to the peak velocity of tricuspid regurgitation, in infants with congenital heart disease undergoing cardiac catheterisation (p=pressure drop in mmHg and v= velocity in metres/second). There was close agreement (95% confidence...
limits -12 mmHg to +8 mmHg) and correlation (r=0.95) between direct and TR measurements, although the TR method slightly underestimated the RV-RA pressure drop, by a mean of 2 mmHg.

A longitudinal study of healthy newborns over the first three days of life was performed using the TR method (chapter 8). 34 babies were at term and 17 were preterm. Right atrial pressure was treated as if it were zero (in the light of previous catheterisation studies) in determining systolic pulmonary arterial pressure. The derived RV-RA pressure drop in the term babies corresponded to known neonatal systolic pulmonary arterial pressure data. The rate of fall in the systolic pulmonary : systemic arterial pressure ratio was very similar in term and preterm babies. This arterial pressure ratio was mirrored by ductal flow patterns anticipated from previous studies correlating direct pressure measurement with ductal flow, (bidirectional flow 0.88:1 - 1.22:1, high velocity left-to-right flow 0.49:1 - 0.66:1) suggesting that the TR method was truly reflecting pulmonary arterial pressure, and in turn suggesting that analysis of ductal flow patterns may itself be a useful technique to assess the pulmonary : systemic arterial pressure ratio in the newborn. However, measurement of TR was only feasible in roughly a quarter of the term babies and a half of the preterm babies.

To determine a reasonable allowance for right atrial pressure in ventilated babies, a review was performed in chapter 9 of right atrial pressure values taken from 49 neonatal cardiac catheterisations for babies with congenital heart disease, and (prospectively) from 13 newborns ventilated for respiratory disease. A literature review was also done. An allowance of 5 mmHg seemed to be most appropriate in babies ventilated for hyaline membrane disease.

The incidence of measurable tricuspid regurgitation was much higher in a longitudinal study of 33 babies ventilated for hyaline membrane disease (chapter 10), at over 90% in the first 36 hours of life falling to about 30% at day ten (or about 50% of those still ventilated). The resulting pulmonary arterial pressure values varied greatly amongst this population. In general, hyaline membrane disease was characterised by a delay in the normal postnatal fall in pulmonary arterial pressure and rise in systemic arterial pressure, with prolonged ductal patency. Statistical analysis revealed little correlation between pulmonary arterial pressure and disease severity, though systemic arterial pressure was reduced by high mean airway pressure and pneumothorax. Babies of lower gestation had lower absolute values of pulmonary arterial pressure, and, in general, a more rapid fall in the pulmonary : systemic arterial pressure ratio, than more mature babies. Again ductal flow patterns mirrored the arterial pressure ratio.

Chapter 11 presents a study of 24 babies with bronchopulmonary dysplasia, in whom it
would be particularly useful to have a reliable non-invasive means of pulmonary arterial pressure determination. Measurement of TR was only feasible in four of the babies (17%). This low percentage might be explained by the fact that these babies often had a hyperinflated chest, and were frequently restless and difficult to examine. Ductal flow patterns could only be recorded in the four babies with a patent duct. Detailed echocardiographic examination revealed some surprises, including one unsuspected large left-to-right ductal shunt, and two babies with a clinical diagnosis of ductal shunting who in fact had a closed duct, but appeared to have a form of high output cardiac failure. Therefore while echocardiography appeared to be of some clinical value in these babies, accurate non-invasive determination of pulmonary arterial pressure was not usually possible, since systolic time intervals were the only feasible method.

After the work for this thesis had started two publications appeared suggesting that the modified Bernoulli equation could be applied to the velocity of ductal flow in the newborn, to derive the pressure drop across the duct, and thereby determine pulmonary arterial pressure by knowing systemic arterial pressure. This was evaluated in chapter 13 by using the TR method as the best available point of reference. The database now contained 741 scans from 203 babies in the first 28 days of life, and there were 223 examinations including concurrent TR, systemic arterial pressure, and ductal flow measurements. Detailed analysis suggested that at large pressure drops (either right-to-left or left-to-right) the ductal pressure drop was usually underestimated by applying the Bernoulli equation to ductal flow velocities, but at low velocities the method was reasonably accurate. Measurement of the velocity across the duct therefore gave no more information than that obtainable from recognition of the type of pattern of flow through the cardiac cycle.

In chapter 14, the relationship of the pattern of ductal flow was related to the quantity of left-to-right ductal flow, assessed using the left atrial : aortic root ratio and left ventricular output. A characteristic pattern was identified in babies with a large left-to-right shunt, consisting of continuous left-to-right flow with low velocity at end diastole and higher velocity in mid systole. This suggested that aortic and pulmonary arterial pressures were roughly balanced at end diastole, presumably due to high left atrial pressure leading to an elevation of diastolic and mean pulmonary arterial pressure, and also to low diastolic pressure in the aorta. This pattern was more frequent amongst babies who had a murmur in association with the left-to-right shunt. Babies with a clinically silent left-to-right ductal shunt tended to have either continuous high velocity flow or low velocity or bidirectional flow.

The relationship of systolic time intervals to pulmonary arterial pressure were then explored in chapter 15, since these techniques are alternatives in babies with neither tricuspid regurgitation nor a patent arterial duct. Again using the TR method as the point of
reference, right ventricular systolic time intervals were compared to estimated systolic pulmonary arterial pressure values. TR was measured concurrently with the TPV/RVET ratio (time to peak velocity at the pulmonary valve/right ventricular ejection time) on 262 occasions, and with the PEP/RVET ratio (right ventricular pre-ejection period/RVET) on 122 occasions. Overall correlation of these ratios with pulmonary arterial pressure estimated using the TR method was poor (PEP/RVET, r=0.28; TPV/RVET, r=0.42). By analysing results from subgroups separately, the ratios were found to be subject to influences other than pulmonary arterial pressure, including patency of the arterial duct, gestational age and possibly other factors associated with respiratory distress such as right ventricular dysfunction. PEP, and the PEP/RVET ratio correlated closely with estimated systolic pulmonary arterial pressure in babies of restricted gestational age (<33 weeks) and with a closed arterial duct (PEP, r=0.85; PEP/RVET, r=0.86). This might explain its usefulness (apparent from other studies) in detecting pulmonary hypertension in babies with bronchopulmonary dysplasia. TPV and the TPV/RVET ratio had a weak correlation with estimated systolic pulmonary arterial pressure in babies ventilated for respiratory distress, but was better in healthy preterm babies (TPV, r=0.72), and in term babies with a closed duct (TPV, r=0.82; TPV/RVET, r=0.83).

Repeatability of measurement of each of the four methods of pulmonary arterial pressure estimation was assessed along with other Doppler indices of blood flow in chapter 16. Repeatability between two observers was very similar to temporal (and within observer) variability over half to one hour. Results were expressed as a repeatability index, representing the percentage variability obtained by applying the coefficient of repeatability (95% confidence limits of repeatability) to an average value. A high index therefore indicated poor repeatability. The systolic time interval ratios fared poorly, with an index greater than 35% (TPV/RVET 36%, PEP/RVET 45%). Ductal velocities were similar (maximal velocity 28%, mean velocity 36%). The index for the TR method was 15%, or 8% with the results expressed as a velocity rather than a pressure drop. A measure of the usefulness for each technique in the study of serial haemodynamic change, was designed by dividing the expected range of values for each parameter in the neonatal population by its coefficient of repeatability, producing a number of “confidence steps”. For example, the range of velocity of maximal left-to-right ductal flow (3.1 m/s; from 0.4 m/s to 3.5 m/s) was high in relation to the repeatability coefficient (0.48 m/s; 6.5 confidence steps within the expected range). This measurement is therefore more likely to be helpful in discriminating different levels of pulmonary arterial pressure than the TPV/RVET ratio with a relatively narrow range of values (3.2 confidence steps). The Doppler techniques with the highest number of confidence steps within the expected neonatal range were tricuspid regurgitation (8.5), maximal left-to-right ductal flow velocity (6.5), and two measurements of blood flow, aortic and pulmonary stroke distance (10.1 and 6.1 respectively).
At this point the advantages and limitations of each of the methods of pulmonary arterial pressure estimation by Doppler had been clarified. Chapters 17 and 18 introduce experimental ideas, and the work has not yet been subject to in-depth peer review. These chapters aim to combine all four methods of pulmonary arterial pressure estimation (TR, ductal flow, PEP/RVET ratio and TPV/RVET ratio) together with parameters of blood flow (aortic and pulmonary stroke distance), in describing haemodynamic changes in relation to expected normal temporal variability.

Firstly (in chapter 17), confidence steps were used in analysing the haemodynamic effects of alteration in inspired and blood oxygen levels in 18 preterm babies with respiratory failure. Arterial oxygen saturation (SaO₂) was changed in stages from 86% to 96% and to 100%. The confidence step analysis allowed the graphical display of the different measurements, with their different units, on the same graph, by indicating amount of change for each technique as a number of confidence steps. The effects of the variation in oxygen levels varied greatly, causing ductal constriction in some, and a fall in indices of pulmonary arterial pressure. However, there were generally equivocal changes from 86-96%, and more marked changes from 96 to 100% SaO₂. Most of the babies were recovering from hyaline membrane disease, and it would be interesting to repeat this study in babies with higher oxygen dependency than those studied here.

Chapter 18 studies thirty babies with persistent transitional circulation. Nine babies did not have a measurable TR signal, even when the pulmonary arterial pressure was known to be high from other measurements. Confidence step analysis of the haemodynamic events during recovery, suggested that serial measurement of ductal flow velocity may be the most sensitive Doppler echocardiographic index of clinical improvement, provided that the duct is patent. Values for the TPV/RVET ratio were mostly within the normal range, despite evidence from ductal flow and tricuspid regurgitation of elevated pulmonary arterial pressure. None of the indices of pulmonary arterial pressure were proven to be related to eventual outcome, but low left ventricular output (<100 ml/kg/min) and low left ventricular stroke volume (1 ml/kg) were associated with subsequent death, in 4/4 and 6/7 babies respectively, suggesting that these measurements are worthy of further prospective evaluation as predictors of outcome in this condition.

In summary, measurement of peak velocity of tricuspid regurgitation and application of the Bernoulli equation in the newborn was found to be accurate, repeatable and reliable, but feasibility was limited, particularly in babies with bronchopulmonary dysplasia. Analysis of the pattern of ductal flow during the cardiac cycle was useful to determine the approximate pulmonary : systemic arterial pressure ratio, and the degree of left-to-right shunting, but while measurement of the velocity of flow was useful in studying serial change
within a baby, the study suggested that it is inappropriate to apply the modified Bernoulli equation to determine pressure drop unless the velocity is low. Systolic time intervals and ratios were subject to considerable error in measurement, and the relationship to pulmonary arterial pressure was not consistent between babies of different gestation and was influenced by other factors such as ductal patency. When there was no tricuspid regurgitation and the arterial duct was closed, the PEP/RVET ratio was probably the best remaining non-invasive technique to estimate pulmonary arterial pressure, but results should always be interpreted with caution.
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Aims

The work in this thesis was performed in order to explore the use of Doppler echocardiography in the non-invasive determination of pulmonary arterial pressure in the newborn.

Specifically the aims were:

1. To study the feasibility, accuracy and repeatability of non-invasive determination of pulmonary arterial pressure estimation in the newborn both in health and with respiratory distress by measuring the maximal velocity of regurgitation through the tricuspid valve with continuous wave Doppler ultrasound and applying the Bernoulli equation.

2. To use this method to examine and compare serial changes in pulmonary and systemic arterial pressure in healthy term and preterm infants and those with hyaline membrane disease.

3. To compare this method with other non-invasive methods of pulmonary arterial pressure estimation in the newborn, including evaluation of feasibility, and temporal and between observer variability of each method.

4. To study the effects of quantity of ductal shunting and also alterations in inspired and blood oxygen levels on pulmonary arterial pressure in newborns with respiratory failure, using Doppler echocardiography.

5. To assess the potential of detailed Doppler echocardiographic examination, including determination of pulmonary arterial pressure, in evaluating babies with persistent transitional circulation.
### Abbreviations

Listed below are some of the abbreviations used frequently in this thesis.

<table>
<thead>
<tr>
<th><strong>General</strong></th>
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<tr>
<td>HMD</td>
<td>Hyaline membrane disease</td>
</tr>
<tr>
<td>BPD</td>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>TTN</td>
<td>Transient tachypnoea of the newborn</td>
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<tr>
<td>PTC</td>
<td>Persistent transitional circulation</td>
</tr>
<tr>
<td>CVP</td>
<td>Central venous pressure</td>
</tr>
<tr>
<td>IPPV</td>
<td>Intermittent positive pressure ventilation</td>
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<tr>
<td>FIO2</td>
<td>Inspired oxygen fraction</td>
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<table>
<thead>
<tr>
<th><strong>Statistics</strong></th>
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<tbody>
<tr>
<td>r</td>
<td>correlation coefficient</td>
</tr>
<tr>
<td>r²</td>
<td>coefficient of determination</td>
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<table>
<thead>
<tr>
<th><strong>Circulation</strong></th>
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<tbody>
<tr>
<td>Pa</td>
<td>pulmonary artery</td>
</tr>
<tr>
<td>Ao</td>
<td>aorta</td>
</tr>
<tr>
<td>PDA</td>
<td>patent arterial duct</td>
</tr>
<tr>
<td>Qp:Qs</td>
<td>pulmonary-systemic blood flow ratio</td>
</tr>
<tr>
<td>SaO2</td>
<td>arterial oxygen saturation</td>
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<tr>
<th><strong>Echocardiography</strong></th>
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<tr>
<td>LA:Ao ratio</td>
<td>left atrial : aortic root ratio (measured on m-mode echocardiography)</td>
</tr>
<tr>
<td>LVEDD</td>
<td>left ventricular end-diastolic dimension</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
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<table>
<thead>
<tr>
<th><strong>Doppler echocardiography</strong></th>
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<tbody>
<tr>
<td>TR</td>
<td>tricuspid regurgitation</td>
</tr>
<tr>
<td>RV-RA drop</td>
<td>peak drop in pressure between the right ventricle and right atrium</td>
</tr>
<tr>
<td>TPV</td>
<td>time to peak velocity</td>
</tr>
<tr>
<td>PEP</td>
<td>pre-ejection period</td>
</tr>
<tr>
<td>RVET</td>
<td>right ventricular ejection time</td>
</tr>
<tr>
<td>TPV/RVET</td>
<td>ratio of TPV at the pulmonary valve to RVET</td>
</tr>
<tr>
<td>PEP/RVET</td>
<td>ratio of PEP at the pulmonary valve to RVET</td>
</tr>
<tr>
<td>PDAMAX</td>
<td>maximal left-to-right ductal flow velocity</td>
</tr>
<tr>
<td>PDAMIDSYS</td>
<td>velocity of ductal flow at 30% of the R-R interval on the electrocardiograph</td>
</tr>
</tbody>
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Declaration of originality

The work of this thesis is that of myself and those in the acknowledgements. It is submitted only to the University of Leicester, and describes entirely original work.
Chapter 1: The fetal and transitional circulation - normal and abnormal

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   2. Mechanism of distribution of cardiac output
   3. Arterial and venous pressure in the fetal lamb

1.3 The transitional circulation
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   2. The four phases of the transitional circulation

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      3. The final phase
      4. Summary
   2. Studies in the human neonate
      1. Direct pressure measurements
      2. Factors influencing arterial pressures
      3. Summary

1.7 Closure of the oval foramen

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   2. Maintenance of ductal patency
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   1 Pulmonary arterial pressure
   2 Systemic arterial pressure
   3 Ductal patency
   4 Patency of the oval foramen
3 Summary

1.10 Failure of the transitional circulation

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2 Incidence
3 Clinical presentation
4 Aetiology
5 Management
   1 Introduction
   2 Vasodilators
   3 Acid base status
6 Invasive studies
7 Non-invasive assessment
Chapter 1: The fetal and transitional circulation - normal and abnormal

Figures (Figures are inserted in the text. There are no tables in chapter 1)

1.1 Factors altering vascular resistance in the fetal pulmonary circulation.
1.2 Changes in pulmonary flow and pressure during and after fetal life.

Figures 1.3-1.7 plot data from healthy human babies in the first 3 days of life from the work of Emmanouilides et al (1964), Saling (1960), and Moss et al (1965):

1.3 a Mean pulmonary arterial pressure.  
   b Serial measurements of mean pulmonary arterial pressure.  
   b Ratio of mean pulmonary : mean aortic pressure.

1.4 Pulmonary : systemic flow ratio (healthy term infants)
1.5 Relationship of pulmonary : systemic flow ratio with pulmonary : systemic mean arterial pressure ratio.
1.6 Ratio of pulmonary : systemic arterial pressures in systole and diastole.
1.7 Pulmonary : systemic mean arterial pressure ratio, comparing preterm and term babies.
Chapter 1: The fetal and transitional circulation - normal and abnormal

1.1. Introduction

(1) Investigation of the circulatory adaptation to postnatal life caused great scientific interest in the 1940s 50s and 60s. Cardiac catheterisation of the fetal and newborn lamb, and subsequently of the human neonate, showed that dramatic changes occur in the circulation after birth and the first breath, associated with elimination of the uteroplacental circulation. In the mid 1940s it was realised for the first time that the pulmonary circulation did not merely accept the output of the right heart passively. Some ten years later came the revelation that the transition from fetal to adult type circulation did not occur suddenly, with the arterial duct clamping shut, but that there was a gradual process over at least several hours. It is now known that there is a recognisable series of events associated with the transition, and that central to the process is the reduction of pulmonary vascular resistance. However there are still many unanswered questions, particularly why the transition sometimes fails. Furthermore, while cross-sectional studies of pulmonary arterial pressure have been performed in the term neonate, relatively little is known of the effect of prematurity, and of hyaline membrane disease, upon this adaptation.

(2) This first section will describe the fetal circulation and some of the early work which lead to our current understanding. There follows a synopsis of contemporary knowledge of the transition to the adult type circulation, concentrating, where possible, on data provided from direct measurement in the human neonate. The influence of prematurity itself is discussed, before the next chapter which concentrates on the circulatory effects of hyaline membrane disease.

1.2. The fetal circulation

1.2.1. General description (Dawes, 1968; Rudolph, 1979)

(1) While this description arises from work with the fetal lamb, the circulation has been confirmed angiocardioangiographically in the human fetus (Lind and Wegelius, 1954).

(2) Umbilical venous blood, rich in nutrient and oxygen passes from the placenta to the portal vein, and thereafter divides to pass equally through the hepatic circulation or directly into the inferior caval vein via the venous duct. Over 70% of blood reaching the right atrium comes from the inferior caval vein, and consists of venous drainage from the lower half of the body, umbilical venous return and hepatic venous blood. Twenty percent returns from the superior caval vein, and 4% from the coronary sinus. The venous return is split into two streams by a ridge in the wall of the atrium (the crista dividen). One stream,
predominantly from the inferior caval vein, passes through the oval foramen to the left atrium, ventricle and ascending aorta and therefore supplies the head and neck, and the heart itself, with nutrient and oxygen rich blood. The other stream enters the right ventricle and pulmonary artery, and the majority is diverted via the arterial duct to the descending aorta. Less than 10% of the total cardiac output enters the pulmonary circulation to return to the left atrium.

1.2.2. Mechanism of distribution of cardiac output

(1) In the fetus the two ventricles do not function in series; blood from both ventricles enters the lower part of the body. Cardiac output in the fetus is therefore usually expressed as combined left and right ventricular output, whereas after birth it is expressed as the volume ejected by either ventricle per minute. The arterial duct, connecting the aorta and pulmonary arteries allows an equalisation of these pressures. The distribution of blood flow to different parts of the circulation, is therefore determined largely by local vascular resistance. Placental vascular resistance is low, and it therefore takes a high proportion of the cardiac output (40-60%). The lungs, which must take all of the cardiac output after adaptation to extrauterine life, have a high vascular resistance, and thus take less than 10% of the cardiac output.

(2) In the fetal lamb, right ventricular output is higher than that of the left ventricle; the ratio of right to left ventricular output is between 2:1 and 3:1. Assuming that brain blood flow in relation to tissue weight is similar in lambs and humans, the ratio would be about 1.3:1 in the human fetus because of the relatively large proportion of the circulation which, supplying the relatively large brain, reaches the systemic circuit before the arterial duct. The figure is consistent with recent Doppler echocardiographic studies (Allen et al, 1987; DeSmedt et al, 1987). The myocardium, kidneys and gastrointestinal tract take between 2 and 6% each of the combined ventricular output.

1.2.3. Arterial and venous pressure in the fetal lamb

(1) Venous pressures are probably higher in the fetus than in the newborn, because of the intra-amniotic pressure to which the whole fetus is subjected. In the fetal lamb peripheral venous pressure is 10-12 mmHg, and umbilical venous pressure is about 15mmHg above atmospheric pressure. However, pressures are normally expressed in relation to amniotic cavity pressure; caval vein pressures are 3-5 mmHg above and left atrial pressure is 2-4 mm Hg above amniotic pressure. Aortic and peripheral arterial pressures in the third trimester average 60-70/40 mmHg with a mean of about 50 mmHg. Right ventricular and pulmonary arterial pressures are often 5 to 8 mmHg higher in late gestation, probably due to mild constriction of the arterial duct.
1.3. The transitional circulation

1.3.1. General description

1. The final outcome of the events triggered by birth is the achievement of a pulmonary vascular resistance approximately one fifth that of systemic vascular resistance. This is associated with functional closure of the oval foramen, as placental venous return decreases and pulmonary venous return increases, and is followed by closure of the arterial duct. The cardiopulmonary circulation is changed from a parallel circuit, where both ventricles eventually pump most of their blood into the aorta, to a series arrangement postnatally.

2. The central event in this sequence is the dramatic fall in pulmonary arterial pressure in relation to the aortic pressure. If this central event does not occur, the transition will fail. It is essentially, therefore, a physiological process, and not an anatomical one. It is not, for example, active constriction of the arterial duct that diverts blood into the pulmonary circulation. Furthermore, it is not a single event, but a process.

3. Leffler (1978), and later Clarke (1990), while accepting that the transition of the circulation is essentially a continuum, divided the transition into distinct phases based on physiological and pharmacological characteristics. Whilst many factors, and in particular oxygen tension, have a similar effect on pulmonary vascular resistance before and after birth, different factors are of different importance at each phase. The role of the eicosanoids- the products of arachidonic acid metabolism, including the prostaglandins, leukotrienes, and thromboxanes- varies with each phase, and some even have opposite effects according to the phase concerned.

1.3.2. The four phases of the transitional circulation (Clarke, 1990)

1. In utero. This is the baseline or starting point. There is a very high pulmonary vascular resistance, and there is no endogenous production of prostaglandins (including prostacyclin (PGI^)) within the fetal lung. Prostaglandins PGI^, D_2 and H_2 infusion decreases pulmonary vascular resistance.

2. 'Immediate' The first respiratory effort. There is expansion of the lungs, and this mechanical effect, aided by surface tension within the alveoli, causes the initial fall in pulmonary vascular resistance. This phase lasts from a few seconds to a few minutes, and initiates the next phase.

3. 'Fast' This begins within minutes of birth and lasts for about 12 to 24 hours. There is a continuous decrease in the pulmonary vascular resistance. Production of prostacyclin (a
potent pulmonary vasodilator) by the lungs begins in large amounts. PGD$_2$ infusion has no effect at all but PGH$_2$ increases pulmonary vascular resistance, opposite to the effect observed in utero. The arterial duct is widely patent through much of this time and alterations in pulmonary and systemic vascular resistance can cause significant changes in the proportion of flow through each circuit.

4. Final The phase of pulmonary vascular reorganisation, is associated with a gradual thinning down of the muscular medial layer, and growth of the pulmonary vascular tree with increased numbers of small arterioles. This phase starts at about 12 to 24 hours of age and continues until at least day 10, though further smaller changes continue for several months.

These four phases are looked at in more detail in section 1.6 but it is helpful to review the historical perspective of research in this area along with anatomical and physiological knowledge of pulmonary vascularity before doing this. These aspects are therefore reviewed in sections 1.4 and 1.5.

1.4. The pulmonary circulation in the fetus and neonate - Background and historical perspective

(1) Before 1946 it was generally believed that the lungs had a toneless vascular structure in adult life, which accepted passively the output of the right heart. In 1946 von Euler and Liljestrand observed that hypoxia causes a rise in pulmonary arterial pressure in the cat, a rise which they correctly attributed to pulmonary vascular constriction. At about the same time it was noticed that some patients with congenital heart disease had a considerable and apparently permanent rise in pulmonary arterial pressure, an observation made using the then new technique of cardiac catheterisation. Over the next ten years many publications established that the pulmonary vascular bed in the adult constricted with hypoxaemia, though the effect of pH and CO$_2$ was less certain. In the early 1950s research on the fetal and transitional circulation began in earnest.

(2) The first direct measurements on the fetal pulmonary vascular bed were done on fetal lambs, born by caesarian section and kept warm with an intact umbilical cord. (It was found that respiration did not commence unless there was a drop in body temperature or the cord was clamped.) These studies were reviewed by Dawes (1968a). Pulmonary arterial pressure was found to be higher than that in the descending aorta. Pulmonary blood flow varied ten fold between different lambs (Dawes et al, 1953) and it was first suggested that the fetal pulmonary circulation might be more labile than was previously supposed. In 1959 and 1962, Dawes et al showed that acetyl choline caused profound pulmonary vasodilation in the fetal lung, as did raising the arterial oxygen saturation by the
administration of oxygen to the mother. On the other hand, asphyxia caused extreme pulmonary vascular constriction (Cook et al 1963), an effect also seen by Cassin (1964) and Rudolph (1966). The importance of these observations is the influence of these factors upon the normal transition of the fetal circulation to that of the newborn baby.

(3) Study of the fetal and perinatal circulation has continued apace since these early experiments. The remainder of chapter 1. reviews some of the more important findings, and they are presented in a systematic rather than historical manner.

1.5. Regulation of fetal pulmonary vascular resistance

1.5.1. Pulmonary vascular morphology

(1) Development of the fetal lung. The development of the fetal lung was reviewed by Strang (1977) and can be divided into four main periods according to the structure of the bronchial tree: the embryonic period, from three to six weeks, with formation of the lung primordium; the pseudoglandular period, from 6-17 weeks, where the main pattern of bronchial branches is laid down; the canalicular period, from 17-24 weeks, when the branches elongate and the epithelial cells change from columnar to cuboidal; and an alveolar sac period, from 24 weeks to term, when thin-walled air passages are formed within the acinus and begin the process of growth and subdivision that continues during the remaining period of lung development. Considerable remodelling of the acinus continues after birth, and in fact new alveoli continue to develop until 8-11 years, though nearly 40% of this development occurs in the first year of life (Dunhill,1962).

(2) Development of pulmonary blood vessels. The main pulmonary artery with its two main branches develops from the left sided sixth aortic arch during embryonic life. From about 37 days of gestation, following division of the aortic sac, the lungs derive blood only from the right ventricle, and the right-sided arch disappears (Congden,1922). The pulmonary artery then communicates only with the aorta through the arterial duct, which is derived from the dorsal part of the left sided sixth arch. Up until four to five weeks, the pulmonary microcirculation drains into a systemic venous plexus which is common to the lung and foregut, but after this, an outgrowth from the atrial region connects with the pulmonary venous system, to complete the pulmonary venous drainage (Auer,1948). The arterial supply at this stage is also effectively a plexus of channels connected both to the systemic and pulmonary circulations. Later in fetal life, the lung parenchyma is supplied from the systemic circulation by bronchial arteries, and the bronchi by pulmonary arteries. However, some (though fewer) bronchopulmonary arterial anastomoses formed in the fetal lung are maintained into infancy. Other less numerous but potentially important pulmonary-systemic anastomoses, are formed by pulmbronchial arteries, present only
during fetal life (Wagenwoort, 1967). These small arteries, of 40 to 120 microns, are branches of pulmonary arteries which leave lung tissue to end in peribronchial or perivascular connective tissue, or to supply the bronchial mucosa. During the pseudoglandular and canalicular periods, pulmonary arteries develop alongside the airways, with dichotomous branching at each airway division. About 25 of these main divisions (the full adult number) are present by 19 weeks, and two to four further arteries come off each main division to penetrate the lung without following the pattern of airway distribution. During the second part of fetal life, new arterial branches develop in the acinus; but even at term, the number of small arteries per unit of lung volume is less than later in childhood.

(3) Structure of the vessel walls All sizes of pulmonary artery have a thicker wall in the fetus than in the 3-12 month infant or adult, and are similar to systemic arteries. Hislop and Reid (1973) demonstrated that the walls of arteries with a diameter of 250-850 microns diameter are approximately twice as thick in proportion to total arterial diameter as in postnatal life. The lumen of these arteries is therefore all but occluded in the last trimester, and only really becomes discernible shortly after birth (Harris and Heath, 1977). There is a smooth muscle media with circularly orientated fibres, sandwiched between internal and external elastic laminae. Pathological studies from the lung of the fetal lamb (Naeye, 1961) showed that the precapillary vessels of 50-200 microns diameter also have a well developed muscular medial layer. These vessels are probably responsible for most of the reactivity of pulmonary vasculature. The amount of muscle in these vessels increases during the third trimester and reaches its peak at term. Studies on the fetal lamb have shown that there is a progressive increase in the vasoconstrictor response to hypoxia with advancing gestation, along with increased vessel wall thickness, although the total baseline pulmonary vascular resistance decreases markedly with advancing gestation. This apparent paradox is thought to be due to the great increase in the number of vessels during growth, resulting in an increase in the cross-sectional area of the vascular bed.

(5) In summary, there are several important features of the fetal lung vasculature and its development which can be expected to influence the transitional circulation. The important features are: frequent pulmonary-systemic anastomoses, the well developed muscular coat of small pulmonary arteries and arterioles, the restricted size of the pulmonary vascular tree, and the fact that these features are constantly changing throughout gestation.

1.5.2. Biochemical factors

(1) The high fetal pulmonary vascular resistance is probably mainly due to hypoxic vasoconstriction. Pulmonary vessels are perfused by relatively low PaO2 (about 4 kPa), consisting, in the most part, venous return from the head. It is known that the fetal
pulmonary circulation is extremely reactive to arterial oxygen tension, since delivering hyperbaric oxygen to the mother causes an increase in fetal pulmonary blood flow (Assali, 1968), and induced hypoxia decreases it. However, other factors are important, and can be additive in their effect. Just as acidosis and hypoxaemia have additive effects, such that hypoxia worsens the vascular constriction already present due to acidosis (Rudolph, 1966), it appears that many other factors have interactive roles, and how these factors interact is sometimes different in the fetus from in the newborn.

(2) The role of biochemical and autonomic factors in the maintenance of pulmonary vascular tone in the fetus is still incompletely understood, even though various manoeuvres can be undertaken to alter it; most of these are summarised in figure 1.1. There have been several reviews on this complex subject over recent years (Voelkel et al, 1987; Kulik and Lock, 1987; Heymann, 1987; Cassin, 1987; Fineman et al, 1991), and the subject is difficult to understand, there being a number of apparent paradoxes. For example, postnatally, hypoxia induces an increase in prostacyclin production in the lungs, but this is not the case in the fetus. However, the administration of indomethacin to the fetus raises pulmonary vascular resistance. While this suggests that prostanooids do play some part in regulating pulmonary vascular resistance, even in the fetus, it is not known how. Although prostaglandins are generally locally synthesised and therefore locally active, readily measurable concentrations are present in fetal plasma. This is particularly true of PGE_2, which has an important role in the maintenance of ductal patency, but is also a pulmonary vasodilator. They probably originate from the placenta, but Heymann (1987) states that important amounts of PGE_2 and prostacyclin are produced by the fetal lung, and this is supported by Terragno (Terragno and Terragno, 1979; Terragno et al, 1980). It is hard to equate this observation with the statements of those who say that prostacyclin production in the lung only starts after the onset of respiration (Leffler et al, 1984; Clarke, 1990).

(3) An in-depth review is not appropriate in this thesis, and one has the impression that there are many more questions to answer. However, there are several general points that can be made. Clearly the oxygen environment plays an important role, and this interacts with vasoactive substances. These are the eicosanoids (in particular the prostaglandins), bradykinin or other vasoactive peptides, and other vasoactive substances such as endothelium derived relaxing factor, growth factors, such as platelet-derived growth factor (which are also vasoactive and produced by the pulmonary vascular endothelium), angiotensin 1, and probably others still to be identified. These factors are opposed by vasoconstricting substances, and in particular, the leukotrienes, which are also products of arachidonic acid metabolism, (via lypoxygenase). There is, therefore, a balance maintained by the interaction of these two interacting and opposing mechanisms. This interaction varies markedly according to the phase of transitional circulation, most notably since prostacyclin and Bradykinin are (probably) not produced by the fetal lung. Furthermore,
PULMONARY FLOW

alpha-stimulation
acetyl choline
vagal discharge
beta-stimulation
adrenaline
isoprenaline
sympathectomy
gaseous expansion
mechanical effects
increased PaO2
alkali
decreased CO2
Bradykinin
Histamine
Prostaglandins, J2, E1, E2, and others
VIP
Tolazoline, nitric oxide
Endothelin
Angiotensin II

Figure 1.1

dilated
fetal

constricted
alpha-stimulation
noradrenaline/adrenaline
tyramine
sympathetic discharge
dopamine
Asphyxia
hyposia
acidaemia
Vagotomy
Leukotrienes
Serotonin
Beta-blockade
Prostaglandins, D2, E2alpha

PULMONARY ARTERIAL PRESSURE
Vascular resistance in the fetal pulmonary circulation
since all of these vasoactive substances are produced by the pulmonary vascular endothelium, it can be stated with confidence that if the endothelium is damaged, perhaps by pneumonia, or meconium aspiration, this delicate balance is likely to be disturbed, and if accompanied by acidosis, hypercarbia and hypoxia, major vasoconstrictive stimuli are likely to be unleashed.

1.6. The postnatal fall in pulmonary vascular resistance

1.6.1. Animal studies

(1) Postnatal circulatory changes have been studied in the human neonate, and the findings are discussed in the next section, but studies of pulmonary flow, pressure and resistance prior to birth, and the immediate postnatal period have only been possible in animals. Rudolph summarised the changes in lambs in pulmonary flow and resistance during gestation and after birth diagrammatically, and this is copied in figure 1.2. Pulmonary blood flow and pressure increase slightly with fetal growth. After birth there is a sharp rise in pulmonary blood flow, and a sharp fall in pressure, followed by a more gradual fall to adult levels at six to eight weeks of life.

(2) The mechanisms underlying the fall in pulmonary vascular resistance, discovered from work with animals, can be described using the phases discussed earlier.

1.6.1.1. The first breath (the immediate phase)

(1) On ventilation of the lungs, pulmonary arterial pressure falls rapidly and pulmonary blood flow increases six to ten fold (Dawes et al, 1953). This increase in flow even occurs when the lungs are ventilated with nitrogen, but increases further when air is used (Born et al, 1955). Cook et al (1963) showed that adding 10% CO2 to the ventilating gas mixture had the opposite effect, causing profound vasoconstriction. Since the fall in pulmonary vascular resistance is seen with nitrogen inhalation, it can be inferred that mechanical inflation of the lung is at least as important as increased oxygen tension. The alveoli expand, allowing the pulmonary vessels to fill, possibly aided by the development of a gas-liquid interface in the alveoli which alters surface forces. This hypothesis was supported by studies where the first lung expansion was given with liquid rather than gas, and the pulmonary vascular resistance did not fall (Cassin et al, 1964).

1.6.1.2. The fast phase

(1) The characteristic of this phase is the sudden activation of cyclooxygenase, beginning the production of prostacyclin. This event is probably triggered by the mechanical stretching
Changes in fetal pulmonary arterial pressure, pulmonary blood flow, and pulmonary vascular resistance (PVR) in the perinatal period.

**Figure 1.2**

(Rudolph, 1979. Data from the fetal and newborn lamb.)
of the pulmonary vessels accompanied by an increase in oxygen tension, but the exact mechanism is unknown. Lock et al (1980) showed that prostaglandins and particularly prostacyclin are almost certainly involved in the process of reducing pulmonary vascular resistance in the lamb. The administration of a single dose of indomethacin, a prostaglandin synthetase inhibitor, to the fetal lamb prior to ventilation of the lungs, interfered with the decrease in pulmonary vascular resistance (confirmed by Velvis et al 1991). However, after chronic administration of indomethacin pulmonary vascular tone fell normally with ventilation. Lock concluded that prostaglandins play a role in, but are not essential for, normal neonatal pulmonary vascular control. This observation was supported and further refined by Morin (1986) who showed that, in the newborn lamb, hyperventilation induced alkalosis caused a rise in prostacyclin with a fall in pulmonary vascular resistance, but the pulmonary vasodilation still occurred after the administration of indomethacin. Lock et al went on, with a series of experiments, to study the relative effects of the different prostaglandins on pulmonary vascular tone under normoxic and hypoxic conditions (the results are included in figure 1.1). They allowed for the general effects of anaesthesia and ventilation, which were felt to have confounded the results of other studies, by injecting only one pulmonary artery and comparing the results with the uninjected lung. PGI₂ (prostacyclin) was the most effective pulmonary vasodilator, particularly under hypoxic conditions, and it caused relatively little systemic vasodilation. It was because of these properties that prostacyclin was proposed as a therapy for persistent pulmonary hypertension in the newborn. However, there are likely to be important interspecies differences, and the relative activity of the different prostaglandins in the human neonate has yet to be clarified.

(2) Similarly the pulmonary production of bradykinin begins with the onset of ventilation (Heymann et al, 1987). It is converted from kininogen, a substance which is found in the blood of fetal lambs early in gestation and falls markedly upon the establishment of respiration. Bradykinin might exert some of its effects via prostacyclin, since it stimulates its production in vitro (Hong et al, 1980).

(3) A third group of substances, mentioned earlier, are the leukotrienes. These are converted from arachidonic acid by 5-lipoxygenase. There is an on-going debate about the role of these substances, though the fact that they are found in large amounts in lung lavage samples from babies with persistent pulmonary hypertension of the newborn (Stenmark et al, 1983), and not from other ventilated babies, suggests that they are probably important vasoactive substances; their infusion certainly causes pulmonary vasoconstriction (Lulik and Lock, 1987).

(4) The vasomotor effects of oxygen are important during the fast phase. In adult animals, both the mixed venous pO₂ and the alveolar pO₂ exert vasomotor effects on the pulmonary
vasculature (Marshall and Marshall, 1983). These rise dramatically postnatally. The vasodilator effects of oxygen described in the fetus also occur in the newborn and adult, and underline the importance of oxygen in the normal transition. There is no dispute about this, although the mode of action remains unclear; probably being mediated locally, either from a direct effect upon the smooth muscle or from a chemical mediator. One such mediator may be bradykinin.

1.6.1.3. The final phase

(1) Wagenwoort et al (1961) and Naeye (1966) showed that pulmonary arterial vessel wall thickness decreases very rapidly in the first two weeks after birth, followed by a slower reduction over the next 18 months, though Hislop and Reid (1973) consider that most of the immediate change is due to distension of small vessels rather than loss of substance from their walls. Hall and Howarth (1986) performed ultrastructural studies on the pulmonary blood vessels in pigs, and they also note that the more distal smaller vessels show a more rapid and greater change in shape than the proximal vessels, particularly in the first thirty minutes of life, but continuing thereafter. After a few months of life, subendothelial tissue begins to acquire much more collagen (rising from about 7% to 20% at six months), and this might be partly responsible for, or be a reflection of, the reduction in pulmonary arteriolar reactivity, along with decreased muscle mass and biochemical changes.

1.6.1.4.

In summary, the initial rapid decrease in pulmonary vascular resistance results from a release of vasoconstriction. The transitional circulation can be described in phases, delineated by the factors most affecting pulmonary vascular tone at that time. It can also be considered as a cascade of events, each one leading on to the other, with the initial trigger being the first breath.

1.6.2. Studies in the human neonate

1.6.2.1. Direct pressure measurements

(1) Pulmonary and aortic pressures were measured by cardiac catheterisation in healthy newborn infants born at term by Adams and Lind (1956), Saling (1960), Rudolph et al (1961), Emmanouilides et al (1964), Arcilla et al (1966) and Moss et al (1964). Arcilla et al studied the effect of early and late cord clamping, but absolute values were not given in their paper. Moss et al studied the effect of hypoxia and hyperoxia. All of the studies were done on unsedated babies, except Adams and Lind who administered general anaesthesia. Of 20 babies studied by Rudolph, there were only five babies who were normal; nine were
babies of diabetics, five had Downs’ syndrome, and two were born of mothers who were eclamptic. For the normal infant therefore, the work of Saling and Emmanouilides has more relevance. However, the babies were studied by Saling on the pretext that they had arterial lines sited for clinical reasons, namely the risk of erythroblastosis fetalis or respiratory distress. It is unclear from the text (even after translation from German into English!) as to whether the babies were actually completely healthy. They were certainly not anaemic at the time of the study, and were breathing air.

(2) The mean pulmonary arterial pressure results from these papers are presented in figure 1.3a. The values obtained by Saling (20 babies) were mostly during the first hour of life, and are considerably higher than those of Emmanouilides, which were taken between one and 54 hours of age in 51 babies. If we accept that the results of these two cross-sectional studies are compatible, there is a dramatic fall in pressure between one and two hours of age, followed by a more steady fall over the next 48 hours.

(3) The only longitudinal pulmonary arterial pressure data available in healthy human neonates was also presented by Saling in the same study. In seven babies the cardiac catheter was left in situ for a variable period up to twelve hours; the results are drawn in figure 1.3b. The great variety in the rate of change within each baby seen in this figure is not apparent from the cross-sectional data and demonstrates the importance of longitudinal data in studying physiological events. However, all babies but one show a downward trend over the time they were studied.

(4) Since it is the fall of pulmonary vascular resistance, in relation to systemic vascular resistance, that is central to a normal transitional circulation, the pulmonary : aortic arterial pressure ratio can be a useful way to examine pressure changes over the transition. Several factors can influence the absolute value of both the systemic and the pulmonary arterial pressures within each baby. For example, early clamping of the umbilical cord results in relative hypovolaemia which results in a lowering of both systemic and pulmonary arterial pressures (Wallgren et al,1964), but it may reduce systemic more than pulmonary arterial pressures, encouraging right-to-left ductal shunting. The balance of the two arterial pressures will dictate the direction of ductal shunting. Expressing the pulmonary arterial pressure as a ratio of systemic pressure potentially allows more meaningful comparison between babies, even babies of different size and gestation, and perhaps also between different studies. Therefore, the ratio is probably of more physiological significance to the baby than absolute arterial pressures. It is interesting to note that the one baby in figure 1.3b (from Saling’s study of healthy neonates) who had a rise in pulmonary arterial pressure over the first hour, from 29 to 42 mmHg, also had a marked rise in aortic pressure, such that the pulmonary arterial pressure actually fell in relation to aortic pressure, from a ratio of 0.97:1 to 0.89:1.
Figure 1.3a
Mean pulmonary arterial pressure in healthy human neonates over the first 3 days of life

Figure 1.3b
Serial measurements of mean pulmonary arterial pressure in the human neonate
(The dots show single values from healthy babies)

Figure 1.3c
Ratio of mean pulmonary : mean aortic pressure in healthy human neonates.

Data of Saling
Data of Emman. et al
The pulmonary to systemic mean arterial pressure ratios from the same two studies, of Saling and Emmanouilides, are presented in figure 1.3c. The result is a relatively smooth, and perhaps more believable, exponential fall from the first hour, levelling out at 36 to 54 hours. The arterial pressure ratio will be employed later in this thesis to compare post-natal adaptation of arterial pressures (derived by Doppler) in babies born at term with premature babies, and healthy with sick babies.

The mean ratio of pulmonary to aortic systolic pressures in newborn lambs (Assali et al, 1967), was 1.03 before birth, but 0.57:1 at 30 minutes after birth, whereas the ratio in the first hour is over 0.9:1 in humans and does not reach 0.6:1 until 36-48 hours after birth. The data of Saling and Emmanouilides therefore provides evidence of a major difference between lambs and humans in post natal circulatory adaptation. The very rapid fall in pulmonary arterial pressure seen in lambs with the first breath, is not as marked in the human. (It is worthy of note however, that in Assali et al's study, the lambs were presumably ventilated mechanically (it is not specified), whereas the human babies breathed spontaneously.) Because of these potentially important differences, it is important to review studies of the human neonate separately.

1.6.2.2. Factors influencing arterial pressures in the healthy human neonate.

(1) Oxygen environment Moss et al (1963) studied the effect of breathing air, 13% oxygen and 100% oxygen in 12 term infants from 2 to 27 hours old. Hypoxia caused a rise in pulmonary arterial pressure in every case, and a significant fall in systemic pressure in five. Hyperoxia caused a fall in pulmonary arterial pressure (a mean of -16%) in nine, whereas aortic pressure remained essentially unchanged. Thus the suggestion from work with fetal lambs that oxygen is a potent pulmonary vasodilator in the perinatal period, was confirmed in the human.

(2) Intravascular volume Ardilla et al (1966) studied 32 normal neonates between 0.5 and 11 hours of age. Babies with early clamping of the umbilical cord had, as expected, relatively lower arterial pressures, but the pulmonary-systemic mean arterial pressure ratio was also significantly lower. At 3 hours the ratio was 0.98:1 in the late clamped babies, and 0.80:1 in the others. At 7 hours, the ratios were 0.77:1 and 0.55:1 respectively. The authors postulated that the high ratios in the late clamped babies were related to the pulmonary circulation being relatively constricted, and non-compliant, in comparison with the systemic circulation, therefore producing higher pressure with the increased volume loading secondary to a completed placental transfusion. Therefore intravascular volume can influence the balance of pulmonary and systemic pressures as well as absolute pressures.
(3) **Mode of delivery**  Delivery by Caesarian section is so different from vaginal delivery, that it is reasonable to expect differences in the transitional circulation. However, relatively little is known about this. Most work with animals involves birth by caesarian section, so comparative analysis in animals is not available. The more rapid postnatal fall in the pulmonary:systemic arterial pressure ratio seen in sheep than in humans, might be not due to interspecies difference at all, but to the different mode of delivery. The relative lack of stress response in caesarian section may result in reduced vascular tone, which will affect the pulmonary vascular tree more than systemic since it is more reactive, and also could result in relatively poor myocardial stimulation. Transient tachypnoea of the newborn is more common after caesarian section, and at least one non-invasive study has suggested that poor myocardial function may be a factor in this condition (Halliday et al,1981). Holland and Young (1956) found that babies born by elective caesarian section had significantly lower systolic blood pressure (obtained by palpation), than vaginally born infants, and this remained significantly lower until after three weeks. The cause of this difference remains unknown but may, in part, be due to the tendency to clamp the cord earlier after caesarian section.

(4) **Maternal pre-eclampsia**  Babies born to hypertensive mothers tend to have marginally higher systemic blood pressure, though the mechanism remains unclear (Cabal et al,1981 and Miller et al 1983).

(5) **Gestational age**  has, of course, a very important influence on systemic systolic pressure, (along with postnatal age).

1.6.2.3 In summary, studies of systemic and pulmonary arterial pressures in the human baby have demonstrated that the human undergoes a similar fall in pulmonary arterial pressure in relation to systemic pressure to that seen in some animals. However, the rate of change seems to be markedly different from that in sheep. This difference between sheep and human transitional circulation is likely to be one of many differences, and emphasises the need for further studies in the human. Studies in the human baby illustrate the important influence of perinatal events on the normal transitional circulation.

1.7. **Closure of the Oval Foramen**

(1) As well as dramatic physiological changes, there are two especially important 'anatomical' changes; the closure of the oval foramen and the arterial duct. These are considered in more detail next, referring to data in humans wherever possible.

(2) In the fetus, over half of the blood of the inferior caval vein is derived from umbilical venous return. With removal of placental venous return, there is a marked fall in blood
returning to the heart and a small drop in right atrial pressure. At the same time, pulmonary blood flow increases, and the increased pulmonary venous return elevates left atrial pressure. The gradient thus created between the atria closes the valve-like flap of the oval foramen. In fact it is common for a small opening to remain, with a left to right shunt, for several months, and even throughout life. In children under one month of age the incidence of right-to-left shunting across a patent oval foramen (at rest) was 55%, and over one month, the incidence was 22% as seen with contrast echocardiography, from a study of 127 children (Van Hare and Silverman, 1989). Lynch et al, (1984) using contrast echocardiography, showed that 5% of adult volunteers had some right-to-left shunting via the oval foramen at rest, increasing to 18% following a Valsava manoeuvre. Using Doppler colour flow mapping, Hiraishi et al (1990) studied the interatrial shunt profiles in 36 term infants over the first five days of life. Shunting was found in 92% within the first hour, and was still present in 47% on the fourth and fifth day. The shunting was bidirectional in 64% at the first hour, and in 19% by day five, and was pure left-to-right in the rest. The arterial duct closed before the oval foramen in every case. Steinfield et al (1988) demonstrated that during bidirectional shunting, the period of right-to-left shunting typically occurred at the start of diastole, when the mitral valve opens marginally before the tricuspid valve; the opposite from the adult situation, and the same as in the fetus. This occurs because left ventricular isovolumic relaxation is completed before the right. Therefore, a pathological persistence of poor right ventricular compliance could lead to significant right-to-left interatrial shunting. However, until recently it was unclear if the patent oval foramen had an important effect on haemodynamics in the normal term infant. Hannu et al (1989), attempting to answer this question, recorded patency of the foramen using colour Doppler flow mapping, and measured left ventricular output with Doppler over the first two days of life. Patency of the oval foramen made no difference to left ventricular output. However, right ventricular output was not measured, and with a left-to-right shunt at atrial level it is this that one would expect to be elevated. A longitudinal study of both ventricular outputs has been done (Shiraishi et al,1988), but while left-to-right ductal shunting increased both outputs transiently, no effect could be attributed to the oval foramen.

(3) Thus, while the oval foramen provides a potentially important site of intracardiac shunting in the neonate, it is probably of little haemodynamic consequence in the healthy term baby.

1.8. Closure of the arterial duct

1.8.1 Anatomy of the duct

The development of the normal human arterial duct during pregnancy, and its closure after birth, based on pathological studies was reviewed by Gittenberger-de Groot (1979). From
about 16 weeks, the duct most resembles a muscular artery. The media contains virtually no elastic tissue, in marked contrast to the pulmonary artery and aorta, which have mostly elastic tissue. The smooth muscle fibres are mostly arranged in a circular fashion, probably in a spiral. During ductal constriction, intimal "cushions" are formed by folds of intima protruding into the lumen. Mucoid lakes appear between the cushions and the media, effectively cutting off the blood supply to the media and cushions, which become necrotic. The outer region is supplied by the vasa vasorum, and the innermost region by diffusion from the lumen. Anatomical closure occurs by three weeks and at the earliest at about 6 days after birth, when there is fusion between the opposed endothelia, usually first at the pulmonary end of the duct, followed by cytolyc necrosis of the inner part of the vessel wall. The central core of the duct shrinks, and the ring of muscle disappears, to leave the ductal ligament. In a study of 22 premature infant post-mortems, (26 weeks onwards) it was found that ductal structure was not strictly related to gestation, and it was suggested that there are no structural reasons why the premature duct (from 26 weeks onwards) should not close. The abnormally persistent arterial duct (after three months) has a classical histological appearance, with a ring of elastic tissue around the lumen just beneath the endothelium. This appearance is also seen in prolonged ductal patency in premature infants.

1.8.2 Maintenance of ductal patency

(1) This subject was reviewed by Olley and Coceani (1987). Ductal patency is maintained by an active process involving prostaglandins, most particularly PGE\(_2\), and to a lesser extent prostacyclin, sensitivity to which is increased by hypoxia (Clyman et al,1980a). Once again, the vast majority of work in this field has been with animals, and statements about the relative activity of different eicosanoids pertain to the animals, and are not necessarily true in the human. PGE\(_2\) is probably produced intramurally, but a subsidiary role for blood borne PGE\(_2\) is not excluded since circulating levels of PGE\(_2\) are three to five times higher in the fetus than in the adult. PGE\(_2\) synthesis begins early in fetal development, and is greater in the less mature duct. Another product of arachidonic acid is probably an antagonist, causing ductal constriction after birth (the 'constrictor substance'). Cytochrome P-450 catalyses the monoxygenation of arachidonic acid, and if it is deactivated (for example by carbon monoxide) ductal constriction is reversed, even in the presence of high oxygen concentrations. It therefore appears that ductal tone is controlled by the opposing activities of cyclooxygenase and monoxygenase products of arachidonic acid, and oxygen levels may be important in dictating which pathway is the most productive. The next target of the physiologist is to find this constrictor substance.

(2) Since the review by Olley, Rabinowitch (1989) has shown that cells from the
endothelium of the duct, the aorta and the pulmonary arteries are quite phenotypically
different in their responses to hyperoxia and hypoxia, in the prostaglandins produced at
these times. For example, hypoxia induces a fall in prostaglandin synthesis in pulmonary
artery endothelial cells, but not in ductal cells. Increased understanding of these events
using isolated tissues may eventually identify tissue specific vasoactive compounds, which
could be of significant therapeutic value in the management of persistent fetal circulation.

1.8.3 Mechanism of ductal closure

(1) Permanent anatomical closure only follows when the endothelial layers make contact,
secondary to ductal constriction. The two principle factors causing ductal constriction
appear to be the postnatal rise in arterial oxygen saturation, and the rapid fall in circulating
$PGE_2$ levels (Clyman et al,1980b). There is possibly also a myogenic element, whereby the
ductal tissue responds to increased perfusion pressure after birth by a reactive constriction;
an effect which is also dependent on $PGE_2$ (Kirska et al,1990). In the very immature fetus,
oxygen induced ductal constriction is less marked, and isolated ductal tissue is more
reactive to prostaglandins (Clyman et al,1980a). This may partly explain the tendency for
prolonged ductal patency in the preterm infant with hyaline membrane disease, along with
the fact that these infants have high circulating $PGE_2$ levels (Clyman et al,1980b), and
could help to explain the success in treating preterm infants with a symptomatic patent
arterial duct (associated with left to right shunting) with indomethacin to block
prostaglandin synthesis. Clyman has also demonstrated that the preterm lamb duct is more
responsive to indomethacin than at term (1980a), and that glucocorticoids (cortisol)
increase the sensitivity of the isolated lamb preterm duct to oxygen, improving ductal
constriction (1981). Thus glucocorticoids, which circulate in large amounts during vaginal
delivery and not before elective caesarian section, seem to have a 'maturing action' on the
duct.

(2) There are therefore no consistent anatomical differences between the preterm and term
duct (except for less ductal mass), but there are important physiological differences in the
balance between the respective roles of prostaglandins, oxygen and glucocorticoids.

1.8.4 Rate of closure and postnatal shunting via the arterial duct

(1) Born (1954) from Dawes' laboratory, first showed that the arterial duct does not clamp
shut immediately at birth, as was previously believed, but that flow through it was common,
at least in sheep, for a few hours after birth. Because no murmur had been heard in the
human immediately after birth, this paper was greeted sceptically. Eldridge et al (1955)
were the first to demonstrate left-to-right ductal shunting in the normal human neonate for
up to 48 hours after birth. The method was crude, using capillary samples from the right hand and a foot to measure the difference in oxygen saturation. However, in 1956, Adams and Lind, using cardiac catheterisation, showed that ductal shunting could be present in the human, with a left to right shunt, several hours after birth, without a murmur - the first recognition of the "silent ductus". Moss et al (1963) and Emmanouilides (1964), working together, showed by cardiac catheterisation that left-to-right ductal shunting was common over the first day of life, the shunt being as high as 3.6:1 in two of the babies. Shunting was bidirectional over the first six hours, then left-to-right, and became insignificant after 15 hours. The results were calculated by oximetry and may be overestimated due to streaming within the pulmonary artery, but qualitatively the results are reliable. The results are presented in figures 1.4 and 1.5. Figure 1.4 shows the high prevalence of left to right ductal shunting over the first 12 hours. Moss (1964) found five of six babies less than 11 hours of age had left to right ductal shunting, but at 18-27 hours only one of nine babies shunted left to right. Figure 1.5 demonstrates the relationship between the ratio of mean pulmonary and systemic arterial pressures with the pulmonary to systemic flow ratio (Qp/Qs). The most significant shunting occurs when the pulmonary arterial pressure is only marginally below systemic. It would appear from this, that the size of the duct is the main factor determining the degree of left to right shunting as pulmonary arterial pressure falls over the first hours of life. On the other hand, Saling's study showed that, in the first hour of life, when the pressures are balanced, right to left ductal shunting is common. Thus in determining the size and the direction of shunting, there is an important interplay of ductal size with the pressure gradient across it. Since resistance is a product of flow and pressure, the high pulmonary flow associated with left-to-right ductal shunting may maintain a high pulmonary arterial pressure, even in the presence of a falling vascular resistance.

(2) In relating pulmonary to systemic arterial pressures, the diastolic pressure ratio falls quicker than the systolic pressure ratio. Emmanouilides' data has been redrawn to include both of these ratios in figure 1.6. At 24 hours, the systolic pulmonary:systemic pressure ratio is about 0.7:1, whereas the diastolic ratio is about 0.3:1. One can safely assume from this data that left to right shunting is likely to be greatest during diastole.

(3) Using Doppler echocardiography it has been shown that the arterial duct in fact remains slightly patent for much longer than demonstrated by cardiac catheterisation. Between 10 and 15% of healthy term babies have a patent arterial duct into the fourth day (Gentile et al,1981; Reller et al,1988; Milne et al,1989).

(4) In summary therefore, the arterial duct constricts rapidly after birth. Catheter studies have shown that there is a variable period of significant ductal shunting in the first hours of life, even in the healthy term infant, and this shunting occurs mostly during diastole. The duct is usually 'functionally' closed by the end of the first day, but Doppler
Figure 1.4  Pulmonary : systemic flow ratio in 51 healthy term infants (Emmanouilides)

Figure 1.5  Relationship of pulmonary and systemic flow ratios with mean arterial pressure ratio. (Emmanouilides)
Figure 1.6
Ratio of pulmonary : systemic arterial pressure in healthy neonates, systole and diastole.

**Arterial pressure ratio**

- systolic Pa:Ao ratio
- diastolic Pa:Ao ratio

Figure 1.7
Ratio of mean pulmonary : aortic pressure. Healthy premature and Term neonates

**Ratio of mean Pa : mean Ao pressures**

- Term (Emmanouilides)
- Preterm (Moss)
- Term (Saling)
echocardiography has demonstrated that a degree of ductal patency is common well into
the first week of life.

Thus, there is a recognisable series of events resulting in the successful adaptation of the
circulation to extraterine life. Central to this process is the reduction of pulmonary
vascular resistance in relation to systemic vascular resistance. The transition can be
disturbed by a number of factors, but how is the process affected by premature delivery and
by hyaline membrane disease?

1.9. Prematurity and the transitional circulation

1.9.1. Introduction

(1) Because of the invasive nature of cardiac catheterisation, good data on the circulation in
the newborn premature infant are scarce. It is to be expected that there will be differences in
postnatal adaptation because there are important physiological and anatomical differences
between the term and preterm neonate. An example where this is most clearly
demonstrated is the cerebral circulation, which has been extensively investigated over the
last decade (Archer and Evans, 1988). The presence of a 'watershed' blood supply to the
periventricular area which carries the corticospinal tracts, means that ischaemic injury is
common in this area, giving a greatly increased risk of spastic cerebral palsy. It has also
been suggested that there is a lack of cerebral autoregulation rendering the premature brain
vulnerable to a mismatch between metabolic demand and cerebral perfusion (Rennie et
al, 1989).

(2) Much less attention has been given to the pulmonary circulation. The lung of the
premature neonate is structurally and physiologically different in a number of ways, and
these differences involve the pulmonary vasculature and the arterial duct. Since alterations
in pulmonary vascular tone are central to the normal transitional circulation, it would be
reasonable to suspect some important differences in either the rate or the mechanisms of the
process compared to the term baby. Certain differences in the way the premature neonate
adapts its circulation to postnatal life might be expected from a knowledge of normal fetal
development:

A. Pulmonary vascularity. Throughout the third trimester, pulmonary vascular resistance
does (in animals), due to a proliferation in the number of pulmonary arterioles, and an
increase in the size of the pulmonary vascular bed. The muscular walls of the arterioles also
become increasingly thick, and also increasingly reactive to various stimuli, such as hypoxia.
Taking these factors alone, it would seem likely that there will be relatively increased
pulmonary vascular resistance after birth in the premature neonate, but at the same time, the
resistance will be less sensitive to external stimuli. The normal stress of vaginal delivery, a minor degree of acidosis and hypoxia, not constituting overt asphyxia, are common. Perhaps the neonate at term will respond to this stress by elevating pulmonary vascular resistance, and the preterm infant will be less able to do so. This may be advantageous to the preterm neonate, because adequate pulmonary blood flow is clearly important, but it could also be seriously disadvantageous in terms of preserving adequate aortic and cerebral blood flow at a time of increased cerebral metabolic demand. With a widely patent arterial duct and a low pulmonary vascular resistance, there may be a cerebral 'steal' as blood poors into the newly released pulmonary circuit through the patent duct, particularly in diastole. In fact, it is not known whether healthy premature neonates have a different rate of fall of pulmonary vascular resistance. It is likely that there is not a straight-forward answer to this question, and factors such as mode of delivery and timing of cord clamping may cause differences in the transitional circulation which are not per se related to prematurity. These issues can now be addressed using Doppler ultrasound. However, some invasive studies of pulmonary and systemic arterial pressure have been done on the healthy human preterm baby and are discussed in the next section (1.9).

B. The arterial duct. The preterm arterial duct is physiologically immature, and just as the pulmonary vasculature becomes increasingly reactive throughout fetal development, the same is true of the arterial duct. At earlier fetal gestation, oxygen induced ductal spasm is less marked. Physiological maturation depends on glucocorticoid activity, but there is a higher incidence of caesarian section for premature delivery. For these two reasons, the preterm duct could, theoretically, be more likely to remain patent after preterm birth.

C. The oval foramen. The initial closure of the oval foramen is brought about by a pressure gradient between the left and right atria. The closure does not depend on prostaglandins or other biochemical events. Therefore 'physiological' immaturity is not an issue with the oval foramen. However, case reports of premature closure of the foramen, which is fatal to the fetus, tend to occur with more advanced gestation (Fraser et al, 1989); the oval foramen is presumably designed to be competent at term. Therefore one might expect that closure of the flap could, theoretically, be anatomically less adequate following preterm delivery.

1.9.2. Circulatory studies in the healthy premature neonate

1.9.2.1 Pulmonary arterial pressure

(1) Moss et al (1965) performed cardiac catheterisation on 77 healthy preterm infants and compared the results with 18 babies with hyaline membrane disease. In fact pulmonary arterial pressure was only measured in nine healthy babies, and only five of these were actually premature (less than 37 weeks). The results are shown in figure 1.7, with mean
pulmonary and systemic arterial pressure expressed as a ratio. The five values fall well within the range of results from Emmanouilides' study of term infants. Mean aortic pressures (from all 77 infants) showed a steady rise over the first three days: the average was approximately 45 mmHg at 12 hours and 55 mmHg at 30 hours. Ductal shunting was not significant, though all but one of the babies studied were over 10 hours old.

(2) There have been a few studies using Doppler ultrasound to estimate pulmonary arterial pressure in the preterm neonate, but it is necessary to discuss the potential inaccuracies and limitations of these techniques before discussing the results, so this will be done after describing Doppler techniques of pulmonary arterial pressure estimation in chapter 4.

1.9.2.2. Systemic arterial pressure

(1) Systemic arterial pressure was shown to be lower in the premature neonate, and the value related to birth weight, by Holland and Young in 1956. There was also a gradual rise in blood pressure up to six months of age. There have since been several cross-sectional studies, but few longitudinal studies. Versmold et al (1981) reported aortic pressure in 61 healthy infants with umbilical arterial catheters, weighing 610 to 4220g from one to 12 hours of age, and the nomograms produced have been used widely. Mean systolic pressure was about 43 mmHg for a baby of 1000g and 62 mmHg for a baby of 3000g. However, this study did not allow for the spontaneous elevation in arterial pressure seen in the first hours of life. This was reported in very low birth weight infants by Moscoso et al (1983): from the second and third hours of life to the seventh and eighth hour, mean (SD) systolic blood pressure rose from 35.1 (7.4) mmHg to 40.9 (4.9) mmHg in babies under 1000g, and from 35.3 (2.8) mmHg to 42.6 (4.0) mmHg in babies between 1000 and 1250 g. A more recent study, using an oscillometric technique (Dinamap) confirmed that term babies also show a significant rise over the first 3 days of life (Hulman et al, 1991), of between 10 and 15 mmHg. Babies of lower birth weight (2000g to 2500g) showed a similar rate of rise over this time period, but these were a mixture of preterm and small for gestational age babies.

(2) Thus it is clear that systemic blood pressure rises in the term and preterm neonate over the first hours of life, and that the absolute values are lower in the preterm neonate. It is not clear if one tends to rise faster than the other.

1.9.2.3. Ductal patency

There have been several studies using Doppler echocardiography to record ductal patency in the newborn, but surprisingly few have concentrated on the healthy premature neonate. When healthy babies of 30-36 weeks gestation were compared with term babies by Keeler et al using colour Doppler flow mapping (1988), there was no difference; all ducts were closed
by day 5. The comparative study by Milne (1989) included some premature babies with respiratory distress and this biased the results such that premature infants had prolonged ductal patency. Prolonged ductal patency is probably not a feature of the transitional circulation in the healthy premature neonate of over 29 weeks gestation.

1.9.2.4. Patency of the oval foramen

Despite the potential importance of this interatrial communication, there have been no studies comparing the rate of closure of the oval foramen between healthy term and preterm neonates. Evans and Archer (1990), demonstrated that seven healthy preterm infants did have a patent oval foramen in the first three days of life, but the numbers were too small to allow comparison with term babies.

In summary, healthy preterm neonates have a similar transitional circulation to the term infant, despite physiological and anatomical differences. Both groups undergo ductal closure within 5 days of birth, and have a marked rise in systemic blood pressure, and also a fall in pulmonary arterial pressure. These changes seem to be of the same order of magnitude in the term and preterm infant. There are several factors which have not been firmly established, including the relative rate of fall of pulmonary arterial pressure, and the rate of closure of the oval foramen and its haemodynamic influence prior to closure, and the haemodynamic effect of the patent duct in healthy babies (particularly preterm) in the first hours of life.

1.10. Persistent transitional circulation

1.10.1. Introduction

While Lind and Wegelius (1954) were the first to recognise the importance of right-to-left atrial and ductal shunting in neonatal cyanosis in the absence of congenital heart disease, the 'FPC' syndrome (persistent fetal circulation) was first described as such by Gersony et al in 1969. They "encountered two term infants who displayed persistent physiological characteristics of the fetal circulation in the absence of recognisable cardiac, pulmonary, hematologic or CNS disease." Both babies had right ventricular failure with cyanosis and clear lung fields. Cardiac catheterisation revealed large right-to-left shunting at both atrial and ductal levels. Both babies died, although in one, capillary oxygen saturation had increased transiently with tolazoline. Post mortem studies showed normal heart and lungs.
(2) 'PFC' syndrome has been extensively researched, and reviews abound. Central to the continued fascination in the subject is the inability to agree on the best form of treatment, coupled with high mortality and morbidity.

(3) There have been no controlled trials comparing different regimens for the management of this condition, perhaps because of a lack of agreement as to what the condition actually is. Burnard (1989) contended that it has been unhelpful to lump all the conditions associated with increased pulmonary vascular resistance together under one label, including such varied aetiologies as left ventricular failure, cardiogenic shock and meconium aspiration. One standard treatment is unlikely to be appropriate for all of these, and any useful comparison of outcome between centres, and following different therapy, is difficult if not impossible. An indication of this confusion is the difficulty in finding the best name to describe the problem. The term 'persistent pulmonary hypertension of the newborn' (PPHN) has been substituted for three reasons: 1. 'PFC' should describe only those babies without an associated recognisable disease, 2. the baby is no longer connected to a placenta, 3. it is said to reflect the underlying physiology more accurately (Tiefenbrunn and Reimensdmeider, 1985). However, this new name seems to imply that pulmonary hypertension must, of itself, be a diagnosis and a clinical problem, and it is therefore also misleading. And why is it 'persistent'? Hypertension denotes a pressure which is too high, a pathological situation, but it is appropriate to have a high pulmonary arterial pressure in the fetus. The condition is truly persistence of the pulmonary circulation appropriate to the fetus, and not persistence of a pathological state. The essence of the syndrome is the failure of the transitional circulation, as a consequence of a failure of the normal postnatal fall in pulmonary vascular resistance. This leads to cyanosis, with a structurally normal heart and lungs, and with a normal blood pCO2. Furthermore, 'PFC' (ie. with cyanosis) can occur without markedly elevated pulmonary arterial pressure, a point made by Reimensdmeider in a previous publication (1975). This point is of considerable importance in designing a non-invasive tool to monitor the progress of the pulmonary circulation, since it would suggest that monitoring pulmonary arterial pressure alone will not give all of the important information. Surely it is decreased pulmonary flow that is the crux of this condition; perhaps Chu et al's words could be borrowed from their paper in 1967 on hyaline membrane disease (discussed later in section 2.4), and PFC could be renamed 'pulmonary hypoperfusion syndrome'.

(4) The condition is therefore not really a syndrome or even a diagnosis, and it is not always associated with pulmonary hypertension. It is, however, a recognisable clinical problem. In reviewing the subject it is probably best to consider the "disease processes (in the newborn) with persistent elevated pulmonary vascular resistance as an important feature" (Gersony, 1984) and a structurally normal heart. Perhaps "persistent transitional circulation (PTC)" would be most appropriate. This term will be used in this thesis to
describe babies with hypoxaemia associated with failure of the normal transitional circulation, babies with 'pfc' being a sub-group in whom no underlying aetiology is clinically apparent.

1.10.2. Incidence (Abu-Osba, 1991)

(1) True "PFC", as originally described by Gersony et al, is rare. There is usually a recognisable underlying cause, and if these are included, the incidence lies between 1/1400 and 1/2600 live births and accounts for about 1% of admissions to intensive care units. Abu Osba said mortality lies between 34 and 60% despite aggressive management with hyperventilation, fluids, vasopressors and vasodilators. Once again, the problem is one of disease definition, and threshold of severity.

1.10.3. Clinical presentation

(1) Hypoxia, acidosis and tachypnoea, are the main presenting features, (Levin et al, 1976) but the hypoxia persists despite correction of the acidosis. It can occur in babies of any gestation, though most are at term or post-term. Tricuspid or mitral regurgitation and myocardial dysfunction are common, with electrocardiographic evidence of myocardial ischaemia, and a clinically overactive right ventricle is frequent (Levin et al, 1976; Riemenschneider et al, 1976; Fox and Duara 1983). Presentation can be immediate, typically following perinatal asphyxia, or with diaphragmatic hernia, subacute, at 4-12 hours, typically with meconium aspiration syndrome, or late, at 12-24 hours, often associated with group B Streptococcal infection or progressive airways obstruction (Abu-Osba, 1991). A very late type, of unknown cause, was recently described in two babies by Raine et al (1991); one baby presented at ten days and the other at two months; both babies died. Chronic lung disease with secondary pulmonary hypertension does not fall into this disease group.

1.10.4. Aetiology

(1) There is a long list of pre and perinatal events that are associated, including hypoxaemia, meconium aspiration, maternal salicylates, premature ductal closure, polycythaemia, hypoglycaemia and hypocalcaemia. The final common pathway is pulmonary vascular underperfusion consequent upon a combination of two factors: constriction of pulmonary blood vessels and/or a reduced number of vessels (restriction). These can be complicated by functional obstruction due to hyperviscosity, pulmonary venous hypertension due to left ventricular dysfunction, (or congenital heart disease) and pulmonary parenchymal disease, such as interstitial emphysema. Both types also have some reactive element of pulmonary vasoconstriction.
The pathological correlates were reviewed by Reid (1987). She suggested that:

**Constrictive pulmonary hypertension** implies a rapidly reversible hypertension and arises from constriction of the contractile elements of the vessel wall, mostly in the muscle coat, but including endothelial and smooth muscle precursor cells.

**Restrictive pulmonary hypertension** implies a structural basis, with reduced cross-section of the vascular bed. This can be due to obliteration or failure to multiply, by a failure to grow or by a restructuring of the vessel wall that encroaches on the lumen.

Both constrictive and restrictive elements are usually present; Reid states that there is almost always a structural abnormality in babies that die from persistent pulmonary hypertension. Most characteristic is precocious or excessive muscularisation of the pulmonary vascular bed, where muscle is located in vessels as far down the bronchial tree as the alveoli. In the normal term baby, the muscle only reaches as far down as the terminal bronchiole. Murphy et al (1981) reported that ten of 11 patients who died of meconium aspiration with right-to-left shunting and hypoxaemia also had these changes. It was concluded that these changes were so extensive that they must have developed prenatally. The cause of this muscularisation is unknown, and fetal animal models of maternal hypoxia have failed to produce these changes, though they have produced persistent pulmonary hypertension (Soifer et al, 1987). Interestingly, large systemic arteriovenous shunts are associated with similar changes, suggesting that high flow before birth could be involved, perhaps causing elevated pulmonary arterial pressure due to the fixed resistance of the system. Premature ductal constriction has been strongly implicated. It is fatal to the fetus if closure is complete and is accompanied by right ventricular and atrial dilation and damage, evident on post-mortem examination (Kohler, 1978). Levin et al (1978 and 1979) showed that ductal constriction in the fetal lamb resulted in precocious pulmonary arterial muscularisation and, after ventilation, right ventricular hypertension, hypertrophy and damage. Maternal non-steroidal anti-inflammatory drugs (prostaglandin synthetase inhibitors) have also been implicated (Wilkinson et al, 1979).

Hypoplasia of the pulmonary vascular bed takes several forms, according to the stage of fetal lung development at which the disturbance occurred. The lung may be perfectly formed, but simply too small, or there may be reduced bronchial airway generations (implying disturbance before the 16th week of fetal development), such as in Potter’s syndrome, congenital diaphragmatic hernia, or idiopathic lung hypoplasia (Reid, 1987). These lungs are simply unable to accept the full cardiac output, and are extraordinarily difficult to manage, because even slight pulmonary vasoconstriction can tip the balance permanently against adequate pulmonary flow.
1.10.5. Management

1.10.5.1. Management can be divided conveniently into three sections:

1. Specific treatment aimed at the underlying cause, for example antibiotic therapy for suspected group B Streptococcal infection, or broad spectrum antibiotics following meconium aspiration, glucose or calcium for hypoglycaemia and hypocalcaemia, plasma exchange for polycythaemia, and surfactant for associated hyaline membrane disease.

2. General supportive therapy, particularly following perinatal asphyxia, including inotropes and diuretics in the management or prevention of renal failure, maintenance of adequate circulating blood volume and blood pressure, anticonvulsants for seizures, maintenance fluid requirements adequate sedation and pain relief. Increasing systemic arterial pressure can also have the direct effect of reversing R-L shunting.

3. Specific therapy to decrease pulmonary vascular resistance, involving intravenous vasodilators and manipulation of the acid-base status. Most management is done on an empirical basis, without monitoring pulmonary arterial pressure or flow in any way, and control trials of different therapies do not exist.

1.10.5.2. Vasodilators

Many vasodilators have been tried in the neonate with PTC. The problem remains that all pulmonary vasodilators are also systemic vasodilators. Tolazoline is the most commonly used, either alone (Goetzman et al, 1976) or in combination with Dopamine, or other pressor drugs (Drummond et al, 1981; Seri et al,1983). Prostacyclin has been used, but is very expensive and is probably only of use in a minority of patients (Kulik and Lock, 1984). Trinitroglycerine looks promising (Tamura and Kawano, 1990). Acetylcholine has, surprisingly, not been carefully evaluated in this condition. A recent publication comparing three pulmonary vasodilators in a newborn calf pulmonary hypertension model (Orton et al, 1988), showed that acetylcholine was a much more effective pulmonary vasodilator than sodium nitroprusside and prostacyclin, and had a less marked systemic hypotensive effect. This was thought to be because prostacyclin and nitroprusside exert their effects via the mediation of the vascular endothelium, which is often damaged in PTC, particularly in association with meconium aspiration, and acetylcholine does not require an intact endothelium to exert its effects. Abu-Obe (1991,1992) put forward a strong case for the use of magnesium and inhaled nitric oxide (biologically identical to endothelium derived relaxing factor (Ignarro, 1991)) is finding increasing favour. Other drugs that have been tried
include hydralazine, nifedipine, captopril and phentolamine, but none have achieved universal acceptance.

1.10.5.3 Acid-base status

The principles learnt from the study of the normal transitional circulation have been applied in the treatment of this condition, in which the transition has failed. Pulmonary arterial pressure is reduced by hyperventilation to lower pCO₂, or by alkalinisation (see below). Hyperoxia has not been evaluated but can be used since, as previously discussed, it is known to reduce pulmonary arterial pressure in healthy neonates and hypoxia is known to increase it. Hyperventilation (more specifically hypocapnia) reduces cerebral blood flow, and has been implicated as a cause of neurological handicap and deafness in follow up studies (Bifano and Pfannenstiel, 1988; Ferrara et al, 1984; Hendricks-Munoz and Walton, 1988).

1.10.6 Invasive studies

(1) Drummond et al (1977) catheterised 7 infants with persistent pulmonary hypertension, between 10 and 38 hours after birth. Pulmonary arterial systolic and mean pressure was equal to, or higher than the systemic arterial pressure. A right-to-left shunt was present at the duct in all cases, and at atrial level in three cases. A large difference between umbilical (post-ductal) and temporal (pre-ductal) pO₂ was also found in four of six babies by Levin et al (1976). This point is of interest because it is Gersony’s contention that most right-to-left shunting occurs at atrial level (1984, and personal communication, 1991), as a consequence of decreased right ventricular compliance. Lind and Wegelius (1954) demonstrated, using angiography, reflux of contrast up the superior vena cava in cyanosed neonates, during atrial contraction, and stressed the likely importance of decreased right ventricular compliance and relaxation in the development of right-to-left atrial shunting. Peckham and Fox (1978) showed, using indwelling pulmonary arterial lines, that pulmonary arterial pressure was extremely labile, with abrupt changes due to no apparent cause, but was reduced by hyperventilation (Tolazoline had a variable and unpredictable effect). Drummond et al (1981) in another five cases, showed that systemic arterial saturation was satisfactory when the pulmonary to systemic systolic arterial pressure ratio was below 1.0:1. This ratio averaged 1.14 with ‘standard therapy’ but was reduced to 0.98 with respiratory alkalosis, to 0.87 with tolazoline and dopamine, and to 0.70 when the two therapies were combined.

(2) Since right-to-left ductal shunting is so common in this condition, support of systemic arterial pressure assumes great importance. Right ventricular hypertension can, per se, severely reduce left ventricular output and systemic arterial pressure, by interfering with left
ventricular function (Behk et al, 1989). Forcibly increasing systemic arterial pressure using distal aortic compression in a hypoxic piglet PTC model caused a marked increase in pulmonary blood flow and arterial oxygen saturation (Ghai et al, 1991). In the human, dopamine infusion alone has been used successfully in the treatment of PTC associated with myocardial dysfunction (Fiddler et al, 1980). Emmanouides presented the pulmonary to systemic mean arterial pressure ratios in 18 babies with PTC (1979), and compared them with his normal data. All of the values were higher than the normals, but three of the eight babies over 48 hours had values below 0.8:1, one was as low as 0.5:1. Fifteen of the 18 had right-to-left ductal shunts, but interatrial shunting was not discussed. Once again the pulmonary to systemic arterial pressure ratio is useful in describing perinatal circulatory events.

1.10.7. Non-invasive assessment

(1) Important non-invasive measurements are already available. These include physical examination, to assess cyanosis, pulse volume, presence of atrioventricular valve regurgitation, presence of hyperinflation and so on. Chest X-Ray shows cardiac size and is a crude measure of pulmonary perfusion and vascularity, and excludes pneumothorax and areas of consolidation. Electrocardiography can demonstrate right ventricular hypertrophy and myocardial ischaemia, but is of little practical use in monitoring therapy.

(2) Transcutaneous oxygen measurement has been shown to be of use in PTC (Boyle and Oh, 1978), though in the presence of poor skin perfusion, values may underestimate arterial saturation. Pulsed-oximetry is also a valuable tool. High concentrations of fetal haemoglobin, the norm in the first days of life, render the results less accurate (Jennis and Peabody, 1987). The method is unreliable in severe hypoxaemia (saturation less than 60%) (Fanconi, 1985), and in the monitoring of hyperoxia (over 92%) (Baeckert et al, 1987) though both of these studies showed reasonably close correlation with directly measured arterial saturation between 65 and 92% saturation. When the two methods were compared in 18 infants with respiratory distress (Wimberley et al, 1987), they were both found to be very good trend monitors, but the fluctuation in fetal haemoglobin, pCO2, pH and diphosphoglycerate concentration rendered the interpretation of pulsed oximetry values rather difficult, and it was suggested that strict limits for hypoxia and hyperoxia should be applied with caution using this method. Both of these methods are now part of routine clinical management of these children already, and can be also useful in the detection of differences in cyanosis due to ductal shunting.

(3) Direct pulmonary arterial pressure measurement has been reserved for the investigation of new treatments since it is invasive, and potentially harmful. A non-invasive measurement of pulmonary arterial pressure, resistance or flow would be most useful in the
routine management of these patients, allowing correct evaluation of therapy and helping to avoid the "cook book" approach, where every baby perceived to have PTC receives the same therapy (Phillips, 1984). A combined approach, using all the facets of Doppler, m-mode and cross-sectional echocardiography, is likely to be the most helpful.

(4) Previous echocardiographic studies in babies with PTC are reviewed in chapter 4 (section 4.2.4), after the echo-Doppler techniques have been discussed in chapter 3. In chapter 18, a study is presented in which 34 babies presenting with PTC underwent detailed echocardiographic assessment.
Chapter 2: Hyaline membrane disease

2.1 Introduction

2.2 Epidemiology and typical presentation

2.3 Historical perspective

2.4 Aetiology- surfactant deficiency or pulmonary ischaemia?

2.5 Pulmonary circulation in hyaline membrane disease.

Figures

2.1 Direct measurements of mean pulmonary : mean systemic arterial pressure ratio in babies with hyaline membrane disease (from the data of Moss et al (1965)).

There are no tables in chapter 2.
Chapter 2. Hyaline membrane disease (respiratory distress syndrome)

2.1. Introduction

Most of the workload of a neonatal intensive care unit revolves around the management of ventilator dependent premature babies most of whom have hyaline membrane disease. The mainstay of management is mechanical ventilation, and more recently, the administration of surfactant, deficiency of which is now believed to be the primary underlying cause of the disease. Premature babies less than 30 weeks gestational age frequently do not have 'pure' hyaline membrane disease, their respiratory failure being complicated by lack of respiratory drive and gross morphological immaturity of the lung. Nevertheless, hyaline membrane disease, now widely known as surfactant deficiency, is important even in this group of babies, and babies of less than 30 weeks are included in this study.

2.2. Epidemiology and typical presentation

(1) The condition is worldwide, and is only seen following premature delivery, more commonly in babies of diabetic mothers, following perinatal asphyxia and following elective caesarian section (Farrell and Avery, 1975). Cyanosis, tachypnoea and an expiratory grunt develop soon after the time of birth, and typically the respiratory distress peaks at the second or third day, followed by a gradual recovery. There is a classical chest X-ray appearance ('ground glass', with air bronchograms, and underinflated lungs). The lungs have reduced compliance, reduced functional residual capacity, poor alveolar stability and poor lung distensibility, and pathologically there is atelectasis, damaged epithelial cells, and the classical eosinophilic hyaline membrane which contains fibrin and cellular products.

(2) Prior to positive pressure ventilation, the outlook for a baby with severe hyaline membrane disease was grim, but with each passing year, the prognosis for premature babies with the disease becomes better, and the youngest gestational age of viability is becoming progressively lower. At the Princess Mary Maternity Unit, Newcastle upon Tyne, a centre specialising in the obstetric and perinatal management of high risk pregnancies, the overall perinatal mortality rate has fallen from 18.9 per thousand live births in 1979, to 11.6 in 1989. Over the same time period, the number of babies less than 1.5 kg birth weight admitted to the nursery over a year rose from 34 to 88, largely due to transfer from other units without high dependency facilities, and the ventilator workload (ventilator nights/year) rose from 147 to 1104. In 1979, mortality was 41% in babies weighing 1-1.5 kg and 12% in babies weighing 1.5 to 2.0 kg. Respective figures were 5% and zero in 1989. While a high mortality still exists for extremely low birth weight babies (61% mortality for babies less than 1.0 kg), there has been a shift in emphasis from reducing mortality to reducing morbidity.
Many of the factors causing significant morbidity are related to the effects the disease and extreme prematurity have on the circulation, most notably the cerebral and gut circulation (Toro et al., 1991; Coombs et al., 1990). A circulatory system designed for many further weeks of warmth and comfort in utero is suddenly exposed not only to the stresses of extrauterine life, but to a situation where the main site of gas exchange is damaged and where huge fluctuations of pressure occur within the thorax. Perinatal asphyxia, and depletion of blood volume through rapid cord clamping add to the cardiorespiratory problems of the sick premature neonate. The systemic circulation is directly connected, at two levels, to the pulmonary circulation, and any change in one system is bound to affect the other. The need for a clear understanding of the behaviour of the pulmonary circulation under these circumstances is obvious.

2.3 Historical perspective

(1) In 1903, pulmonary hyaline membranes were first described by Hochheim, and were considered to represent aspirated amniotic fluid. Over the next 47 years, various suggestions were put forward ascribing significance to the hyaline membrane. In 1950, an interval of air breathing was proposed as a prerequisite to the development of the membrane, the association with prematurity, fetal anoxia, maternal diabetes and caesarean section were recognised, and the clinical presentation of respiratory failure was described (Miller and Jennison). In 1951 the hyaline membrane was recognised as resulting from tissue damage and transudation of plasma protein and was therefore a secondary phenomenon, and atelectasis was proposed as the significant factor (Bruns and Shields). In 1953 the classical reticulogranular radiographic appearance was described (Donald and Steiner). In 1955, the clinical pattern of respiratory distress syndrome was clarified (Miller and Conklin), allowing indices of disease severity to be developed, and surfactant was discovered in adults, from pulmonary oedema and lung extracts (Pattie).

(2) In 1959, Avery and Mead demonstrated pulmonary surfactant deficiency in babies succumbing to hyaline membrane disease. However, abnormalities of the transitional circulation were thought to be a likely cause of the disease, and numerous publications suggested the important role of pulmonary vascular tone and shunting at ductal or atrial level. Reduced phosphatidyl choline in the lungs of affected infants was demonstrated in 1967 (Brumley et al.) and 1970 (Adams et al.). At around the same time, assisted ventilation was shown to improve survival rates (Swyer, 1969).

(3) In 1970-1, there were several important advances: the lecithin to sphingomyelin ratio in amniotic fluid was found to predict severity of respiratory distress in premature babies (Gluck et al., 1971), positive end expiratory pressure was shown to markedly reduce mortality (Gregory et al., 1971), and the effectiveness of regionalised perinatal care was
demonstrated (Swyer, 1970). Abnormalities of the pulmonary circulation were no longer felt to be the underlying cause of hyaline membrane disease, and research into this aspect became scarce.

(4) In 1973, the antenatal administration of corticosteroids was shown by Liggins and Howie to reduce the incidence of hyaline membrane disease.

(5) The next decade saw the steady improvement of the survival of the preterm neonate, coupled with improved and rationalised regional services, and advances in techniques of ventilation and the management of fluid balance and nutrition. The high incidence of brain damage and, in particular, cerebral palsy led to studies attempting to identify the nature and potential causes of this damage (reviewed recently by Toro et al, 1991). Increasing numbers of premature neonates were left with chronic respiratory disease.

(6) Prolonged patency of the arterial duct, recognised as a feature of hyaline membrane disease for over forty years (Rudolph et al, 1963), was increasingly recognised as a potential cause of increased morbidity through left-to-right shunting (Siassi et al, 1976). Surgical ligation and later indomethacin treatment, were found to be important and effective treatments for babies developing heart failure (Merritt et al, 1978, Cooke et al, 1978; Obeyesekere et al, 1980; Yanagi et al, 1981; Harris et al, 1982, Gersony et al, 1983; Rudd et al, 1983). McGrath et al, in 1978, showed that there may be clinically silent left-to-right ductal shunting, but early prophylactic ductal closure, shortly after birth, has failed to reduce mortality or morbidity (Cotton et al, 1978; Merritt et al, 1981; Hammerman et al, 1987; Cassady et al, 1989).

(7) The last ten years has seen the introduction of surfactant to neonatal intensive care. Several different preparations have been the subject of randomised controlled trials. These were reviewed recently by Morley (1991). Trials giving surfactant prophylactically have shown a decreased incidence of intraventricular haemorrhage, pneumothorax, bronchopulmonary dysplasia, and an average reduction in mortality of about 20%. Trials giving surfactant after the disease has reached a certain threshold of severity ("rescue") are slightly less impressive, particularly since it does not apparently reduce the incidence of bronchopulmonary dysplasia. There has been no change in the incidence of patent arterial duct going on to require treatment.

(8) Surfactant therapy is therefore beneficial, but is not the whole answer. The duct remains patent, so the balance of pulmonary and systemic pressures remains crucial. The present study was completed prior to the introduction of surfactant therapy to Newcastle. Since surfactant therapy is here to stay, this work therefore represents one of the last opportunities to study the circulatory effects of the disease in its 'pure' form.
2.4 Aetiology-surfactant deficiency or pulmonary ischaemia?

(1) The mid 1960's was a period of great controversy over the aetiology of the disease. In the midst of all the interest in surfactant deficiency, came a publication, from some of the leading researchers in the field, saying, "In our view, idiopathic respiratory distress of the newborn, or hyaline membrane disease, results from, and primarily involves, pulmonary ischaemia and that secondary changes in structure, composition and physical properties of the lungs have tended to divert attention from it." Such was the conviction of the authors (Chu and Clements et al 1967), that the disease was referred to by a new name throughout the publication: "Neonatal pulmonary ischaemia". After a preliminary report ("The pulmonary hypoperfusion syndrome", 1965), the authors outlined their detailed argument in a 73 page supplement to Pediatrics in 1967. The starting point was the recognition of three characteristics of the disease: atelectasis, severe hypoxia and hypercarbia, and the development of anaerobic metabolism with accumulation of organic acids. They suggested that, due to the hypoxia and acidemia, pulmonary vasoconstriction would develop, leading to pulmonary ischaemia, deterioration of alveolar tissue, and further interference with the alveolar lining.

(2) To reverse this vicious cycle of events, they took two approaches, firstly giving an artificial surfactant, and secondly, administering a potent pulmonary vasodilator, acetylcholine. The affected babies had decreased pulmonary blood flow, as compared to controls. They were also extremely sick, and 15 of the 27 babies died; all but two died in the first two days. The surfactant increased pulmonary compliance in some of the babies, but did not improve gas exchange. Acetylcholine had a dramatic effect on some of the babies, and greatly improved gas exchange. It also caused an increase in cardiac output and effective pulmonary flow and a decrease in fractional right-to-left extrapulmonary shunt. Neither therapy had any conclusive effect on eventual survival. They concluded that the pulmonary ischaemia presented a greater functional difficulty than did pulmonary atelectasis and hyaline membranes. They did not go so far as to suggest that acetylcholine should be used in regular treatment; (in fact it was not until tolazoline therapy was used by McIntosh and Walters (1979) in some babies ventilated for the disease that a pulmonary vasodilator was used in the clinical management of hyaline membrane disease). Chu et al concluded, "We are convinced that whatever (management) regimen proves most successful, it will have early pulmonary vasodilation as an important effect."

2.5 The pulmonary circulation in hyaline membrane disease

(1) Chu’s paper was not the first to implicate disturbance of the circulation in causing hyaline membrane disease. Lendrum in 1955 described the pulmonary hyaline membrane as a "manifestation of heart failure" in a newborn infant. However, it was the simultaneous
work on the normal transitional circulation that began speculations about its role in hyaline membrane disease. James and Rowe (1957) then provided evidence, from cardiac catheterisation, that hypoxia in the human infant causes a fall in systemic blood pressure in relation to pulmonary arterial pressure, and that blood from the right heart can temporarily revert to the fetal pattern, and avoid the lungs by passing through the foramen ovale and the open duct.

(2) A less commonly quoted paper had appeared earlier. Lind and Wegelius (1954) had recognised right-to-left interatrial shunting in 30 cyanosed newborn infants, and described the importance of functional disturbance of the right atrium with pulmonary hypertension in the development of this shunting. In angiographic studies, they described reflux of contrast up the superior vena cava during diastole in these cyanosed babies. They also discussed the possibility of the arterial duct reopening after birth in the presence of hypoxia. I assume the reason this paper is not widely quoted is related to the ethical considerations of a procedure which was part of this publication. Live human fetuses, of 12 to 25 weeks gestation, were delivered by caesarian section, and angiocardiology was performed on them prior to ligature of the cord.

(3) In 1961, Rudolph reported the first formal cardiac catheter studies comparing healthy newborns with those with hyaline membrane disease, mostly over the first 24 hours of life. Interpretation of the results is made more difficult by the inclusion of babies with Downs' syndrome and babies of diabetics and eclamptics in the normal group. There were no differences in the haemodynamic data between the healthy and mildly distressed infants, but the severely distressed infants (none of whom were ventilated) had markedly lower pulmonary and systemic pressures, although the pulmonary : systemic arterial pressure ratios were similar. The distressed infants had larger arterial ducts and greater amounts of both left-to-right and right-to-left ductal and foraminal shunting. Left atrial pressure was not increased, (though it was always higher than right atrial pressure) which was against the theory that left ventricular failure may be a cause of the disease, although the large negative intrathoracic pressures generated by these babies could generate a high transmural pressure, and oedema could, theoretically, then develop. Therefore, despite the presence of low or normal left atrial pressures, Rudolph postulated that left ventricular failure, possibly as a consequence of left-to-right ductal shunting, may have an important role in hyaline membrane disease, and “serious consideration should be given to attacking the disease from the circulatory point of view”.

(4) Important right-to-left shunting with respiratory failure in the newborn was found by Strang and MacLeish (1961), who took serial samples from umbilical vein and iliac arteries in seven babies with hyaline membrane disease before and after the administration of 100% oxygen, used as a nitrogen "washout". The size of the shunt varied from 0 to 80% of the
cardiac output, all but one sample being over 20%. The right-to-left shunt could have occurred at any level, including within the lungs, but it seems most likely, because of the method used, to have occurred at ductal and foraminal levels.

(5) In 1963 Moss et al performed a study testing a possible association of early cord clamping with the pathogenesis of respiratory distress. It was suggested that the sudden pressure rise from the raised systemic vascular resistance as the umbilical circulation is discontinued, could be transmitted via the arterial duct to the pulmonary circulation and cause transudation or even rupture through the capillary-alveolar membrane. The authors concluded that their study provided supportive evidence. In fact the study was far from conclusive; the babies who underwent early cord clamping had a higher incidence of respiratory distress, but the incidence of perinatal asphyxia was also much higher in this group. Other studies showed that early cord clamping can dramatically reduce the eventual circulating blood volume in the newborn baby (Jegier et al, 1963; Arcilla et al, 1966); this is likely to have dramatic circulatory effects in the asphyxiated premature neonate, though just what these effects are remains uncertain. The suggested link with respiratory distress still remains unproven.

(6) In another study by Moss et al (1965), distressed premature babies were found to have lower systemic, and higher pulmonary arterial pressures than a large control group of healthy infants. The lower arterial pressures of Rudolph et al (1961), were presumably a consequence of profound biventricular failure secondary to prolonged hypoxaemia and acidosis. The results, expressed as the mean pulmonary : mean systemic arterial pressure ratio are shown in figure 2.1. It may be important however, that the majority of babies were in room air during the catheter, despite breathing 'maintenance' oxygen beforehand, and thus hypoxia is likely to have influenced these results. Left-to-right ductal shunts were detected in two of eight distressed infants over 15 hours of age, and none of the eight healthy infants over this age. Low PO$_2$ values in the ascending aorta in some babies indicated important right-to-left intrapulmonary and /or inter-atrial shunting (via the oval foramen) was probably more significant than right-to-left ductal shunting.

(7) Elebute et al, (1966) investigated the effects of atelectasis, a well recognised feature of hyaline membrane disease, on pulmonary haemodynamics using anaesthetised and ventilated dogs. They showed neatly, for the first time, that areas of collapsed lung received more blood than the aerated lung. The concept of a ventilation/perfusion mismatch within the lung clearly had important potential implications in hyaline membrane disease.

(8) Roberton and Dahlenburg (1969) further investigated ductal shunting in hyaline membrane disease by comparing right radial and descending aorta oxygen tensions in 21 infants on 139 occasions, whilst estimating total right to left shunt using the same method as
Figure 2.1  Ratio of mean pulmonary : aortic pressure.
Healthy babies -v- babies with HMD

NOTE: Measurements were made by cardiac catheterisation.
Strang and Macleish. While 15 of the babies had some degree of right-to-left ductal shunting, it was never more than 39% of the total shunt, and usually much less, averaging about 15%. However, the contribution was larger when the babies were actually hypoxic (\( PaO_2 \) less than 100mmHg), and the right-to-left ductal shunt diminished dramatically when 100% oxygen was given, which was taken to indicate ductal constriction. Presumably it could also have indicated a reduction in pulmonary arterial pressure. The authors' conclusion was that the majority of right-to-left shunting in hyaline membrane disease must pass through the foramen ovale or the lungs.

(9) Stahlman (1972) reported circulatory studies in 168 babies with hyaline membrane disease. Aortic and atrial pressures were measured and dye dilution curves were used to investigate the location, magnitude and direction of persistent fetal shunts. Aortic pressures rose over the first three days in babies who survived, but gradually fell in babies who subsequently died. 19 of 40 infants had large right-to-left shunts at 12 hours or less, and 8 of 27 at 13-36 hours, and these shunts were associated with significant hypoxia. However, when acidosis was corrected, only one of 17 infants had right-to-left shunting at 13-36 hours. A degree of left-to-right shunting was almost always present and became increasingly important with age. Less than 20% had large left-to-right shunts under 12 hours of age. Experimentally induced hypoxia caused systemic hypotension and an increase in right to left shunt, especially in infants under 12 hours of age. Correction of acidosis had the opposite effect. Left atrial 'a' and 'v' wave pressure was consistently 1-2 mmHg higher than right atrial pressure, but in 7 babies, differential pressures were recorded between oesophageal pressure, (representing intrathoracic pressure) and atrial pressures, and in five of these babies mean inferior vena caval pressure was higher than mean left atrial pressure. In summary, right-to-left foramen ovale shunting was common, but only severely affected hypoxic infants were thought to maintain persistent right to left ductal shunts. Left to right ductal shunting was common after 12 hours of life and was frequently combined with right-to-left interatrial shunting.

(10) The paper by Stahlman appeared to mark the end of the era during which investigations of pulmonary haemodynamics were at the forefront of research into hyaline membrane disease. These studies had made it abundantly clear that pulmonary vascular tone and extrapulmonary shunting were important parts of hyaline membrane disease. Surprisingly, very little work has been done to follow this line of research over the succeeding twenty years. More recently, a few echocardiographic studies have been done, but before discussing these papers it is necessary to review the methods of pulmonary arterial pressure estimation available using Doppler and m-mode echocardiography.
Chapter 3: Doppler echocardiographic methods to determine pulmonary arterial pressure in the neonate

3.1 Introduction

3.2 Right ventricular systolic time intervals

3.3 Tricuspid regurgitation and the Bernoulli equation
   1 Introduction
   2 The Bernoulli Principle
      1 Historical perspective
      2 The physics
   3 Factors causing underestimation of the pressure drop
   4 Validation against direct measurement
   5 Summary

3.4 Analysis of ductal flow

3.5 Summary

Figures

3.1 Diagrammatical representation of the measurement of systolic time intervals.

Tables

3.1 Publications comparing direct measurement of pulmonary arterial pressure with systolic time intervals

3.2 Publications comparing direct measurement of pulmonary arterial pressure with pressure determined from tricuspid regurgitation and the modified Bernoulli equation.
Chapter 3. Doppler echocardiographic methods to determine pulmonary arterial pressure in the neonate

3.1 Introduction

3.1.1 Background

(1) Doppler echocardiography has radically altered management of babies and children with congenital heart disease by allowing rapid and noninvasive diagnosis. All of the different facets of echocardiography, initially applied to these babies, have been applied to babies with structurally normal hearts as each method has been developed.

(2) M-mode echocardiography allowed non-invasive assessment of ventricular function by measurement of the ejection fraction, and accurate timing of events during the cardiac cycle lead to the investigation of systolic time intervals in the assessment of ventricular function and pulmonary arterial pressure. A crude assessment of ductal shunting was possible by measurement of the width of the left atrium in relation to the aorta (Silverman, 1974).

(3) Cross-sectional echocardiography was the next stage of development, allowing direct visualisation of cardiac structures. Congenital cardiac defects were diagnosed or excluded more easily at the bedside in babies with heart failure or cyanosis secondary to birth asphyxia or persistent fetal circulation. The arterial duct could be visualised, but flow through the duct could still only be quantified using m-mode echocardiography, or by obtaining a visual impression of left atrial and ventricular volume loading.

(4) Doppler ultrasound, the most recent addition, has the potential to quantify flows and pressures, and is already of value in the intensive care unit (Rein et al, 1986; Morrow et al, 1985). Doppler measurements of left ventricular output have been validated (Alverson et al, 1982), and normal values in infants and neonates established (Sholler et al, 1987b; Hirsamaki et al, 1988). While there is little data from longitudinal studies, the method has been used successfully for clinical and research purposes in neonatology (Alverson et al, 1988). Left to right ductal shunting, which carries a significant morbidity (Cotton et al, 1988), can be detected several days before becoming clinically apparent (Mellander et al, 1987; Walther et al, 1989). Various different Doppler techniques have been employed to quantify ductal flow (Swenson et al, 1986; Liao et al, 1988; Milne et al, 1989; Hirsamaki et al, 1990), and this is an area of active research. Doppler measurements of cerebral, renal and gut blood flow have been studied extensively over recent years (Archer and Evans, 1989; Coombs et al, 1990).

(5) Doppler therefore already has an important place in neonatology. However, there has
been comparatively little research into the factor which is central to the normal transition from the fetal to the adult type circulation; pulmonary arterial pressure. Some studies in neonates used Doppler techniques to reflect pulmonary arterial pressure indirectly, using timing of cardiac events, and these will be discussed in more detail later. However the methods are complicated, and involve measurement of systolic time intervals from the pulmonary valve, or attempting to describe the shape of the pulmonary waveform numerically. These methods have not been validated for use in the neonate, and are influenced by myocardial function, heart rate and preload as well as pulmonary arterial pressure.

3.1.2 Determination of pulmonary arterial pressure

(1) There are three methods of pulmonary arterial pressure estimation using Doppler echocardiography which have been investigated for use in older children with congenital heart disease, and have potential for use in the neonate. None of the methods have been validated against direct pressure measurement in the mature or premature neonate.

1 Right ventricular systolic time intervals.

2 Measurement of maximal tricuspid regurgitant velocity with application of the Bernoulli equation.

3 Analysis of ductal flow patterns, and/or measurement of flow velocity through the duct and application of the Bernoulli equation.

(2) Since systolic time intervals were the first method to be introduced, and have already been applied in neonatology, this method will be discussed first.

3.2 Right ventricular systolic time intervals

(1) Right ventricular systole can be divided into time periods which alter in length, both in absolute terms and in relation to each other, depending on changes in pulmonary arterial pressure or pulmonary vascular resistance.

(2) Isovolumic contraction occurs during the pre-ejection period (PEP); this starts from the Q-wave of the ECG and ends with the opening of the pulmonary valve. The ejection phase follows, and the pulmonary blood flow velocity begins at zero, and following the opening of the valve accelerates to a peak velocity. This is the acceleration time or 'time to peak velocity', (TPV' or 'AT'). The whole time that the valve is open is termed the right ventricular ejection time (RVET). This sequence is shown diagrammatically, using Doppler...
Figure 3.1 Measurement of right ventricular pre-ejection period (PEP), time to peak velocity (TPV) and ejection time (RVET)

\[ P = PEP \]
flow through the pulmonary valve, in figure 3.1.

(3) Using m-mode echocardiography, it was possible, for the first time, to record accurately the opening and closing of valves during the cardiac cycle non-invasively (Hirshfeld et al, 1974). The left ventricular pre-ejection period was found to be prolonged with left ventricular dysfunction, but was also found to be inversely related to heart rate, rendering the test less useful in the assessment of left ventricular function (Spitaels et al, 1974). However, by dividing the pre-ejection period by the total ejection time, an index was produced which was independent of heart rate and age. With the advent of Doppler echocardiography, the events became easier to record, and furthermore, differences in the pattern of blood flow during systole were discovered. The left ventricular acceleration time was found to be a reliable index of myocardial performance under different haemodynamic states (Wallmeyer et al, 1986). These same principles were applied to right heart events, and it is reasonable to group together studies of m-mode and Doppler echocardiography, since they are different ways of measuring the same thing.

(4) 13 studies investigating the use of right ventricular systolic time intervals by comparing results obtained from cardiac catheterisation are summarised in table 3.1. All the studies were able to produce a correlation of different time intervals with pulmonary arterial pressure or resistance. TPV and TPV/RVET ratio are negatively correlated and PEP/RVET is positively correlated. However, there is still no agreement as to which is the best method because all of the measurements are influenced by factors other than pulmonary arterial pressure. RPEP, RVET and TPV are all decreased by heart rate, and increase with age (Hirshfeld et al, 1975b; Gardin et al, 1986). Dividing the PEP by RVET produced a ratio, (PEP/RVET) which was also inversely related to pulmonary arterial pressure, and was not affected by heart rate (Hirshfeld, 1975b). However, the ratio was prolonged by myocardial dysfunction (Riggs et al, 1977b).

(5) Kitabatake et al (1984) found that TPV had a closer inverse correlation with the logarithm of mean pulmonary arterial pressure than pulmonary arterial pressure itself, with which it had a curvilinear relationship, whereas Chan et al (1987) and Mahan et al (1983) found a direct linear relationship. Cooper et al (1988) found only an extremely weak correlation of TPV with mean pulmonary arterial pressure (r=0.38). There are other factors which can influence TPV. Matsudu (1986) found that TPV directly correlates with pulmonary blood flow (r=+0.46). Since mitral regurgitation shortens aortic TPV (Elkins et al, 1967), tricuspid regurgitation can be expected to shorten TPV, and analysis of Kitabatake's results seems to support this, despite a statement to the contrary in the discussion. However, Chan et al found no relationship of TPV with clinically evident tricuspid regurgitation.
### Table 3-1: Papers comparing direct measurement of pulmonary arterial pressure with sphygmomanometer techniques

<table>
<thead>
<tr>
<th>Author/Method</th>
<th>Year</th>
<th>No. Methods None</th>
<th>No. Notes None</th>
<th>Patient Selection</th>
<th>Time of Doppler Study</th>
<th>Group</th>
<th>Doppler Mean Diastolic</th>
<th>Sphygmomanometer Mean Diastolic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davie et al.</td>
<td>1977</td>
<td>29</td>
<td>7</td>
<td>12</td>
<td>7</td>
<td>CHF</td>
<td>22</td>
<td>64</td>
<td>Hypnosis</td>
</tr>
<tr>
<td>Leitch et al.</td>
<td>1978</td>
<td>22</td>
<td>3</td>
<td>10</td>
<td>6</td>
<td>CHF</td>
<td>16</td>
<td>54</td>
<td>Hypnosis</td>
</tr>
</tbody>
</table>

Note: CHF = Congestive Heart Failure; PVR = Pulmonary Vascular Resistance; PWP = Pulmonary Wedge Pressure;

Additional notes or details may be included in the comments column.
(6) Other authors found better correlation when correcting for heart rate, either by dividing the TPV or the TPV/RVET ratio by the R-R interval or its square root respectively, or by using a regression equation derived from the ratio versus heart rate relationship from a population with normal pulmonary arterial pressure (Chan et al 1987). These authors found that the TPV/RVET ratio was in fact very poorly correlated to pulmonary arterial pressure and resistance, but that TPV, corrected using the regression equation, was more closely correlated. Martin-Duran (1986) found that TPV, the TPV/RVET and the PEP/RVET ratios all correlated best with a logarithmic function of pulmonary arterial pressure (TPV was best, r=-0.77). Graettinger (1987) demonstrated that the TPV/RVET ratio correlated best (r=-0.72) with \(0.8 \times \text{mean pulmonary arterial pressure} + 3\).

(7) Because of the lack of consistent good results using the above techniques, other ratios have been tried, most claiming success. An example is Morera et al (1989) who used a system whereby a formula was multiplied by the systemic systolic pressure obtained from the arm, including the 'mean acceleration to peak velocity' (ACCm): \((\text{RPEP} \times \text{RACCm}/\text{RVET}) / (\text{LPEP} \times \text{LACCm}/\text{LVET}) \times \text{systolic blood pressure} = \text{systolic pulmonary arterial pressure.}\) Results were correlated with direct measurement. The correlation coefficient was an extraordinarily high one (r=0.98) with a standard error for the estimate of 5.2 mmHg. These results are hard to accept when seen in the light of validatory studies (Reder et al,1978); the measurement of systolic blood pressure alone by oscillometry (these authors used Dynamap), has, at best, a correlation coefficient of 0.84, with a large standard error (much higher than 5 mmHg). Further differences must arise from interobserver and temporal variability.

(8) Aside from all of these potential difficulties, there are at least five further problems pertinent to the use of these ratios in the neonate:

1. The validatory studies only include a few neonates, and none of the studies using TPV or TPV/RVET ratio, included more than a few infants, despite marked differences in age, body surface area and heart rate in this age group. All of these factors influence systolic time intervals. Despite this, the TPV/RVET ratio has been used recently in clinical studies of term and premature neonates by Evans and Archer (1989,1990,1991).

2. Despite the correlation of the various time interval indices and ratios with pulmonary arterial pressure, they do not reliably differentiate subjects with normal pulmonary arterial pressure from those with moderate or severe pulmonary hypertension. For instance, data from Hirschfeld et al(1975) showed that a PEP/RVET ratio of 0.25 can represent a mean pulmonary arterial pressure of between 15 mmHg and 55 mmHg, and a ratio of 0.35 of between 35 and 80 mmHg. In a study of six babies with bronchopulmonary dysplasia (Newth et al, 1984) the same ratio did not differentiate babies with pulmonary hypertension.
by catheterisation. The TPV/RVET ratio has the same problem; a ratio of 0.30 can occur with a mean pulmonary arterial pressure of 15 mmHg or 45 mmHg (Kosturakis et al, 1984; Martin-Duran et al, 1986; Cooper et al, 1988). Friedman et al (1986) examined TPV and TPV/RVET ratio in eight children with severe idiopathic pulmonary arterial hypertension. Many of the values lay within the 'normal' range from other publications, and their data shows that TPV the TPV/RVET ratio is insensitive to extreme changes in pulmonary vascular resistance.

3 There are technical difficulties in measuring some of the intervals accurately, most notably RVET. Turbulence in the pulmonary artery can make the end of the RVET difficult to ascertain; (Kosturakis et al, 1984) and such turbulence is common with pulmonary regurgitation and with a patent arterial duct.

4 The positioning of the pulsed wave Doppler sample is critical. Moving the sample up and down the right ventricular outflow tract, or across the pulmonary artery alters results markedly, doubling the TPV or halving the TPV/RVET ratio (Pandis et al 1986). Since the pulmonary artery of the premature infant is very small, very small movements of the Doppler sample will affect the results. There is in fact no agreement about the ideal sampling site, and the validatory studies used different sampling positions. For example, Kitabatake et al (1983) and Martin-Duran et al (1986) used the distal right ventricular outflow tract, Kosturakis et al (1984) used the distal main pulmonary artery, and Cooper et al (1988), who showed the weakest correlation of systolic time intervals with pulmonary arterial pressure of all of the studies, used the area within 2 cm of the pulmonary valve, the position used by Evans and Archer in their neonatal studies. Stevenson (1987) compared two positions for determining the TPV/RVET ratio: the right ventricular outflow tract (RVOT) and just above the pulmonary valve. Values in the RVOT were significantly larger than those beyond the valve for a given pulmonary arterial pressure, but showed a good correlation with mean pulmonary arterial pressure (0.94, Standard error of the estimate (SEE) 7.7mmHg). Values from beyond the valve showed a weak correlation (0.63) and large SEE (16.4 mmHg) and Stevenson wrote, "There is no useful correlation between actual pressures and Doppler estimates". Further confusion is added by the observation of Matsudu et al (1986) that there was no difference in TPV/RVET ratios measured in the RVOT and at the pulmonary valve! This study is alone in this conclusion.

5 The ratios do not reflect serial changes in pulmonary vascular resistance or pressure consequent upon 100% oxygen therapy, at least in children with a left-to-right intracardiac shunt (Cooper et al, 1988; Vogel et al, 1991).

(9) Because of the numerous potential technical difficulties (particularly 3 and 4 above) studies of inter-observer error assume particular importance in the neonate, but no such
studies have been done. In the first publication of Evans and Archer (1990), interobserver variability was said to be acceptable, but the method of investigation was for a second observer to analyse the video tape produced by a first observer. This does not allow for error in obtaining the recording, particularly the positioning of the pulsed Doppler sample.

(10) Systolic time intervals in neonates cannot be reliable reflectors of pulmonary arterial pressure, and studies using these techniques should be interpreted with due caution. Nevertheless, they are certainly influenced by pulmonary arterial pressure, and the studies with the poorest correlation with direct measurement were in children with large left-to-right intracardiac shunts. They may have a place in research in making serial measurements within the same baby, however, systolic time intervals should, at present, probably only be used when other methods are not available. TPV/RVET should probably be measured at the RVOT and not at the pulmonary valve in children and adults: the ideal position in neonates is not known.

3.3 Tricuspid regurgitation and the Bernoulli equation

3.3.1 Introduction

Doppler ultrasound in patients of all ages, including neonates, has demonstrated that tricuspid regurgitation often exists even when not clinically apparent (Waggoner et al, 1981; Mahoney et al, 1985; Kostucki et al, 1986; Yoshida et al, 1988). This fact, along with extensive validation of the modified Bernoulli equation (table 3.2), potentially allows, for the first time, reliable non-invasive estimation of right heart pressure.

(2) The Bernoulli equation is derived from fluid mechanics, and relates the pressure drop between two chambers to the velocity of the fluid passing between them (Hatle and Angelsen, 1985). The peak velocity of blood is measured using continuous wave Doppler ultrasound, which can measure high velocities (unlike pulsed-wave Doppler). The velocity is converted to a pressure drop by application of the simplified and modified Bernoulli equation: \[ P = 4V^2 \], where \( P \) is the pressure drop (mmHg) and \( V \) is the velocity of blood (metres/second). In the right heart, the drop in pressure from the right ventricle to the right atrium in systole can be assessed by applying the modified Bernoulli equation:

\[
\text{right ventricular pressure - right atrial pressure} = 4 \times (\text{peak tricuspid regurgitation jet velocity})^2
\]

Systolic pulmonary arterial pressure is equal to right ventricular pressure if there is no pulmonary stenosis. Hence systolic pulmonary arterial pressure is equal to the drop in
pressure in systole between the right ventricle and the right atrium plus the right atrial pressure. In healthy neonates shortly after birth, atrial pressure is close to zero (Burnard and James, 1963; Blankenship et al, 1965; Young and Cottom, 1966); and application of the Bernoulli equation to the tricuspid jet velocity should therefore approximate closely to systolic pulmonary arterial pressure. Under different circumstances, such as with persistent pulmonary hypertension or asphyxia, right atrial pressure may elevated, and the measured value should be added to the derived pressure drop to estimate pulmonary arterial pressure. If the right atrial pressure is not measured in sick or ventilated neonates, a fixed allowance for right atrial pressure may be appropriate. This issue will be further discussed in chapter 9.

3.3.2 The Bernoulli principle

3.3.2.1 Historical perspective

The principle was conceived by Daniel Bernoulli, who was born in Holland in 1700, and was part of the second generation of Swiss mathematicians in the Bernoulli family. He was a most remarkable man. He won ten prizes from the distinguished Paris Academy of Science for work in astronomy, gravity, tides, magnetism, ocean currents and the behaviour of ships at sea. He was also a lecturer in medicine, mechanics and physics in St. Petersburg, Russia, and later lectured in botany and philosophy in Basel. There was great rivalry between Daniel and his father, Johann, whose work on calculus and differential equations created a problem for generations of school children! Daniel established the kinetic theory of gases and heat, and in 1738 he wrote "Hydrodynamica", which considered the basic properties of fluid flow, especially pressure, density and velocity, and set forth their fundamental relationship. This relationship has been central to the understanding of fluid mechanics, particularly in the design of engines. However, it was only recently, that Holen et al (1976) and subsequently Håtle et al (1978) realised the potential of this relationship for use with Doppler ultrasound. Doppler ultrasound can measure velocity of blood, and therefore has the potential to measure the pressure difference causing the movement of the blood.

3.3.2.2 The physics

1. The driving force for blood flow through a vessel is the pressure drop along the vessel. For time steady flow (ie neither accelerating nor decelerating), in a tube with constant cross-section, the viscous friction outbalances the pressure drop:

   \[ \text{Pressure drop} = \text{Resistance} \times \text{Flow} \]
This equation is analogous to Ohm’s law for electric current and voltage (V=IR).

If the blood flow is accelerated, additional pressure drop is required to overcome inertial forces. Furthermore, the flow velocity profile across the vessel changes from laminar to turbulent flow. In the development of turbulent flow (during acceleration), small, rapidly changing eddies form, moving along the main stream. In effect, these eddies, known as convection currents, waste some of the energy designed to push the bulk of the fluid through a narrow lumen. The whole process is termed convective acceleration. The pressure drop required for convective acceleration is

\[ P_1 - P_2 = 0.5 \times \rho \left( V_2^2 - V_1^2 \right) \]

The subscripts 1 and 2 indicate two positions along the line of flow, and \( \rho \) is the mass density of blood. The result of the equation is a pressure drop expressed as the increase in kinetic energy per unit volume of the fluid, (similar to the increase in kinetic energy of a falling stone in the gravitational field). Importantly, the pressure drop is related solely to the increase in velocity, and is independent of the size of the orifice, assuming viscous friction can be neglected. This effect is analogous to large and small stones having the same increase in velocity in a gravitational field.

(2) In calculating a pressure drop across a valve, the velocity in front of the jet \( (V_1) \) is usually much smaller than the maximal velocity in the jet \( (V_2) \). Therefore, \( V_1 \) can usually be neglected. Inserting \( \rho = 1.06 \times 10^3 \text{ kg/m}^3 \) we obtain approximately

\[ P_1 - P_2 = 4V_2^2 \]

\( V_2 \) is in metres/second and the pressure drop is in mmHg.

This equation has been termed the modified Bernoulli equation, because it only gives the part of the pressure drop that comes from convective acceleration. The viscous friction and the inertial pressure drop that results from a change of the flow rate itself with time are neglected. When these terms are included we obtain the full Bernoulli equation:

\[ P_1 - P_2 = 0.5 \times \rho \left( V_2^2 - V_1^2 \right) + \text{flow acceleration + viscous friction} \]

(3) Numerous publications have now validated the use of the modified Bernoulli equation in determining pressure gradients across stenosed or regurgitant valves (Holen et al, 1976;
These testify that the simplified equation is satisfactory for most clinical purposes. However, there may be circumstances when the two factors of flow acceleration-generated pressure drop and viscous friction cannot be neglected, and these factors might distort the results in the newborn.

Viscous friction depends not only on the local velocity, but also on the whole velocity profile, as it includes friction between neighbouring fluid elements. Provided the centre of the flow profile is flat, the equation should hold, and viscous friction can be neglected. In vitro experiments by Holen et al (1976), and later Requarth et al (1984), showed that the pressure drop across a stenosis could be accurately determined from the modified Bernoulli equation provided the orifice was greater than 3.5 mm diameter. Presumably the centre of the flow profile was still flat until this point, but beyond it the pressure drop was underestimated. This inaccuracy was larger for velocities under 3 metres per second, a velocity range encountered in preterm infants with their relatively low ventricular pressures. Newborn infants also have a relatively high packed cell volume, and this can elevate blood viscosity.

Factors which can cause underestimation of pressure drop

1. The two factors which could cause underestimation of pressure drop across the tricuspid valve particularly in the newborn are: 1- Small size of the valve orifice and 2- High blood viscosity. A third factor- inability to align the Doppler beam with the peak flow will lead to underestimation at any age, but should not be a particular problem in the newborn because of the relatively large "echo window" at this age. Finally in determining systolic pulmonary arterial pressure, right atrial pressure is added to the RV-RA pressure drop; this needs to be measured or a reasonable estimate made.

1- Premature neonates have a small heart and therefore a small tricuspid valve. The physical properties of a healthy, but slightly regurgitant valve, are very different from the stiff, firm-edged orifice created in Holen’s experiments, and the shape, and its surface morphology are important in the generation of friction. The size of the area of leak through a regurgitant tricuspid valve almost certainly to varies considerably but there is no known normal range in the newborn. The only available pertinent data is the width of the right atrium in the term infant, above the attachment of the tricuspid valve, which is about 13 to 23 mm (Hanscusc et al, 1988), as opposed to 30 to 50 mm in the adult. Data does not exist to refute the possibility that a small area of tricuspid regurgitation may cause underestimation of pressure gradient using the modified Bernoulli equation.

2- The principle factor raising blood viscosity is the haematocrit. This can be as high as 65% in the newborn, though the average is about 54% at birth, and this falls rapidly over the
first few days. Vasko et al (1984), using in vitro experiments, found that viscosity within the physiological range did not affect results comparing Doppler measured velocity with directly measured pressure drop. Furthermore, at a fixed haematocrit of 60%, Linderkamp et al (1983) showed that preterm neonates have a lower whole blood viscosity than term neonates, and term neonates lower than adults. This effect is due to the relatively low concentration of plasma proteins, and has the advantageous effect of allowing high haemoglobin concentrations, and therefore high oxygen carrying capacity, in the fetus, without causing studding in the capillary circulation. It would seem unlikely therefore, that viscosity per se will significantly reduce flow velocity in neonates.

3- Maintaining an angle of incidence less than 20 degrees to the direction of flow is very important, since angles over 20 degrees will lead to significant underestimation of the actual blood velocity. How this is achieved will be discussed under the methods section.

4- To estimate systolic pulmonary arterial pressure it is important to make a reasonable estimate of right atrial pressure when it is not measured directly. There is a shortage of data on right atrial pressure in the ventilated neonate, so this subject is addressed in more detail later, (in chapter 9). However, changes in right atrial pressure will usually be much smaller than changes in pulmonary arterial pressure, such that with serial measurement it becomes less important. High right atrial pressure should be expected when tricuspid regurgitation on Doppler echocardiography is severe. Pneumothorax, where the high intrathoracic pressure is also likely to be associated with right atrial hypertension (Cabal and Hodgmann; 1979), but pneumothorax is usually clinically obvious, and should not present a diagnostic problem. Other causes of elevated right atrial pressure, including ventilation itself, are discussed later.

(2) In summary, there are some factors which might, theoretically, lead to underestimation of pulmonary arterial pressure in the newborn using tricuspid regurgitation and the modified Bernoulli equation.

3.3.4 Validation of the method against direct measurement

(1) In measuring the gradient across stenosed valves, the modified Bernoulli equation has been validated extensively, and is now in regular use in clinical cardiology (Holen et al,1976; Hatle et al,1980 etc). Eleven publications investigating its use in determining peak pulmonary arterial pressure are listed in table 3.2. All of these used continuous wave Doppler, unguided by cross-sectional echocardiography, and compared results against direct catheter measurement.

(2) There seems to be no disagreement regarding methodology, only one single measurement...
<table>
<thead>
<tr>
<th>Time of Doppler study (in months)</th>
<th>Treatment</th>
<th>Condition</th>
<th>No.</th>
<th>Sex ratio</th>
<th>Mean ± SD of PE, mm Hg</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3.9 months</td>
<td>0-6.3 days</td>
<td>COOP</td>
<td>30</td>
<td>0</td>
<td>5.0 ± 1.5</td>
<td>0.71</td>
</tr>
<tr>
<td>0-3.9 months</td>
<td>0-6.3 days</td>
<td>CHD</td>
<td>70</td>
<td>0</td>
<td>6.0 ± 2.5</td>
<td>0.65</td>
</tr>
<tr>
<td>0-3.9 months</td>
<td>0-6.3 days</td>
<td>AVP</td>
<td>36</td>
<td>0</td>
<td>7.0 ± 3.5</td>
<td>0.71</td>
</tr>
<tr>
<td>0-3.9 months</td>
<td>0-6.3 days</td>
<td>COOP</td>
<td>9</td>
<td>0</td>
<td>9.0 ± 4.5</td>
<td>0.69</td>
</tr>
<tr>
<td>0-3.9 months</td>
<td>0-6.3 days</td>
<td>CHD</td>
<td>34</td>
<td>0</td>
<td>11.0 ± 5.5</td>
<td>0.65</td>
</tr>
<tr>
<td>0-3.9 months</td>
<td>0-6.3 days</td>
<td>AVP</td>
<td>40</td>
<td>0</td>
<td>13.0 ± 6.5</td>
<td>0.71</td>
</tr>
<tr>
<td>0-3.9 months</td>
<td>0-6.3 days</td>
<td>COOP</td>
<td>12</td>
<td>0</td>
<td>15.0 ± 7.5</td>
<td>0.69</td>
</tr>
<tr>
<td>0-3.9 months</td>
<td>0-6.3 days</td>
<td>CHD</td>
<td>89</td>
<td>0</td>
<td>18.0 ± 8.5</td>
<td>0.71</td>
</tr>
</tbody>
</table>

The peak velocity of the ductus and application of the modified Bernoulli equation.

Previous studies evaluating Doppler determination of pulmonary arterial pressure by measurement of
is required, that of the maximal velocity of the regurgitant jet through the tricuspid valve. Some authors advocate a standard allowance of 5 to 10 mmHg for right atrial pressure in determining systolic pulmonary arterial pressure, and others suggest estimating the jugular venous pressure. However, this factor is small in relation to the right ventricle to right atrium pressure difference, particularly in the presence of pulmonary hypertension, and more importantly, changes in right atrial pressure are very small in relation to changes in right ventricular pressure.

(3) Overall, validatory studies are much more consistent than those using systolic time intervals. The correlation coefficients are higher, and the standard error of the estimates are lower, so that low pulmonary arterial pressure can be reliably differentiated from moderately elevated pulmonary arterial pressure. There were two exceptions to this trend. The study of Laabman et al, (1989) and Tramarin et al (1991) both had lower correlation coefficients, of 0.65 and 0.73 respectively. However, these were studies of adult patients with chronic obstructive airways disease, who are technically difficult to scan because of hyperinflated lungs and the consequent poor "echo window". Furthermore, the Doppler studies were not simultaneous with the cardiac catheterisation, and a significant temporal variability is to be expected in this group.

(4) The studies including significant numbers of infants (Currie et al, 1985; Chan et al, 1987; Stevenson et al, 1989) showed remarkably high correlation coefficients and narrow standard errors. The two studies comparing systolic time intervals with the tricuspid regurgitation (TR) method against direct measurement both concluded that the TR method was superior, provided that regurgitation was actually present. (Chan et al, 1987; Stevenson et al, 1989)

3.3.5

In summary, the use of the modified Bernoulli equation with Doppler ultrasound has been validated extensively in clinical cardiology. It is a simple, one measurement technique, which is not influenced by heart rate or myocardial function, and does not require reference to a complex regression equation. It produces a value in mmHg which can be related to simultaneous systemic arterial pressure, and previous invasive pressure studies. However, the method has not been extensively validated in the neonate and there are some theoretical reasons why it may underestimate the pressure gradient across the tricuspid valve in premature babies. Finally, the incidence of tricuspid regurgitation with a maximal velocity measurable on Doppler ultrasound is not known in the neonate, and this factor may limit the feasibility of its use in this age group.
The arterial duct is a direct communication between the systemic and pulmonary circulations and flow across it reflects the pressure difference between the two. Marx et al (1986) showed that the modified Bernoulli equation could be used successfully in assessing the pressure drop across aorto-pulmonary shunts, when the velocity was measured by Doppler. Musewe et al (1987) followed this, using the same principle, measuring the pressure drop across the arterial duct in 29 patients in a variety of haemodynamic states. The method of measurement used in this study will be discussed in the methods section, but involves the use of pulsed wave Doppler for low velocities, and continuous wave Doppler for high velocities. There were very high coefficients of correlation for peak, mean and diastolic left-to-right gradients, r= 0.94, 0.95, and 0.96 respectively, but with relatively large standard errors of 13 mmHg, 10 mmHg and 8 mmHg. Bidirectional shunting (right-to-left in systole, left-to-right in diastole) was found with pulmonary arterial pressures at or near systemic levels, though the right-to-left velocity did not closely correlate with the corresponding pressure gradient. Houston et al (1989) used the same method, on 37 patients catheterised for congenital heart disease. Their analysis showed a much larger discrepancy between Doppler-derived and directly measured pressure gradients, even when the studies were performed simultaneously. 95% confidence limits of agreement for the peak pressure gradients were approximately ±25 mmHg, and errors were higher at higher pressure differences. Both under and over estimation of the true pressure drop occurred. Similar results were reported by Hiraishi et al (1987). However, it was found that the pattern of flow through the duct during the cardiac cycle closely followed the balance of pulmonary and systemic pressures. Houston et al described four patterns:

1- Continuous left-to-right flow, maximal in late systole with a gradual fall throughout diastole.

2- Continuous left-to-right flow, high in systole falling rapidly to a low velocity during diastole.

3- Continuous low velocity left-to-right flow, maximal in late diastole.

4- Bidirectional flow.

Pattern 1 was associated with normal, or slightly elevated pulmonary arterial pressure, 2 with raised pulmonary arterial pressure, and 3 and 4 with pulmonary arterial pressure at systemic levels. Pure right-to-left flow was not encountered in this study, but had been recognised by Cloez et al (1986) in association with aortic coarctation, where the descending aorta is supplied only via the duct, and in persistent fetal circulation, with suprasystemic
pulmonary arterial pressure.

(3) Musewe et al were interested in validating the use of ductal flow velocities in determining pulmonary arterial pressure in the premature neonate. This was done in their subsequent study (1990) by subtracting the pressure drop in mid systole, (derived from ductal flow velocity and application of the Bernoulli equation) from the systemic arterial pressure (measured through an arterial line). Results were compared with pulmonary arterial pressure values derived from tricuspid regurgitation (allowing 10 mmHg for right atrial pressure) which were taken as the 'gold standard'. Mid systole was determined by superimposing ascending aortic Doppler tracings onto the ductal waveform, and marking the time of peak aortic velocity. The resulting correlation, $r=0.95$, with a standard error of the estimate of 8 mmHg, is certainly impressive. It was even better for the subgroup with bidirectional shunting: $r=0.95$, standard error 4.5 mmHg. It is surprising that when relating two non-invasive measurements, dependent on four different measured variables, there was such a close agreement. The correlation is better than that obtained by the same author against direct measurement. Nevertheless, taken as it stands, this publication goes some way towards validating both the ductal flow method and the tricuspid regurgitation method of determining pulmonary arterial pressure in the newborn. The same study analysed bidirectional flow further; if the duration of right-to-left flow exceeded 60% of systole, this was associated with suprasystemic pulmonary arterial pressure (measured using tricuspid regurgitation), and if it were less than 60%, it was at systemic levels or less.

(4) The statistical analysis used by Houston et al, introduced by Bland and Altman (1986), was specifically designed to test the agreement between two measurements of the same phenomenon. Houston also used it to investigate Doppler interrogation of pressure drop across ventricular septal defects (1988). This method will be discussed in more detail later. However Houston’s study sets an important example in comparing direct and indirect measurements. Correlation examines the relationship between two variables, not the agreement between them; two measurements of the same thing are bound to be highly correlated. Had the Bland-Altman method been employed with systolic time intervals, it is likely that the weaknesses of this method would have been more apparent earlier. The Bland-Altman method will be employed in the Doppler-catheter validation using tricuspid valve regurgitation and the modified Bernoulli equation in infants later in this thesis.

(5) There are several possible reasons why Houston et al did not find close agreement between Doppler and invasive measurement.

1- In a small duct it may be difficult to obtain a clear signal of peak velocity due to the small amount of blood passing through.
2- The duct is a tunnel, and not a discrete orifice, and this may effect the validity of the modified Bernoulli equation. This aspect was evaluated in an in vitro model by Tierstein et al (1985), who created tunnel-like and irregular obstructions to blood flow and measured blood velocity with Doppler ultrasound. Long tunnel length (>3 cm) and small cross-sectional area (<0.25 cm²) induced underestimation of the pressure difference.

Whether the area of obstruction is tunnel-like or not, it is reasonable to assume that ductal constriction, particularly just preceding closure in the newborn, will produce such a small orifice that the modified Bernoulli equation is no longer valid. The Doppler signal will become weak and difficult to record at this point, and Houston et al found that occasionally the spectral frequency was of low intensity.

3- At low velocities, (with bidirectional flow peak velocity values are frequently less than one metre/sec) blood viscosity may become more important by causing loss of kinetic energy and invalidate the modified Bernoulli equation. Holen et al's experiments (1977) indicated that velocities under 3 metres/sec will result in underestimation of the true pressure drop.

4- The Doppler probe may not have been in direct line with flow.

(6) All of these factors may cause underestimation of the pressure drop. It is harder to understand how they may overestimate it. It could be that the catheter measurements may be underestimates, due to a phenomenon known as 'pressure recovery'. In an elegant series of experiments, Levine et al (1989) used in vitro models of different shaped tunnel-like obstructions, at different flow rates and orifice sizes, to show that withdrawal of the catheter tip away from the site of the stenosis, caused a marked drop in the apparent pressure difference. This effect was most marked in longer tunnels and with higher flow rates.

(7) Since the duct is a tunnel, usually narrowest at the pulmonary end, when blood travels from left-to-right, it may accelerate before it meets the narrowest part. Since gradient = 4 x \((V_{\text{distal}}^2 - V_{\text{proximal}}^2)\), failure to include the proximal velocity in the modified Bernoulli equation will result in under-estimation of the pressure drop by the Doppler method.

(8) There are therefore, several plausible explanations for the inaccuracies of this technique. It is perhaps not surprising that Musewe et al are, at present, alone in showing such a close agreement between the Doppler and catheter measurements, though some of this apparent agreement might disappear if appropriate statistical analysis was applied. Houston's careful study points out the difficulties but does not rule out the clinical usefulness of ductal flow evaluation. The main difficulty from a technical point of view is probably achieving a
position on the front of the chest which is directly in line with blood flow. Therefore, serial measurements within the individual subject, with the Doppler probe in the same position, may still be of value, and in comparing different population groups it may have a place, provided absolute individual values are not used for clinical decision making. The flow patterns described by Houston et al categorising subjects into groups with normal, moderate, and severe pulmonary hypertension remain the most important product of Doppler studies of ductal flow.

3.5

In summary, there are three types of technique for pulmonary arterial pressure estimation available in the newborn, none of which have been validated against direct measurement in this age group, and all of which have potential advantages and disadvantages.
Chapter 4: Echocardiographic studies in the neonate

4.1 Introduction

4.2 Determination of pulmonary arterial pressure

1 Systolic time intervals
   1 Healthy term neonates
   2 Healthy preterm neonates
   3 Hyaline membrane disease
   4 Persistent transitional circulation
   5 Transient tachypnoea of the newborn
   6 Bronchopulmonary dysplasia
   7 Summary

2 Analysis of ductal flow
3 Tricuspid regurgitation

4.3 Interatrial shunting

4.4 Left ventricular output

4.5 Right ventricular output

4.6 M-mode echocardiography

4.7 Echocardiographic evaluation of ductal shunting (summary)

4.8 Summary

Figures (previous studies)

4.1 PEP/RVET ratio in healthy term babies
4.2 PEP/RVET ratio in healthy preterm babies
4.3 PEP/RVET ratio in babies with hyaline membrane disease and persistent transitional circulation

Tables
Results of four studies of right ventricular systolic time intervals in healthy term babies:

4.1 PEP/RVET ratio
4.2 TPV
4.3 TPV/RVET ratio
Chapter 4. Echocardiographic studies in the neonate

4.1 Introduction

This section discusses previous echocardiographic studies in babies (without structural heart disease), over the period of transitional circulation. This includes healthy term and preterm babies, as well as babies with respiratory distress, myocardial dysfunction, persistent pulmonary hypertension and bronchopulmonary dysplasia. Studies of ductal patency and interatrial shunting in healthy neonates are excluded since they have already been discussed in the section on the transitional circulation (sections 1.7 and 1.8).

4.2 Determination of pulmonary arterial pressure

The studies are reviewed under three headings according to the echocardiographic technique employed, namely systolic time intervals (including the PEP/RVET ratio and the TPV/RVET ratio), analysis of ductal flow and tricuspid regurgitation.

4.2.1 Systolic time intervals

4.2.1.1 Healthy term neonates

(1) The results from four studies are summarised in tables 1 to 3, and figure 4.1 with the values grouped into ages, as presented in the publications. Riggs et al (1977c) used m-mode echocardiography and the other three used pulsed-wave Doppler, with the sample at different positions. Since the TPV/RVET ratio varies with position of the sample (Panidis et al, 1986), comparison between the studies is difficult. Takenaka et al (1985) and Evans and Archer (1990) placed the pulsed Doppler sample at the pulmonary valve, (the position used by Kitabatake et al (1983) in their validatory study in adults) whereas Shiraishi placed it just below the valve in the right ventricular outflow tract (the position shown by Stevenson (1989) to be optimal in his validatory study in children).

(2) All of the studies showed that the time intervals changed significantly after the first 12 hours of life. Paired serial values of PEP/RVET ratio, plotted by Riggs et al in 25 babies, showed a downward trend, indicating a fall in pulmonary arterial pressure.

(3) TPV and TPV/RVET showed a more marked change with time than the PEP/RVET ratio. However, the difference in absolute values for the ratio (TPV/RVET) between the studies of Shiraishi et al and Evans and Archer is striking. The mean ratio at 2-12 hours found by Shiraishi et al (0.37) is almost identical to that found by Evans and Archer at 25-36 hours (0.36). This major difference is probably due to variation in sampling positions.
Systolic time intervals in healthy term babies - a summary of four studies

Table 4.1 PEP/RVET ratio

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>2-12 h</th>
<th>12-24 h</th>
<th>24-48 h</th>
<th>&gt;48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riggs</td>
<td>1977</td>
<td>0.39 (0.05)</td>
<td>0.32 (0.03)</td>
<td>0.31 (0.05)</td>
<td>0.28 (0.03)</td>
</tr>
<tr>
<td>Hiraishi</td>
<td>1987</td>
<td>0.51 (0.12)</td>
<td></td>
<td></td>
<td>0.34 (0.07)</td>
</tr>
<tr>
<td>Takenaka</td>
<td>1987</td>
<td>0.43 (0.09)</td>
<td></td>
<td></td>
<td>0.32 (0.07)</td>
</tr>
</tbody>
</table>

Table 4.2 TPV (ms)

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>2-12 h</th>
<th>12-24 h</th>
<th>24-48 h</th>
<th>&gt;48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiraishi</td>
<td>1987</td>
<td>69 (17)</td>
<td></td>
<td></td>
<td>121 (19)*</td>
</tr>
<tr>
<td>Takenaka</td>
<td>1987</td>
<td>46 (7)</td>
<td>82 (14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*TPV was then lower at one month, at 101.0 (20.8)

Table 4.3 TPV/RVET ratio

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>2-12 h</th>
<th>12-24 h</th>
<th>24-48 h</th>
<th>&gt;48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiraishi</td>
<td>1987</td>
<td>0.37 (0.12)</td>
<td></td>
<td></td>
<td>0.56 (0.07)^</td>
</tr>
<tr>
<td>Evans</td>
<td>1990</td>
<td>0.23 (0.035)</td>
<td></td>
<td>0.36 (0.037)</td>
<td>0.38 (0.023)</td>
</tr>
</tbody>
</table>

^TPV/RVET ratio was 0.52 (0.05) at one month.

Note:
Hiraishi used the area just below and Evans used the area just above the pulmonary valve.
Figure 4.1 Healthy term infants PEP/RVET ratios

- 0.60 - from Riggs et al
- 0.50 - from Hiraishi et al
- 0.40 - from Takenaka et al
- 0.30 -
- 0.20 -

AGE HOURS (approximate mean)
Serial values in ten babies from Shiraishi et al all rose from the first to the fifth day, indicating a fall in pulmonary arterial pressure.

(4) Thus, systolic time intervals may be useful in studying serial changes within the same, healthy, baby when the studies are done by the same observer, using a constant site for the Doppler sample. Unfortunately Takenaka, and Evans and Archer, did not utilise this important feature because they did not present serial values from individual babies.

(5) Because the ratios change over the first few days of life, it has been assumed that the changes reflect the changes in pulmonary arterial pressure which are known to occur at this time. However, other changing factors including ductal patency, heart rate and ventricular compliance could also influence these ratios.

(6) Studies of left ventricular systolic time intervals in healthy term babies show that these do not change significantly over the period of the transitional circulation (Riggs et al, 1977; Shiraishi et al, 1987; Takenaka et al, 1987), suggesting that left ventricular function does not change much over this period. Absolute values were similar in these studies (mean LPEP/LVET = 0.36 - 0.37, LVTPV = 44-61 ms).

4.2.1.2 The healthy preterm neonate

(1) Halliday et al (1977) included a control group of healthy preterm neonates, in their study of hyaline membrane disease using the PEP/RVET ratio measured by m-mode. The mean value at 0-12 and 24-48 hours was 0.33 and 0.28 respectively, compared with 0.39-0.51 and 0.28 respectively in studies of term babies. This could suggest that pulmonary arterial pressure is lower in preterm neonates in the first six hours, and falls slower thereafter (see figure 4.2).

(2) The only study to compare pulmonary arterial pressure in the healthy preterm neonate with term neonates using Doppler echocardiography was that by Evans and Archer (1990). Nineteen preterm infants, of 28 to 34 weeks, were compared with 18 full term neonates over the first four days of life, using the TPV/RVET ratio. There was a rapid rise in ratios over the first 24 hours, followed by a more gradual rise to day four. The ratios were always lower in the preterm infants, and appeared to show a slower rise. The authors concluded that pulmonary arterial pressure falls more slowly in the preterm neonate. Since this is the first time this has been claimed, it is important to analyse the study closely.

(3) The study was flawed in two respects:

1 Study design and statistical analysis. No longitudinal data were presented. Instead the
Figure 4.2  Healthy infants PEP/RVET ratios

AGE HOURS (approximate mean)
results were presented in a cross-sectional manner, dividing the results into age groups, with different numbers at each age, and comparing preterm and term values by t test. This is an unsuitable statistical method for assessing rate of change, since it is not making full use of the age relationship. For example, differences between the term and preterm babies, within an age group, may be due to differences in age. This is especially important when the parameter is likely to change rapidly, such as pulmonary arterial pressure over the first twelve hours of life; the value at 1 hour is likely to be different from the value at 6 hours. Furthermore, half of each group were studied at 0-6 hours and half at 6-14 hours; the text does not state if it was the same half. If it was not, or if some were represented at both ages, then comments on the rate of change of the whole group are inappropriate.

A further statistical point is that when using the t test, the two groups to be compared must have normal distributions. At 37 to 48 hours, the mean and standard deviation of two values are compared with that of six. The values were statistically different, p<0.001!

It would have been better to analyse each baby separately.

2. Comparison of systolic time intervals between subjects of different size. The assumption that these two groups, of vastly different size and maturity, produce systolic time intervals which are comparable at equivalent pulmonary arterial pressure is probably invalid. The assumption is that body weight and heart rate can be ignored. If the values obtained in this study are plotted on the regression line produced by Kosturakis et al (1984), relating TPV/RVET ratio with mean pulmonary arterial pressure in infants and children, a TPV/RVET ratio of 0.2, the mean value in premature babies at 0-6 hours, would represent a mean pulmonary arterial pressure of about 50 mmHg; the expected value for systolic systemic pressure in these babies. Furthermore, the lower ratios seen in the preterm infants implies higher absolute values than in the term group.

It is not correct to conclude, from the evidence presented in this study, that pulmonary arterial pressure falls slower in preterm infants, nor can it even be concluded that the TPV/RVET ratio rises slower. Therefore the question of the relative rate of fall in pulmonary arterial pressure of term and preterm infants remains unanswered.

4.2.1.3 Hyaline membrane disease

(1) Stahlman's paper in 1972 was the last in that era of intense interest in the pulmonary haemodynamics of the premature neonate. There have since been three papers using echo-Doppler to study pulmonary arterial pressure in hyaline membrane disease. It appears that since surfactant deficiency was finally accepted as the primary underlying cause of the disease, pulmonary haemodynamics have received remarkably little attention.
(2) Halliday et al (1977) compared 22 healthy premature neonates with 60 babies with mild or severe respiratory distress secondary to hyaline membrane disease using the PEP/RVET ratio. Babies with severe distress had markedly higher ratios over the first 72 hours than babies with mild or no distress. The 31 babies with severe distress could be divided into two groups with high or low ratios. Babies with high ratios had a higher mortality (7/17) than the others (1/14). The ratios were not related to concurrent blood gas status or oxygen requirements, but it seems unlikely that there would be a close correlation with these indices, because many of the severely effected infants had normal ratios. However, the correlation of high ratio with poor outcome is highly significant, and could, as the authors discuss, be due to disordered right ventricular contractility, particularly if combined with elevated pulmonary vascular resistance.

(3) Evans and Archer have produced two reports, (1991a and b) from a cohort of 38 infants with hyaline membrane disease, again using the TPV/RVET ratio, and compared the results from the healthy neonates in their previous paper discussed above. The values in babies with hyaline membrane disease were, as a group, significantly lower after about 15 hours, and remained so until at least day 5. Prolonged ductal patency was noted, and a high proportion had bidirectional ductal shunting even into the third and fourth day. There was a weak correlation with concurrent arterial pH, but there was no correlation with other indices of disease severity, including inspired oxygen fraction. During the recovery phase, longitudinal analysis identified three distinct patterns of change in the ratio over time. In group 1 (12 infants), the ratio rose to 'normal' as the inspired oxygen requirements fell. In group 2 (13 infants), the ratio rose to normal after a delay of over 24 hours after the reduction in FiO2. In group 3 (12 infants), the ratio rose somewhat during initial recovery, and then fell again to remain below the normal range for the duration of their hospital stay, suggesting that pulmonary arterial pressure remained high. Eleven of these twelve infants were breathing air at the time of discharge; one died with bronchopulmonary dysplasia. Upon discharge, the mean TPV/RVET ratio (0.26) in this group was the same as in the acute phase of the disease when over a third of the babies had bidirectional ductal flow. This is surprising; surely, well babies breathing air cannot be expected to have pulmonary arterial pressure approaching systemic levels? This observation is so surprising that there must be some doubt that these babies truly have pulmonary hypertension.

(4) In summary, these three studies indicate that pulmonary hypertension is indeed an important part of hyaline membrane disease, and that systolic time intervals can be measured serially in these babies. They suggest that the TPV/RVET ratio may prove to be useful as an indicator of the risk of respiratory disease in infancy following neonatal intensive care.
4.2.1.4 Babies with persistent transitional circulation

(1) To eliminate congenital heart disease, all ultrasound modalities are needed in the cyanosed baby (Linday et al 1983). Pulmonary hypertension is part of many conditions, including anomalous pulmonary venous drainage, left heart hypoplasia, coarctation of the aorta and transposition of the great arteries, all of which present early in the neonatal period. Once congenital heart disease has been excluded, does echocardiography assist in the diagnosis and treatment of persistent pulmonary hypertension?

(2) There have been surprisingly few ultrasound studies of this condition. Three reports described the use of m-mode echocardiography to determine the PEP/RVET ratio. Riggs et al (1977a) showed that 17 babies with PPHN all had higher values than healthy normal controls. Serial values fell in babies who survived. Three babies who died had serial measurements, and the ratio remained unchanged from the first value onwards, though absolute values were not different from those in the survivors. The LPEP/LVET ratio was also high, indicating left ventricular dysfunction. Johnson et al (1980) studied 16 ventilated babies with severe parenchymal disease and profound hypoxia, and found that these right-sided systolic time intervals clearly differentiated (by a large margin) the eight babies who subsequently responded to tolazoline, with an increase in \( Pao_2 \), from those who did not. Again, left sided ratios were also prolonged. Valdez-Cruz et al (1981) found that higher ratios from both ventricles predicted the development of persistent transitional circulation amongst babies requiring oxygen in the first 36 hours of life. If the results from these three papers are taken together with the results of Halliday et al (1977) in hyaline membrane disease; a ratio of over 0.49:1 was associated with persistent transitional circulation, whereas values above 0.45:1 were not found in healthy babies after 6 hours of age. Hyaline membrane disease was associated with the whole range up to 0.75:1 but not exceeding 0.49:1 after day three. These results are summarised in figure 4.3.

(3) In summary, systolic time intervals can be used to monitor progress in PTC, and may differentiate babies who will respond to tolazoline. However, due to the heterogeneous nature of this condition there is a need for a combined approach, using all of the facets of echocardiography, to determine which indices of flow and pressure are the most useful in haemodynamic assessment. It would seem unlikely that one single measurement will be of much clinical use in this situation.

4.2.1.5 Transient tachypnoea of the newborn

25 infants with transient tachypnoea of the newborn (TTN) were studied by Halliday et al (1981), again using right and left-sided systolic time intervals (LPEP/LVET). The findings suggested that there are two distinct types of TTN. Babies with mild, classical TTN had
Figure 4.3
PEP/RVET ratios:
Distribution in HMD and PTC

AGE HOURS (approximate mean)
prolonged LPEP/LVET ratios, indicating mild left ventricular failure, and babies with more severe disease, needing over 60% oxygen, had prolonged right sided ratios, indicating pulmonary hypertension and/or right ventricular dysfunction. An alternative interpretation of these results is that the 'severe' group in fact had an element of PTC, since as previously discussed, prolonged left and right sided PEP/ET ratios are a feature of PTC.

4.2.1.6 Bronchopulmonary dysplasia

There have been three studies of bronchopulmonary dysplasia using the PEP/RVET ratio, because of the known association with pulmonary hypertension and right ventricular failure. Halliday et al (1980) showed that the ratio increases with hypoxia (PaO2 less than 55 mmHg), and recommended that the ratio be kept below 0.35:1 to avoid right heart failure. Fouron et al (1980) showed that infants with a ratio below 0.30:1 eventually had a good outcome, despite grossly abnormal chest X-ray appearances, and they proposed that measurement of the ratio should be part of routine clinical management. However, Newth et al (1984) compared ratios with directly measured pulmonary arterial pressure and showed that two of six babies with pulmonary hypertension had normal ratios; both had ratios of 0.25:1 with systolic pulmonary arterial pressures of 58 and 33 mmHg respectively, and one baby had a ratio of 0.30:1 with a pressure of 54 mmHg whilst breathing 100% oxygen.

4.2.1.7

In summary, the problems with systolic time intervals that were apparent when comparing direct and indirect measurement in older children, are also apparent in the neonate. They do not reliably differentiate babies with high pulmonary arterial pressure from those with normal pulmonary arterial pressure, and are seriously limited in clinical application because of this. However, they have provided interesting research haemodynamic information for comparing groups of babies with different respiratory disorders, and can be used in serial measurements within the same baby. Furthermore, since not all babies have tricuspid regurgitation or a patent duct, an alternative non-invasive method is still required.

4.2.2 Analysis of ductal flow

(I) There have been few studies analysing ductal flow in babies with structurally normal hearts. Cloez et al (1986) analysed ductal flow using pulsed wave Doppler in six babies with persistent transitional circulation. Four of them had pure right-to-left flow, and two had bidirectional flow. During recovery, left-to-right flow increased during diastole. Musewe et al (1990), found that three of four patients with PTC showing pure right-to-left ductal flow at any time died (there were 6 deaths in all amongst 21 babies). Thus it is a bad prognostic sign if diastolic pulmonary arterial pressure exceeds systemic. Clinical
improvement was associated with reversion of bidirectional or pure right-to-left flow, to pure left-to-right flow.

4.2.3 Tricuspid regurgitation

(1) The prevalence of tricuspid regurgitation detectable by Doppler echocardiography in the healthy neonatal population has not been established, though it is likely to be high. Mahoney et al (1985) detected tricuspid regurgitation in a small group of healthy term neonates using pulsed wave Doppler (between 55% and 64% in the first three days of life). Kelley and Guntheroth (1988) suggested that tricuspid regurgitation was a frequent cause of pansystolic murmur in the healthy newborn. Tricuspid regurgitation also occurs as part of the clinical syndrome of ‘PFC’ and of myocardial ischaemia (Rowe et al, 1972; Reimenschneider et al, 1976; Bucciarelli et al, 1977; Nelson et al, 1978; Finley et al, 1979; Gewilch et al, 1988), and can occur as a consequence of premature (in utero) ductal closure (Berry et al, 1983). In a post mortem study by Setzer et al (1980), 24 of 84 neonates with structurally normal hearts had papillary muscle necrosis. In babies over 3 Kg, papillary muscle necrosis was more likely with a preceding history of perinatal asphyxia, but this was not true in low birth weight babies, in whom papillary muscle necrosis was more frequent overall. Asphyxia, and/or low birth weight is therefore likely to be associated with atrio-ventricular valve regurgitation.

(2) Therefore, it would seem likely that a considerable proportion of healthy and distressed term and preterm neonates have sufficient tricuspid regurgitation to generate a measurable peak velocity on Doppler ultrasound, allowing estimation of pulmonary arterial pressure.

(3) ReUer et al (1987), was the first to use tricuspid regurgitation to estimate pulmonary arterial pressure in respiratory disorders of the newborn. They studied 17 infants, of 36 weeks gestation or more, requiring supplemental oxygen for a variety of respiratory problems. Using the modified Bernoulli equation, and allowing 10 mmHg for right atrial pressure (justified by reference to validatory studies in adults), peak right ventricular pressure was greater than 60% of systemic pressure, and on nine occasions it was over 90%. A systolic murmur, felt to be consistent with tricuspid regurgitation, was found in eight of the fourteen babies who had pansystolic regurgitation. The pulmonary to systemic arterial pressure ratio fell as oxygen requirements fell, but the relationship between the ratio and oxygen requirements varied greatly between babies. The relationship to age was not discussed, and there was no control group of normal babies.

(4) The prevalence of tricuspid regurgitation in babies with bronchopulmonary dysplasia is not known, though White and Houston (1990), in a report of nine babies, found measurable tricuspid regurgitation in six (67%). Serial estimates of pulmonary arterial pressure were
possible in all six, showing a fall with clinical improvement.

4.3 Interventricular shunting.

(1) Contrast echocardiography was used by Sahn et al (1977) to investigate interatrial and ductal shunting in critically ill infants; right-to-left atrial and ductal shunting was demonstrated in PTC. Interventricular shunt flow profiles were studied by Hiraishi et al (1991) in six babies with PTC, using colour and pulsed wave Doppler echocardiography, and showed that the right-to-left phase of bidirectional shunting was prolonged in comparison to healthy babies. Evans and Archer (1991) found, using pulsed wave Doppler, that babies with hyaline membrane disease had more bidirectional or right-to-left flow than seven healthy babies, in whom left-to-right flow predominated.

(2) These studies demonstrate the difficulties in quantifying interatrial flow. It would be better to quantify flow across each atrio-ventricular valve or semilunar valve, were this reliable. The right-to-left flow ratio could then be calculated, as has been done with some success in congenital heart disease (Goldberg et al, 1982; Meijboom et al, 1983; Cloez et al, 1988), and in utero (Mayrse et al, 1987), though work in Newcastle has suggested that interobserver variability is unacceptably high in the fetal studies (Beeby et al, 1991) and accurate measurement of the diameter of the pulmonary artery is technically difficult in the infant (Goldberg et al, 1982). Furthermore, the rapidly changing dimensions of the neonatal heart are likely to render flow measurements across the atrio-ventricular valves unreliable, and pulmonary arterial shunt measurements can also be unreliable because turbulence in the pulmonary artery from a patent arterial duct disturbs the Doppler signal.

(3) New developments in 'dual beam' Doppler echocardiography may eliminate some of these problems (Kapusta et al, 1991) by avoiding both the need to measure the arterial dimensions with cross-sectional echocardiography and the angle of incidence of the beam to blood flow. The cross-sectional area of the vessel is determined by the ratio of the power returns of two beams which are set at angles to each other. This new ultrasound tool is still under development and was not used in the present study.

4.4 Left ventricular output

(1) Measurement of left ventricular output is simple, requiring three measurements: 1. The aortic flow integral, ('stroke distance') calculated from either continuous or pulsed wave Doppler 2. The Aortic diameter, to derive the cross-sectional area 3. Heart rate. The methodology will be discussed further under the methods section, but the calculation is summarised overleaf.
Left ventricular output (mls/kg/min) = Aortic flow integral ('stroke distance') (cm) 
\times 
cross-sectional area of the aorta (cm^2) 
\times 
heart rate (beats per minute)

(2) The technique was validated against cardiac catheterisation measurement (using the Fick principle) or thermodilution, in adults (Loeppky et al, 1983; Elkyam et al, 1983; Fast et al, 1988) and in children and neonates (Alverson et al, 1982). It has proved to be a very popular tool in paediatric and neonatal intensive care, and, with care, can produce clinically useful results in this setting (Rein et al, 1986; Morrow et al, 1988). The chief technical difficulty and source of error is in measurement of the aortic diameter (Hudson et al, 1990; Robson et al, 1988b), but serial measurements within an individual (Robson et al, 1988a), or measurement of the Doppler signal alone, have proven clinical value.

(3) A detailed review of publications on this subject would be inappropriate in this thesis, but some papers are of relevance.

(4) Walther et al (1985a), in a study of 121 healthy neonates with a mean age of 5 days found left ventricular output values (ml/min/kg) of, mean and (standard deviation):

Term infants  241 (33) ml/kg/min 
Preterm infants (less than 1.5kg)  265 (32) ml/kg/min.

(5) These values are somewhat lower than those obtained by Burnard et al (1966) with thermodilution; left ventricular output was 348 ml/kg/min in infants aged 2 to 8 hours, though this value fell as the arterial duct closed, and average systemic flow was 232 mls/kg/min. A serial study of the transitional circulation in term infants using Doppler showed a rise in stroke volume at 2-5 hours, followed by a fall in total output by 24 hours (Winberg et al, 1989). Other studies have confirmed that left ventricular output is raised with left-to-right ductal shunting, mediated via an increase in stroke volume (Alverson et al, 1983; Hirsimaki et al, 1988; Linder et al, 1990). The mean (standard deviation) value in preterm babies with symptomatic ductal shunting was 343 (16) mls/kg/min (Alverson et al, 1983) and 419 (range 305-562) mls/kg/min (Lindner et al, 1990). In a longitudinal study rising cardiac output predicted symptomatic shunting (Walther et al, 1989).

(6) Thus, Doppler echocardiographic measurement of left ventricular output can be a useful measure of pulmonary flow. Hausdorf et al (1987) and Trang et al (1988) found that increasing positive end expiratory pressure over 8 or 9 cm H\textsubscript{2}O on mechanical ventilation, caused a significant fall in left ventricular output due to decreased pulmonary flow. Left
ventricular output is also obviously related to myocardial performance, and this method has been used to examine the effect of inotropes (Walther et al, 1985). Correction of anaemia in bronchopulmonary dysplasia caused a detectable fall in output (Alverson et al, 1988).

(7) This technique is useful, but is also incompletely validated in the neonate. The problem is that there is no 'gold standard', all methods of cardiac output measurement are prone to considerable error at all ages (Leeuw and Birkenhager, 1990; Conway and Lund-Johansen, 1990). Provided the reproducible measurements, i.e. the Doppler measurements, are used in trend analysis within the individual, the technique is a useful non-invasive serial measure of pulmonary venous return (and systemic flow when the arterial duct is closed) and myocardial function in the neonate.

4.5 Right ventricular output

(1) This is measured in the same way as the left ventricular output, but there are three problems:
1- Accurate measurement of the pulmonary arterial dimension is difficult, because of poor lateral resolution with most phased-arrays, the posterior angulation of the pulmonary artery and its variability in size during the cardiac cycle (Robson et al, 1988).
2- Continuous wave Doppler may pick up signals from a patent duct, and high velocities from branch pulmonary arteries, in which mild or physiological stenosis is common in the newborn. Therefore only pulsed wave Doppler should be used, but the positioning of the pulsed Doppler sample is so critical that observer variability is likely to be high.
3- Turbulence at the pulmonary valve is common, due to ductal shunting or pulmonary regurgitation. A clear signal is not then obtained.

(2) Measurement of right ventricular output has not been validated properly in the neonate. A recent publication by Walther et al (1990) compared right and left ventricular output in healthy babies. Naturally one expects a close correlation between these two measurements when there is a closed duct, and this paper showed this. However, even though the level of agreement was incompletely evaluated (Bland-Altman type analysis was not applied), the results appeared to be remarkably good. Other studies have suggested much larger measurement error than quoted in this paper (Goldberg et al, 1982; Colvin et al, 1983). It will be interesting to see if the findings of Walther et al are confirmed by others working with neonates.

(3) Right ventricular output measurement is potentially very useful, since it represents systemic venous return, or effective systemic circulation, provided that interatrial shunting is negligible.
4.6 M-mode echocardiography (other than systolic time intervals)

(1) M-mode has been superseded by cross-sectional and Doppler echocardiography in many respects, but with regard to neonatal haemodynamic assessment, it is still of particular use in the assessment of ventricular function and ductal shunting.

(2) M-mode echocardiography provides a high resolution image from a single line of ultrasound passing through the heart, plotted against time. It allows clear delineation of the edges of cardiac structures, particularly when they lie perpendicular to the ultrasound beam, and accurate timing of movement due to the rapid sweep speed of the ultrasound beam. These features make it the best tool to study motion of chamber walls and valves during the cardiac cycle. The method of measurement has been standardised by the American Society of Echocardiography, allowing comparison between studies and minimising interobserver error (Sahn et al, 1978).

(3) Left ventricular ejection fraction, or fractional shortening, can be easily calculated from left ventricular dimensions, but are influenced not only by intrinsic ventricular contractility, but also by volume loading, particularly due to left-to-right ductal shunting, and by afterload. Diastolic ventricular function can also be assessed by analysing wall motion, and in particular, rate of relaxation. By digitising the recordings, subtle abnormalities of wall motion can be detected (Murphy et al 1986).

(4) Both left atrial and left ventricular dilation occurs with ductal shunting, due to increased pulmonary venous return. The end diastolic chamber dimensions can be expressed as a ratio of the root of aorta, allowing comparison with babies of different size. Silverman et al (1974) were the first to use this idea; prior to ductal ligation 14 premature infants had left atrial to aortic root (LA:Ao) ratio, mean (standard deviation) of 1.28:1 (0.23), which fell afterwards to 0.86:1 (0.10). In a similar study, Halliday et al (1979) found a mean LA:Ao ratio of 1.69:1 pre and 1.16:1 post ductal closure, with a marked reduction in left ventricular end diastolic dimension. Fractional shortening of the left ventricular dimension during systole fell from 40.4% to 34.8%, demonstrating the relationship of an index of ventricular function to preload and afterload. Mellander et al (1987) found that a high LA:Ao ratio predicted subsequent development of a symptomatic L-R ductal shunt. Johnson et al (1983) compared m-mode echocardiograms in 415 babies (less than 1.75 kg) with clinical left-to-right ductal shunting with those of 1,496 babies without. The best discriminators were an LA:Ao ratio greater than 1.40, a left ventricular to aortic (LVEDD/Ao) root ratio greater than 2.1, or a LPEP/LVET ratio less than 0.27.

(5) A study by Valdez-Cruz and Dudell (1981a) suggested that these ratios are much less sensitive in detecting left-to-right shunting when babies are fluid restricted. However, the
gold standard for significant left-to-right shunting was contrast aortography which is itself extremely sensitive, and detects trivial shunting; this factor lead to a rather over-stated conclusion. The problem now with such studies lies in the absence of a gold standard for comparison. Cardiac catheterisation is not done on these babies, so should the gold standard be the clinical diagnosis, as in Silverman's study (1974), or should it be the very sensitive methods of contrast aortography, colour or continuous wave Doppler?

4.7 Echocardiographic evaluation of ductal shunting

(1) To summarise the features from the aforementioned studies, in assessing ductal shunting, there are three questions to answer:

1- Is the duct patent?
Colour, continuous and pulsed wave Doppler in the pulmonary artery or duct are the most sensitive and specific tests, combined with cross-sectional echocardiography. Retrograde flow in cerebral or other systemic arteries is also very sensitive (Kupferschmid et al, 1988).

2- How big is the duct?
This is assessed by direct visualisation with cross-sectional echocardiography.

3- What is the volume of left-to-right flow?
This can be addressed using a combination of measurements, all of which are either qualitative or at best semi-quantitative:
- M-Mode, (LA:Ao >1.4, LVEDD/Ao> 2.1, LVPEP/LVET <0.27)
- Cross-sectional, interatrial septum bulges into RA, volume loaded LV.
- Doppler, by assessing elevated LV output, (sensitivity/specificity not established, upper limit of normal about 300-325 mls/kg/min.) or by quantifying antegrade diastolic flow in the left pulmonary artery (Hiraishi et al, 1987).

4.8 Atrioventricular valve flow

(1) Recent studies in adults have shown that diastolic ventricular function can often be present in myocardial disease, even when systolic function appears to be normal (Cohn et al, 1990; Sampson et al, 1990). A classic example of this is hypertrophic cardiomyopathy. Spirito (1990) and others have shown that one manifestation of this reduced ventricular compliance is a change in the pattern of flow through the mitral and tricuspid valves. Normally there are two peaks in flow velocity during diastole, an early "E" peak, due to passive ventricular filling and a second "A" peak due to atrial contraction. The E wave is normally considerably higher than the A peak, such that the E:A ratio is much greater than
1:1. In hypertrophic cardiomyopathy, the A wave is higher, and the E wave is lower. Experimental animal models have shown that increasing myocardial hypertrophy is associated with increasing E:A ratio. Unfortunately, the E:A ratio cannot, in isolation, be used as a reliable indicator of diastolic dysfunction, because the ratio is influenced by a number of other factors, most particularly mitral regurgitation and left atrial pressure (Myreng et al,1990), and dilation of the left ventricle (Ng and Gibson,1990).

(2) There have been few studies thus far in the neonate. Johnson et al (1988) recorded values in 10 term and 18 preterm neonates under 10 days old. The E:A ratio at the mitral valve was, mean (SD), 1.13 (0.30) in term babies and 1.01 (0.11) in preterm babies. At the tricuspid valve, the ratio was 0.71 (0.13) in term babies and 0.67 (0.10) in preterm babies. Similar figures were reported by Riggs et al (1989).

(3) Thus it appears that there is impaired right ventricular diastolic function in the first days of life. This reversed ratio is the norm in the fetus in both left and right ventricles, but while the mitral valve ratio 'normalises’ straight after birth, the tricuspid valve ratio does not (Allen, 1986). It would be too speculative to read very much into this observation. However, these values can act as a normal group for comparison against babies with cardiac or respiratory disease. A reversed E:A ratio in the right ventricle cannot, in isolation, be taken as indicative of right ventricular dysfunction.

(4) There have, as yet, been no studies of diastolic atrio-ventricular valve flow in hyaline membrane disease, or other cardiopulmonary disease of the newborn.

4.8.

In summary, there are many measurements that can be made in the neonate using Doppler, cross-sectional and m-mode echocardiography. Interpretation of these measurements can be difficult, since very few flow and pressure estimates have been adequately validated in the neonate. Despite this, studies have been able to obtain new haemodynamic information and give new insight into neonatal cardiopulmonary function. Further progress in this exciting field is dependant on careful scientific evaluation of each of the methods, and care in interpreting results from clinical studies.
The work in this thesis was performed in order to explore the use of Doppler echocardiography in the non-invasive determination of pulmonary arterial pressure in the newborn.

Specifically the aims were:

1. To study the feasibility, accuracy and repeatability of non-invasive determination of pulmonary arterial pressure estimation in the newborn both in health and with respiratory distress by measuring the maximal velocity of regurgitation through the tricuspid valve with continuous wave Doppler ultrasound and applying the Bernoulli equation.

2. To use this method to examine and compare serial changes in pulmonary and systemic arterial pressure in healthy term and preterm infants and those with hyaline membrane disease.

3. To compare this method with other non-invasive methods of pulmonary arterial pressure estimation in the newborn, including evaluation of feasibility, and temporal and between observer variability of each method.

4. To study the effects of quantity of ductal shunting and also alterations in inspired and blood oxygen levels on pulmonary arterial pressure in newborns with respiratory failure, using Doppler echocardiography.

5. To assess the potential of detailed Doppler echocardiographic examination, including determination of pulmonary arterial pressure, in evaluating babies with persistent transitional circulation.
Chapter 6: Methods

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   3 Measurement of agreement
   4 Fisher's Exact test

The numerous figures and photographs are listed at the end of the chapter

There are no tables in this chapter
Chapter 6

Methods

6.1 Introduction

This section outlines the method of recruitment of the subjects, and the details of the examination and data collection. Preparation of the data for computer analysis and statistical methods are discussed in the next chapter. The details about the subjects studied, and the timing of examinations is included in the relevant subsequent chapters.

6.2 Recruitment

(1) There were two main types of subject, namely healthy babies and those with some form of respiratory distress. In validatory studies, some babies with congenital heart disease were included.

(2) To recruit healthy term babies for serial echocardiographic examination over the first three days of life, midwives at a local antenatal class asked pregnant ladies who were in their third trimester for volunteers. A standard advice sheet was given, (Appendix A) and I obtained written consent for up to four Doppler ultrasound examinations of the newborn baby, over the first three days of life. Most mothers-to-be were enthusiastic and interested; many were medical or paramedical by profession. Forty volunteers were obtained. Healthy preterm babies were recruited as they arose on the neonatal units (Princess Mary Maternity Hospital, Newcastle upon Tyne, and Newcastle General Hospital). The same advice sheet was used. Verbal consent from both parents was obtained where possible, but consent from one parent was considered adequate when only one was available.

(3) The same procedure was used for babies undergoing intensive care, except that in some cases, the initial examination was sometimes carried out prior to informed parental consent if it was felt by the attending neonatologist that echocardiography was clinically indicated. This was common for babies with persistent fetal circulation or asphyxia, where it was necessary to exclude congenital heart disease and to assess ventricular function.

(4) Special consent was obtained for repeatability studies and the study of the haemodynamic influence of arterial oxygen saturation.

(5) Ethical approval was obtained from the district ethics committee for each stage of the study.
6.3 Method of examination

6.3.1 Data sheets

Each patient was assigned an identification number, and basic patient details were recorded. All information was recorded on a data sheet, which was laid out in a manner allowing rapid transfer of data into a data base for use with the university main-frame SPSS\textsuperscript{X} statistical package (Appendix B). Some of the less obvious categories and abbreviations on these sheets are explained in appendix C. Some of the sections are not relevant for the healthy babies, and not all of the sections are directly relevant to this thesis. The first sheet contains information about the mother, including details of the pregnancy. Sheet two contains information about the baby (such as gestation, birth weight and sex) and its condition at delivery (time in minutes until heart rate exceeded 100 beats per minute, whether intubated or not, cord pH etc.). Then follow five sheets which are repeated for each examination. The first two ("patient status") outline the clinical status at the time of examination, eg. the age in hours, the main respiratory diagnosis, presence of a heart murmur, packed cell volume, and ventilation status with recent blood gas result. The next three sheets record the blood pressure and central venous pressure when available and detailed results of the echocardiogram. This section, which evolved during the study period, was modified to include more information, particularly about the pattern of flow through the arterial duct (bottom of the first sheet). Most of the sections are self-explanatory, but there are several abbreviations which are explained in appendix C. The first of these three sheets contains mostly m-mode and cross-sectional echocardiographic information, in particular, the size of the arterial duct (graded from 0-3), and left ventricular, atrial and aortic root dimensions. The second sheet contains Doppler flow results from the pulmonary and aortic valves, peak tricuspid regurgitant velocity, ductal flow velocity and flow patterns. The final sheet records peak flow velocity at the atrio-ventricular valves, and systolic time intervals at the outflow valves. The repeatability and oxygen saturation studies were recorded on smaller, more simple sheets (Appendix D).

6.3.2 The examination

6.3.2.1 General approach

(1) The examinations were usually done with the mother in attendance, particularly with the healthy babies. The baby was placed on his or her back in the cot or incubator (plates 1.2 and 3). Healthy babies were usually most settled when "tucked-in" comfortably with sheets (plates 3-5). Examination was only done if the baby was resting quietly; if the baby became unsettled during the procedure and could not be calmed down, the examination was abandoned, and results were included from the section of the examination when the baby
was well settled. The systolic upper limb blood pressure was recorded manually by Doppler sphygmomanometry.

(2) The ultrasound examination was performed using one of two Hewlett-Packard ultrasound machines (plates 1 and 2). Both were equipped with cross-sectional imaging, pulsed and continuous wave Doppler ultrasound. In the intensive care unit, the electrocardiograph was transmitted via a connector from the back of the Kontron monitoring module into the ultrasound machine, to allow accurate timing of cardiac events. The pulsed-wave Doppler sample could be superimposed onto the cross-sectional image, but the continuous wave probe was a non-imaging 1.9 MHz free-standing probe (plates 3-7 and 9). At the first ultrasound examination, normal intracardiac anatomy was confirmed using cross-sectional echocardiography. A routine examination procedure then followed, with all images being recorded on video tape for subsequent analysis. Measurements were later made with the on-screen system software and results were recorded on the data sheet. Each recorded measurement was an average of four cardiac cycles, except for peak velocities, for which the highest value was taken. Important features of each measurement are outlined below.

6.3.2.2 Cross-sectional m-mode and pulsed Doppler echocardiogram.

Subcostal and apical views were obtained, and patency of the oval foramen was assessed. Atrioventricular valve velocities were recorded with the pulsed Doppler sample at the tip of the valves, in line with the ventricular septum. The presence of atrio-ventricular valve regurgitation was noted. The arterial duct was visualised from the high left parasternal or parasternal short axis position (plates 11 and 12) and the pulsed Doppler sample was placed at the pulmonary end of the duct and the flow was recorded (eg. plate 13). Ductal size was graded as absent (0), small (1), moderate, with clear constriction (2) and large, with little or no constriction (3). The pulmonary valve was visualised from the parasternal short axis position, and the pulsed sample was placed at the tips of the pulmonary valve. The position of the probe was adjusted until it was directly in line with flow. Plate 14 shows blood flow velocity at the pulmonary valve. Right ventricular systolic time intervals were measured from this Doppler tracing, as shown earlier in figure 3.1, including the pre-ejection period (PEP, onset of the QRS complex to onset of pulmonary flow), the time to peak velocity (TPV, from onset of pulmonary flow to the peak velocity, as measured in plate 14), and total right ventricular ejection time (RVET). A parasternal long axis view was then obtained (plate 25), and several beats recorded to allow subsequent freeze-frame measurement of the aortic root diameter. An m-mode echocardiogram of the left ventricle and atrium was then recorded according to the methods recommended by the American society of echocardiography (Sahn et al, 1978).
6.3.2.3 Continuous wave Doppler

(1) Continuous wave Doppler studies were then performed.

(2) Ductal flow was recorded from the pulmonary area, in the second or third left intercostal space directing the probe posteriorly and adjusting the position finely to record the maximal left-to-right velocity (plates 7 and 8). The optimal position was usually with the probe tilted 10-15 degrees cranially and to the left of the subject from the position giving the optimal right ventricular outflow waveform (with opening and closing valve clicks).

(3) Pulmonary flow was not recorded with continuous wave Doppler, because of the difficulty in differentiating signals arising from the branch pulmonary arteries (where there is often a higher velocity), the arterial duct and the descending aorta.

(4) Tricuspid regurgitation was sought for from the lower left chest (plates 4 and 5). The probe was directed towards the tricuspid valve. Slight angulation of the probe was required (note the subtle difference in position of the probe in plates 4 and 5). When the regurgitation was pansystolic, the highest velocity obtainable was recorded, and it was assumed that the probe was directly in line with flow at this point. An example of a pansystolic recording is shown in figure 6, with a peak velocity of 2.78 metres/second.

(5) Ascending aortic blood flow velocity was obtained from the suprasternal notch (plates 9 and 10). The angulation of the tip of the probe is designed to allow the ultrasound beam to be directed downwards towards the aortic valve. The probe was assumed to be in line with flow if the Doppler recording showed:
   a) Opening and closing clicks.
   b) No downward deflection during systole.
   It was found that pulsed wave Doppler interrogation of the aortic valve from the apical position invariably produced a lower velocity than that obtained with continuous wave from the suprasternal notch, probably because of difficulty in achieving an angle of incidence less than 20 degrees to the direction of blood flow from the apical position. Only the continuous wave measurement was used.

6.3.2.4 Analysis of the echocardiogram

(1) With practice, the whole examination could be completed in ten minutes. The most difficult subjects were very low birth weight babies recovering from hyaline membrane disease who were unsedated, hungry and receiving intermittent mandatory ventilation. They tended to be irritable. However, warming the contact jelly, keeping the environment warm, and applying very little pressure improved their tolerance.
The analysis (digitising) of the video recording took about 30 minutes. When this time is added to the time for data collection from the intensive care charts, and the interview with the parents, each examination took at least 90 minutes. In intensive care, examinations were done at the start of "handling periods" which are designed to reduce the frequency of times the babies are handled.

6.4 Summary of the relevant echocardiographic information obtained

The mean ultrasound measurement from four cardiac cycles was used, with the exception that all maximal Doppler velocities were the maximum recordable. This applied to ductal, tricuspid regurgitation, aortic and pulmonary maximal velocities.

M-mode From these measurements, the left atrial to aortic root (LA:Ao) and left ventricular end diastolic dimension to aortic root (LVEDD:Ao) ratios were calculated. Fractional shortening was calculated from the formula $\frac{\text{LVEDD}-\text{LVESD}}{\text{LVEDD}} \times 100$.

Doppler

1. At the pulmonary valve: (pulsed-wave) Systolic time intervals, including pre-ejection period, time to peak velocity and ejection time. Maximal velocity, and pulmonary stroke distance (mean of four beats) were also recorded. The 'stroke distance' was measured on screen by tracing around the Doppler flow contour during systole.

2. Tricuspid regurgitation: The presence of tricuspid regurgitation was noted in five grades, 0 = no regurgitation, 1 = just detectable, 2 = easily detectable but not pansystolic, 3 = pansystolic, but not with every beat, 4 = pansystolic, measurable peak velocity with every beat. Grades 1 and 2 therefore constituted "detectable" but not measurable TR, where the maximal velocity was not recordable, and grades 3 and 4 constituted "measurable" TR. The maximal velocity, (not the average of four beats) in metres/second was recorded.

3. Arterial duct: Ductal patency can be assessed in terms of three characteristics:
   1. The diameter, or size of the duct.
   2. The velocity and pattern of flow through the duct (see figure 6.2).
   3. The volume of flow through the duct.

The size was graded as above, from 0 to 3 on cross-sectional echocardiography. The index of volume of flow was the left atrial : aortic root (LA:Ao) ratio (see above). The flow velocity was measured at a number of points during the cardiac cycle, and the flow pattern varied greatly.
An attempt was therefore made to categorise the pattern of flow into 8 types:

1. Pure right-to-left. (plate 17)
2. Bidirectional (plate 13, 15 and 16).

Patterns 3 to 8 are all left-to-right:

3. Not a recognisable pattern, or too weak a signal to define the pattern accurately.
4. Low velocity in systole (<1 metre/sec.), higher in diastole (plate 20).
5. High in mid systole, and low at end diastole (plate 21).
6. High velocity throughout, peak at end systole/early diastole (plate 22).
7. Complex, two peaks during systole, trough in mid systole (plate 23).
8. Complex, two peaks, one during early systole, another in early diastole.

These patterns are shown diagrammatically in figure 6.1. Blood flow velocity was recorded at a number of times during the cardiac cycle, as illustrated in figure 6.2.

**Maximal and mean left-to-right velocity** was measured by tracing over 2-4 consecutive beats (see figure 6.2). If pulsed and continuous wave values were different, the higher value of the two was taken.

In the presence of bidirectional flow, the mean velocity was measured by

1. Assuming negative values were zero. Recorded as "PDA MEAN" (This was done because of the suggested lack of correlation between right-to-left velocity and aorto-pulmonary pressure gradient (Houston et al, 1989).

2. Tracing over the entire waveform from the pulsed wave signal (figure 14), including negative velocities. This was recorded as "true mean flow".

**Minimum left-to-right velocity** was also measured, down to zero. A negative value was recorded as zero.

**Velocity at end diastole** (at the R wave on the ECG) and **at end systole** were measured (at the end point of forward flow in the pulmonary artery-easily seen in plate 8, occurring just
after the highest left-to-right velocity).

For bidirectional flow, *the ratio of the time period of right-to-left flow and left-to-right flow was measured* (figure 6.2 and plate 14).

4. **The ascending aorta.** Measurements were made using continuous wave Doppler. Systolic time intervals, maximal velocity and stroke distance were measured in the same way as for the pulmonary valve (see plate 10).

Several other measurements were made during the scan, as noted on the data sheet in appendix B. These are not of direct relevance to this thesis, but will be the subject of a later analysis to be published separately. These other measurements will not therefore be described in detail.

6.5. **Computing and statistical analysis**

6.5.1 Data preparation

(1) The data sheet shown in appendix B was prepared after consultation with the Newcastle University data preparation department, and the departments of computing and statistics. Each page represents a line of up to 80 digits in the SPSS® database. At the start of each line (and therefore at the top of each page) is the patient identification number (three digits), the line or page number (two digits), and the 'level', from 1-4, so that the computer can be instructed to differentiate the different types of data. Level 1 is basic data about the mother, level 2 is the data about the birth of the baby, level 3 is clinical details, and level 4 is ultrasound data.

(2) Some babies had up to 68 lines of data (thirteen examinations). Data was recorded from over 140 babies. There were over 10,000 lines of data, each with up to 80 digits.

(3) Because of the large quantity of data from the longitudinal studies, the professional data preparation team at the university punched the numbers into the database. Two independent operators put the data in, and any mistakes made by one were automatically detected by the other. After this, a number of random checks were performed by myself, and the entire database was listed to check for strange characters and incorrectly placed decimal points, prior to performing analysis on the data.

(4) Smaller data sets, such as those from the repeatability studies, were put in by myself.
6.5.2 Computing software

(1) Most of the statistical analysis was done using "SPSS" or "Minitab".

(2) Graphs were drawn using Apple Macintosh "Cricket Graph". Some simple statistical analyses, such as mean and standard deviation, were done using "Statworks" on the Apple Macintosh. Diagrams were drawn using "Microsoft Works" and "Macdraw".

6.6 Statistical analysis

6.6.1 Introduction

Most of the statistical analysis is discussed in the relevant chapters. However, there are three issues worthy of separate discussion here.

1) Analysis of serial data.
2) Measurement of agreement between two techniques.
3) Fishers' Exact test.

6.6.1 Analysis of serial data

(1) Serial data are frequently obtained in medical studies, yet interpretation of the data is difficult, and incorrect conclusions can be drawn from inappropriate analysis.

(2) The most frequent method of analysis used is to group patients together into different age bands, produce a mean and standard deviation of the measured parameter for that group, and compare it with a comparison group, or a different age band, by t test. For this approach to be valid, certain criteria must be met: there must be very little difference in age within in each age band, every subject must be included in every age band, and the distribution of the measured value within each age band must be 'normal'. Unfortunately, usually at least one of these factors is missing. A typical example of this is in the paper studying serial change in systolic time intervals in healthy babies discussed earlier (in section 4.2), by Evans and Archer (1990), where none of these three criteria are met. This method could also be misleading in the longitudinal studies in the present study, primarily because it is not possible to perform examinations on every baby at an exact time. Furthermore, even if all of the above three criteria are met, the analysis excludes a lot of important information about individual variability. For example, let us assume systolic blood pressure amongst 20 babies changes rises from, mean (SD), 50 mmHg to 60 mmHg from 12 hours to 48 hours. This gives the impression that all of the babies showed a rise of 10 mmHg. The truth may be quite different; in some babies the value may have decreased; there could even be two
distinct sub-groups, one rising and one falling.

(2) A neat method of comparing serial measurements between subjects was described recently by Matthews et al (1990). The method entailed plotting the serial values against time, calculating the area under the curve, and comparing subjects using standard statistical tests. From the point of view of the present study, the limitation of the method is that it is essential that values are measured at exactly the same time intervals. Therefore even this technique cannot be used in the present study.

(3) Since much of statistical analysis is essentially a way of summarising what can best be seen graphically, the general approach adopted in this thesis is to display the measured parameters graphically against time, and to visually interpret the results. The descriptive interpretation of the results may vary between observers, but at least the over-interpretation of indices of confidence is avoided, and valuable data is not obscured by grouped statistics.

(4) Despite this general approach, there is still a need to provide some statistically derived confidence limits, primarily to allow direct comparison with other studies, so these are usually presented alongside the graphical displays.

6.6.2 Measurement of agreement.

(1) When a new measurement is introduced into clinical medicine, a comparison with an established method is required. This is the case in the validation section of this thesis, where the pressure difference between the right ventricle and the right atrium is measured directly by cardiac catheterisation, and indirectly using the measurement of the peak velocity of tricuspid valve regurgitation. As mentioned previously, it is inappropriate to use correlation coefficients in this setting. There are several reasons for this:

1- $r$ measures the relationship between two variables, not the agreement between them. A perfect correlation occurs when the two variables lie along any straight line, but perfect agreement occurs only if the values lie along the line of equality (and passing through zero).

2- Correlation depends on the range of the true quantity in the sample. If it is wide, the correlation will be greater than if it is narrow. Hence a wide sample range, eg right ventricular pressure from 15 to 115 mmHg, is likely to produce a high correlation, even with relatively poor agreement.

3- The test of significance is designed to show if the two measurements are related. It would be amazing if two methods designed to measure the same thing were not related. The test of significance is irrelevant to the question of agreement.
4- Data with quite poor agreement can produce quite high correlations. This was the case with several of the papers mentioned earlier, testing the value of systolic time intervals in measuring pulmonary arterial pressure.

5- A change of scale of the measurement does not affect the correlation of two measurements, but it certainly affects the agreement.

(2) Because of these difficulties, Bland and Altman (1986), described the new technique previously mentioned as used by Houston et al (1988) investigating the Doppler estimation of pressure gradient across ventricular septal defects. There are three stages to 'Bland-Altman' analysis. Firstly, a plot is drawn of the difference between the methods against their mean difference. This shows any relationship between the true value and measurement error. Houston et al (1988) demonstrated that when the pressure difference across a ventricular septal defect was larger, the error margin became larger. Secondly, confidence limits are calculated. When there is no obvious relation between the differences and their mean, the lack of agreement between the measurements can be summarised by calculating the mean difference and the standard deviation of the differences. Limits of agreement can be defined as ± 2 SD around the mean difference. These can be drawn as lines on the initial plot.

(3) Thirdly, the precision of the estimated limits of agreement can be calculated, as confidence intervals for the limits of agreement. This analysis makes allowance for the sample size. (This last step has been employed in the repeatability section of this thesis, and is described in more detail there).

6.6.2 Fisher's Exact test.

(1) Fisher's exact probability test was designed for use under the same circumstances as the chi-squared test (ie, to compare the distribution of a discrete variable in a sample with the same variable in another sample), but where the sample is too small to use the chi-squared test reliably. Experts differ as to how small the sample can be with the chi-squared test, but it is probably best not to use it if the total in the four fold table is less than 40 (Swinscow, 1982).

(2) In this thesis, the Fishers exact test is preferred throughout, because there is no ambiguity about the validity of the test with lower numbers.
Chapter 6: Methods

Figures:
6.1 Diagrammatic representation of ductal flow patterns 1-8
6.2 Measurement of ductal flow velocity

Plates (photographs)
1. Echocardiographic examination in low dependancy area of the nursery.
2. Ventilated baby undergoing examination; (only a single port-hole of the incubator is open).
3. Position of the imaging probe for the apical four-chamber view.

Measuring velocity of tricuspid regurgitation-
4. from the apex
5. from between the apex and subcostal area.
6. the Doppler trace on-screen.

Recording ductal flow-
7. the probe is placed at the upper left sternal edge.
8. an example of ductal flow trace; (above the zero line is continuous left-to-right ductal flow, towards the probe).

Measurement of aortic stroke distance-
9. the probe is placed in the suprasternal notch
10. the Doppler trace on-screen (aortic stroke distance= 8.98 cm)

Pulsed-wave Doppler interrogation of ductal flow-
11. the imaging probe, high up the right sternal edge
12. the pulsed-Doppler sample is at the pulmonary end of the arterial duct (upper part of picture) recording a Doppler trace of bidirectional ductal flow.
Chapter 6: Methods

Plates (photographs) continued

Analysis of ductal flow

13 -Measurement of the 'true mean' ductal flow velocity (39 cm/sec).
14 -Measurement of the right-to-left phase of bidirectional flow (100 msec).
15 -Pure right-to-left flow (type 1), in a baby with persistent transitional circulation.
16 -Same patient as plate 15, ductal flow becoming bidirectional with increased ventilation.
17 -Same patient as plates 15 and 16, now bidirectional ductal flow (type 2)
18 -Pure left-to-right flow, low in systole (type 4).
19 -High velocity in systole, low at end diastole (type 5).
20 -Continuous high velocity left-to-right flow (type 6).
21 -Complex, low velocity left-to-right flow (type 7). Note brief right-to-left spike on this example.

Measurement of right ventricular systolic time intervals.

22 -Recording pre-ejection period (PEP), as 35 msec and time to peak velocity (TPV) as 95 msec. Right ventricular ejection time (RVET) was 210 msec. (Baby had low pulmonary arterial pressure determined by tricuspid regurgitation). Peak velocity was 51 cm/sec at the pulmonary valve.

23 -The pre-ejection period is long (95 msec) in this baby with high pulmonary arterial pressure and persistent transitional circulation. Note also the pulmonary incompetence (upward deflection), and the low velocity flow through the pulmonary valve (downward deflection about 15 cm/sec), with a qualitatively different, less rounded, signal from the baby with low pulmonary arterial pressure in figure 22.

Change in ductal flow with increasing arterial oxygen saturation (see chapter 17)

24 -At 85% SaO2 there is bidirectional ductal flow.
25 -At 100% SaO2 there is pure left-to-right ductal flow.
Doppler traces with simultaneous aortic pressure recordings. (These photographs are discussed in chapter 13, but are also listed here for the convenience of the reader). Note how the pattern of ductal flow mimics the aortic pressure trace.

26 (fig 13.2) - Bidirectional ductal flow recorded with continuous wave Doppler.
27 (fig 13.3) - Tricuspid regurgitant jet precedes aortic pressure peak (Same patient as plate 26).
28 (fig 13.4) - Bidirectional ductal flow on pulsed-Doppler.
29 (fig 13.5) - Peak velocity of tricuspid regurgitation coincides with peak aortic pressure
30 (fig 13.6) - Pure L-R flow (type 6) with symptomatic left-to-right ductal shunt.
31 (fig 13.7) - The delay in transmission of ascending aortic flow (the Doppler trace) to descending aortic pressure impulse.
Figure 6.1 Diagrammatic representation of types of pattern of ductal flow

1. PURE RIGHT-TO-LEFT

2. BIDIRECTIONAL

3. L-R BUT SIGNAL TOO WEAK TO CLARIFY PATTERN, OR PATTERN NOT IN ANY OTHER CATEGORY

4. L-R LOW SYSTOLE HIGHER DIASTOLE

5. L-R HIGH MID SYSTOLE / LOW END DIASTOLE

6. L-R CONTINUOUS HIGH VELOCITY

7. L-R, COMPLEX, 2 PEAKS IN SYSTOLE

8. L-R, COMPLEX, 1 PEAK IN SYSTOLE, 1 IN EARLY DIASTOLE
Figure 6.2: Measurements of velocity of flow through arterial duct.

Bold line = "PDA MAX"

Open line = "PDA MIN"

(End diastole)

R-L

Maximum L-R (zero)

Minimum L-R (zero)

PDA MAX

PDA MIN
Chapter 7: Comparison of Doppler and catheter measurement of right ventricle to right atrial pressure drop.

7.1 Introduction

7.2 Study group

7.3 Methods

7.4 Statistical analysis

7.5 Results

7.6 Discussion

7.7 Summary

Figures:

7.1 Correlation of Doppler-determined and directly measured right-ventricle to right atrial pressure drop.

7.2 Bland-Altman plot of difference between TR- determined RV-RA pressure drop and catheter measured RV pressure.

7.3 Bland-Altman plot of difference between RV-RA pressure drop measured from TR and from catheterisation.

7.4 Bland-Altman plot of difference between RV-RA pressure drop measured from TR and from catheterisation, but with results expressed in metres/second.

There are no tables in chapter 7
Chapter 7. Comparison of Doppler and catheter measurement of right ventricle to right atrial pressure drop.

7.1 Introduction

The main aim of this study was to investigate the validity of the TR method in neonates. However, comparison with direct measurement is no longer ethically acceptable in healthy babies, and neonatal catheterisation is now rare in paediatric cardiology (a fact which may in part be due to the widespread clinical application of Doppler methods of pulmonary arterial pressure estimation as yet unvalidated for this age group). Therefore the study group was expanded to include babies up to one year of age.

7.2 Study group

The study group comprised 28 infants (less than one year of age) with congenital heart disease found to have Doppler evidence of tricuspid regurgitation. 30 paired measurements were made on the 28 babies. Three babies with indwelling pulmonary arterial and right atrial pressure lines in intensive care were included. Two of these babies had paired measurements on consecutive days. The other babies underwent formal cardiac catheterisation. Two values were excluded because of haemodynamic instability (predefined, as in section 7.3 (1)) between Doppler and catheter measurements. There were therefore 28 completed studies from 26 babies. Weight range was 3.1 to 9.0 kg (median 4.7 kg) and age range was 10 days to 12 months (median 4.5 months). 18 babies weighed less than 5 kg and 20 were under 6 months of age. The study population included three post-operative patients (two babies who had anomalous pulmonary venous drainage, and one with a ventricular septal defect), eleven babies with a ventricular septal defect, four with a complete atrio-ventricular septal defect (one also had Fallots tetralogy), three with isolated pulmonary stenosis, one with cardiomyopathy, one with arterial trunk, one with partial atrio-ventricular septal defect, one with pulmonary atresia with VSD, and one baby with a hypoplastic left heart.

7.3 Methods

(1) All infants were under general anaesthesia when the Doppler and catheterisation measurements were taken. Doppler measurements were made prior to venepuncture. Catheter measurements were made with a single catheter, prior to angiography, recording peak right ventricular pressure, and then withdrawing to record mean right atrial pressure. This method was used in preference to two catheters recording simultaneous pressures to avoid enlargement of the area of tricuspid regurgitation caused by leaving a catheter through the tricuspid valve. Oscillometric systemic blood pressure was recorded with the Doppler
and catheter measurements. Since some haemodynamic variability is expected at all times, when the systolic systemic pressure changed by more than 10 mmHg between the two measurements, the values were excluded from the study.

(2) Doppler measurements were made by the author with a Sonos 1000 ultrasound machine, using a stand-alone 2.2 Mhz continuous-wave Doppler probe in the manner described earlier (see figures 6.4-6.6). The spectral display was adjusted to achieve a clear velocity profile, and the low velocity (noise) filter was set on maximum. The maximal velocity was taken as being in line with flow. In four babies with complete atrio-ventricular septal defect, colour flow guided continuous wave Doppler was used. Catheterisation pressures were measured using a strain gauge with either a Bentley-Trantec or a Trumex transducer. Signals were transmitted via isolation amplifiers at the foot of the bed to pressure amplifiers in the main console. Measurements for this study were made from a Siemens Elema Mingograph strip chart recording, by a single independent observer who was unaware of the Doppler results. Mean right atrial pressure was subtracted from peak right ventricular pressure to determine the maximal RV-RA pressure drop.

(3) The catheter derived measurements were re-analysed by a third observer to determine observer error associated with the catheter measurement.

7.4 Statistical analysis

Measurements were compared using Spearman correlations and the method introduced by Bland and Altman.

7.5 Results

(1) The results are presented in figures 7.1 to 7.4. In figure 7.1, the two values of the peak right ventricle to right atrial (RV-RA) pressure drop are plotted against each other in the same manner as previous validatory studies, \((r=0.95, r^2=0.90)\). Standard error for the estimate was 5.1 mmHg. There is considerable spread around the correlation line. Three 'Bland-Altman' plots (figures 7.2 to 7.4) give more insight into the level of agreement between the methods. Doppler derived values are compared with peak right ventricular pressure in figure 2: there is a mean underestimation of 5.8 mmHg (95% confidence limits of -17.4 mmHg to +7.0 mmHg). Comparison of the Doppler and catheter measured RV-RA pressure difference (figure 3) shows closer agreement, but the Doppler values still tend to underestimate the true pressure drop (mean = -2.0 mmHg, 95% confidence limits -11.8 to +7.8 mmHg).

(2) To determine the confidence limits for the velocity measured by Doppler, the RV-RA
Figure 7.1 Correlation of catheter and Doppler-determined RV-RA pressure drop.

Figure 7.2 Difference between TR determined RV-RA pressure drop and catheter RV systolic pressure.
Figure 7.3
Difference between Doppler and catheter determined RV-RA pressure drop

Figure 7.4
Difference between Doppler and catheter determined RV-RA pressure drop:
expressed in metres/second
pressure drop measured by catheter was calculated in metres/sec by using the Bernoulli equation in reverse \( p = 4v^2 \), therefore \( v = \sqrt{p/4} \). For example, an RV-RA pressure drop of 36 mmHg = 3 m/sec. The derived values have been plotted against the Doppler measurements in figure 4. The resulting 95% confidence limits for the TR jet velocity are -0.41 to +0.26 m/sec.

(3) Catheter measurements were reanalysed by a third observer. All but one measurement agreed to within ± 4 mmHg, one differed by 6 mmHg. Therefore some of the disagreement between the two methods can be explained by subjectivity in interpretation of the catheterisation results.

7.6 Discussion

(1) This study shows close agreement between direct and indirect measurement of the RV-RA pressure drop, although the tricuspid regurgitation technique marginally underestimated the true pressure drop, by 2 mmHg on average. This underestimation may be due to energy loss due to viscous friction through the small valve orifice, or due to failure to align the Doppler beam accurately with the direction of the regurgitant jet. There were only two babies with a pressure gradient of more than 65 mmHg, and Doppler measurements in both showed considerable underestimation of the true pressure drop, when expressed in mmHg. However, when the values are expressed in metres/sec (figure 7.4), the margin of error is no different from that seen at lower pressures.

(2) Comparison of figures 7.3 and 7.4 suggests that it is better to express the confidence limits of the Doppler measurement in terms of velocity (-0.41 to + 0.26 m/sec) rather than pressure because the same measurement error at higher velocities results in a larger error in calculated pressures. This is logical since measurement errors at the higher velocities are also squared and multiplied by four. When these confidence limits are applied, the method is seen to be more accurate, in terms of the derived pressure drop in mmHg, at lower velocities. For example, a tricuspid regurgitant velocity of 2 m/sec indicates a true RV-RA pressure drop of 13 to 23 mmHg (range = 10 mmHg), and a velocity of 4 m/sec indicates 58 to 77 mmHg (range = 19 mmHg). The confidence interval, in terms of mmHg, has almost doubled with a doubling of the velocity. Furthermore, a given change in pressure drop at lower velocities will produce a bigger change in regurgitant velocity than at higher values. For example, when there is a change of 10 mmHg in the RV-RA pressure from 20 to 30 mmHg, velocity changes from 2.24 to 2.74 m/sec (a rise of 0.5 m/sec), whereas if the pressure rises by the same amount, from 50 to 60 mmHg, velocity changes from 3.54 to 3.87 (a rise of 0.33 m/sec). The first 10 mmHg change can be detected 'with confidence' by the TR technique, whereas the second cannot.
(3) Previous validatory studies of the TR technique (see table 3.2) have compared results of direct and indirect measurement using linear regression analysis, the drawbacks of which were discussed in the last chapter (section 6.6.3). The alternative (Bland-Altman) method allows the production of confidence intervals, which are of more clinical value than a correlation coefficient. Visual interpretation of the plots in this study demonstrate that there was no obvious variation across the range of pressures encountered, particularly when the results were expressed in metres/sec. This is in contrast to the large variation in agreement over the pressure range in determining pressure drop across ventricular septal defects by Doppler and catheter (Houston et al, 1988).

(4) There were, unfortunately, only three neonates in the first part of this study, because neonatal catheterisation is now rarely necessary. However, 18 babies weighed less than 5 kg, so that small subject size does not appear to influence the validity of this method adversely, and between observer error, studied in neonates, was acceptable. It is therefore fair to assume that the technique is valid in the term neonate. Furthermore, lower RV-RA pressure drops, below 40 mmHg, are more frequent in this study than in previous studies and they were determined accurately by the TR technique. However, this study alone cannot be taken as validation for the use of the tricuspid regurgitation technique in the low birth weight or preterm neonate. The next chapter (chapter 8), is particularly important in this respect since this technique is used in healthy term and preterm neonates over the first three days of life, and results are compared with concurrent systemic arterial pressure and ductal flow patterns.

(5) Small valve orifice and low blood velocity, the theoretical sources of error of this technique in neonates, did not lead to serious underestimation of pressure drop. Perhaps the reason is that the physical properties of a healthy, but slightly regurgitant valve, are very different from the stiff, firm-edged orifice created in Holen's in vitro experiments, and the shape of an orifice, and its surface morphology are important in the generation of friction.

7.7

(1) In summary, the measurement of peak tricuspid regurgitation and application of the modified Bernoulli equation predicts the right ventricle to right atrial pressure drop in infants and neonates with reasonable accuracy, and provides a more reliable estimate of pulmonary arterial pressure than systolic time intervals, or velocity across a ventricular septal defect, but it is only feasible in babies with tricuspid regurgitation. An allowance for right atrial pressure in determining peak pulmonary arterial pressure may need to include a small allowance, of about 2 mmHg, for the tendency of the method to slightly underestimate the true pressure drop, as well as the estimated right atrial pressure. An average total allowance of about 6 mmHg would be appropriate from the present study, in ventilated...
infants with congenital heart disease. This allowance should probably vary between different categories of patients, and in intensive care concurrent right atrial pressure may be known. However, this study suggests that it may be better, in the setting of congenital heart disease and when individual values are of clinical importance, to express TR jet values in terms of velocity (m/s) rather than as a pressure drop (mmHg).

(2) In the rather different context of neonatal haemodynamic research, expressing RV-RA pressure drop as a velocity has the disadvantage that the values cannot be expressed as a ratio of systemic arterial pressure, nor can they be compared with previous studies using direct measurements. Therefore, for the bulk of the rest of this thesis values are expressed in mmHg. An aim of a subsequent chapter (chapter 9) is to produce an appropriate reasonable allowance for right atrial pressure in preterm babies ventilated for hyaline membrane disease.
Chapter 8: Longitudinal Doppler study of pulmonary arterial pressure in healthy neonates over the first three days of life.

8.1 Introduction

8.2 Study group and methods

8.3 Results

1. Prevalence of tricuspid regurgitation
2. Systolic pulmonary and systemic arterial pressure
3. Ductal flow patterns

8.4 Discussion

Figures

8.1 Systolic pulmonary arterial pressure (derived from TR) in healthy term babies, compared with Catheterisation data obtained by Emmanouilides et al (1964).

8.2 Systolic pulmonary arterial pressure (derived from TR) in healthy preterm babies.

8.3 Systolic pulmonary : systemic arterial pressure ratio in term and preterm babies.

Tables

Tables summarise results from both term and preterm neonates, divided into three age groups; 0-12, 13-36, and 37-72 hours.

8.1 Incidence of detectable and measurable tricuspid regurgitation.

8.2 Systolic upper limb blood pressure.

8.3 Ductal patency and flow patterns.
Chapter 8. Longitudinal Doppler study of pulmonary arterial pressure in healthy neonates over the first three days of life.

8.1 Introduction

There were three main objectives in this part of the study:

1) To establish the prevalence of tricuspid regurgitation detected by Doppler ultrasound in healthy neonates in the first three days of life.

2) To estimate systolic right heart pressures utilising tricuspid regurgitant jet velocity and the modified Bernoulli equation, and compare values in term and preterm babies.

3) To see how changes in ductal flow patterns correlate with the estimated systolic pulmonary : systemic arterial pressure ratio.

8.2 Methods and study group

1) Serial Doppler ultrasound examinations were performed on 34 term infants (birth weight 2615-4659 g) and 17 preterm infants (28-35 weeks gestation, 1165-2290 g). Each child was examined within 12 hours of birth and daily thereafter for three days unless discharged sooner. All were born in good condition without evidence of perinatal asphyxia and none had respiratory distress requiring oxygen. The term infants were recruited antenatally at parent-craft classes and the preterm infants were enrolled as they arrived in the nursery provided they were not oxygen dependent after 20 minutes. All but 4 babies in each group were born vaginally.

2) Systolic upper limb blood pressure was determined by Doppler sphygmomanometry. Patency of the arterial duct was established using continuous wave Doppler ultrasound (2.2 Mhz) by recording flow velocities from the pulmonary artery. Evidence of tricuspid regurgitation was looked for and where found maximal velocities were recorded. (Further details of the examination technique are described in section 6.3.2.)

3) In neonates shortly after birth, right atrial pressure is known to approximate to zero (Burnard et al, 1963; Blankenship et al, 1965; Young and Cotton, 1966). Therefore, in this part of the study, dealing with healthy (unventilated) babies, pulmonary arterial systolic pressure was calculated treating right atrial pressure as if it was zero.

4) Babies with any Doppler evidence of tricuspid regurgitation were recorded as having "detectable tricuspid regurgitation". In a subgroup of these babies the systolic regurgitant
jet was detectable throughout the whole of systole and the maximal velocity was easily seen. These were recorded as having "measurable tricuspid regurgitation", and systolic pulmonary arterial pressure was derived in these babies.

8.3 Results

8.3.1. Prevalence of tricuspid regurgitation.

The prevalence of ("detectable") tricuspid regurgitation is shown in table 8.1. Doppler studies were positive in the majority of babies in both groups and at some stage in all preterm babies. Detectable tricuspid regurgitation was more common in the preterm group at all ages and this reached statistical significance at 37-72 hours using Fisher's Exact Test. Measurable tricuspid regurgitation was significantly more common in the preterm group in the first 12 hours than in the term group, the proportion falling significantly with time. Neonates who had measurable tricuspid regurgitation on the third examination were re-examined 24 hours later but measurable tricuspid regurgitation was found in only two term babies who were still under 72 hours of age. The preterm babies were all re-examined after 72 hours and none had measurable tricuspid regurgitation.

8.3.2. Systolic pulmonary arterial pressures.

(1) The non-invasively determined systolic pulmonary arterial pressures for the term and preterm groups are plotted in figures 8.1 and 8.2 respectively. The values in the preterm babies are lower than those in the term babies, but they show a similar pattern of change against time. Furthermore when pulmonary arterial pressure is expressed as a ratio of systemic blood pressure (figure 8.3) the results from the two groups become almost identical. Differences in the pulmonary : systemic arterial pressure ratio between the preterm and term groups were assessed by relating group and age to the logarithm of the ratio using multiple linear regression. (It was necessary to take the logarithm because the relationship of the absolute pressures to age appears to be roughly exponential, and a linear relationship is required for multiple linear regression analysis). Taken overall there was no statistically significant difference between the groups (P > 0.8). The fall in the ratio is partly related to the fall in pulmonary arterial pressure, but is also related to an increase in systemic blood pressure, which is most marked in the preterm group. The systemic blood pressure measurements are presented in table 8.2.

(2) The data are compared with the cardiac catheterisation data of Emmanouilides et al (1965) in figure 8.1 and show similar absolute values and similar changes with time. Statistical comparison was done using the same method as used to compare the term and preterm groups- ie. the logarithm of pulmonary arterial pressure was related to group and
Figure 8.1
Systolic pulmonary arterial pressure, determined by Doppler TR jet velocity, in 15 healthy term babies (22 values), compared with catheterisation data from Emmanouilides et al.

![Graph showing systolic pulmonary arterial pressure over age in hours, with data points indicating measurements from Doppler and catheterisation methods.](image-url)
Figure 8.2

Systolic pulmonary arterial pressure (determined by Doppler from TR jet velocity) in healthy preterm babies (21 values from 11 babies)

Figure 8.3

Systolic pulmonary : systemic arterial pressure ratio in healthy term and preterm neonates.

- preterm
- term
age using multiple linear regression. Some babies in this study had serial measurements, but Emmanouilides’ study was entirely cross-sectional. To allow valid statistical comparison between these two different types of data, one value was selected at random from each baby who had multiple values. The data exhibit considerable variability and this is only partially explained by the regression model. There was no significant difference between the groups overall ($P > 0.5$) and no significant difference in the way the pressure fell with time ($P > 0.8$).

8.3.3. Ductal flow patterns

(1) The pattern of ductal flow (patterns are summarised diagrammatically in figure 6.1) was compared with the simultaneous pulmonary : systemic arterial pressures in those babies with both measurable tricuspid regurgitation and a patent duct. Bidirectional flow (‘pattern type 2’) was present in 11 babies with measurable tricuspid regurgitation. The ratio of pulmonary to systemic arterial pressure in these babies was $0.88:1 - 1.22:1$. High velocity left-to-right flow with maximal velocity in late systole (pattern type 6) was seen in seven babies with measurable tricuspid regurgitation and in them the arterial pressure ratio was $0.49:1 - 0.66:1$. An intermediate type of flow was seen in five babies with continuous low velocity left-to-right flow, lowest in systole and higher in diastole (pattern 4); in these the ratio was $0.74:1 - 0.92:1$. One baby with a ratio of $0.79:1$ had a ductal wave form varying with respiration from bidirectional to intermediate in type.

(2) Thus, when derived pulmonary arterial pressure approached systemic pressure, bidirectional flow was seen in the pulmonary artery and conversely low pulmonary arterial pressures were associated with continuous retrograde high velocity flow, indicating that systolic pulmonary arterial pressure determined from tricuspid regurgitation do truly reflect pulmonary arterial pressure.

(3) Not all babies with bidirectional flow in the pulmonary artery (indicating high pulmonary arterial pressure) had tricuspid regurgitation measurable on Doppler. In the term group there were 19 babies with bidirectional flow in the first 12 hours. Only 7 of these (37%) had measurable tricuspid regurgitation. In the preterm group 5 of the 7 (71%) with bidirectional flow had measurable tricuspid regurgitation, suggesting that preterm infants are more prone to have physiological tricuspid regurgitation than term infants in the presence of pulmonary hypertension. The proportion of babies with a patent duct at each examination and the ductal flow patterns seen are recorded in table 3. In the first 12 hours bidirectional flow was seen in 19 of the 30 term babies (63%) and 7 of the 16 preterm babies (44%) with a patent duct. The fact that 56% of preterm babies had pure left to right flow in the first 12 hours of life suggests that the pulmonary to systemic arterial pressure ratio falls faster in the preterm babies during this time. After 13 hours of age pure left-to-
right flow predominates in both groups and bidirectional flow was seen in only one term baby. At 21 hours, this was the only baby to present with a transient soft systolic heart murmur consistent with tricuspid regurgitation. The data point representing a relatively high pulmonary arterial pressure (pulmonary to systemic arterial pressure ratio 1.1:1) can be seen as an outlier in figure 8.3.

8.4 Discussion

(1) This section has shown that most healthy neonates have Doppler evidence of tricuspid regurgitation in the absence of clinical signs, and in a significant proportion it is possible to measure the maximal velocity. Derived systolic pulmonary arterial pressure values fell quickly in both the premature and term babies, and the pulmonary : systemic arterial pressure ratio was similar in the two groups. This pattern of change with time was also mirrored by ductal flow patterns. This finding of a changing pattern of ductal flow as the ratio of pulmonary : systemic arterial pressure falls is consistent with the studies discussed earlier, in chapter 3, comparing ductal flow velocities with simultaneous cardiac catheterisation data (Musewe et al, 1987; Houston et al, 1989).

(2) The observation that pulmonary arterial pressure falls as quickly in the preterm as in the term baby, is in conflict with the findings from the study of healthy neonates by Evans and Archer (1990) discussed earlier. Some of the weaknesses of that study, and the many difficulties in interpreting the TPV / RVET ratio have already been discussed (sections 3.2 and 4.2.1). However, in comparing the preterm and term babies, while the method used in this study has the advantage that it should not be affected by either heart rate or myocardial performance, a major disadvantage is that pulmonary arterial pressure could only be estimated in the babies with measurable tricuspid regurgitation, and these were a minority, particularly amongst the term babies. This subgroup might not be truly representative of the whole group; it is possible that babies without tricuspid regurgitation have different pressures. However, evidence from this study does not support this. The results are consistent with previous catheter studies, and ductal flow patterns showed a similar fall of pressure with time in babies with and without tricuspid regurgitation. Furthermore if the presence of measurable tricuspid regurgitation were dependent merely on pulmonary hypertension then it would not have been possible to make sequential measurements in babies as the pulmonary arterial pressure fell. Factors other than pulmonary artery pressure are obviously affecting the competence of the tricuspid valve.

(3) This study has shown that two different Doppler techniques for pulmonary arterial pressure estimation correlate well and that the derived pressures are consistent with known neonatal cardiac catheterisation data. The only thing that has not been done is to compare direct and indirect measurement in the same baby at the same time. Clearly this is no
longer an ethical option in the healthy neonate. Combining the evidence from this study, and the validation study in infants presented in chapter 7, suggests that measurement of the peak tricuspid jet regurgitant velocity with application of the modified Bernoulli equation is a valid method of systolic pulmonary arterial pressure estimation in the newborn term or preterm baby.

(4) Another important message is that since there was Doppler evidence of tricuspid regurgitation at some stage in most healthy babies in the first three days of life, detection of tricuspid regurgitation by Doppler cannot be interpreted, in isolation, as a sign of cardiopulmonary distress at this age.

8.5.

In summary, measurement of the maximal tricuspid regurgitant jet velocity and application of the modified Bernoulli equation appears to be a valid and useful way of measuring systolic pulmonary arterial pressure non-invasively in a high proportion of babies shortly after birth. The values presented in this paper show how systolic pulmonary arterial pressure falls in relation to systemic pressure over the first 72 hours in term and preterm babies, and the results suggest that the rate of fall in the pulmonary : systemic arterial pressure ratio is similar in term and preterm infants. Ductal flow patterns mirrored the fall in this ratio with age: bidirectional flow was associated with a ratio of 0.88:1 - 1.22:1 and high velocity L-to-R flow with a ratio of 0.49:1 - 0.66:1. This both suggests that analysis of ductal flow patterns can also be a useful a means of assessing pulmonary arterial pressure in the newborn, and in itself confirms that the method utilising tricuspid regurgitation truly reflects pulmonary arterial pressure.
TABLE 8.1  Prevalence of detectable and measurable tricuspid regurgitation (TR) in preterm and term neonates divided into three age groups.

<table>
<thead>
<tr>
<th></th>
<th>Term</th>
<th>Preterm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-12hr</td>
<td>13-36hr</td>
<td>37-72hr</td>
</tr>
<tr>
<td></td>
<td>0-12hr</td>
<td>13-36hr</td>
<td>37-72hr</td>
</tr>
<tr>
<td>mean age (hours)</td>
<td>5</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>TR detected (%)</td>
<td>23/32 (72)</td>
<td>18/30 (60)</td>
<td>15/27** (56)</td>
</tr>
<tr>
<td>TR measurable (%)</td>
<td>7/32* (22)</td>
<td>8/30 (27)</td>
<td>5/27 (19)</td>
</tr>
</tbody>
</table>

*p<0.05  **p<0.02 , Fisher's exact test.

TABLE 8.2  Systolic upper limb blood pressure (mmHg), mean and Standard Deviation, for term and preterm neonates divided into three age groups.

<table>
<thead>
<tr>
<th></th>
<th>0-12hr</th>
<th>13-36hr</th>
<th>37-72hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>49.4 +9.3**</td>
<td>56.3 +6.4**</td>
<td>58.8 +9.3</td>
</tr>
<tr>
<td>Term</td>
<td>60.6 +6.3</td>
<td>63.0 +8.0*</td>
<td>71.6 +6.0*</td>
</tr>
</tbody>
</table>

significant rise within each group:  
* and **p<0.005 , paired t test.
**TABLE 8.3** Ductal patency and flow patterns in term and preterm neonates divided into three age groups.

<table>
<thead>
<tr>
<th></th>
<th>TERM</th>
<th></th>
<th></th>
<th>PRETERM</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-12hr</td>
<td>13-36hr</td>
<td>37-72hr</td>
<td>0-12hr</td>
<td>13-36hr</td>
<td>37-72hr</td>
</tr>
<tr>
<td>number examined</td>
<td>34</td>
<td>31</td>
<td>28</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>bidirectional</td>
<td>19</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>intermediate L-R</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>high velocity L-R</td>
<td>5</td>
<td>11</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>patent duct (%)</td>
<td>88</td>
<td>48</td>
<td>14</td>
<td>94</td>
<td>47</td>
<td>18</td>
</tr>
</tbody>
</table>
9.1 Introduction

9.2 Study group and methods

9.3 Results

9.4 Review of the literature

9.5 Summary

9.6 Addendum

Figure

9.1 Right atrial pressure in 42 neonates with congenital heart disease plotted against base deficit.

Tables

9.1 Summary of right atrial pressure values from 42 neonates with congenital heart disease.

9.2 Summary of right atrial pressure values from thirteen neonates ventilated for respiratory failure.
Right atrial pressure

9.1 Introduction

(1) Before moving on to studies of pulmonary arterial pressure in ventilated babies, an important issue to address is the allowance for right atrial pressure (or central venous pressure) in estimating systolic pulmonary arterial pressure, since the method using peak velocity of tricuspid regurgitation only estimates the right ventricle to right atrial (RV-RA) pressure drop. Publications comparing direct and Doppler determined systolic pulmonary arterial pressure using this method have discussed the allowance for right atrial pressure, with varying conclusions. Chuwa et al (1983) found that measuring right atrial pressure did not improve the correlation of direct and indirect measurements of pulmonary arterial pressure; a standard estimate of 10 mmHg was just as good. Chan et al (1987) found the best right atrial pressure allowance was 14 mmHg. On the other hand, Gallett et al (1989) found that correlation improved with a clinical estimate rather than a standard figure; r = 0.88 with a fixed 10 mmHg, r = 0.91 with clinical estimate, and Vasquez de Prada et al (1987) also found the correlation rose from 0.91 to 0.96 if clinically estimated right atrial pressure was used.

(2) Putting these observations together, it seems likely that even in the adult population, where a rough estimate of right atrial pressure can be made from clinical assessment of jugular venous pressure, a standard allowance for right atrial pressure is acceptable.

(3) In following serial change in right heart pressures, RV-RA pressure drop changes much more than right atrial pressure. Thus, when the right atrial pressure is not known, the RV-RA pressure drop alone can usefully be reported instead of pulmonary arterial pressure. Since this is usually the case, and right atrial pressure can only be an estimate, serial change in the RV-RA pressure drop is reported in part of the next chapter on babies with hyaline membrane disease. Nevertheless, systolic pulmonary arterial pressure is a more readily understandable measurement which allows comparison of data obtained with previous direct measurements in neonates, and with concurrent systemic arterial pressure. Therefore there is a need to find a reasonable approximation for right atrial pressure to add to the RV-RA pressure drop. This chapter sets out to establish such an estimate.

(4) There is little published data available on central venous pressure (CVP) in the sick neonate, and only limited data in the healthy neonate. This is particularly surprising as the myocardium of the sick neonate is highly dependent on an adequate preload, (Maayan et al, 1986) and frequently functions against a high afterload in the form of pulmonary hypertension.
Central venous pressure is not monitored routinely in neonatology, and there is no non-invasive measure of preload. There is a shortage of such data in the ventilated neonate, and indeed some of the reference manuals of neonatal intensive care barely mention the subject. Most available data were obtained from healthy babies, and these values, of around -2 to + 4 mmHg, (Adams and Lind, 1957; Rudolph et al, 1961; Young and Cotton, 1966) may not be relevant to the ventilated baby. In order to try to obtain 'normative reference data' for the ventilated newborn baby, the available published data has been reviewed and further case material assembled from 62 neonates of two different categories. Group 1. was 49 babies with congenital heart disease undergoing cardiac catheterisation and, group 2. was 13 babies with respiratory disease who had central venous pressure measurements while undergoing intensive care. This new data is presented first, and is followed by a literature review.

9.2 Patients and methods

1. Babies with congenital heart disease.

(1) Data were available from 49 neonates with a variety of congenital heart defects who were catheterised at the regional cardiothoracic unit in Newcastle, between 1977 and 1979. This represents an unselected sample from a period prior to the routine clinical use of cross-sectional and Doppler echocardiography in neonatal cardiac diagnosis. Median age was five days (range 0.5-30 days); 29 (59%) were less than eight days old. Mean weight was 3.3 Kg (range 1.6-4.5kg).

(2) All of the babies were ventilated and under general anaesthesia. Measurements were made using a strain gauge with either a Bentley-Trantec or a Truck transducer. Signals were transmitted via isolation amplifiers at the foot of the bed to pressure amplifiers in the main console. Recordings were made with Siemens Elema Mingograph chart recorder and were reported by one of two consultant paediatric cardiologists.

2. Babies ventilated for respiratory disease.

(3) Values from 13 neonates ventilated for a variety of respiratory disorders were collected between 1988 and 1991. Gestation was between 28 and 42 weeks, and birth-weight between 860 g and 4390 g. Further details are given in table 9.2.

(4) Central venous access was obtained via the umbilical or the internal jugular vein. Measurements were supervised by a clinician (the author or a consultant neonatologist). A Gould P50 minidome transducer was used, connected to a Kontron Supermon pressure module.
In both groups, the catheter tip was in the right atrium and zero calibration was at the mid thorax, corresponding approximately to the level of the tricuspid valve.

9.3 Results

1. Babies with congenital heart disease.

(1) The results are summarised in table 9.1 and figure 9.1. No values below +1 mm Hg were encountered, and only five babies had values of 1 to 2 mm Hg. Of these five, three babies had a marked metabolic acidosis (pH<7.22, base excess > -8), and all three had transposition of the great arteries with ventricular septal defect. At the other extreme, there were 13 babies with a CVP of over eight mmHg. All but two (who had tricuspid atresia or pulmonary atresia with ventricular septal defect) were in overt cardiac failure; eight had aortic coarctation, two had persistent fetal circulation and one had a hypoplastic left heart. Nine of these 13 babies had a severe metabolic acidosis. Twelve babies had coarctation: eight had a CVP of more than 8 mmHg and seven of these were profoundly acidic, (as was the only baby with a CVP of 8 mmHg) indicating circulatory failure. The other three babies with coarctation had CVP values of 4 to 6 mmHg and were not acidic. There were 22 babies with a CVP of 4 to 8 mmHg and available blood gas results, and only three were significantly acidic (two had CVP values of 8 mmHg and the other of 4 mmHg).

2. Babies ventilated for respiratory disease.

(2) The results are summarised in table 9.2, though this presentation does not demonstrate the most useful feature of CVP measurement, which comes from serial measurement. However, on all occasions when the CVP was zero, there was clinical evidence of hypovolaemia. In general, higher values were seen in the larger babies, but this observation could be explained by the nature of their illness, rather than size per se, with a preponderance of asphyxia and myocardial ischaemia. Low values, from 0-3 mmHg were particularly badly tolerated in this group. The four babies with uncomplicated hyaline membrane disease who survived had CVP values within a relatively narrow band when clinically stable, (2-6 mmHg most of the time).

9.4 Review of the literature

9.4.1 Preterm babies with hyaline membrane disease.

(1) Rudolph et al (1961) recorded CVP in six babies with hyaline membrane disease; values ranged between -6.5 mm Hg and zero. In such early studies of hyaline membrane disease, the babies were usually unventilated and generating large negative intrathoracic pressures.
Figure 9.1 CVP versus base deficit in 42 neonates with congenital heart disease.

Other
Atrial Tntrm
Normal Heart
Transposition + VSD
Persistent Fetal Circulation
Hypoplastic left heart
Coarctation + VSD

Mean right atrial pressure (mmHg)
Because of this influence of intrathoracic pressure, Stahlman et al (1972) did not report mean CVP in their studies. Siassi et al (1980) reported a mean CVP of +1.6 mm Hg in healthy preterm neonates, and negative values in 12 babies with respiratory distress; values varying from -16 to +3 mm Hg. Six of these 12 babies were ventilated, and they were reported to have higher values within this range. Cabal and Hodgmann (1979) reported that a ventilated premature neonate developed a mean CVP of 12 mm Hg with a tension pneumothorax, returning to 6 mm Hg after successful drainage.

(2) Todres et al (1979) performed Swan-Ganz catheterisation in 11 ventilated preterm neonates. In two of these babies CVP was reported; both had hyaline membrane disease and sepsis. One baby had a CVP of 2 mm Hg and the other a CVP of 0-2 mm Hg. The latter baby was clinically hypovolaemic when right atrial pressure was zero. In another study by Cabal et al (1980) four asphyxiated, ventilated, preterm neonates of 30-34 weeks gestation with respiratory distress and heart failure were managed successfully with inotropes. Mean CVP was 12 mm Hg at one hour of age (prior to treatment), 6.2 mm Hg at six hours, 5 mm Hg at 12 hours and 4 mm Hg at 24 hours.

9.4.2 Term babies with persistent pulmonary hypertension

(1) Peckham et al (1978) catheterised ten ventilated babies with persistent fetal circulation, and found a mean CVP of 6.6 mm Hg. Tamura et al (1990) investigated the clinical efficacy of nitroglycerine in the management of heart failure and persistent pulmonary hypertension. Six babies had CVP recordings, two were 32 weeks gestation and the rest were at term; all were ventilated. The initial CVP was, mean (SD), 13.8 (6.7) mm Hg falling to 10.8 (4.4) mm Hg with clinical improvement. However, this was a mixed group of babies; one had Ebstein's anomaly, one had hypertrophic cardiomyopathy, and two had diaphragmatic hernias.

9.4.3 Older babies with congenital heart disease

Burnell (1970) catheterised 131 infants under one year of age with congenital heart disease; those in heart failure had a mean right atrial pressure of 7.7 mm Hg compared to 3.5 mm Hg in those without heart failure. Some of the babies were ventilated and some were not.

9.5 Discussion

(1) It is clearly difficult to establish 'normal' values for central venous pressure, since the optimal filling pressure for any individual is unique and varies with changes in ventricular performance, compliance and afterload. However this review shows that, in the ventilated neonate, a central venous pressure of zero is likely to be associated with hypovolaemia and
inadequate right ventricular preload. In term babies with heart failure and pulmonary hypertension, higher pressures are found, so a value below 3 mmHg in this situation may also indicate inadequate preload. Thus, while values of 2-6 mmHg are 'normal' in clinically stable preterm babies requiring ventilation for hyaline membrane disease, such values may indicate inadequate preload in the bigger baby with pulmonary hypertension.

(2) Central venous pressure values over 7 mmHg usually indicate myocardial dysfunction and/or pulmonary hypertension, but the measured value may be “artificially” high due to raised intrathoracic pressure, secondary to pneumothorax or overventilation of compliant lungs (this may be an important factor when therapeutic alkalosis is induced by hyperventilation). Central venous pressure is related, not only to the volume of intravascular blood within the venous system and the function of the cardiac pump, but also to intrathoracic pressure (Siassi et al, 1980; Maayan et al, 1986; Musewe et al, 1990)

(3) The haemodynamically stable babies with congenital heart disease, ventilated for catheterisation, most of whom were at term, had mean CVP values between 4 and 8 mmHg. Babies with circulatory failure secondary to aortic coarctation, manifesting as a metabolic acidosis, had higher CVP values (over 7mmHg) than those who did not.

9.5 Summary

(1) In preterm babies ventilated for hyaline membrane disease, right atrial pressure should be expected to be higher than zero and usually within a fairly narrow range, of about 2-6 mmHg provided the babies are not suffering from marked right or left ventricular failure or from a pneumothorax. Babies with these latter features, and larger term babies can be expected to have marginally higher values on average.

(2) Thus 3-4 mmHg may be a reasonable estimate of average right atrial pressure in the ventilated premature neonate. Adding 2 mmHg for the anticipated marginal underestimation of the true pressure drop, (from the validation study in chapter 7), 5 mmHg seems to be a reasonable average allowance for right atrial pressure in determining systolic pulmonary arterial pressure from the peak velocity of tricuspid regurgitation in this group of patients.

9.6 Addendum

(1) Central venous pressure values provide unique haemodynamic information, which is of particular importance to the very sick neonate. A message from this review is that it should, perhaps, be measured more frequently.
There is experimental evidence that the cardiovascular system in the human neonate is much less able to cope with hypervolaemic conditions than the adult (Wallgren et al. 1964). Hypovolaemic shock, possibly an important factor in the development of respiratory distress (Moss et al. 1963; Dobbs et al. 1961) is common following perinatal asphyxia or preterm delivery. Early cord clamping can deprive the baby of over 40% of its circulating volume (Jegier et al. 1963). Hypotension is known to be associated with an increased risk of intraventricular haemorrhage (Mial-Alen et al., 1987) and an early increase in preload by colloid administration may reduce the risk (Beverly et al., 1985). In the assessment of all these dramatic haemodynamic changes and interventions, it is remarkable how infrequently CVP is measured.

The principal use of CVP measurement is in trend analysis, but interpretation of initial or isolated measurements in the ventilated neonate assumes special importance during an episode of cardiorespiratory collapse. This review suggests that single measurements can be of value, but that correct interpretation of the result will depend on the context in which it is made.
Table 9.1  Central venous pressure measurements (mmHg) from 49 neonates with congenital heart disease, whilst ventilated and under general anaesthesia.

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>No.</th>
<th>'a' wave</th>
<th>'v' wave</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent fetal circulation</td>
<td>3</td>
<td>12 (6.0)</td>
<td>10 (6.0)</td>
<td>8.3 (3.1)</td>
</tr>
<tr>
<td>Obstructive left heart lesions~</td>
<td>15</td>
<td>11.3 (4.2)</td>
<td>10.6 (4.6)</td>
<td>8.9 (3.2)*</td>
</tr>
<tr>
<td>Remainder</td>
<td>31</td>
<td>8.0 (3.5)</td>
<td>6.4 (3.6)</td>
<td>5.2 (2.5)*</td>
</tr>
<tr>
<td>Whole group</td>
<td>49</td>
<td>9.3 (4.3)</td>
<td>7.7 (4.4)</td>
<td>6.5 (3.2)</td>
</tr>
</tbody>
</table>

* p<0.001, comparing groups 2 and 3.

'a-wave' represents atrial contraction, 'v-wave' represents venous filling of the right atrium.

~coarctation (12), aortic stenosis (1), hypoplastic left heart syndrome(2).
| Range Mean | No. (%) | Outcome | Gestation Birth Weight Diagnosis
---|---|---|---
| 2-9 | 2 | Alive, well | Preterm, meconium aspiration, RDS, renal failure, NEC, and pneumonia
| 10-13 | 1 | Alive, well | Preterm, meconium aspiration, RDS, renal failure, NEC, and pneumonia
| 14-17 | 1 | Alive, well | Preterm, meconium aspiration, RDS, renal failure, NEC, and pneumonia
| 18-21 | 2 | Alive, well | Preterm, meconium aspiration, RDS, renal failure, NEC, and pneumonia
| 22-25 | 1 | Alive, well | Preterm, meconium aspiration, RDS, renal failure, NEC, and pneumonia
| 26-29 | 3 | Alive, well | Preterm, meconium aspiration, RDS, renal failure, NEC, and pneumonia
| 30-33 | 1 | Alive, well | Preterm, meconium aspiration, RDS, renal failure, NEC, and pneumonia
| 34-37 | 1 | Alive, well | Preterm, meconium aspiration, RDS, renal failure, NEC, and pneumonia
| 38-41 | 2 | Alive, well | Preterm, meconium aspiration, RDS, renal failure, NEC, and pneumonia
| 42-45 | 1 | Alive, well | Preterm, meconium aspiration, RDS, renal failure, NEC, and pneumonia

Table 4.2: Central venous pressure in 13 neonates ventilated for respiratory failure.
e. THREE episodes of hypotension/circulatory collapse, all with pulmonary hemorrhage; CVP fell to zero. Clinical findings included hemodynamic instability, evidence of severe right ventricular failure.

f. CTV pressures are stable on inotropic support.

C. Two recordings at zero with clinical evidence of hypovolemia.

C. Two recordings at zero with clinical improvement.

b. Three recordings at zero with poor peripheral perfusion and mild hypotension at the time of an intraarterial bleed.

a. One record of zero CVP coincided with circulatory collapse and

Footnotes to Table 9.2
Chapter 10: Pulmonary and systemic arterial pressure in hyaline membrane disease

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   1. Ductal patency
   2. Flow patterns
   3. Aorta-pulmonary artery pressure difference
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Chapter 10: Pulmonary and systemic arterial pressure in hyaline membrane disease

10.1 Introduction

The main aim of this chapter was to obtain serial measurements of pulmonary arterial pressure by non-invasive means in babies ventilated for hyaline membrane disease, relate values to concurrent systemic arterial pressure, and correlate results with severity of disease, blood gas status and gestational age during the first ten days of life.

10.2 Study group

(1) The study group consisted of 33 ventilator dependent neonates diagnosed clinically and radiographically as having hyaline membrane disease in the two regional neonatal units in Newcastle. Babies were of 25-39 weeks gestation (median 30.5). Birth weight was between 892g and 3020g (median 1651g). Three babies died at 12 hours, 9 days and 11 days respectively. None of the babies received exogenous surfactant.

(2) The results were compared with those obtained in the first 72 hours of life from the 17 healthy premature neonates first presented in chapter 8, who were unventilated, not oxygen dependent and had no history of perinatal asphyxia. Birth weight in this group was between 1143g and 2290g (median 1608g) and gestational age was between 28 and 35 weeks (median 32 weeks). Parental permission for serial study was obtained in all cases and ethical approval was granted by the District Ethics Committee.

10.3 Methods

(1) Examinations were performed by a single observer (the author) when the babies were clinically stable, starting during the first 24 hours of life, three or four times in the first 5 days of life and intermittently until successful extubation. At the first examination normal cardiac anatomy was confirmed with cross-sectional and pulsed Doppler echocardiography. At all examinations a detailed Doppler echocardiographic study was done using one of two Hewlett-Packard ultrasound machines. The maximal velocity of the jet of tricuspid regurgitation was measured as previously described. Ductal patency was established, and flow velocities recorded, using a combination of cross-sectional echocardiography, pulsed and continuous wave Doppler. Detailed clinical status was recorded on the data sheets. The arterial/alveolar (a/A) oxygen tension ratio was calculated as described by Tarnow-Mordi et al (1990) from current arterial or transcutaneous oxygen tension, blood gas data and inspired oxygen fraction, and was used as a measure of disease severity. Systolic blood pressure was determined by indwelling
arterial line or Doppler sphygmomanometry.

(2) In determining systolic pulmonary arterial pressure, 5 mmHg was added to the calculated RV-RA pressure drop in babies ventilated at the time of the examination; no addition was made in unventilated babies. This 5 mmHg allowance was made when presenting the results shown in figures 10.2 and 10.3 and tables 10.3 and 10.5. However, because this allowance can only be approximate, and to permit direct comparison between the ill and healthy babies, the actual observed pressure difference across the tricuspid valve is presented in table 10.2.

(3) The pattern of ductal flow during the cardiac cycle was observed and recorded along with the peak left to right flow velocity. The maximal pressure difference between the systemic and pulmonary circulations was also assessed by applying the Bernoulli equation to the maximal left to right flow velocity across the duct. (The accuracy of this technique is questionable (Houston et al, 1989) and is investigated further in chapter 13).

10.4 Results

10.4.1 Incidence of tricuspid regurgitation

(1) The incidence of measurable tricuspid regurgitation (where the peak velocity is seen clearly) in the healthy preterm babies and the babies with hyaline membrane disease is shown in table 10.1. The incidence was significantly higher in babies with hyaline membrane disease throughout the first 72 hours. After this, none of the healthy babies was found to have measurable tricuspid regurgitation, and the incidence in babies with hyaline membrane disease began to fall, although it was possible to follow the course of pulmonary arterial pressure in half of the babies requiring oxygen for up to ten days.

(2) The examination procedure was well tolerated by even the sickest babies as long as they were kept warm. On some occasions measurement of the peak velocity of tricuspid regurgitation was hampered by the presence of a pneumothorax, the small amounts of interposing air being impervious to ultrasound. In one baby, with a pneumothorax on day one, no measurements were obtainable despite some Doppler evidence of tricuspid regurgitation.

(3) After day 6 (144 hours), fewer babies were examined because some were extubated and well. Therefore the values derived from those babies who were studied may not be descriptive of the group as a whole. If none of the babies with hyaline membrane disease who were well by day 9-10 (193-240 hours) had measurable tricuspid regurgitation, then the true incidence of regurgitation at this time would be 35% (see table 10.1).
10.4.2 Right ventricular and systemic arterial pressures

Measurements of systemic blood pressure, and the RV-RA pressure difference are shown in table 10.2. Over the first 24 hours, systolic blood pressure rose by a mean of 7 mmHg in the healthy babies. A significant rise was not seen until day four in the ill babies. The RV-RA pressure difference was similar in the two groups in first 12 hours, but then fell rapidly in the healthy babies, and more slowly in the babies with hyaline membrane disease. A comparison between the ill and healthy babies is shown in figure 10.1, where the RV-RA pressure difference is expressed as a ratio of systemic blood pressure.

10.4.3 Ductal flow

10.4.3.1 Ductal patency

Ductal patency was prolonged in hyaline membrane disease. By day 4, all but one of the healthy premature babies had a closed duct, while in the diseased group it was still patent in 24 of 32 (75%). Only two of these 24 babies (8%) had a clinically audible ductal murmur.

10.4.3.2 Flow patterns

The incidence of bidirectional flow (indicating balanced pulmonary and systemic arterial pressures) was higher in the ill babies at all ages. The difference between the groups was most marked at 13-36 hours when 53% of the babies with hyaline membrane disease had a patent duct with bidirectional flow, while all the healthy babies with a patent duct had pure left to right flow.

10.4.3.3 Aorto-pulmonary pressure difference

The derived maximal pressure difference is shown for each age group in table 10.4. Comparing babies with hyaline membrane disease with well babies, values are similar in the first 12 hours but become strikingly different after 12 hours. This confirms the rapid fall in pulmonary arterial pressure in relation to systemic pressure in healthy babies, and a slower fall in babies with hyaline membrane disease.

10.4.3.4 Comparison of ductal flow patterns with arterial pressure ratio.

The pulmonary : systemic arterial pressure ratio was compared with concurrent ductal flow patterns. There were 42 examinations with bidirectional flow and measurable tricuspid regurgitation. With no allowance for right atrial pressure the mean ratio (and its standard deviation) was 0.87 (0.17):1. Allowing 5 mmHg for right atrial pressure in the ventilated...
Figure 10.1

RV-RA pressure difference as a ratio of systemic arterial pressure: Hyaline membrane disease v healthy preterms

(Age (hours))

(RV-RA):BP ratio

Healthy preterm

HMD
babies the ratio was 0.97 (0.18) :1. Since the pressures can be expected to be approximately equal, this analysis supports the use of a 5 mmHg constant for right atrial pressure. Therefore, for the rest of the analysis, this constant has been added when determining systolic pulmonary arterial pressure during the time period for which the babies were ventilated. The results are summarised in table 10.3.

10.4.4. Factors influencing pulmonary and systemic arterial pressure.

(1) Multiple linear regression analysis was performed to determine which factors most influenced systemic and pulmonary arterial pressures, and their ratio. If a baby had more than one measurement within a single time band, one value was selected for analysis at random; (this process was utilised for all the comparative analyses reported in this chapter). The predictive factors tested in the analysis were: age, arterial alveolar (a/A) oxygen tension ratio, inspired oxygen fraction, mean airway pressure, transcutaneous pO2, and pH and pCO2 from the most recent blood gas.

A. Pulmonary : systemic arterial pressure ratio.

(2) The regression model only explained 48 % of the variability of the pulmonary : systemic arterial pressure ratio. Clearly factors other than those included in the analysis were influencing the ratio, including random variation. There was some evidence of a negative correlation with inspired oxygen fraction, and a positive correlation with pCO2. However the most significant correlation was with age (negative) and with mean airway pressure (positive). Therefore the downward trend in the pulmonary : systemic arterial pressure ratio persisted with increasing age even with continuing severe respiratory distress. A higher mean airway pressure was associated with a higher pulmonary : systemic arterial pressure ratio. This relationship was mediated by low systemic arterial pressure and not high pulmonary arterial pressure.

B. Systemic arterial pressure.

(3) Systemic arterial pressure correlated negatively with mean airway pressure and positively with age.

C. Pulmonary arterial pressure.

(4) The regression model explained less than 20% of the variability of pulmonary arterial pressure. There was a strong negative correlation with age, and a weaker correlation with pCO2.
(5) None of these variables correlated with the a/A oxygen tension ratio.

(6) Utilising the serial measurements to determine the effect of disease severity, paired t tests were done comparing the final low value for the arterial pressure ratio with the immediate previous higher value in each baby. There was no consistent correlation with a fall in the ratio with any of the selected predictive factors.

10.4.5 Individual variability

(1) Serial values for the pulmonary : systemic arterial pressure ratio for the whole group are plotted in figure 10.2a. All the babies with hyaline membrane disease in whom three or more measurements were obtained are shown. The figure demonstrates considerable variability and a downward trend with age. In figure 10.2b the values derived from the healthy babies are superimposed, showing the dramatic difference between the groups despite this variability.

(2) Examination of the serial plot (fig 10.2a) shows six babies with a sharp rise in the ratio at around 48 hours of age, against the trend of the whole group. These are highlighted in figure 10.2c. Two babies, represented by the open symbols, were remarkable in having a very low ratio initially, accompanied by pure left-to-right ductal flow, then rising to a much higher value, with bidirectional ductal flow. They were two mature babies (34 and 37 weeks gestation) who were initially unventilated with relatively mild hyaline membrane disease. They both developed worsening respiratory distress, requiring a brief period of ventilation on days three and four. The three highest values in figure 10.2c were associated with systemic hypotension, two, as indicated, following a recently treated pneumothorax, and the third with myocardial dysfunction secondary to myocardial ischaemia. The sixth baby was the 39 week gestation baby, who was felt clinically to have an element of persistent fetal circulation, and was receiving inotropic support. In these six cases the pulmonary : systemic arterial pressure ratio was closely related to oxygen requirements.

(3) Two other babies (of 32 and 36 weeks gestation) were also unventilated until the third day but had high initial pulmonary arterial pressure values. In one of these babies the pressure value fell soon after ventilation was started while in the other it did not.

(4) One baby (36 weeks gestation, 2760 g) received tolazoline at 22 hours of age. Arterial pH was 7.34 and pCO₂ 6.1 KPa. Arterial oxygen saturation rose from 78% to 90%. Derived pulmonary arterial systolic pressure was 66 mmHg and fell only marginally, to 60 mmHg. The pulmonary : systemic arterial pressure ratio was elevated (1.4:1), and is the earliest peak in figure 3a; the ratio had risen from 1.2:1 over the 2 hours prior to treatment.
Legend for figure 10.2

Serial measurements of the pulmonary : systemic arterial pressure ratio in babies with hyaline membrane disease. Systolic pulmonary arterial pressure is derived from maximal tricuspid regurgitant velocity, (adding 5 mmHg for right atrial pressure in ventilated babies). Only babies with three or more values are included. Points of measurement are excluded for clarity but are indicated by angulation changes.

a. The whole group with hyaline membrane disease. The ratios show considerable variability and a downward trend with age.

b. All the values from the healthy preterm babies (open triangles, dark lines) are superimposed on those from the babies with hyaline membrane disease. The rate of fall in the pulmonary to systemic arterial pressure ratio is much faster in the healthy babies.

c. In six babies with hyaline membrane disease, the ratio rose between the second and third day of life, against the trend (see text).

ptx, recent pneumothorax.
(5) After 48 hours, no babies with uncomplicated hyaline membrane disease (ie. no pneumothorax or myocardial dysfunction) had a pulmonary : systemic arterial pressure ratio over 1.0:1.

10.4.6. Gestational age

(1) Using the arterial pressure ratio, rather than pulmonary arterial pressure alone, it was possible to compare babies of differing size and maturity directly. Babies of less than 30 weeks (mean 27.6) were compared with those of over 32 weeks gestation (mean 35.7). The serial values are plotted in figure 10.3. The course over time is very varied amongst the larger babies, but remarkably consistent in the more premature babies. Since the ratio may be transiently raised by pneumothorax, these values were excluded from the comparison presented here and in table 10.5. Pulmonary arterial pressure is significantly lower in the babies of lower gestation. The pulmonary : systemic arterial pressure ratio is initially similar, but is significantly lower in the more premature babies at 37 -72 hours; due mostly to their larger rise in systemic arterial pressure between the two time periods.

(2) There were no significant differences in the a / A oxygen tension ratio or inspired oxygen levels between the two groups. However, these are small numbers, and it may be important that these figures show a trend suggesting that the more mature babies had worsening respiratory distress between the first and second age band.

10.5. Discussion

(1) These two methods of assessing pulmonary arterial pressure are new to neonatology, so are the results reliable? It is possible to underestimate peak flow velocities if the Doppler probe is not directly in line with flow, so while overestimation is unlikely, some of the values could have underestimated the true pressure. However, this seems unlikely from the evidence of the validatory study presented in chapter 7 and other validatory studies (discussed in section 3.3.4). In the study of healthy babies in chapter 8, bidirectional ductal flow was associated with a ratio of between 0.88:1 and 1.22:1 (mean 0.96:1), which would not suggest serious underestimation of pulmonary arterial pressure. Musewe et al (1990) found that, in neonates with respiratory distress, an allowance of 10 mmHg for right atrial pressure improved the correlation of pulmonary arterial systolic pressure values obtained simultaneously from tricuspid regurgitation and from ductal flow. 10 mmHg may be appropriate in large babies with asphyxia or persistent fetal circulation, but (on the evidence presented in chapter 9) seems too high for a preterm neonate with hyaline membrane disease. This high figure may therefore represent a tendency for the tricuspid regurgitant technique to underestimate pulmonary arterial pressure in the premature neonate. This is partly supported by the observation that some babies in the present study
A comparison of the way the pulmonary : systemic arterial pressure ratio changed with time:

a in eight babies > 32 weeks' gestation
b in seven babies < 30 weeks' gestation
had bidirectional ductal flow with pulmonary : systemic arterial pressure ratio below 0.8:1, even allowing 5 mmHg for right atrial pressure. It is, however, equally possible that the ductal flow method may slightly overestimate pulmonary arterial pressure. It would seem prudent therefore to combine these two methods where this is possible, and conclusions here are drawn using both of the methods. In observing trends within a subject, the allowance for right atrial pressure is less important, since this will change much less than arterial pressure.

(2) The most striking feature in this study is the marked difference between the healthy preterm babies and those with respiratory distress. Pulmonary hypertension is indeed a significant part of hyaline membrane disease. This finding is consistent with those of Halliday et al (1977) and Evans and Archer (1991) who used systolic time intervals to estimate pulmonary arterial pressure in hyaline membrane disease. The present study has shown that there is a delay in the normal postnatal fall in pulmonary arterial pressure and the normal post natal rise in systemic blood pressure. This is accompanied by persistent patency of the arterial duct. Even when the respiratory distress remains severe, the pulmonary : systemic arterial pressure ratio usually continues to fall, though at a much slower rate than in the healthy baby.

(3) In contrast with Halliday et al, this study and that of Evans and Archer, found no consistent relationship with disease severity, although there was a suggestion in this study that arterial pCO2 was important, and in Evans' study that pH had an influence. Oxygen levels in the pulmonary artery may also have influenced pulmonary arterial pressure because oxygen is known to be a potent pulmonary vasodilator (Dawes, 1968; Peckham and Fox, 1978; etc., see section 1.6.2) Oxygen saturation levels only varied over a fairly narrow range in most of the babies reported here, but the levels were almost always lower than those seen in the healthy preterm neonate (Poets et al, 1991). It would be necessary to undertake serial studies in individual babies, while varying oxygen saturation over a wider range, to demonstrate how much influence hypoxia had on the persistent pulmonary hypertension. Such a study was done by Halliday et al (1980) using m-mode echocardiography in babies with bronchopulmonary dysplasia, and a small study in hyaline membrane disease is reported later in this thesis, in chapter 17.

(4) The negative influence of mean airway pressure on systemic blood pressure was independent of disease severity and is presumably related to high intrathoracic pressure impeding venous return, and thereby reducing cardiac output (Furzan et al,1981; Maayan et al,1986). The high pulmonary : systemic arterial pressure ratio is thus partly maintained by ventilation itself.

(5) There was considerable temporal variability in both arterial pressures, and pneumothorax had a profound impact. It also appears that gestation is an important
factor. Less mature babies had lower absolute pulmonary arterial pressures and a steadier
fall in the pulmonary : systemic arterial pressure ratio over time. This latter feature may be
a chance finding, because of the small sample size, or it could be due to a genuine difference
in the disease at different gestations, or to management differences. In the classical disease
there is steadily worsening respiratory distress over the first two to three days, followed by
steady improvement. This was seen in the four relatively mature babies who were not
ventilated until they were about 48 hours old. In three of these babies, pulmonary arterial
pressure fell soon after ventilation, suggesting that it was higher at a time of alveolar
collapse. The less mature babies were all ventilated early, and structural lung immaturity
may be a further important ingredient of the disease in these babies.

(5) A spectrum of maladaptation of the transitional circulation to extra-uterine life was
described by Reimenschneider (1976) who presented 13 newborn babies who were cyanosed
in oxygen, without structural heart disease. There were three categories; pulmonary
hypertension with normal myocardial function and blood pressure, pulmonary hypertension
with decreased myocardial function, and systemic hypotension alone without marked
pulmonary hypertension. The present study suggests that these circulatory disturbances can
also occur without overt cyanosis and can be part of hyaline membrane disease (though
they will not usually present as a clinical problem). The observation that babies can be
clinically stable and acyanotic with pulmonary arterial pressure at systemic levels and a
patent duct suggests that despite pulmonary hypertension, pulmonary blood flow is
adequate. This distinction is important; merely having pulmonary hypertension does not
imply that it should be treated pharmacologically. Indeed, drugs such as tolazoline and
prostacyclin may cause systemic hypotension, (McIntosh and Walters, 1979) and therefore
cause clinical deterioration.

(6) The present analysis has concentrated on the pressure ratios seen in systole, but pure
right-to-left ductal shunting was never seen in any of the babies in this study. Therefore, it
can be inferred that, during diastole (which is longer than systole), pressure in the
pulmonary artery was always lower than systemic pressure, allowing a period of left-to-
right flow with each cardiac cycle. Furthermore, it is probably that right-to-left shunting
across the foramen ovale is at least as important in the development of persistent fetal
circulation (Gersony et al, 1984), and in this context, right ventricular diastolic dysfunction
may be as important as pulmonary arterial pressure. The method used by Halliday et al
(1977) to estimate pulmonary arterial pressure (the PEP/RVET ratio) is influenced by right
ventricular dysfunction, and this might explain why their values followed the severity of
hyaline membrane disease more closely.

(7) In conclusion, there is a spectrum of post-natal circulatory adaptation amongst babies
with hyaline membrane disease. At one extreme there are babies in whom the pulmonary :
systemic arterial pressure ratio is always relatively low, even with severe disease, and at the other extreme there are babies who have marked pulmonary hypertension, some of whom have problems related to persistent transitional circulation, even with relatively mild disease, and some of whom do not. The uniting feature of all of these babies with hyaline membrane disease is that post-natal circulatory adaptation is delayed.
Comparing babies with respiratory distress with healthy babies:

<table>
<thead>
<tr>
<th>No. examined</th>
<th>No. with respiratory distress</th>
<th>Mean age (hours)</th>
<th>Mean age (hours)</th>
<th>p-value</th>
</tr>
</thead>
</table>
| Healthy      | Healthy, trend                | Healthy, trend  | Healthy, trend  | Healthy,
|              |                               |                 |                 | trend   |
| 11 (69)      | 11                            | 11              | 221             | 0.005   |
| 1 (41)       | 21                            | 11              | 169             | 0.005   |
| 16 (57)      | 16                            | 24              | 119             | 0.005   |
| 0             | 17                            | 88              | 16              | 0.73    |
| 5 (31)       | 96                            | 44              | 24              | 0.005   |
| 8 (30)       | 96                            | 42              | 30              | 0.005   |
| 8 (33)       | 51                            | 6               | 12              | 0.012   |

Table 10.1: Incidence of respiraory distress measured on Doppler ultrasound in 33 babies with pterygium and 17 healthy premature babies.
The numbers examined at each age, and the proportion in whom right ventricular pressure could be derived from measurable BP, systolic blood pressure (SR-a), mean right ventricular to right atrial pressure difference.

Comparing babies with respiratory distress with the healthy babies: *not significant, p>0.05.

<table>
<thead>
<tr>
<th>Age range (months)</th>
<th>Healthy premature babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>3.8 (0.9)</td>
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</tbody>
</table>

Table 10.2. A comparison of systemic and right heart pressures in 33 babies with hyaline membrane disease and 17
Values are compared between distressed and healthy babies: *p<0.05, **p<0.0005

<table>
<thead>
<tr>
<th></th>
<th>193.0±14.4</th>
<th>145.1±22.1</th>
<th>119.3±13.7</th>
<th>115.0±12.3</th>
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</thead>
<tbody>
<tr>
<td>T3</td>
<td>2.0±1.1</td>
<td>1.7±0.9</td>
<td>1.2±0.8</td>
<td>1.1±0.7</td>
</tr>
<tr>
<td>%</td>
<td>0.1±0.1</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
</tr>
<tr>
<td>No. (N)</td>
<td>17 (10)</td>
<td>8 (4)</td>
<td>5 (3)</td>
<td>6 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean (Range)</th>
<th>Mean (Range)</th>
<th>Age examined (No. of cases)</th>
<th>Mean (Range)</th>
<th>Age examined (No. of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy premature infants with hyaline membrane disease</td>
<td>and 17 healthy premature babies.</td>
<td>and 13 healthy premature babies.</td>
<td>and 17 healthy premature babies.</td>
<td>and 13 healthy premature babies.</td>
<td>and 17 healthy premature babies.</td>
</tr>
<tr>
<td>Mean (10 cases)</td>
<td>16 (53)</td>
<td>30 (94)</td>
<td>23 (47)</td>
<td>20.5 (41)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Age range</td>
<td>0-12.0</td>
<td>0-13.0</td>
<td>0-13.0</td>
<td>0-12.0</td>
<td>0-13.0</td>
</tr>
</tbody>
</table>

Table 10.3 Ductal patent and Doppler flow characteristics from 33 babies with hyaline membrane disease...
Table 10.4 Corrected estimates of pulmonary arterial pressure (mean ± SD) in babies with hyaline membrane disease.

<table>
<thead>
<tr>
<th>Age (hours)</th>
<th>Systolic Pulmonary arterial pressure (mmHg)</th>
<th>Pulmonary:systemic arterial pressure ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>42.4 (9.2)</td>
<td>0.86 (0.16)</td>
</tr>
<tr>
<td>13-36</td>
<td>40.2 (7.1)</td>
<td>0.86 (0.18)</td>
</tr>
<tr>
<td>37-72</td>
<td>40.2 (7.3)</td>
<td>0.82 (0.19)</td>
</tr>
<tr>
<td>73-96</td>
<td>39.3 (8.9)</td>
<td>0.69 (0.13)</td>
</tr>
<tr>
<td>97-144</td>
<td>39.1 (6.2)</td>
<td>0.69 (0.14)</td>
</tr>
<tr>
<td>145-192</td>
<td>34.7 (5.2)</td>
<td>0.53 (0.12)</td>
</tr>
<tr>
<td>192-240</td>
<td>29.1 (6.1)</td>
<td>0.43 (0.11)</td>
</tr>
</tbody>
</table>

Data as in table 10.2, after allowing for an average right atrial pressure of 5 mmHg in babies ventilated at the time of examination.
<table>
<thead>
<tr>
<th></th>
<th>&lt; 30 weeks gestation</th>
<th>&gt; 32 weeks gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13-36h</td>
<td>37-72h</td>
</tr>
<tr>
<td>No. of observations</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Systemic arterial pressure (mmHg)</td>
<td>44.8 (7.6)</td>
<td>51.3 (8.7)</td>
</tr>
<tr>
<td>Pulmonary arterial pressure (mmHg)</td>
<td>37.0 (6.1)*</td>
<td>36.0 (6.4)*</td>
</tr>
<tr>
<td>Pulmonary:systemic pressure ratio</td>
<td>0.83:1(0.20)</td>
<td>0.70:1(0.11)*</td>
</tr>
<tr>
<td>FIO2</td>
<td>0.65 (0.19)</td>
<td>0.59 (0.19)</td>
</tr>
<tr>
<td>a/A ratio</td>
<td>0.15 (0.03)</td>
<td>0.19 (0.08)</td>
</tr>
</tbody>
</table>

All values are compared with more mature babies, *p<0.05, **p<0.005.
Chapter 11: Doppler echocardiographic evaluation of bronchopulmonary dysplasia

11.1 Introduction

11.2 Aims

11.3 Methods and study group

11.4 Results

1. Determination of pulmonary arterial pressure.
   1. Tricuspid regurgitation
   2. Ductal flow patterns
   3. TPV/RVET ratio

2. Other haemodynamic data.
   1. Patency of the arterial duct
   2. Heart murmurs
   3. Aortic and pulmonary stroke distance
   4. Diastolic atrioventricular valve flow.

11.5 Discussion

11.6 Summary

Tables

11.1 Summary of the clinical condition of 24 babies with bronchopulmonary dysplasia and their Doppler echocardiographic findings.
Chapter 11: Doppler echocardiographic evaluation of babies with bronchopulmonary dysplasia

11.1 Introduction

(1) Previous non-invasive studies of pulmonary arterial pressure in bronchopulmonary dysplasia (BPD) were reviewed in section 4.2. The PEP/RVET ratio was used mostly, with its inherent limitations (which are discussed in more detail in sections 3.2. and 4.2.1.6). The fall in incidence of measurable tricuspid regurgitation during recovery from hyaline membrane disease seen in the preceding chapter might suggest that tricuspid regurgitation will be less prevalent amongst babies with bronchopulmonary dysplasia. The feasibility of methods other than the PEP/RVET ratio have not been evaluated formally, although White and Houston (1990), in a report of nine babies, found measurable tricuspid regurgitation in six babies (67%) allowing serial estimation of pulmonary arterial pressure. Previous studies have also not assessed the clinical value of more detailed echocardiography in these babies.

11.2 Aims

(1) The main aim of this study was therefore to evaluate the feasibility of estimating pulmonary arterial pressure by measuring peak velocity of tricuspid regurgitation and application of the modified Bernoulli equation, or analysis of ductal flow, in babies with bronchopulmonary dysplasia.

(2) A secondary aim, of less direct relevance to this thesis, was assess the value of a single, detailed echocardiographic assessment of babies with BPD.

11.3 Methods and study group

(1) 23 premature babies with BPD over 28 days of age, and one baby aged 23 days, were examined in the standard manner described earlier. Systolic blood pressure was measured by Doppler sphygmomanometry, and the latest blood gas analysis (usually a capillary sample) was recorded. Each baby had a clinical and radiological diagnosis of BPD, and was receiving mechanical ventilation and/or supplementary oxygen.

(2) The clinical details are listed in table 11.1, in descending order of FiO2. Gestation ranged from 23 to 32 weeks, and birth weight ranged from 660g to 1380g. One baby was breathing air whilst on mechanical ventilation, but all of the others were receiving between supplementary oxygen; all but six were receiving ventilatory support. Eleven babies had particularly severe disease, requiring over 60% oxygen.
Eighteen of the babies were examined purely because of the present study, but in six babies there were pre-existing clinical indications for cardiological evaluation. Two babies (ID numbers 2 and 21) were referred to the regional cardiothoracic centre for ligation of the arterial duct, but were found to have a closed arterial duct on echocardiography. Both of these babies had cardiomegally on chest X-ray, a loud systolic heart murmur (grade 3/6) in the pulmonary area, and a gallop rhythm. They were unequivocally in heart failure. Both of these babies were light for dates, but baby 21 was remarkably growth retarded, born weighing 688g at 32 weeks gestation. Four other babies had a soft systolic heart murmur in the pulmonary area, and a patent arterial duct was considered possible.

11.4 Results

(1) The results are listed in table 11.1. Values of particular interest are highlighted in bold type.

(2) The results section is divided into two parts: firstly, those observations directly related to the non-invasive determination of pulmonary arterial pressure, and secondly those relating to the rest of the haemodynamic assessment.

11.4.1 Determination of pulmonary arterial pressure

11.4.1.1 Tricuspid regurgitation

Only four of these babies (17%) had measurable tricuspid regurgitation; three had severe disease; baby 8 was in overt right heart failure, and was intubated and ventilated shortly after the examination. The RV-RA pressure drop ranged from 41 to 55 mmHg, and the calculated pulmonary : systemic systolic arterial pressure ratio was 0.46:1 to 0.99:1. Some of the other babies had detectable regurgitation, usually the velocity of the detected signal was greater than 3 m/s (36mmHg), but the systolic peak was not recordable. One baby (subject 1) had an indwelling pulmonary arterial pressure line recording supra-systemic pressure, but tricuspid regurgitation was barely detectable and not pansystolic.

11.4.1.2 Ductal patency

(1) Four babies had a patent arterial duct. In three it looked small, but in one (subject 6) it was of moderate size. Subject 6 had bidirectional ductal flow, consistent with the pulmonary : systemic arterial pressure ratio of 0.92:1. Subject 24 had a Pa:Ao pressure ratio of 0.67:1 and pure left-to-right flow highest in mid systole and lowest at end diastole ("type 5") and subject 19 had low velocity L-R flow, lowest in systole (type 4). Subject 15 had high velocity continuous L-R flow (type 6) suggesting a lower pulmonary arterial
pressure; this baby was receiving indomethacin.

(2) Combining the TR and ductal flow measurements, it was therefore possible to obtain useful information about pulmonary arterial pressure in only six babies (25%).

11.4.1.3 TPV/RVET ratio

(1) The TPV/RVET ratio was recorded in 19 of the 24 babies. Four of the earlier examinations were incomplete and the ratio was not measured, but in two babies with patent arterial duct, subjects 4 and 24, turbulence in the pulmonary artery prevented reliable measurement of the systolic time intervals. The values obtained were compared with the 'normal range' from the data of Evans and Archer (1990) in healthy premature babies after the fourth day of life (0.34 to 0.41). The range of values in the present study was 0.24 to 0.59. The values less than 0.34 are highlighted in table 11.1.

(2) Interpretation of these results is difficult because hugely different pulmonary arterial pressures have produced the same TPV/RVET ratio. Subject 3, with a directly measured systolic pulmonary arterial pressure of 100 mmHg, had a TPV/RVET ratio of 0.30, whereas subjects 20 and 24 had a TR-determined pulmonary arterial pressures of 60 and 50 (allowing 5 mmHg for right atrial pressure), and had ratios of 0.26 and 0.33 respectively. However, these three babies all had pulmonary hypertension, and all had low TPV/RVET ratios. Furthermore, all of the babies with a very high capillary CO$\text{2}_2$ (>11 KPa), when a degree of pulmonary hypertension can be expected, had low ratios (<0.34).

(3) The relationship of TPV/RVET ratio with capillary CO$\text{2}_2$ is plotted in figure 11.1. Some babies with CO$\text{2}_2$ values in the lower range also had low TPV/RVET ratios.

11.4.2. Other haemodynamic data.

11.4.2.1. Patency of the arterial duct

(1) Four babies had a patent duct. In subjects 6 and 19 this was an entirely unexpected finding. In subject 6 there was evidence of a considerable left-to-right shunt, with an enlarged left atrium and high aortic stroke distance (representing a left ventricular high stroke volume). The duct was surgically ligated, and the baby made slow but steady improvement after this. Subject 19 had previously been treated with indomethacin on day 5. There was no evidence of a significant left-to-right shunt, no treatment was given, and he made a full recovery with later spontaneous ductal closure. Baby 24 had clinical evidence of a considerable L-R ductal shunt which was confirmed by the echocardiographic findings,
Figure 11.1
Bronchopulmonary dysplasia:
Capillary CO2 -v- TPV/RVET ratio

[Graph showing the relationship between capillary CO2 and TPV/RVET ratio with markers for \( FIO2 > 0.55 \) and \( FIO2 < 0.55 \).]
and the duct was surgically ligated. Baby 15 had received two doses of indomethacin prior to this scan; there was no murmur at the time of examination, and the duct was small.

11.4.2.2. Heart murmurs and cardiac failure

(1) Five other babies had systolic murmurs in the pulmonary area, but did not have a patent duct. In three (subjects 2, 16 and 21) the attending consultant neonatologists were convinced that patent arterial duct was to blame. Two of these babies, mentioned earlier, (2 and 21) were in overt cardiac failure and had been referred for surgical ligation. The echocardiographic features were striking in these babies, particularly in subject 21. Both had a large patent oval foramen, with torrential left-to-right flow across it recorded with colour flow mapping. Both babies had very high right and left ventricular outputs (represented by high stroke distances in table 11.1) and in baby 21 they were hugely elevated. The aortic and pulmonary valves were of average size and showed no evidence of stenosis to explain the high velocities. Arterio-venous fistulae were considered as a possible cause, but cerebral and abdominal ultrasound examinations were normal. Colour flow mapping did not reveal any major aorto-pulmonary collaterals. In baby 21, a high velocity (2.5 m/s) was recorded at the origin of the left pulmonary artery, and was noted as a possible cause of the pulmonary flow murmur. Both babies returned to their referring hospital, but neither baby was ever successfully extubated and both eventually died. Post mortems revealed no anatomical cause for the high cardiac output.

11.4.2.3. Left and right ventricular stroke distance

(1) The babies with high stroke distances are discussed above. However, since a high pulmonary vascular resistance might be expected to produce a low pulmonary flow, low pulmonary and aortic stroke distances might be expected in the severe cases. This is certainly not the case, although subject 1, with preterminal disease and suprasystemic pulmonary arterial pressure, had the lowest pulmonary stroke distance of the group (5.5cm).

11.4.2.4. Diastolic flow patterns at the atrio-ventricular valves

(1) All but five of the 17 babies in whom transmitral flow was recorded, had an E:A ratio less than 1.0:1. Of the three babies with a ratio >1.0:1, two had a patent duct with left atrial dilation, and the other was baby 21, who had gross left atrial and left ventricular dilatation. (As mentioned in a previous section, these factors can 'normalise' the E:A ratio in the presence of abnormal diastolic ventricular function (Myreng et al, 1990).) Three babies had no E peak at all.
Trans-tricuspid valve flow was recorded in the same 17 babies. Eight babies had a single A peak, and in all the rest the ratio was 1.0:1 or less.

11.5. Discussion

(1) This study was primarily a feasibility study of the use of the TR measurement technique in bronchopulmonary dysplasia, and the clear conclusion is that it is of limited use in this patient group. Tricuspid regurgitation is not usually present in sufficient quantity to generate a measurable velocity. However, with hindsight, by noting the highest recordable velocity of a detected TR jet that is not pansystolic, a 'minimum' RV-RA pressure drop could, theoretically, have been estimated. This practice might help detect pulmonary hypertension when the measured jet is of high velocity, but, of course, could not exclude it if the jet were of low velocity.

(2) Part of the reason for the low incidence of measurable tricuspid regurgitation probably lies in technical difficulties with this group of patients. The hyperinflated lungs make any echocardiographic assessment difficult, and the babies tended to be rather irritable, their chest and body movements making it difficult to align consistently with any TR jet. Colour Doppler was only available in two patients and this, particularly with in-line continuous wave Doppler, may well be helpful in future studies, and improve the feasibility of measuring the TR jet when it is present. Even allowing for this, the author has obtained considerable experience at measuring TR in small babies, so it does seem likely that this measurement technique will be of value only in a minority of babies with BPD. It seems that the tricuspid valve of newborn babies is remarkably competent, even in the presence of pulmonary hypertension, after recovery from hyaline membrane disease.

(3) The TPV/RVET ratio may find a place in serial analysis of babies with BPD, (unless there is turbulence in the pulmonary artery from a patent duct) though this study has not attempted to address this issue. Newth et al (1984) demonstrated that the PEP/RVET ratio was unreliable in detecting pulmonary hypertension in babies with BPD. This question, with regard to the TPV/RVET ratio, cannot be addressed here, because there are two few estimates of pulmonary arterial pressure from TR. However TPV/RVET ratios were not linked consistently with disease severity. While high values (>0.40) were not present with marked CO₂ retention, the whole range of values occurred in babies with relatively mild disease, in whom it would be very surprising to find severe pulmonary arterial hypertension.

(4) It is a shame that the PEP/RVET ratio was not measured in the majority of babies, (because an ECG was not used routinely). It would have been interesting to compare results with earlier studies, and with concurrent estimates of systolic pulmonary arterial pressure.
from TR. However, this was not an aim of this part of the thesis.

(5) The variety of other interesting, and sometimes unexpected echocardiographic findings, would suggest that echocardiographic assessment should be undertaken at intervals in babies with BPD. Of particular importance was the discovery of a clinically silent patent arterial duct with a considerable left-to-right shunt. Whether or not stopping such a shunt is of help to the baby is a separate, and difficult issue to resolve, but since left-to-right ductal shunting decreases pulmonary compliance (Naulty et al, 1978) ductal closure should, theoretically, be beneficial under these circumstances, provided the procedure can be tolerated.

(6) Evidence from this study suggests that pulmonary murmurs, in the presence of high output cardiac failure and cardiomegally, can occasionally deceive even experienced clinicians into the incorrect diagnosis of L-R ductal shunting. One wonders if this is a frequent occurrence, and if so, how many babies in the past have received indomethacin (or even ductal ligation) unnecessarily.

(7) The two babies with high output cardiac failure and a large left-to-right atrial shunt, are most interesting and puzzling. Why should the patent oval foramen apparently be so haemodynamically important in these babies and not in others? Perhaps poor left ventricular compliance (in diastole), a potential consequence of right ventricular hypertension, encourages left-to-right flow, just as the reverse happens with persistent transitional circulation (Gersony, 1984). This is supported by the reversal of the normal E:A ratio at the mitral valve seen in the majority of the whole group. Furthermore, both of these babies were growth retarded, and Siassi (1988) has suggested that left ventricular dysfunction may be important in growth retarded babies with respiratory distress.

11.6

(1) In summary, pulmonary arterial pressure cannot be accurately determined non-invasively in the majority of babies with BPD, because the majority have neither measurable tricuspid regurgitation nor a patent arterial duct. However, a high TPV/RVET ratio (>0.45) probably excludes severe pulmonary hypertension in this group. The methods evaluated in this study are therefore no more useful than the PEP/RVET ratio evaluated by Halliday et al (1980). The feasibility of measurement of TR might be improved by the use of colour Doppler and in-line continuous wave Doppler ultrasound, and possibly also by the judicious use of sedation.

(2) Detailed echocardiographic assessment was clinically helpful by revealing a clinically silent left-to-right ductal shunt, and two babies with high output heart failure and left-to-
right interatrial shunting.

(3) Diastolic flow across the mitral valve suggests that babies with BPD have diastolic left ventricular dysfunction, possibly as a consequence of right ventricular dominance.

(4) While echocardiography cannot accurately determine pulmonary arterial pressure in the majority of babies with BPD, it can reveal other useful haemodynamic information not available by other means. This study suggests that echocardiographic assessment should be part of the routine management of babies with BPD, at least to detect clinically silent ductal shunting.
Table 11.1: Echocardiographic study of 24 babies with bronchopulmonary dysplasia: Subjects and results.
Chapter 12: Interpretation of pattern and velocity of ductal flow - an introduction to chapters 13 and 14.

(1) The work of Musewe et al (1987), Hiraishi et al (1987) and Houston et al (1989), discussed earlier in section 3.4, demonstrated the relationship of ductal flow patterns to pulmonary arterial pressure, measured invasively in children with congenital heart disease. Musewe et al (1990) also showed close correlation between pulmonary arterial pressure derived by applying the modified Bernoulli equation to peak TR velocity and to ductal flow velocities (subtracting the derived pressure drop from systemic arterial pressure) in neonates. If ductal flow velocities do truly reflect the gradient between the pulmonary artery and the aorta, they can provide information about pulmonary arterial pressure throughout the cardiac cycle, whereas TR only provides the peak systolic pressure. Houston et al suggested application of the modified Bernoulli equation to velocity of ductal flow velocity was not always reliable, whereas Musewe et al have been more confident of the value of this technique. Ductal flow patterns were correlated with TR-derived pulmonary arterial pressures in chapters 8 and 10, but this section attempts a more extensive analysis.

(2) There has been no attempt previously to study the effect of the quantity of ductal shunting upon the pattern of ductal flow through the cardiac cycle in the newborn. Does a baby with a large left-to-right ductal shunt have a different ductal flow pattern from one with a small shunt?

(3) Chapter 13 studies how ductal flow patterns and velocities relate to pulmonary arterial systolic pressure derived from tricuspid regurgitation, the pulmonary to systemic arterial pressure difference and the pulmonary : systemic arterial pressure ratio.

(4) Chapter 14 studies how ductal flow patterns and velocities relate to quantity of left-to-right ductal shunt assessed by the left atrial to aortic root (LA: Ao) ratio and left ventricular output, including a longitudinal study of the effect of ductal constriction on the pattern of ductal flow.

Methods and study group

(1) A cross-sectional study of the echocardiographic data base was carried out in chapters 13, 14 (and 15) such that 741 scans were reviewed from 203 babies in the first 28 days of life. Most were from the longitudinal studies of normal healthy babies and of those with hyaline membrane disease presented earlier in chapters 8 and 10, but other babies were examined to assess ductal shunting or ventricular function, and some babies had persistent transitional circulation (and are presented in more detail in chapter 18). The number of studies from each group is summarised in the table overleaf.
Table 12.1. Number of babies and scans in the database from babies less than 29 days of age.

<table>
<thead>
<tr>
<th></th>
<th>preterm</th>
<th>term</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>well</td>
<td>resp failure*</td>
<td>well</td>
</tr>
<tr>
<td>No. Babies</td>
<td>22</td>
<td>119</td>
<td>38</td>
</tr>
<tr>
<td>No. Scans</td>
<td>72</td>
<td>500</td>
<td>94</td>
</tr>
</tbody>
</table>

* All of these babies had neonatal respiratory failure, mostly due to hyaline membrane disease. Some preterm babies were ventilated for prematurity. Most of the term babies had suffered perinatal asphyxia, and are presented in more detail in chapter 18 on persistent transitional circulation.

(2) Amongst these 741 scans, there were 475 recordings of ductal flow from 192 of the 203 babies. Of these 475 recordings of ductal flow, 392 were from babies with respiratory failure and 83 were from healthy babies (see table 14.1). There were 223 examinations with concurrent measurements of peak velocity of tricuspid regurgitation, systemic arterial pressure and ductal flow.

(3) The statistical analysis uses the combined approach of linear regression and the method of Bland and Altman. Serial values within the same baby are compared using the paired t test.
Chapter 13: Relationship of pattern of ductal flow and flow velocities to systolic pulmonary: systemic arterial pressure ratio.

13.1 Study group

13.2 Results

1. Ductal flow patterns and the PA:Ao pressure ratio
2. Relationship of ductal flow patterns to aortic pressure wave-form.
3. Velocity of ductal flow
   A. Velocity at mid-systole (PDA MIDSYS)
   B. Peak left-to-right velocity (PDAMAX)
   C. Mean and minimum velocity.

13.3 Discussion

13.4 Summary

Figures are listed on the next page

Tables

Table 13.1 (inserted in the text, in section 13.2)

Shows the 10th, 50th and 90th centiles of estimated pulmonary: systemic systolic arterial pressure ratio for each pattern of ductal flow.

Table 13.2

This table lists the 85 studies of systemic arterial pressure, mid-systolic ductal flow velocity, pattern of ductal flow and estimated systolic pulmonary arterial pressure values derived from both peak velocity of tricuspid regurgitation (allowing 5 mmHg for right atrial pressure in ventilated babies), and from subtracting mid-systolic pressure gradient (derived from ductal flow) from systemic arterial pressure. It is the data used in the first part of chapter 13, and records a maximum of one value for each flow pattern from each baby, to a maximum of two values for each baby.

Table 13.3

The gestational age, mean airway pressure and FiO2 of the subjects generating the data for table 13.1.
Chapter 13: Relationship of pattern of ductal flow and flow velocities to systolic pulmonary : systemic arterial pressure ratio.

Figures

13.1 Relationship of ductal flow patterns to estimated systolic pulmonary:systemic arterial pressure ratio.

Recordings of aortic pressure and Doppler flow:
13.2 (plate 26) Bidirectional ductal flow (continuous wave Doppler).
13.3 (plate 27) Tricuspid regurgitation (peak velocity precedes peak aortic pressure).
13.4 (plate 25) Bidirectional ductal flow (pulsed wave Doppler).
13.5 (plate 29) Tricuspid regurgitation (peak velocity coincides with peak aortic pressure).
13.6 (plate 30) Continuous L-R ductal flow.
13.7 (plate 31) Ascending aortic flow.
13.8 Mid-systolic ductal flow velocity v PA:Ao pressure ratio.

Estimation of systolic pulmonary arterial pressure gradient by two methods: A. Systemic pressure - (TR derived RV-RA pressure drop + 5mmHg in ventilated babies) B. Application of the Bernoulli equation to mid-systolic ductal flow velocity.

13.9 Relationship of the two measurements.
13.10 Agreement of the two measurements.

Estimation of systolic pulmonary arterial pressure by two methods: A. TR derived RV-RA pressure drop + 5mmHg in ventilated babies B. Systemic pressure - pressure drop across duct from mid-systolic flow velocity.

13.11 Relationship of the two measurements (all flow patterns).
13.12 Agreement of the two methods in relation to pattern of ductal flow.

Exploration of the disagreement between the two estimates...

13.14 Difference v concurrent ductal flow pattern, using RV-RA pressure drop and no right atrial pressure allowance.
13.15 Difference v systemic blood pressure.
13.16 Difference v PA:Ao pressure ratio
   a) using a right atrial pressure allowance of 5 mmHg in ventilated babies and zero in others, to derive systolic pulmonary arterial pressure
   b) using a right atrial pressure allowance of 10 mmHg in all babies.

Using maximal left-to-right ductal velocity to calculate aorto-pulmonary pressure gradient instead of mid-systolic gradient...

13.17 Difference in aorto-pulmonary pressure gradient calculated from ductal velocity and from systemic pressure-TR derived PA pressure.
13.18 Correlation of the same two measurements.
13.19 As figure 13.18 with only left-to-right ductal flow.
13.20 As figure 13.18 with only bidirectional ductal flow.
13.21 Maximal ductal flow velocity v PA:Ao pressure ratio
Chapter 13: Relationship of pattern of ductal flow and flow velocities to systolic pulmonary:systemic arterial pressure ratio.

13.1 Study group.

(1) There were 223 examinations with both a patent arterial duct and measurable tricuspid regurgitation. These were taken from 109 babies. Of the 223 examinations, 188 were in preterm babies, and 28 were in babies without any respiratory distress.

(2) Many babies had serial examinations. The ductal flow pattern typically changed from bidirectional to pure left-to-right with advancing age, as presented in the preceding chapters on healthy babies and babies with hyaline membrane disease. However, in some babies the flow pattern remained unchanged during several examinations, so that several babies with hyaline membrane disease, for example, had a number of scans with bidirectional flow. To ensure that the results from these individuals do not produce a bias in the subsequent analyses, one examination per flow pattern was selected (at random) from each baby, to a maximum of two examinations from each baby.

(3) The analysis is divided into two sections. The first correlates pulmonary arterial systolic pressure derived from TR (allowing 5 mmHg for right atrial pressure in ventilated babies), and the pulmonary:systemic arterial pressure ratio with ductal flow patterns. The second section correlates these values with flow velocity through the duct. In the second section, the analysis includes the actual velocities in metres/sec., the pressure drop across the duct in mmHg, (derived by application of the modified Bernoulli equation), and an estimated pulmonary arterial pressure derived by subtracting pressure drop across the duct from systolic blood pressure.

13.2 Results

13.2.1 Ductal flow patterns and the PA:Ao ratio

(1) These patterns are described in detail in the methods chapter, but are summarised overleaf, along with the total number of each type in whom simultaneous peak velocity of tricuspid regurgitation was measurable. A second copy of figure 6.1, representing the ductal flow patterns diagrammatically, is also inserted.
Ductal flow patterns:

1/ Pure right-to-left (n = 5).
2/ Bidirectional (n = 66).

Patterns 3 to 8 are all pure left-to-right:

3/ Not a recognisable pattern, or (mostly) too weak a signal to define the pattern accurately.
4/ Low velocity in systole, higher in diastole (n = 41).
5/ High in mid systole, and low at end diastole (n = 6).
6/ High velocity throughout, peak at end systole/early diastole (n = 30).
7/ Complex, two peaks during systole, trough in mid systole.
8/ Complex, two peaks, one during early systole, another in early diastole.

Patterns 7 and 8 are lumped together in this section (n = 10).

(2) The relationship of each type of flow pattern to the systolic PA:Ao ratio is presented in table 13.1 below.

Table 13.1

<table>
<thead>
<tr>
<th>Flow pattern</th>
<th>Centile</th>
<th>1 (n=5)</th>
<th>2 (n=66)</th>
<th>4 (n=41)</th>
<th>5 (n=6)</th>
<th>6 (n=30)</th>
<th>7&amp;8 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90th</td>
<td>1.65</td>
<td>1.19</td>
<td>0.97</td>
<td>0.89</td>
<td>0.72</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>50th</td>
<td>1.06</td>
<td>0.94</td>
<td>0.79</td>
<td>0.70</td>
<td>0.55</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>10th</td>
<td>1.02</td>
<td>0.75</td>
<td>0.61</td>
<td>0.53</td>
<td>0.38</td>
<td>0.70</td>
<td></td>
</tr>
</tbody>
</table>

Results are presented in centiles because the values do not all follow a normal distribution. Figure 13.1 presents the results diagrammatically. The progression from type 2 to 4 and then 6, (the progression in healthy neonates during the first 72 hours of life), represents a sequential fall in the systolic pulmonary : systemic arterial pressure ratio.

(3) Types 1, 5, 7 and 8 were never seen in healthy babies. Type 1, pure right-to-left flow, only occurred when systolic pulmonary arterial pressure exceeded systemic pressure, and was only found in babies with persistent transitional circulation. Type 5 was associated with modest systolic pulmonary hypertension (0.5:1 to 0.9:1) and was common in babies with a large left-to-right ductal shunt; this will be discussed further in chapter 14. Types 7 & 8 were found with a pulmonary : systemic arterial pressure ratio between about 0.7:1 and 1.0:1, and many also had a large left-to-right shunt.
Figure 6.1 Diagrammatic representation of types of pattern of ductal flow

1. PURE RIGHT-TO-LEFT

2. BIDIRECTIONAL

3. L-R BUT SIGNAL TOO WEAK TO CLARIFY PATTERN, OR PATTERN NOT IN ANY OTHER CATEGORY

4. L-R LOW SYSTOLE HIGHER DIASTOLE

5. L-R HIGH MID SYSTOLE/LOW END DIASTOLE

6. L-R CONTINUOUS HIGH VELOCITY

7. L-R, COMPLEX, 2 PEAKS IN SYSTOLE

8. L-R, COMPLEX, 1 PEAK IN SYSTOLE, 1 IN EARLY DIASTOLE
Figure 13.1

TYPE 1
(right-to-left)

TYPE 2
(Bidirectional)

TYPE 4

TYPE 5

TYPE 6

TYPES 7 and 8

Relationship of ductal flow patterns to estimated systolic pulmonary to systemic arterial pressure ratio
13.2.2. Relationship of ductal flow pattern to the aortic pressure waveform.

(1) In a small group of patients with indwelling aortic pressure lines, the pressure waveform was transmitted to the ultrasound scanner from the bedside monitor. This waveform was superimposed on simultaneous Doppler tracings of ductal flow. Some examples are shown in figures 13.2-13.6 (plates 26-31). The striking feature is the close relationship of the diastolic pressure waveforms in the aorta to the Doppler waveform in the duct. This close relationship is particularly important in understanding the relationship of the quantity of ductal shunting to ductal flow patterns, and its influence on diastolic pulmonary arterial pressure. This will be discussed further in chapter 14.

13.2.3. Velocity of ductal flow

A. Velocity at 'mid-systole'

(1) Explanatory note: Application of the Bernoulli equation to the ductal flow velocity in mid-systole gives a pressure drop, which, when subtracted from systemic systolic pressure, should produce a pressure value similar to pulmonary arterial systolic pressure derived from tricuspid regurgitation. Peak velocity at the pulmonary valve occurred at an average of between a quarter and a third (28%) of the way through of the whole cardiac cycle in this study group. This was calculated by adding the pre-ejection period to the time to peak velocity. It did not vary significantly with ductal flow patterns. For ease of calculation, and allowing a small period for flow to reach the arterial duct, a point on the ductal flow pattern was selected for measurement corresponding to 30% of the R-R interval, and 103 ductal waveforms were reanalysed to include this measurement. This measurement was called for convenience 'velocity at mid-systole' (PDA MIDSYS). However, it is merely a very rough estimate as to the time of the systolic pressure peak at the pulmonary end of the arterial duct.

(2) Some difference between the two derived systolic pulmonary arterial arterial pressures can be expected even if the modified Bernoulli equation holds true for ductal flow velocities. Some of this variation is likely because pulmonary arterial pressure (measured by TR), and peak aortic pressure occurs at different times, and peak pulmonary arterial pressure may not be at 'mid-systole'. Furthermore it is unlikely that the pressure gradient across the duct is ever precisely the same as the peak to peak pulmonary to systemic pressure gradient. In other words, the peak pulmonary arterial pressure is unlikely to occur at exactly the same time as peak aortic pressure. Bidirectional ductal flow may occur when systolic pulmonary arterial pressure is lower than systemic systolic pressure because the aortic pressure impulse takes longer to reach the arterial duct than the pulmonary arterial impulse. This is demonstrated in figures 13.2, and 13.4 in which an aortic pressure waveform, from an arterial catheter
placed above the diaphragm, is superimposed on a simultaneous Doppler tracing at the pulmonary end of the duct. Figure 13.3 shows that, in the same patient, peak tricuspid regurgitation velocity marginally precedes peak aortic pressure. Figure 13.7 shows the delay in transmission between the ascending aortic flow (Doppler signal) and the descending aortic pressure trace.

(3) In the subsequent presentation it is important to bear these limitations in mind.

A. Velocity at 'midsystole': Results

(1) There were 103 measurements of 'velocity at midsystole' with simultaneous systolic pulmonary arterial pressure measurements from TR. Limiting the values to one for each pattern of flow from each baby, to a maximum of two values from each baby, (as above) left 85 observations. The values are presented in tables 13.2 and 13.3. Estimated systolic pulmonary arterial pressure ranged from 21 mmHg to 100 mmHg (mean 41 mmHg, SD ± 11 mmHg), and systemic systolic arterial pressure ranged from 20 to 71 mmHg (mean 50 mmHg, SD ± 11 mmHg).

(2) In figure 13.8, ductal velocity at mid-systole is plotted with the PA:Ao pressure ratio. A negative correlation is evident. A velocity greater than 1 metre/sec. is found with a systolic PA:Ao ratio less than 1.0:1, and a velocity less than zero is found with a PA:Ao ratio greater than 0.7:1.

(3) The pressure drop across the duct was calculated in two different ways, firstly by applying the Bernoulli equation to velocity at midsystole, and secondly by subtracting the pulmonary arterial systolic pressure (derived from peak velocity of tricuspid regurgitation and application of the Bernoulli equation, allowing 5 mmHg for right atrial pressure in ventilated babies) from the systemic arterial pressure.

(4) The relationship between these paired values are shown in figure 13.9. The figure has an explanatory note with it. In essence the result is that the aorto-pulmonary pressure gradient measured by applying the Bernoulli equation to the mid-systolic ductal velocity is smaller than expected from subtracting estimated systolic pulmonary arterial pressure from the systemic arterial pressure. This is apparent when the aortic pressure exceeds pulmonary arterial pressure (in quadrant “a” on the graph, where most of the points lie below the line of identity), and also when pulmonary arterial pressure exceeds systemic (in quadrant “b” on the graph, where most of the points lie above the line of identity, although there are few data here).

(5) When the aortic pressure exceeds pulmonary arterial pressure there can be three reasons
Figure 13.8

Mid-systolic flow velocity in arterial duct v systolic pulmonary:systemic arterial pressure ratio.

- Systolic pulmonary:systemic arterial pressure ratio
- Systolic L-R flow velocity in arterial duct (meters/sec)
why the aorto-pulmonary pressure gradient determined from ductal flow is lower than that
derived from subtracting the TR derived estimate of pulmonary arterial pressure from
systemic blood pressure: the systolic pulmonary arterial pressure determined from peak
velocity of tricuspid regurgitation is too low, the systolic blood pressure measurement is too
high, or the pressure gradient determined from mid-systolic ductal flow is too low.

(6) Similarly there can be three reasons why the pulmonary-aortic pressure gradient is
underestimated when the pulmonary arterial pressure exceeds systemic. The systolic
pulmonary arterial pressure determined from peak velocity of tricuspid regurgitation is too
high, the systolic blood pressure measurement is too low, or the pressure gradient
determined from mid-systolic ductal flow is too low.

(7) The only factor which can explain both the difference in left-to-right and right-to-left
directions is therefore that the pressure gradient determined from mid-systolic ductal flow is
too low.

(8) The correlation line in figure 13.9 has a surprisingly high coefficient of determination
(0.38), suggesting that there may be a proportionate disagreement between the two
measurements of aorto-pulmonary pressure difference. The correlation equation
\( y = 0.3 + 0.33x \) in a sense represents the average disagreement; the ductal flow gradient is, on
average, roughly one third of that expected from subtracting the TR derived estimate of
pulmonary arterial pressure from systemic blood pressure.

(9) The difference between these paired values are shown in the Bland-Altman type plot in
figure 13.10. This figure confirms that the larger the pressure drop across the duct,
regardless of whether pulmonary or aortic pressure is highest, the more the ductal flow
estimate is lower than that from subtracting the TR derived estimate of pulmonary arterial pressure from systemic blood pressure.

(10) The only time when the pressures agree closely is at zero ductal flow. Near this point,
the application of the Bernoulli equation to an extremely low velocity makes little difference
to the "ductal estimate" of pulmonary arterial pressure; the pulmonary arterial systolic
pressure (derived from TR) roughly equals systemic systolic arterial pressure.

(11) In figure 13.11, the pulmonary arterial pressure derived from subtracting mid-systolic
ductal flow from systemic arterial pressure, is plotted against that derived from tricuspid
regurgitation (allowing 5 mmHg for right atrial pressure in ventilated babies). While there is
some correlation, there is wide scatter around the line of identity, and as expected from the
relative underestimation of aorto-pulmonary pressure gradient, the ductal flow method
tends to overestimate the pulmonary arterial pressure, particularly with pure left-to-right
Relationship of two estimates of systolic aorto-pulmonary pressure difference:
1. Mid-systolic ductal flow (y axis)
2. Systemic BP - systolic PAP (estimated from TR) (x axis)

Equation:
\[ y = 0.3 + 0.33x \]

Figure 13.9

This figure shows the relationship of two different non-invasive ways to estimate the systolic pressure gradient between the aorta and the pulmonary artery; subtracting estimated systolic pulmonary arterial pressure from the systemic blood pressure, and applying the Bernoulli equation to the mid-systolic ductal flow velocity.

a) The arrow indicates that many points lie below the line of identity. There can be three reasons why they do this:
   1. The systolic pulmonary arterial pressure determined from peak velocity of tricuspid regurgitation is too low,
   2. The systolic blood pressure measurement is too high,
   3. The pressure gradient determined from mid-systolic ductal flow is too low.

b) This arrow indicates that most of the points are above the line of identity. There can be three reasons:
   1. The systolic pulmonary arterial pressure determined from peak velocity of tricuspid regurgitation is too high,
   2. The systolic blood pressure measurement is too low
   3. The pressure gradient determined from mid-systolic ductal flow is too low.

The upper left quadrant of the graph is clear; i.e., when pulmonary arterial pressure estimated from TR is greater than systemic, ductal flow was negative (right-to-left). The lower right quadrant is also clear; when pulmonary arterial pressure estimated from TR was less than systemic, ductal flow was positive (left-to-right).

The correlation line has a high coefficient of determination (0.38), and the equation in a sense represents the average disagreement \( y = 0.3 + 0.33x \); the ductal flow gradient is, on average, roughly one third of that expected from TR derived values.
13.10 Difference in estimated pressure drop across the duct using
1 mid-systolic ductal flow and
2 BP - systolic PAP (estimated from TR)

Average pressure drop (mmHg)

Figure 13.10

This is a 'Bland-Altman' type plot, evaluating the agreement between the two non-invasive methods of determining the aorto-pulmonary pressure gradient. It demonstrates that the two measurements are only similar when the average ("true") pressure drop (the average of the two measurements), is around zero. More importantly it shows that the two techniques disagree as the aorto-pulmonary pressure gradient becomes bigger, when either the pulmonary or systemic pressure is higher. The disagreement becomes larger with increasing pressure gradient.

As in figure 13.9a, in the quadrants labelled "a" and "b" the ductal flow estimated aorto-pulmonary pressure gradient is lower than that from subtracting pulmonary arterial pressure (estimated from tricuspid regurgitation) from systolic blood pressure. Very few points lie in quadrants "c" and "d"; it was unusual therefore, for the ductal flow method to overestimate the gradient.
Figure 13.11
Relationship of systolic pulmonary arterial pressure values determined from systolic ductal flow and from TR.

(R = 0.60, R^2 = 0.33, SEE = 8.4 mmHg)

Figure 13.12
Relationship of systolic pulmonary arterial pressure values determined from systolic ductal flow and from TR: bidirectional flow only

y = 8.0 + 0.9x
R = 0.79, SEE = 6.4 mmHg
R^2 = 0.63
ductal flow (represented as open symbols). The correlation is much better when limited to bidirectional flow patterns, as shown in figure 13.12 ($r = 0.79$, $r^2 = 0.63$, standard error for the estimate 6.4 mmHg).

(12) The disagreement between values is explored further in figure 13.13. The difference between the two estimates of systolic pulmonary arterial pressure are plotted against the type of flow pattern. With pure right-to-left flow (pattern 1), the ductal method underestimates the true pulmonary arterial pressure, the agreement is best for bidirectional flow, but the left-to-right flow patterns lead to over-estimation of the true pressure.

(13) What factors influence this disagreement between the two methods?

(14) Could this discrepancy between the two methods be due to the arbitrary allowance of 5 mmHg for right atrial pressure in ventilated babies when calculating pulmonary arterial systolic pressure? When this allowance is excluded, and the RV-RA pressure drop alone is used, the overall picture remains unchanged, as shown by figure 13.14. Overall, the mean difference between the estimates was 10 mmHg (12 mmHg including only left-to-right ductal flow). This is the same as found by Musewe et al (1990), (this paper is discussed further in the discussion section).

(15) Figure 13.15 demonstrates a trend towards a greater discrepancy at higher systemic arterial pressure.

(16) In figure 13.16a, the discrepancy between the two methods varies with the pulmonary : systemic arterial pressure ratio. There is a strong negative correlation. The greater the difference between the aortic and pulmonary arterial pressures, the larger is the disagreement between the two measurements. Figure 13.6b is the same but the right atrial pressure allowance was 10 mmHg in every baby (regardless of whether or not the babies were ventilated) as in the study by Musewe et al (1990). The same trend is evident, excluding the possibility that the few babies with a right atrial pressure allowance of zero (breathing spontaneously) influenced the result.

(17) Overall, the ductal flow estimate of systolic pulmonary arterial pressure was a mean of 5.2 mmHg higher than the TR estimate when the right atrial pressure allowance was 5 mmHg in ventilated babies. The range of disagreement was -34 mmHg to +24 mmHg, (SD ± 9.8 mmHg), representing a percentage error range of -38% to +69% (Mean +2%, SD ± 22%). The figures were the same when a fixed right atrial pressure of 10 mmHg was used except that the mean difference was 0.2 mmHg (range -39 to +24, SD ± 9.8 mmHg).
Figure 13.13

Difference between systolic PAP estimated from systolic ductal flow and from TR: Influence of type of ductal flow pattern.

(Diagram showing a scatter plot of differences between systolic PAP estimated from two Doppler measurements and TR. The x-axis represents the type of ductal flow pattern, and the y-axis shows the difference in PAP estimated from ductal methods and TR. The graph illustrates that the ductal estimate of PAP is higher than the TR estimate.)

Figure 13.14

Difference between systolic PAP estimated from mid-systolic ductal flow, and RV-RA pressure drop from TR.

(Graph showing the average PAP from ductal estimate and RV-RA pressure drop. The y-axis represents the average PAP, and the x-axis shows the average of PAP from ductal estimate and RV-RA pressure drop. The graph includes a line of agreement and shows an average overestimate of 12 mmHg by ductal method for L-R flow.)

(Note: This graph uses the RV-RA drop i.e., no allowance for RA pressure.)
Figure 13.15
Difference between systolic PAP determined from mid-systolic ductal flow and from TR: the relationship to systemic arterial pressure.

Figure 13.16a
Difference between systolic PAP determined from mid-systolic ductal flow and from TR: the relationship to PA:Ao pressure ratio.
Figure 13.16b

Difference between systolic PAP estimated from TR allowing 10 mmHg for right atrial pressure: effect of PA:Ao pressure ratio

NOTE:
This figure is derived in the same way as figure 13.16a, except that RA pressure allowance is 10 mmHg in every baby.
B. "PDAMAX" (maximal L-R flow velocity)

(1) The pressure drop assumed to represent "mid-systole" may sometimes underestimate the true systolic pressure drop because of the timing of the measurement during the cardiac cycle (at 30% of the R-R interval). The suggestion that the ductal flow velocities lead to underestimation of the true pressure drop would be supported if maximal pressure drop across the duct during the cardiac cycle, calculated using maximal ductal velocity (PDAMAX) is still less than that estimated from subtracting pulmonary arterial systolic pressure (estimated by the TR method) from systolic blood pressure.

(2) Figure 13.17 shows the agreement between these two different pressure drops. On this figure, all of the points on the y axis should be above, or at least equal to the zero line (line of perfect agreement) because the maximal pressure drop across the duct must be at least as big as the systolic PA:Ao pressure difference. In fact, the majority of points are below the zero line; the ductal estimate of maximal pressure drop is less than that obtained by subtracting systolic pulmonary arterial arterial pressure from systolic aortic pressure. Figures 13.18-13.20 show the correlation of the two derived pressure values. Figure 13.18 shows all of the values, and there is wide scatter around the line of identity. Figure 13.19 shows that there is no correlation for values derived from pure left-to-right ductal flow patterns, whereas in 13.20 a correlation is evident for bidirectional flow patterns.

(3) Therefore, the pressure drop across the arterial duct is frequently underestimated by application of the modified Bernoulli equation to ductal flow velocities. Derived pressure drops only agree with the 'true' pressure drops when there is little pressure difference between the pulmonary and systemic circulations.

(4) Can PDAMAX, (in metres/second) be a useful predictor of the PA:Ao pressure ratio, without applying the Bernoulli equation and subtracting from systemic pressure? This question is addressed in figure 13.21. There is clearly a relationship. Values less than 1 metre/sec. are found with a PA:Ao ratio of > 0.7:1 and values above 3 metres/sec. are found with a ratio <0.7:1. However, there is a wide spread of values around a curvilinear relationship, such that the information provided by an individual velocity measurement is no more useful than analysis of the type of ductal flow pattern.

C. Mean and minimal velocities across the duct

These velocities, and the derived pressure drops from the modified Bernoulli equation, provided no further useful correlation with systolic pulmonary arterial pressure or the systolic PA:Ao ratio.
Figure 13.17

Difference between two estimates of Ao-Pa pressure gradient:
Maximal L-R ductal flow v (BP-TR estimate of PAP)

"Ductal estimate" underestimates "true" L-R pressure drop.
Figure 13.18  
Relationship of (systolic blood pressure-maximal pressure drop across duct) vs systolic PAP

Ductal flow pattern
- Type 1 (R-L)
- Type 2 (Bidirect.)
- Type 3 (L-R)
- Type 4 (L-R)
- Type 5 (L-R)
- Type 6 (L-R)
- Types 7 & 8 (L-R)

Systolic pulmonary arterial pressure (RV-RA drop + 5 mmHg if ventilated) (mmHg)
Figure 13.19  
Relationship of (systolic blood pressure-maximal pressure drop across duct) v systolic PAP

Systolic pulmonary arterial pressure (mmHg)  
(RV-RA drop + 5 mmHg if ventilated)

Figure 13.20  
Relationship of (systolic blood pressure-maximal pressure drop across duct) v systolic PAP

Systolic pulmonary arterial pressure (mmHg)  
(RV-RA drop + 5 mmHg if ventilated)
Figure 13.21

Relationship of maximal L-R ductal flow velocity to the systolic PA:Ao pressure ratio

PDAMAX (metres/sec)

Systolic pulmonary:systemic arterial pressure ratio
13.3 Discussion

(1) This study shows that if the TR method is accepted as the 'gold standard' of Doppler methods to determine pulmonary arterial pressure, applying the modified Bernoulli equation to ductal flow velocities usually results in an underestimation of the true pressure drop.

(2) The results are surprising, in view of the results of Musewe et al (1990) and are difficult to explain. The wide scatter of values and discrepancies in every figure is to be expected from the fact that three measurements are made, each with their own variability and error; limiting useful comment to general trends. Nevertheless, it appears that Doppler assessment of pressure drop across the arterial duct is usually an underestimate of the 'true' pressure drop, in either direction, unless the pulmonary and systemic pressures are approximately balanced. Since this observation appears to be in conflict with those of Musewe et al it is important to discuss why this may be, and look at the differences in methodology and analysis of results between the two studies.

(3) Musewe et al (1990) were interested in validating the use of ductal flow velocities in determining pulmonary arterial pressure in the neonate. This was done by subtracting the pressure drop in mid systole, (derived from ductal flow velocity and application of the Bernoulli equation) from the systemic arterial pressure (measured through an arterial line), as in the present study. The study group comprised 21 babies in whom tricuspid regurgitation could be measured, from 37 newborns most of whom had either persistent transitional circulation (n = 16) or hyaline membrane disease (n = 16). Results were compared with systolic pulmonary arterial pressure values derived from tricuspid regurgitation which were taken as the 'gold standard'. The method of measurement was also similar, using continuous wave Doppler for higher velocities and pulsed Doppler for lower velocities, and measuring velocity at the pulmonary end of the arterial duct for left-to-right flow, and at the aortic end for right-to-left flow. The first important difference was the allowance for right atrial pressure (10 mmHg), significantly higher than in the present study. The argument for using this figure was based on two factors. Two previous reports were quoted as showing that babies such as those being studied were likely to have a right atrial pressure of the order of 10 mmHg. In fact one of these reports was from a study of the newborn lamb, and the other was from a study by Peckham and Fox (1978), who reported a mean right atrial pressure of 6.6 mmHg amongst nine term babies with persistent transitional circulation. This paper was among the many reviewed in chapter 9, wherein there is a discussion leading to the choice of 5 mmHg as the logical average allowance for right atrial pressure. The other factor leading to the choice of 10 mmHg for right atrial pressure was that using this allowance in determining systolic pulmonary arterial pressure lead to the best agreement with systolic pulmonary arterial pressure derived from subtracting the mid-systolic ductal velocity from systemic arterial pressure. In other words,
it was assumed that the measurement of mid-systolic aorto-pulmonary pressure gradient from ductal flow was accurate, even though it was this method which was under examination. Had this approach been used in the present study, the best average allowance for right atrial pressure would also have been 10 mmHg, or 12 mmHg if only subjects with left-to-right flow were included, (see figure 13.14). However, it would seem probable that both values are too high given the previous reports of right atrial pressure in this population (presented in chapter 9), even allowing for the average expected underestimate of the RV-RA pressure drop of 2 mmHg from measurement of peak velocity of tricuspid regurgitation (chapter 7). The most logical conclusion from both the work of Musewe et al, and the present study, is that aorto-pulmonary pressure gradient is underestimated by an average of 5-7 mmHg when the modified Bernoulli equation is applied to mid-systolic ductal flow.

(4) The second important difference was that mid-systole was determined by a more complicated technique than used in this study, superimposing ascending aortic Doppler tracings onto the ductal waveform, and marking the time of peak aortic velocity. The reason given for this was that duration of flow and timing of peak flow velocity were not significantly different from that in the descending aorta (amongst a sub-group of ten patients). The suggestion that peak velocity of ascending aortic flow represents the mid-systolic pressure gradient at the pulmonary end of the arterial duct has not been proven, and a clear example that this can be an incorrect assumption is shown in figure 13.7 (plate 31), where the peak descending aortic pressure lags well behind ascending aortic flow. Nevertheless, this was an attempt to standardise the timing of measurement of ductal velocity in systole, and as such it is certainly no less appropriate than the standard timing (30% of the R-R interval) used in the present study, and it would seem unlikely to be the reason for the different results. Was the timing of the velocity measurement at the 'fixed' time of 30% of the R-R interval appropriate in the present study? It is well known that right ventricular systolic events alter in timing during the cardiac cycle with differing pulmonary vascular resistance; the time relationship of peak arterial pressures could change, such that the velocity at 30% of the R-R interval could represent the pressure drop at different phases of the cardiac cycle. However, as pulmonary arterial pressure falls, (for example) pulmonary PEP becomes shorter, and TPV becomes longer. In the present study, the time from Q-wave to peak velocity at the pulmonary valve did not change significantly between flow patterns. Thus, the timing of peak pulmonary flow during the cardiac cycle was not altered significantly (or consistently) by changing pulmonary vascular resistance, making this an unlikely source of discrepancy between the two pulmonary arterial pressure estimates (or between this study and that of Musewe et al).

(5) A third important difference between this study and that of Musewe et al, is that they compared derived systolic pulmonary arterial pressure values, rather than the aorto-pulmonary pressure gradient, and it is the derivation of the latter which is truly in question,
because this is what is measured by application of the Bernoulli equation to ductal flow. Looking at figure 13.11, excluding a few outliers, one can see a reasonable correlation between the estimates of systolic pulmonary arterial pressure, and this figure, (and figure 13.14) reveals no obvious change in the error across the range of pulmonary arterial pressure studied, as demonstrated by Musewe et al. Yet figures 13.9 and 13.10, comparing derived aorto-pulmonary pressure gradient, reveal that the error does not seem to be just a chance phenomenon in some babies, but tends to increase according to the size of the pressure drop. How might this be explained? When the arterial pressures are balanced, ductal flow velocities are low, and, (if the modified Bernoulli equation can be applied despite such low velocities) only small changes in pressure gradient will produce very big changes in ductal flow velocity. For example if the left-to-right pressure gradient changes by 3 mmHg, from 1 mmHg to 4 mmHg, the velocity would double from 0.5 to 1.0 m/sec., (0.5^2 x 4 =1, to 1^2 x 4 =4), a rise of 0.5 m/sec., but if it changes rise by 3 mmHg from 22 to 25, the velocity would change from 2.35 to 2.5 m/sec. (2.35^2 x 4 =22, to 2.5^2 x 4 =25), a rise of only 0.15 m/sec. Therefore, there can be considerable error in measurement of ductal flow velocity if it is low, without altering the derived pressure gradient significantly, but at high velocities, or higher pressure gradients, much more error, in terms of derived pressure drop, can be expected. The phenomenon of increasing error at bigger aorto-pulmonary pressure gradients was observed by Houston et al (1989), in their Doppler-catheterisation studies of ductal flow. Failure to accurately align with the ductal flow, leading to an underestimation of the true velocity, would lead to more significant underestimation of the pressure drop at a bigger aorto-pulmonary pressure difference. If the patients studied by Musewe et al (1990) had mostly a low aorto-pulmonary pressure difference, (the data is not available in their report) then relatively little error would result in the determination of systolic pulmonary arterial pressure after the estimated pressure drop were subtracted from systemic blood pressure, and this could explain the relatively good correlation of the two estimates of systolic pulmonary arterial pressure seen by them, and hence some of the difference between their results and those of the present study.

(6) Musewe et al (1990) found that the resulting correlation from 14 values in babies with uni-directional shunting (left-to-right or right-to-left) was 0.97, with a standard error of the estimate of 8 mmHg. This is certainly impressive, and we were unable to reproduce this accuracy (r = 0.60); it was even better for the sub-group with bidirectional shunting: (r = 0.95, standard error 4.5 mmHg), as it was in the present study (r = 0.79, standard error 6.4 mmHg). The correlation is better, with lower standard error, than that obtained by the same authors (1987) against direct measurement of instantaneous systolic gradient (r = 0.94, standard error 13 mmHg), although this was over a wider range of pressures. It is quite remarkable that two non-invasive measurements of haemodynamic variables, dependent on four different measurements, can agree so well, particularly when it is unlikely that the
instantaneous pressure gradient across the duct (to which ductal flow is compared in the catheter validation studies) is ever precisely the same as the peak to peak pulmonary to systemic pressure gradient to which it is being compared here.

(7) In summary, some possible reasons for disagreement between the present study and that of Musewe et al (1990), relate to selection of patients (including the balance of systemic and pulmonary arterial pressures), methodology (particularly the estimation of pulmonary arterial pressure rather than the aorto-pulmonary pressure gradient), and the assumption of different average right atrial pressures.

(8) The degree of underestimation of the pressure drop across the duct is related in a linear way to the systolic pulmonary : systemic arterial pressure ratio (figures 13.16a and 13.16b). This relationship was so strong that it is clearly of significance. It is presumably due to the phenomenon described above, whereby the bigger pressure differences are more likely to result in significant error, and this error was almost invariably an underestimation, tending to become more significant with increasing pressure difference. Unfortunately this means that the error of the ductal measurement cannot be predicted, since the pulmonary : systemic arterial pressure ratio is not known before the measurement is taken.

(9) Are there any remaining theoretical explanations for the apparent underestimation of the pressure drop using ductal flow?

(10) Could the source of error in fact be the determination of RV-RA pressure drop from tricuspid regurgitation? This would seem unlikely, because previous evidence suggests little difference in accuracy with changing pulmonary arterial pressure, and in particular no tendency to underestimate true RV-RA pressure drop with high or low pressures that could explain the trend evident in this study. Furthermore, the underestimation of right-to-left pressure gradients by ductal flow could only be caused by over-estimation of the RV-RA pressure drop, which would seem to be extremely unlikely.

(11) Could the source of error be the determination of systemic arterial pressure from the arterial line or Doppler sphygmomanometry? Blood pressure measurement, like any physiological measurement, is prone to error, but this could not explain the systematic alteration in agreement with increasing aorto-pulmonary pressure gradient.

(12) Thus the conclusion is that the most likely source of error is the estimation of aorto-pulmonary pressure gradient using ductal flow velocity and the modified Bernoulli equation.

(13) Before 1985, the modified Bernoulli equation had only been validated for use with discrete orifices. While the arterial duct usually narrows most markedly at the pulmonary
end, it is to a certain degree, a tube or tunnel, and morphology can vary greatly. Musewe et al. showed in an example of gradual acceleration across an arterial duct in their paper of 1987. At the distal end, the retrograde flow velocity from the aorta into the duct was almost zero at end diastole (at the R-wave of the ECG), in the middle part it was 1.5 m/sec. and at the narrowest pulmonary arterial end, the blood accelerated still further to 2.5 m/sec. (coinciding with the R-wave). In 1985 Tierstein et al. studied in-vitro the accuracy of Doppler measurement of pressure gradients across tunnel-like obstructions to blood flow. The cross-sectional area of the tunnels studied was between 0.06 cm$^2$ and 1.25 cm$^2$, and the length was between 0.1 and 4 cm. They found that decreasing cross-sectional area and increasing tunnel length resulted in underestimation of manometer-derived values by Doppler, (probably due to the effect of viscous friction) and this underestimation became significant at tunnel areas below 0.25 cm$^2$ or tunnel lengths above 3 cm. The diameter of the arterial duct, at its narrowest point, was frequently less than 1 mm in the present study. Musewe et al. (1990), in their study of neonates, found a ductal diameter of 0.5 to 7 mm. The cross-sectional area ($\pi r^2$) therefore varied from approximately 0.08 cm$^2$ to 0.38 cm$^2$. Thus the 'tunnel effect' might lead to underestimation of the aorto-pulmonary pressure gradient in some babies.

(14) Even without the possible tunnel effect, the modified Bernoulli equation will eventually not be applicable as the duct becomes very small. Usually, in early postnatal life, the pressure gradient becomes bigger at the same time as the duct becomes smaller. Thus when there is bidirectional flow, there is usually a large duct, (either in the first few hours, or during hyaline membrane disease) and at the same time as pulmonary arterial pressure falls and high velocity pure left-to-right flow develops, the duct usually becomes smaller. Therefore most of the smallest ducts are found with the highest aorto-pulmonary pressure gradients. When the duct becomes so small that the limits found by Holen et al. (1976) are exceeded, then the ductal velocities will be lower than would normally be expected for a given pressure gradient. This feature may be unique to babies, especially preterm babies because of the tiny size of the arterial duct prior to physiological closure, and could explain why this feature was not found by Musewe et al. (1987) and Houston et al. (1989) in their validating studies in older children. This does not explain the underestimation with pure right-to-left flow, but both Houston et al and Musewe et al. found that right-to-left velocity did not correlate well with the directly measured pressure gradient, and there may be a separate phenomenon to explain the error in this group. On the other hand, the strikingly straight regression line in figure 13.15 incorporates values from the babies with pure right-to-left flow, suggesting that the disagreement between values may simply be an extension of the same phenomenon; using high ductal flow velocities in the modified Bernoulli equation usually (but not always) results in underestimation of the true pressure drop.

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(15) Colour flow Doppler, which was not routinely available in the present study, can show the direction of left-to-right flow from the duct and into the pulmonary artery. Anecdotally, I have seen that with a large duct and unrestricted flow, such as in the first hours of life or during hyaline membrane disease when the pulmonary arterial pressure is still high, the blood flows mostly into the centre of the main pulmonary artery. With ductal constriction, the flow tends to be directed upwards and to the left in the main pulmonary artery (as observed by Aziz et al 1990). Therefore it can become more difficult to align with flow during ductal constriction. The angle of insonation to the direction of blood flow must be less than 20 degrees from zero in order to avoid significant underestimation of flow velocity (as discussed in section 3.3.3). Thus the changing direction of the jet of blood into the pulmonary artery during ductal constriction, which usually coincides with falling pulmonary arterial pressure, might also explain why the higher pressure gradients were frequently underestimated. This idea needs to be explored further.

(16) Measurement of ductal flow velocities are shown later, (in chapter 16), to be repeatable, and useful in serial assessment of haemodynamic change within a baby. However, this chapter has shown that application of the modified Bernoulli equation to these velocities does not always produce a reliable estimate of the pressure gradient across the duct. The values frequently underestimate the true pressure drop, particularly at higher pressure gradients, in either left-to-right or right-to-left direction.

(17) The ductal velocities and derived pressure drops, due to the wide margin of error, provide little further useful information with respect to the true ductal pressure drop (or the PA:Ao ratio) than that obtainable from studying the type of flow pattern alone. For example, bidirectional ductal flow implies a systolic pulmonary : systemic arterial pressure ratio greater than 0.7:1, as does a 'mid-systolic' or maximal ductal flow velocity of less than 1 metre/second.

13.4

In summary, analysis of ductal flow patterns can provide useful information regarding the relationship of the pulmonary and systemic arterial pressures, (and serial measurement of ductal flow velocity can also be helpful). However, the evidence presented in this chapter suggests that in the newborn, application of the modified Bernoulli equation to ductal velocities frequently leads to an underestimate of the aorto-pulmonary arterial pressure gradient and is therefore not a reliable technique to determine systolic pulmonary arterial pressure.
Table 13.2. Eighty seven values for systemic arterial pressure and non-invasively determined pulmonary arterial pressure from the database. Results are from all of the babies in whom mid-systolic flow velocity through the arterial duct was measured, but are limited to one value for each flow pattern from each baby.

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<th>Pa:Ao pressure ratio</th>
<th>MIDSYS ΔAo-Pa fr</th>
<th>BP-PAP est (duct-TR)</th>
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**Δ Ao-Pa fr MIDSYS**, aorto-pulmonary pressure gradient in systole determined from mid-systolic velocity through the arterial duct and application of the Bernoulli equation.

**Δ Ao-Pa fr (BP-TR)**, aorto-pulmonary pressure gradient in systole determined from subtracting systolic pulmonary arterial pressure (estimated from peak tricuspid regurgitation and application of the Bernoulli equation), from systolic, systemic arterial blood pressure.

**PAP**, systolic pulmonary arterial pressure estimated from the RV-RA pressure drop from peak velocity of tricuspid regurgitation and the modified Bernoulli equation, allowing 5 mmHg for right atrial pressures in babies who were ventilated.

**Difference Δ Ao-Pa (duct-TR)**, difference in aorto-pulmonary pressure gradient estimates, subtracting the gradient determined from the TR estimate of pulmonary arterial pressure from the gradient determined from the ductal flow method.
Table 13.3. Details of subjects in whom systolic pulmonary arterial pressure was derived from mid-systolic ductal flow and from peak velocity of tricuspid regurgitation.

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<th>Mean airway pressure (cm H2O)</th>
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* no respiratory distress

continued...
Table 13.3. Details of subjects in whom systolic pulmonary arterial pressure was derived from mid-systolic ductal flow and from peak velocity of tricuspid regurgitation. (continued)

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Chapter 14. Relationship of pattern of ductal flow to quantity of ductal flow.

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Chapter 14. Relationship of pattern of ductal flow to quantity of ductal flow.

14.1 Introduction

(1) This section investigates whether there was any relationship between the pattern of flow through the arterial duct during the cardiac cycle and the volume of left-to-right ductal flow. A secondary aim was to look for any relationship between flow pattern and the presence or absence of a heart murmur in systole (or systole/diastole) suggestive of a left-to-right ductal shunt.

(2) This analysis was undertaken because ductal flow patterns showed serial changes in babies with hyaline membrane disease as they developed an increasingly large left-to-right ductal shunt. In healthy babies, the normal sequence over the first two days of life was from bidirectional (type 2), to low velocity left-to-right, lowest in systole (type 4), to high velocity continuous left-to-right (type 6). In some babies with hyaline membrane disease the sequence was similar, although the phase of bidirectional flow lasted longer, but in others the sequence was rather different. Bidirectional flow (type 2), was followed by type 4, and then by type 5 (high in mid-systole & low end diastole) or less frequently types 7 or 8 (complex). These latter patterns were usually accompanied by left atrial dilatation. Type 6 then followed during ductal constriction, followed by ductal closure.

(3) Of the 33 babies studied serially and presented in chapter 10 on TR-determined pulmonary arterial pressure, six developed flow pattern type 5. All developed a large left atrium, although one baby initially had a low LA:Ao ratio in the presence of this pattern. This baby later went on to develop a large L-R shunt, (LA:Ao ratio 1.9:1) but never presented clinically. The flow pattern changed to type 6 prior to the duct closing spontaneously. The other five already had or developed overt clinical signs and required therapeutic ductal closure.

(4) It was decided therefore to analyse this phenomenon in more detail, using the classifications of ductal flow patterns described in chapter 6.

(5) It was also noted that babies may have prolonged periods of clinically silent left-to-right shunting prior to presentation. The clinical signs were assessed daily by the attending neonatologists, and the consultant or registrar was asked at around the time of the echocardiogram whether or not there was a systolic heart murmur (yes or no), and, putting all of their clinical assessment together, whether they felt a left-to-right ductal shunt was unlikely, possible or probable. This assessment was therefore based on the full clinical examination, and sometimes included chest radiography. In the serial study of hyaline membrane disease, the babies who developed overt clinical signs (either a heart murmur...
and/or clinical assessment of probable left-to-right shunt) did so a mean of 72 hours after significant ductal shunting was detected echocardiographically (LA:Ao > 1.4:1, and widely open (moderate or large) duct). This phenomenon of the "silent ductus" is well known (McGrath et al 1978), but why is shunting sometimes clinically silent, and at other times clinically obvious? Is the clinically audible murmur related to the timing of flow through the arterial duct, or to the quantity or speed of flow?

14.2 Study group and methods

(1) All of the scans from all of the babies were included in the analysis (see table 12.1). The SPSSx database and statistical package was used. In comparing results from different flow patterns, results are presented in centiles because the distribution of values across the groups was frequently skewed.

(2) The size of the shunt was assessed semi-quantitatively by comparing ductal flow patterns with concurrent left atrial : aortic root ratios (LA:Ao ratio) and left ventricular output. Both of these echocardiographic measurements are known to rise with ductal shunting, as a consequence of increased pulmonary venous return (Silverman et al 1974, Alverson et al 1983, respectively). These are discussed in more detail in sections 4.4, 4.6 and 4.7.

(3) The same categorisation of flow patterns is used as in chapters 6 and 13.

(4) Left ventricular output and stroke volume were indexed in relation to birth weight. The aortic root diameter was averaged over the time period of the scans to avoid fluctuations in calculated output due to the large observer error associated with this part of the measurement.

(5) Some statistical values are presented, but most of the interpretation of the results presented is best achieved by direct reference to the tables and graphs. It should be remembered that most babies are represented more than once in each category of flow patterns. To help in this subjective interpretation, the tables show not only the total number of scans, but the number of babies from whom they were taken.

(6) The study was divided into four parts:

1. Cross-sectional analysis. This section studies the relationship of the different flow patterns to echocardiographic indices of ductal shunting and includes all scans.

2. Ductal flow patterns in symptomatic babies prior to therapeutic ductal closure.

4. Relationship of flow patterns and indices of left-to-right shunting to the presence of the typical heart murmur.

14.3 Results

14.3.1. Cross-sectional analysis.

(1) The results are summarised in table 14.1, and in figures 14.1 to 14.3. The figures are "box plots" which represent centile distribution of each group. The central line in the box is the 50th centile, the edge of the box shows the 25th and 75th centiles, and the error bars show the 10th and 90th centiles. The outlying bottom and top 10% are shown as individual points.

(2) Patterns 1, 5 and 8 were never seen in healthy babies, and type 7 was seen only once in a healthy preterm baby of 30 weeks gestation aged 4 hours. (This baby had a large duct and an LA:Ao ratio of 1.44:1, but the duct was closed within 24 hours.) Type 1 was only seen in babies with persistent transitional circulation. The other flow patterns occurred both in well babies and those with respiratory distress.

(3) Figure 14.1 demonstrates that the LA:Ao ratio is clearly higher with flow pattern 5, but the most striking feature of these results is in the left ventricular output (figure 14.2) and stroke volume (figure 14.3) measurements. Babies with pure right-to-left flow, all of whom had persistent transitional circulation, had a remarkably low stroke volume index, presumably reflecting little pulmonary venous return to the left atrium. In contrast, flow patterns 5, 7 and less so type 8, were associated with very high stroke volumes, as a consequence of high pulmonary venous return.

(4) Of the 27 babies in this study who had pattern type 5, all but three had a large L-R ductal shunt which eventually required treatment. Two of these three babies had a large shunt which resolved spontaneously.

(5) In summary, pattern type 5 was almost always, and types 7 and 8 were frequently, associated with a large left-to-right shunt.

14.3.2. Babies with symptomatic left-to-right ductal shunt.

(1) 42 babies received indomethacin therapy, on a total of 52 occasions, and 8 babies (in
This box plot shows the relationship of LA:A0 ratio with the type of ductal flow. (Pattern 0= closed duct.)

For this figure, and subsequent box plots, the central line in the box is the 50th centile, the edge of the box shows the 25th and 75th centiles, and the error bars show the 10th and 90th centiles. The outlying bottom and top 10% are shown as individual points. (These are drawn using "Statview"™ software.)
Figure 14.2

Box plot comparing values for left ventricular output in babies with different patterns of ductal flow.

Figure 14.3

Box plot comparing values of left ventricular stroke volume index in babies with different ductal flow patterns.
whom indomethacin failed) required surgical ligation. It is important to stress that the
decision to treat these babies was in the hands of the clinical staff who did not know the
scan findings when the decision was made. The ductal flow patterns in these babies before
treatment are presented in table 14.2.

(2) Of particular note is the fact that seven of the eight babies presenting for ductal ligation
had type 5 flow, (the other had type 4 flow). Overall, immediately prior to therapy for
symptomatic left-to-right ductal shunt (either ligation or indomethacin) 72% of the scans
demonstrated either type 5 or type 7 flow.

(3) What do the flow patterns 5 and 7 have in common?

(4) A uniting feature of flow patterns 5 and 7 (and also of type 8) is that the velocity at
end diastole was usually low (<1.2 m/s), particularly in relation to the maximal velocity,
which occurred at some time in systole. These two velocities can be expressed as a ratio of
each other; maximal velocity : end diastolic velocity ("PDAMAX:ENDDIAS"). When this is
done, the ratio effectively describes the main features of patterns 5, 7 and 8 which are in
common to each other but different from the other patterns; the velocity is high in systole
and low at end diastole. The mean ratio was 3.1:1, 2.3:1 and 2.3:1 for types 5, 7 and 8
respectively, compared to 1.4:1, 1.2:1 and 1.4:1 for types 2, 4 and 6 respectively. In other
words, babies who had a large left-to-right shunt usually had a peak velocity more than
twice the end diastolic velocity.

(5) The feature distinguishing type 7 from type 8, was the timing of the second peak; in
type 7 it was during systole, but in type 8 it was during diastole. With type 8, the highest
peak was frequently the second one (during diastole); it was not recorded which of the two
peaks were highest. Therefore, the reason type 7 is more common amongst babies with large
shunts may relate to the highest peak flow (and the longer duration of high flow) being
during systole and not diastole.

(6) Therefore the fact that types 5 and 7 are usually found with a big shunt, may be because
they both combine low end diastolic velocity with higher systolic velocity. Since the
pattern of ductal flow reflects the changing pressure gradient across the duct throughout the
cardiac cycle, we can conclude that there is a significant gradient between aorta and
pulmonary artery in systole but that the pulmonary and systemic pressures are almost equal
in diastole.

(7) With only one exception, flow pattern type 5 was always found in a baby who had, or
was developing, other unequivocal echocardiographic signs of a large shunt. Therefore,
recognition of this flow pattern itself may prove to be a useful indicator of significant
shunting. However, identification of flow patterns is subjective. Because of this it would be useful to identify a particular velocity during the cardiac cycle which could differentiate babies with large shunts from those with small shunts. To investigate this the scans were divided into two groups for comparison:

**Group 1 (Big shunt):** 41 scans from babies about to receive treatment (either indomethacin or ligation) for symptomatic shunting, who also had an LA:Ao ratio >1.4:1.

**Group 2 (Small shunt):** 106 scans from babies with a small or moderate sized patent arterial duct on cross-sectional echocardiography, an LA:Ao ratio <1.3:1 and a left ventricular output <325 mls/kg/min. (the 90th centile for babies with a closed arterial duct).

(8) Only babies with pure left-to-right ductal flow were included in this analysis.

(9) The results are shown in table 14.3, and in figures 14.4-14.6. Figure 14.4 shows that there was little difference between the maximal left-to-right velocity in the two groups. Figure 14.5 shows that the minimal, mean and end diastolic velocities were all lower in babies with a large shunt. There is a good deal of overlap between the two groups, such that a single velocity measurement cannot usefully distinguish one group from the other. However, 90% of the babies with a large shunt had a minimal velocity less than 1 metre/sec., and an end diastolic velocity less than 1.5 metres/sec. whereas approximately 75% of babies with a small shunt had respective velocities higher than these.

(10) The two groups were best differentiated by using the ratio of maximal velocity : end diastolic velocity (figure 14.6). 76% (23 of 30) of the scans in babies with a large shunt had a ratio >2.0:1 compared to only 4% (3 of 72) of the small shunt group.

(11) In summary, babies with a large, symptomatic left-to-right ductal shunt characteristically had a high left-to-right velocity during systole accompanied by a low velocity at end diastole, though this is not always the case. When this pattern was identified it was almost always associated with a large shunt, clinically requiring ductal closure. This analysis would not suggest that measurement of a particular velocity, or ratio of velocities would be sufficient, in isolation, to differentiate small from large shunts across a population. However, a high velocity at end diastole (>1.5 m/s) or a high minimal velocity (>1 m/s) was uncommon with a large shunt.
Figure 14.4  (data from table 14.3)

Box plot comparing PDAMAX in babies with a large L-R ductal shunt, with those with a small one (see table 14.3).
Figure 14.5 Box plot comparing minimal, mean and end diastolic ductal velocities in babies with a small shunt, with those in babies with a large shunt.

The three boxes on the left are from babies with a small shunt, and those on the right are from babies with a big shunt; they are in the same sequence. (Values are also shown in table 14.3).
Figure 14.6

Box plot comparing the ratio of PDAMAX : ENDDIAS in babies with a small left-to-right ductal shunt with those with a large shunt.
14.3.3. Serial evaluation of ductal flow during ductal constriction.

14.3.3.1. Patients and methods

(1) Serial studies were available from 11 babies receiving indomethacin for a large left-to-right ductal shunt, in whom the duct was still patent on the second scan but showed clear evidence of ductal constriction on cross-sectional echocardiography. Ductal flow velocities and flow patterns were compared from before and during ductal constriction, along with measurements of left ventricular output. In four babies it was possible to follow ductal constriction in three stages.

(2) The details of the patients and their clinical status are shown in table 14.4. Babies were of 26-30 weeks gestation and all but two were ventilated. The studies were a mean of 47 hours apart, but patients 6 to 11 had studies between only 1 and 16 hours apart. Table 14.5 also lists the LA:Ao ratios before and during constriction.

(3) Statistical comparisons were made by paired t test.

14.3.3.2. Results

(1) The Doppler echocardiographic changes are shown in a cross-sectional manner in table 14.5, and serially for each baby in figures 14.7a-14.7i.

LA:Ao ratio-The LA:Ao ratio is seen to fall in all but one baby in figure 14.7a. This baby had mitral regurgitation during ductal closure, which resolved over a few days.

Left ventricular output-Left ventricular output fell in every baby (figure 14.7b), confirming that the enlarged left atrium in subject 1 was indeed due to mitral regurgitation and not to increased pulmonary venous return.

(2) Was this fall in left ventricular output due to a fall in heart rate or stroke volume?

(3) There were only small changes in heart rate (mean fall of 4%), 7 fell, 3 rose and one was unchanged (figure 14.7c). Stroke volume index fell in every baby, by a mean of 29% (figure 14.7d), and aortic stroke distance is seen to mirror the changes in stroke volume index (figure 14.7e).

(4) It is clear therefore that the reduction in left ventricular output with reduced left-to-right ductal shunting is primarily due to a reduction in stroke volume rather than heart rate.
Figure 14.7a. Sequential LA:Ao ratios with ductal constriction following indomethacin.

Figure 14.7b. Sequential LV output with ductal constriction following indomethacin.
Figure 14.7c  Sequential heart rates with ductal constriction following indomethacin.

Figure 14.7d.  Sequential LV stroke volume index with ductal constriction following indomethacin.
Figure 14.7e. Sequential Aortic stroke distance with ductal constriction following indomethacin.

Figure 14.7f. Sequential systolic blood pressure during ductal constriction following indomethacin.
Systolic blood pressure-Systolic blood pressure rose marginally in all but 3 babies (figure 14.7f), suggesting that effective systemic cardiac output rises as the high left ventricular output falls. Fewer results are available for mean and diastolic pressures, though they also tended to rise.

Ductal flow velocities-Maximal left-to-right ductal flow rose in all but two babies (figure 14.7g). The mean rise of 0.78 m/sec. shows that most changes were large enough to be detected 'with confidence' by the measurement (see chapter 16). Mean left-to-right velocity rose in all but one baby (figure 14.7h), and minimal left-to-right velocity rose markedly in all but one baby (subject 6) who had bidirectional ductal flow throughout (figure 14.7i).

Type of flow pattern - Results are summarised in table 14.4. 8 babies had type 5 flow before treatment, and this changed to type 6 in all but 1. One baby with type 8 flow also changed to type 6 (subject 1). The one baby with bidirectional flow (subject 6) showed little change in velocities and the pattern remained unchanged. One baby (subject 2) initially had type 6 flow, and this remained, although there were higher velocities after constriction.

14.3.3.3.

(1) In summary, ductal constriction in the presence of a large left-to-right shunt leads to a reduction in left ventricular output, via a reduction in stroke volume (much more so than heart rate). This is accompanied by a rise in systemic blood pressure, and an increase in flow velocity across the duct, particularly during late diastole. The rise in flow velocities presumably reflects increasing difference between aortic and pulmonary arterial pressures.

(2) These results can be interpreted as follows. As left-to-right shunting decreases, there is an increase in effective systemic output causing a rise in systemic blood pressure. The fall in pulmonary venous return causes a reduction in left atrial volume loading and pressure, leading in turn to a fall in diastolic and mean pulmonary arterial pressure. There is thus an increase in aorto-pulmonary arterial pressure gradient, particularly during late diastole. This increasing gradient is reflected by the increase in ductal flow velocities.

14.3.4. Why do some babies with a large ductal shunt have a murmur when others do not?

14.3.4.1. Patients and methods

Referring again to the original database, scan results were first selected if there was at least a moderate sized duct on cross-sectional imaging and an LA:Ao ratio >1.4:1. These scans were then divided into two groups; those taken at a time when the baby had a heart murmur and clinical signs suggestive of a patent arterial duct with left-to-right shunt, (ie heart
Figure 14.7g. Sequential PDAMAX velocity with ductal constriction following indomethacin.

Figure 14.7h. Sequential mean L-R flow velocity with ductal constriction following indomethacin.
Figure 14.71. Sequential minimal L-R velocity (PDA MIN) with ductal constriction following indomethacin.
murmur and clinical assessment of possible or probable ductal shunt), and those without a heart murmur or other overt clinical signs ("silent", ie no heart murmur and clinical assessment indicating ductal shunt was unlikely).

14.3.4.2. Results

(1) The results are presented in tables 14.6, 14.7 and 14.8.

(2) Table 14.6 shows that two thirds of the babies with a heart murmur and a large shunt had flow pattern type 5, whereas only one fifth of the silent group had type 5 flow. (This is significantly different by Fishers' exact test.)

(3) Analysis of the actual measured ductal flow velocities (Table 14.7) shows that there were no significant differences in the actual measured velocities between the two groups, although the ratio of maximal left-to-right flow velocity : end diastolic velocity tended to be higher in the group with a heart murmur.

(4) Table 14.8 shows that while the LA:Ao ratios and heart rates were similar in the two groups, the babies with a murmur tended to have a higher left ventricular output, as a result of a higher stroke volume (a mean of 39% higher).

(5) In serial analysis within the same baby, the murmur and overt clinical signs often coincided with peak left ventricular stroke volume. Some babies already had type 5 ductal flow, but no murmur, but at the next scan the murmur had presented, and the major echocardiographic change was a rise in stroke volume, with little change in the LA:Ao ratio or the pattern of ductal flow.

14.3.4.3.

In summary, while it was not always possible to determine why a large left-to-right ductal shunt was "silent", in many cases, the presence of the heart murmur and overt clinical signs was associated with a higher stroke volume, suggesting a larger left-to-right shunt despite similar LA:Ao ratios, and type 5 pattern of ductal flow, with low velocity at end diastole accompanied by a higher velocity through a large part of systole. The typical systolic murmur of the patent arterial duct in the newborn may be due to limitation of high volume left-to-right ductal flow to systole alone. Presumably, high left atrial pressure causes a rise in pulmonary arterial pressure such that pulmonary and systemic arterial pressures are balanced during diastole, but during systole the systemic pressure remains sufficiently high to generate a significant pressure gradient.
14.4. Discussion

(1) This study demonstrates that the pattern of blood flow through the arterial duct during the cardiac cycle is greatly influenced by the quantity of left-to-right flow. The patterns that are characteristic of a large left-to-right ductal shunt are those with a low velocity in late diastole, accompanied by a higher velocity in systole. When the peak velocity in systole is only brief, there is not usually an associated ductal flow murmur, even in the presence of a large shunt. When the systolic flow is more prolonged (type 5), there is frequently a systolic murmur. However, the presence of the murmur was dictated not only by the ductal waveform but by the quantity of blood passing through the duct, as shown by the fact that babies with murmurs usually have a higher left ventricular stroke volume than those without. Thus a ductal shunt can be 'silent' because the timing of flow in the cardiac cycle does not produce a sustained peak in systole, or because the volume of ductal flow is not enough to generate a murmur, despite echocardiographic evidence of an enlarged left atrium.

(2) This pattern of flow ("type 5") has been observed by others during simultaneous Doppler-catheterisation studies. Low left-to-right velocity through the duct in diastole (<1.5 m/sec.) was shown by Hiraishi et al (1987) to indicate pulmonary arterial hypertension. Houston et al (1989) identified this pattern of flow in patients with moderately raised pulmonary arterial pressure, the ratio of systolic to diastolic velocities ranged from 2:1 to 5:1. They commented that the pressures in the aorta and pulmonary artery were almost equal during diastole. In the older patient, therefore, this pattern of flow indicates elevated pulmonary arterial pressure. In some of the patients in each of the studies, the pulmonary vascular resistance was elevated as a consequence of pulmonary vascular disease, but it is not clear in how many the pulmonary arterial pressure was elevated purely as a consequence of high pulmonary blood flow. Aziz and Tasneem (1990) showed that patients with high pulmonary arterial pressure had a ratio of systolic velocity to diastolic velocity of greater than 2:1, whereas it was less in those with normal pulmonary arterial pressure. They divided their patients into two groups, group 1 with low and group 2 with high mean pulmonary arterial pressure (<24 mmHg and >24 mmHg), and also presented the mean pulmonary : systemic flow ratio (Qp:Qs) for each group calculated from the Fick principle. In group 1 Qp:Qs was (mean) 2.1:1 and in group 2 it was 3.4:1. The four subjects in group 1 had an end diastolic ductal flow velocity above 2 m/sec., whereas amongst the 13 subjects in group 2 it was below 2 m/sec. The systolic:end-diastolic flow velocity ratio was <2:1 in group 1 and >2:1 in group 2. Thus, while the absolute values for velocity were higher in their study of older children, the systolic:end-diastolic ratio of 2:1 was the same as the present study in differentiating a big shunt from a small one (see figure 14.6). In the premature neonate, this flow pattern may occur because of a combination of high flow and mildly elevated pulmonary vascular resistance. It is possible that left atrial hypertension (as a consequence of increased pulmonary venous return) has a more marked
influence upon diastolic and mean pulmonary arterial pressure than on systolic pressure, particularly in the presence of a reactive neonatal pulmonary vascular bed which is also of restricted capacity in relation to the adult pulmonary vasculature. The presence of left atrial hypertension was supported by the observation in some babies of a high velocity left-to-right jet through a restrictive patent oval foramen. In three babies (it was not measured in all of them) this was over 2 metres/second, suggesting a significant pressure difference between left and right atriums.

(3) Ductal flow during diastole is thus low velocity due to balanced pulmonary and aortic pressures. The systolic pressure gradient across the duct might be affected by systemic pressure changes accompanying resolution of respiratory distress such as improving left ventricular function, or increasing systemic vascular resistance. This could explain why the typical systolic murmur of ductal shunting can first appear at a time when a baby is actually going through a phase of clinical stabilisation or even improvement. During the preceding period of silent ductal shunting, the left ventricle was less able to respond to the high left atrial preload. Additionally, as pulmonary vascular resistance falls during resolution of hyaline membrane disease, systolic pulmonary arterial pressure may fall further leading to an increased aorto-pulmonary gradient during systole, but not so much in diastole because of left atrial hypertension.

(4) Unfortunately the other methods for estimating pulmonary arterial pressure are less good when the left-to-right shunt is large; TR was usually not measurable by this stage, and the flow at the pulmonary valve is often too turbulent to allow accurate timing of the peak velocity. However, type 5 flow has been shown to be associated with elevated pulmonary arterial pressure in chapter 13 (and by the catheterisation studies mentioned above), so the babies with a large shunt have a high systolic pulmonary arterial pressure, at around two thirds of systemic pressure. Presumably, during ductal constriction, as the gradient across the duct increases, the elevated pulmonary arterial pressure falls at the same time as systemic pressure rises.

(5) Twenty eight percent of the scans before treatment for a large shunt showed flow patterns other than types 5 and 7. Therefore, while it is clear that the quantity of left-to-right shunting has an important influence on the pattern of flow through the duct, some babies can apparently have a large left-to-right shunt with flow patterns that occur normally during the transitional circulation in the healthy neonate. Furthermore, it is possible to have a murmur without a ductal flow pattern that can explain the nature of the murmur. It is particularly difficult to understand how low velocity bidirectional ductal flow can give rise to a flow murmur through the duct. One must speculate that the murmur in fact arises from elsewhere, for example from the aorta due to the high stroke volume, or from the branch pulmonary arteries. The peak velocity at the origin of left pulmonary artery was not always
measured, but velocities over 2 metres/second were frequent. Anecdotally this velocity seemed usually to increase during ductal constriction, rather than at the time of maximal left-to-right shunt, and probably gave rise to transient murmurs in some premature babies who were examined while convalescing, as observed recently by Tsuda et al (1993). Clearly the origin of the murmur needs to be examined in more detail, including a detailed clinical examination by an experienced cardiologist identifying subtle differences between murmurs in different babies, coupled with a detailed Doppler echocardiogram by an independent observer.

(6) The serial studies during ductal constriction showed that ductal velocities may be a useful way of documenting ductal constriction in response to indomethacin therapy; the velocities (particularly diastolic and mean velocities) increase as the duct closes. Using this observation as a new research tool, ductal constriction could be related temporally to systemic circulatory changes caused by therapeutic intervention, particularly those which have been ascribed to indomethacin per se, such as reduction in cerebral and gut blood flow, to see if ductal constriction itself plays any part in these general circulatory changes.

(7) Measurement of left ventricular output revealed that the rise in output associated with ductal shunting is mediated primarily by an increase in stroke volume and not heart rate. This might be seen to go against the conclusions of work done on newborn animals which has suggested that cardiac output in the newborn is regulated mainly by changes in heart rate (Rudolph, 1976). While the differences could be due to interspecies variation, it is more likely to be due to the lower systemic vascular resistance associated with ductal shunting presenting a reduced afterload to the left ventricle. Serial measurement of heart rate is clearly of little practical value in assessing ductal shunting clinically in the premature neonate. On the other hand, measurement of left ventricular stroke volume may prove to be a most useful clinical tool. Serial measurement of aortic stroke distance avoids the inaccuracy inherent in measurement of aortic root dimensions, and could be a useful tool for monitoring ductal flow.

14.5.

In summary, these studies have shown a relationship between ductal flow velocities and the pattern of flow during the cardiac cycle and quantity of left-to-right ductal shunting. A plausible theory as to the usual origin of the typical systolic ductal flow murmur is presented, as high volume ductal flow is restricted to systole. A murmur is more likely to be heard when high volume flow is intermittent rather than continuous across the whole of the cardiac cycle. Perhaps the rapidly changing flow patterns cause more turbulence, and hence more noise, than continuous, even flow patterns. The study has outlined the haemodynamic events associated with ductal constriction, including a rise in systemic pressure, a fall in
pulmonary arterial pressure (particularly in late diastole), and a fall in left ventricular output mediated by a fall in stroke volume. In so doing the chapter has introduced two new indices of left-to-right ductal flow which may have clinical applications: left ventricular stroke volume or stroke distance, and ductal flow patterns and velocities.
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Table 14.2. Type of ductal flow pattern in symptomatic babies.

<table>
<thead>
<tr>
<th>Type of ductal flow*</th>
<th>Pre-indomethacin</th>
<th>Pre-indomethacin &amp; LA:Ao ratio &gt; 1.4</th>
<th>Pre-ligation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number</td>
<td>52</td>
<td>34</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>59</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

*Values are percent of each column.
Table 14.3. Comparison of ductal flow velocities in small and large shunts.

<table>
<thead>
<tr>
<th>Doppler measurement (Metres/sec)</th>
<th>1. LARGE SHUNT-</th>
<th>2. SMALL SHUNT^</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>centiles</td>
<td>centiles</td>
</tr>
<tr>
<td>PDAMAX</td>
<td>1.2</td>
<td>1.8</td>
</tr>
<tr>
<td>PDAMIN</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>PDAMEAN</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>ENDDIAS*</td>
<td>0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>RATIO**</td>
<td>1.3</td>
<td>2.7</td>
</tr>
</tbody>
</table>

- pre treatment for symptomatic shunt with LA:Ao ratio>1.4:1 and pure L-R ductal flow. n=41.
^ LA:Ao ratio <1.3:1, LV output <325 mls/kg/min, small-mod duct on imaging, pure L-R flow. n=106
* Enddias (velocity at end diastole) was measured in 30 scans in group 1 and 72 in group 2.
** ratio of "PDAMAX : ENDDIAS".
Table 4.4: Data on patients in serial study of ductal condensation

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Gestation</th>
<th>Birth Weight</th>
<th>Age (Ft)</th>
<th>MAP (mmHg)</th>
<th>FGF (ng/ml)</th>
<th>MAP (mmHg)</th>
<th>FGF (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.94</td>
<td>1.60</td>
<td>0.90</td>
<td>0.06</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>1.22</td>
<td>1.22</td>
<td>1.22</td>
<td>1.22</td>
<td>1.22</td>
<td>1.22</td>
<td>1.22</td>
<td>1.22</td>
</tr>
<tr>
<td>1.06</td>
<td>1.06</td>
<td>1.06</td>
<td>1.06</td>
<td>1.06</td>
<td>1.06</td>
<td>1.06</td>
<td>1.06</td>
</tr>
<tr>
<td>1.18</td>
<td>1.18</td>
<td>1.18</td>
<td>1.18</td>
<td>1.18</td>
<td>1.18</td>
<td>1.18</td>
<td>1.18</td>
</tr>
</tbody>
</table>

Details of second study, during ductal condensation.
Table 14.5: Doppler echocardiographic data on 11 patients before and during ductal occlusion.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before</th>
<th>During</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow velocity</td>
<td>10.0</td>
<td>0.17</td>
</tr>
<tr>
<td>PDAMIN (m/s)</td>
<td>0.33</td>
<td>0.44</td>
</tr>
<tr>
<td>PDAMEAN (m/s)</td>
<td>1.00</td>
<td>0.10</td>
</tr>
<tr>
<td>PDAMAX (m/s)</td>
<td>1.77</td>
<td>0.52</td>
</tr>
<tr>
<td>Ductal flow velocity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>25</td>
<td>46</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>35</td>
<td>55</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>47</td>
<td>70</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>50</td>
<td>75</td>
</tr>
</tbody>
</table>

Doppler echocardiographic data on 11 patients before and during ductal occlusion.

| LV cardiac output (L/min) | 251 | 521 |
| Heart rate (beats/min) | 101 | 101 |
| LV stroke volume (mL) | 352 | 114 |
| Ao stroke distance (cm) | 352 | 10 |
| Index of LV output | 141 | 22 |

LV = left ventricle
Ao = aortic
LV cardiac output = left ventricular output
Heart rate = heart rate
LV stroke volume = left ventricular stroke volume
Ao stroke distance = aortic stroke distance
Index of LV output = index of left ventricular output

*Note: Data presented as mean (SD).*
Table 14.6. Ductal flow pattern & presence of heart murmur in babies with a large ductal shunt

<table>
<thead>
<tr>
<th>Type of ductal flow*</th>
<th>MURMUR</th>
<th>NO MURMUR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of scan</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>number of baby</td>
<td>30</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

*Values are percent of each group, rounded to nearest 1%.

**Moderate-big duct (size 2 or 3) and LA:Ao ratio>1.4:1
Table 14.7. Comparison of ductal flow velocities in babies with a large shunt, with & without heart murmur

<table>
<thead>
<tr>
<th>Doppler measurement (Metres/sec)</th>
<th>MURMUR</th>
<th>NO MURMUR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>PDAMAX</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>PDAMIN</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>PDAMEAN</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>ENDSYS</td>
<td>0.6</td>
<td>1.4</td>
</tr>
<tr>
<td>ENDDIAS</td>
<td>0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>RATIO*</td>
<td>1.5</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*Ratio of "PDAMAX : ENDDIAS"
Table 14.8. Comparison of indices of left ventricular output in babies with & without heart murmur (& large L-R ductal shunt)

<table>
<thead>
<tr>
<th></th>
<th>MURMUR</th>
<th></th>
<th>NO MURMUR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>50</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>LA:Ao ratio</td>
<td>1.45</td>
<td>1.64</td>
<td>1.92</td>
<td>1.41</td>
</tr>
<tr>
<td>Heart rate</td>
<td>138</td>
<td>155</td>
<td>169</td>
<td>130</td>
</tr>
<tr>
<td>LV stroke vol. index (mls/kg)</td>
<td>2.5</td>
<td>3.2</td>
<td>4.4</td>
<td>1.4</td>
</tr>
<tr>
<td>LV output (mls/kg/min)</td>
<td>378</td>
<td>501</td>
<td>712</td>
<td>190</td>
</tr>
</tbody>
</table>
Chapter 15: Relationship of right ventricular systolic time intervals to systolic pulmonary arterial pressure determined from tricuspid regurgitation

15.1 Introduction

15.2 Patients and methods

15.3 Results

1. Influence of heart rate
2. Influence of ductal patency
3. Influence of gestational age
   1. TPV/RVET ratio
   2. PEP/RVET ratio
4. Healthy babies
5. Restricted gestational age and closed duct
   1. Babies < 33 weeks with a closed duct
   2. Term babies with a closed duct.

15.4 Discussion

15.5 Summary

Figures are listed on the next page

Tables: The tables are small, and are included in the text.

15.1 All babies, relationship of PEP/RVET and TPV/RVET to systolic pulmonary arterial pressure (PA pressure) and the PA:Ao ratio.
15.2 Influence of ductal patency on TPV/RVET and PEP/RVET ratios.
15.3 Influence of ductal patency on TPV, PEP and RVET.
15.4 Comparison of TPV, PEP and RVET values at estimated systolic PA pressure of 35-45 mmHg, with closed and patent duct.
15.5 Influence of gestational age on TPV/RVET ratio.
15.6 Influence of gestational age on PEP/RVET ratio.
15.7 All systolic time intervals -v- PA pressure and PAP:Ao ratio in babies < 33 weeks gestation and with a closed duct.
15.8 TPV/RVET ratio -v- PA pressure and PAP:Ao ratio in term babies with a closed duct.
Chapter 15: Relationship of right ventricular systolic time intervals to systolic pulmonary arterial pressure determined from tricuspid regurgitation

Figures

All of the figures plot right ventricular systolic time intervals against either systolic pulmonary arterial pressure ("PA pressure") determined from TR jet (allowing 5 mmHg for right atrial pressure in ventilated babies), or the systolic pulmonary : systemic (Pa:Ao) arterial pressure ratio.

Figures 15.1 to 15.8 include a maximum of two measurements from each baby.

15.1 PEP/RVET ratio -v- PA pressure
15.2 PEP/RVET ratio -v- PA:Ao ratio.
15.3 TPV/RVET ratio -v- PA pressure.
15.4 TPV/RVET ratio -v- PA:Ao ratio.
15.5 PEP/RVET ratio -v- PA pressure, with and without patent duct.
15.6 PEP/RVET ratio -v- PA pressure, only babies with closed duct.
15.7 TPV/RVET ratio -v- PA pressure, with and without patent duct.
15.8 TPV/RVET ratio -v- PA pressure, indicating babies <33 weeks gestation, and term babies.

Figures 15.9 to 15.12 include all values from all of the healthy babies.

15.9 TPV/RVET ratio -v- PA pressure, healthy babies only.
15.10 TPV/RVET ratio -v- PA:Ao ratio, healthy babies only.
15.11 TPV -v- PA pressure, healthy babies only
15.12 TPV -v- PA:Ao ratio, healthy babies only.

Figures 15.13 to 15.16 include only babies with a closed duct, with a maximum of two values from each baby.

15.13 PEP -v- PA pressure, babies less than 33 weeks gestation (and closed duct).
15.14 TPV/RVET -v- PA pressure, term babies (and closed duct).
15.15 TPV -v- PA pressure, term babies (and closed duct).
15.16 TPV -v- PA:Ao ratio, term babies (and closed duct).
Chapter 15: Relationship of right ventricular systolic time intervals to systolic pulmonary arterial pressure determined from tricuspid regurgitation

15.1 Introduction

(1) It is clear from the preceding chapters, that indices derived from tricuspid regurgitation and ductal flow indicate pulmonary arterial pressure more reliably than right ventricular systolic time interval ratios. However, tricuspid regurgitation and ductal flow are not always present. There is therefore a need for alternative noninvasive ways of assessing pulmonary arterial pressure in the neonate, and systolic time intervals are at present the only feasible alternative. It is therefore important to explore these further. One approach is to attempt to identify factors other than pulmonary arterial pressure which influence these time intervals, and cause them to be unreliable indices of pulmonary arterial pressure. Heart rate has been shown to be such a factor, and authors have tried to allow for this in various ways, discussed earlier in section 3.2. Once such confounding factors are eliminated, systolic time intervals might become more useful.

(2) It has been argued previously in this thesis that the results of Evans and Archer's study on healthy neonates (1990), suggest that the TPV/RVET ratio is influenced by the size or maturity of the subject. This aspect, and the effect of a patent arterial duct on this ratio has not previously been explored. The patent arterial duct may theoretically have a number of different effects on right ventricular systolic time intervals. For example, turbulence in the pulmonary artery may disturb the Doppler signal and increase observer error. It might, theoretically, shorten RVET as a torrent of blood from the arterial duct forces relatively premature closure of the pulmonary valve. The early right-to-left ductal flow during the cardiac cycle when flow is bidirectional might effectively reduce the resistance to flow at that time, and lead to a more rapid rise to peak velocity at the pulmonary valve.

(3) Strong evidence has been presented that measurement of systolic pulmonary arterial pressure by the TR technique is accurate and reproducible in this population. In this section, TPV, PEP and the TPV/RVET and PEP/RVET ratios, are evaluated against simultaneous systolic pulmonary arterial pressure values determined by measurement of peak TR velocity in the neonate. The independent effects of gestational age and patency of the arterial duct on the relationship of the systolic time interval ratios to systolic pulmonary arterial pressure are explored.

15.2 Patients and Methods

During the course of the longitudinal Doppler echocardiographic studies presented earlier in
this thesis, the TPV/RVET ratio was measured on 262 occasions and the PEP/RVET ratio was measured on 122 occasions in babies who also had pulmonary arterial pressure determined by the TR method. Pulmonary arterial pressure values ("PA pressure") derived from TR (allowing 5 mmHg for right atrial pressure in ventilated babies, and zero in those breathing spontaneously) were correlated with systolic time interval ratios. Some babies had several simultaneous TR and systolic time interval measurements. To avoid individual babies causing a bias in the results, a maximum of two observations was taken from each baby, comprising the highest and lowest TR value (this was usually the first and the last value for each baby).

15.3 Results

(1) The correlation coefficients (r) and coefficients of determination (r^2) of the PEP/RVET and TPV/RVET ratios against estimated systolic pulmonary arterial pressure and the pulmonary : systemic arterial pressure ratio (PA:Ao ratio) are presented in Table 15.1 below. This includes all babies. A maximum of two values per baby are included.

Table 15.1

<table>
<thead>
<tr>
<th></th>
<th>PEP/RVET ratio</th>
<th>TPV/RVET ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number  r  r^2</td>
<td>number  r  r^2</td>
</tr>
<tr>
<td>PA pressure*</td>
<td>87   0.28  0.08</td>
<td>191   -0.42  -0.18</td>
</tr>
<tr>
<td>PA:Ao ratio</td>
<td>85   0.36  0.13</td>
<td>189   -0.40  -0.16</td>
</tr>
</tbody>
</table>

* "PA pressure", systolic pulmonary arterial pressure estimated from peak TR velocity, allowing 5 mmHg for right atrial pressure in ventilated babies only. (This abbreviation is used frequently in the tables of this chapter).

(2) The correlations are presented graphically in figures 15.1 to 15.4.

(3) A weak correlation of both systolic time interval ratios with estimated systolic pulmonary arterial pressure is evident. As expected, there are clearly factors influencing these ratios other than systolic pulmonary arterial pressure. The next sections investigate how the relationship of the time interval ratios with systolic pulmonary arterial pressure is affected by ductal patency, gestational age and heart rate.
Figure 15.1  PEP/RVET ratio -v- systolic pulmonary arterial pressure determined from TR.

(Maximum of two examinations from each baby)

Estimated systolic pulmonary arterial pressure (mmHg)

Figure 15.2  PEP/RVET ratio v pulmonary:systemic arterial pressure ratio. (All babies).

(Maximum of two examinations from each baby)

Pulmonary : systemic arterial pressure ratio
Figure 15.3  TPV/RVET ratio and systolic pulmonary arterial pressure.

Systolic pulmonary arterial pressure

Figure 15.4  TPV/RVET ratio v pulmonary : systemic arterial pressure ratio.

Pulmonary : systemic arterial pressure ratio
15.3.1. The influence of heart rate

Overall, neither TPV/RVET or PEP/RVET were affected by heart rate. PEP showed a weak correlation only (r=-0.20) and the mean changed surprisingly little across the range. The mean PEP at 130 beats per minute was approximately 63 msec, and at 170 beats per minute was 58 msec (a change of 8%). TPV showed a stronger correlation with heart rate (r=-0.38) and changed more noticeably across the range of heart rates. The mean TPV at 130 beats per minute was approximately 70 msec, and at 170 was 50 msec (a change of 29%).

15.3.2. The influence of ductal patency

(1) The values were separated into those taken at a time when the arterial duct was moderate or large (size 2 or 3) and compared with values taken when the duct was closed. The same baby may be represented in both dosed and patent duct groups, to a maximum of two occasions in each group.

Table 15.2

<table>
<thead>
<tr>
<th></th>
<th>PEP/RVET ratio</th>
<th></th>
<th>TPV/RVET ratio</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>r</td>
<td>r²</td>
<td>no.</td>
</tr>
<tr>
<td>Closed duct</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA pressure</td>
<td>37</td>
<td>0.64</td>
<td>0.40</td>
<td>84</td>
</tr>
<tr>
<td>PA:Ao ratio</td>
<td>35</td>
<td>0.63</td>
<td>0.40</td>
<td>82</td>
</tr>
<tr>
<td>Moderate/Large duct</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA pressure</td>
<td>60</td>
<td>0.14</td>
<td>0.02</td>
<td>120</td>
</tr>
<tr>
<td>PA:Ao ratio</td>
<td>60</td>
<td>0.07</td>
<td>0.00</td>
<td>120</td>
</tr>
</tbody>
</table>

(2) Both systolic time interval ratios correlate better with systolic pulmonary arterial pressure when the duct is closed. This effect is most striking for the PEP/RVET ratio, and is reflected in figure 15.5 and 15.6. Many babies with a patent duct have a relatively high ratio at low pulmonary arterial pressures. Figure 15.7 is in the same format as 15.5, but shows the TPV/RVET ratio. There may be a tendency for babies with a patent duct to have a comparatively low ratio at pulmonary arterial pressures between 40 and 60 mmHg, but this is not clear cut.
Figure 15.5  PEP/RVET ratio and systolic PAP: The influence of ductal patency.

Figure 15.6  PEP/RVET ratio and systolic PAP: Babies with a closed duct.

Estimated systolic pulmonary arterial pressure (mmHg)
Ductal patency alters the relationship of both systolic time interval ratios with systolic pulmonary arterial pressure. Is this due to changes in PEP, TPV or RVET? The correlation of the individual time intervals with systolic pulmonary arterial pressure is shown in Table 15.3 below. (The number of studies is the same as in Table 15.2 for PEP as PEP/RVET, and for TPV and RVET as TPV/RVET.)

Table 15.3

<table>
<thead>
<tr>
<th></th>
<th>PEP</th>
<th></th>
<th>TPV</th>
<th></th>
<th>RVET</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>r</td>
<td></td>
<td>r</td>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Closed duct</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA pressure</td>
<td>0.47</td>
<td>0.22</td>
<td>-0.52</td>
<td>-0.27</td>
<td>0.29</td>
<td>0.08</td>
</tr>
<tr>
<td>Moderate/Large duct</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA pressure</td>
<td>0.02</td>
<td>0.00</td>
<td>-0.29</td>
<td>-0.08</td>
<td>0.06</td>
<td>0.00</td>
</tr>
</tbody>
</table>

The striking, and surprising, feature of these results, is that TPV correlates slightly better with systolic pulmonary arterial pressure than the TPV/RVET ratio, in babies with a closed arterial duct, despite the wide range of heart rates. PEP shows no correlation at all with systolic pulmonary arterial pressure in babies with a patent duct.

In Table 15.4 overleaf, values within a single pulmonary arterial pressure band, 35-45 mmHg, are taken, and the individual time intervals are compared in babies with and without a patent duct, to see which factors cause the relative rise in PEP/RVET and fall in TPV/RVET ratio with a patent duct. To limit the effect of heart rate on the results (because of the known influence of heart rate on these time intervals), only values from babies with a heart rate between 130 and 160 beats per minute are included.

Mean systolic pulmonary arterial pressure for the two groups was the same (40 ± 3 mmHg), and the mean heart rates were not significantly different (146 and 147 with and without patent duct respectively).

PEP is significantly shorter at a given systolic pulmonary arterial pressure when there is a patent duct. Both TPV and RVET tended to be shorter, though this was not statistically significant.
Figure 15.7  
TPV/RVET ratio and systolic PAP: The influence of ductal patency.

- ○ patent duct
- □ closed duct

Figure 15.8  
TPV/RVET v systolic pulmonary arterial pressure: Term babies v <33 weeks

- △ <33 weeks
- • >36 weeks
**Table 15.4**  (Systolic pulmonary arterial pressure estimate 35-45 mmHg)

<table>
<thead>
<tr>
<th></th>
<th>PEP (msec)</th>
<th>TPV (msec)</th>
<th>RVET (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>mean (SD)</td>
<td>no.</td>
</tr>
<tr>
<td><strong>Closed duct</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA pressure</td>
<td>8</td>
<td>49^ (10)</td>
<td>16</td>
</tr>
<tr>
<td><strong>Moderate/Large duct</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA pressure</td>
<td>20</td>
<td>66^ (20)</td>
<td>44</td>
</tr>
</tbody>
</table>

* values are significantly different, p=0.03.

15.3.3. The influence of gestational age

15.3.3.1. TPV/RVET ratio

(1) To explore the influence of gestational age on TPV and TPV/RVET, the babies were divided into those at term and those less than 33 weeks gestation. The results are shown in table 15.5 (overleaf) and figure 15.8. Values in the preterm infants are lower at a given systolic pulmonary arterial pressure. To test the significance of this apparent difference, the values were then divided into bands of systolic pulmonary arterial pressure, 20-30 mmHg, 31-40 mmHg etc., and the time intervals in each band were compared using the (unpaired) students t test. Only one value was taken from each baby within each pressure band.

(2) The way in which the TPV / RVET ratio is related to systolic pulmonary arterial pressure is altered by gestational age. Ratios are lower at a given pulmonary arterial pressure at lower gestation. Is this difference due to TPV or RVET?

(3) The pressure band where the difference is most significant is 41-50 mmHg. The mean RVET within this pressure band was virtually identical: 171 and 172 msec. The mean TPV in babies less than 33 weeks was 52 msec, compared to 67 in the more mature babies (p=0.02). The mean heart rates were 151 and 148 respectively. The mean pulmonary : systemic arterial pressure ratio was also virtually the same in each group within this pressure band (0.89 and 0.88 respectively). The group of babies of lower gestation had a similar frequency of patent arterial duct (30/35 v 8/11) and comparing only those babies with a moderate sized duct in each group (11 and 6 respectively), the TPV was still significantly shorter in the less mature babies (48 msec v 69 msec).
Therefore TPV is shorter at a given systolic pulmonary arterial pressure in preterm babies than in term babies.

Table 15.5 Relationship of TPV/RVET and systolic pulmonary arterial pressure: the influence of gestational age

<table>
<thead>
<tr>
<th>PA pressure range (mmHg)</th>
<th>Gestation &lt;33 weeks</th>
<th>Gestation &gt;36 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>PA pressure mean (mmHg)</td>
</tr>
<tr>
<td>20-30</td>
<td>30</td>
<td>26.5 0.38 (.11)</td>
</tr>
<tr>
<td>31-40</td>
<td>26</td>
<td>35.9 0.30 (.06)*</td>
</tr>
<tr>
<td>41-50</td>
<td>35</td>
<td>43.7 0.29 (.09)**</td>
</tr>
<tr>
<td>51-60</td>
<td>6</td>
<td>54.2 0.24 (.09)</td>
</tr>
</tbody>
</table>

*p=0.01, **p=0.006.

(PA pressure, estimated systolic pulmonary arterial pressure from TR jet)

Table 15.5 shows that the way in which the TPV/RVET ratio is related to systolic pulmonary arterial pressure is altered by gestational age.

15.3.3.2 PEP/RVET ratio

There were fewer measurements of the PEP/RVET ratio in this study. Gestational ages compared were <30 weeks and 31-37 weeks, because there were too few values in term babies. Graphical display showed no obvious difference. There were fewer pressure bands with sufficient data to allow meaningful comparison between babies of different gestation. However, some attempt has been made in the table overleaf.
Table 15.6 Relationship of PEP/RVET to systolic pulmonary arterial pressure: the influence of gestational age

<table>
<thead>
<tr>
<th>PA pressure range</th>
<th>no.</th>
<th>PA pressure mean (mmHg)</th>
<th>PEP/RVET mean (SD)</th>
<th>no.</th>
<th>PAP pressure mean (SD)</th>
<th>PEP/RVET mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-30</td>
<td>7</td>
<td>26.4</td>
<td><strong>0.30</strong> (.09)</td>
<td>10</td>
<td>26.3</td>
<td><strong>0.26</strong> (.08)</td>
</tr>
<tr>
<td>31-40</td>
<td>9</td>
<td>35.9</td>
<td><strong>0.41</strong> (.12)</td>
<td>11</td>
<td>36.0</td>
<td><strong>0.41</strong> (.11)</td>
</tr>
<tr>
<td>41-50</td>
<td>8</td>
<td>43.6</td>
<td><strong>0.37</strong> (.07)</td>
<td>12</td>
<td>42.7</td>
<td><strong>0.34</strong> (.12)</td>
</tr>
</tbody>
</table>

There were no significant differences.

15.3.4. Healthy babies

(1) By studying healthy babies alone, some potentially important influences upon the systolic time intervals are excluded. In particular, right ventricular function should be normal and there is no positive pressure ventilation, and no allowance for right atrial pressure was made. Too few PEP/RVET ratios were available for analysis in this group. The relationship of the TPV/RVET ratio, and TPV alone was therefore studied in the comparatively few babies who were completely healthy and had both TPV/RVET recorded and measurable tricuspid regurgitation in the first three days of life. These are the same babies as presented in the earlier longitudinal study of pulmonary arterial pressure in healthy neonates using peak velocity of tricuspid regurgitation (chapter 8).

(2) The major limiting factor in this analysis is the small numbers, and because of this, all values are included. There were 23 values from 16 premature babies and 18 from 13 term babies. Some babies had three simultaneous TR and TPV/RVET ratios, and this might cause a bias in the results, although the measurements were at 24 hour intervals when the pulmonary arterial pressure was falling markedly. Correlation coefficients should therefore be interpreted with caution. Subjective interpretation of the results is possible by studying figures 15.9 and 15.10, which plot TPV/RVET against pulmonary arterial pressure, and figures 15.11 and 15.12 which plots TPV against pulmonary arterial pressure.
(3) Figure 15.9 confirms the tendency for preterm babies to have a lower TPV/RVET ratio at systolic pulmonary arterial pressure values between about 35 and 50 mmHg. The correlation of TPV/RVET with systolic pulmonary arterial pressure in healthy premature babies is 0.65 \( (r^2=0.43) \). Analysis of figure 15.10 suggests that the TPV/RVET ratio is related to the pulmonary:systemic arterial pressure ratio in a similar way in term and preterm babies, though the values are widely scattered across the graph.

(4) Figures 15.11 and 15.12 show the same plots with TPV instead of the TPV/RVET ratio. Figure 15.11 shows the close correlation of TPV with pulmonary arterial pressure in the healthy premature babies, \( (r=0.72, r^2=0.51) \).

(5) All these figures still demonstrate considerable spread around any correlation, although in the healthy premature infants, it appears that reasonable differentiation of high pressures from low pressures is possible. For example, a TPV of over 70 msec was associated only with systolic pulmonary arterial pressures of less than 35 mmHg. The correlations are closer amongst these healthy babies, than for the whole group.

15.3.5. Restricted gestational age and closed arterial duct

(1) The previous results have shown that correlation of systolic time intervals with systolic pulmonary arterial pressure improves by excluding results from babies with patent arterial duct, and by limiting the gestational age range. This final section combines these two factors in studying firstly only babies less than 33 weeks gestation with a closed arterial duct, and secondly only term babies with a closed arterial duct.

15.3.5.1. Babies less than 33 weeks gestation with a closed arterial duct

(1) This section may have particular clinical importance, because this describes most babies with bronchopulmonary dysplasia, who as previously described, do not normally have tricuspid regurgitation or a patent duct, yet frequently have pulmonary hypertension requiring assessment.

(2) One value was taken at random from each baby, and results are tabulated overleaf (table 15.7).
Figure 15.9  
TPV/RVET ratio v systolic pulmonary arterial pressure from TR in healthy babies:  
Term v preterm

Estimated systolic pulmonary arterial pressure (mmHg)

Figure 15.10  
TPV/RVET ratio v pulmonary : systemic arterial pressure ratio in healthy babies:  
Term v preterm

Pulmonary:systemic arterial pressure ratio
Figure 15.11  TPV v pulmonary arterial pressure in healthy babies: term v preterm

Estimated systolic pulmonary arterial pressure (mmHg)

Figure 15.12  TPV v Pulmonary:systemic arterial pressure ratio in healthy babies: term v preterm.

Pulmonary:systemic arterial pressure ratio
Table 15.7  Correlation of systolic time intervals with estimated systolic pulmonary arterial pressure and PA:Ao pressure ratio in babies of less than 33 weeks gestation with a closed arterial duct

<table>
<thead>
<tr>
<th></th>
<th>PA pressure (est)</th>
<th>PA:Ao ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>r</td>
</tr>
<tr>
<td>PEP</td>
<td>18</td>
<td>0.85</td>
</tr>
<tr>
<td>PEP/RVET</td>
<td>18</td>
<td>0.86</td>
</tr>
<tr>
<td>TPV</td>
<td>26</td>
<td>0.39</td>
</tr>
<tr>
<td>TPV/RVET</td>
<td>26</td>
<td>0.39</td>
</tr>
</tbody>
</table>

The heart rate ranged from 138 to 187 beats per minute.

Figure 15.13 shows the strikingly good correlation of PEP with systolic pulmonary arterial pressure in this selected population.

15.3.5.2. Term babies with a closed arterial duct

(1) There were insufficient data to investigate PEP in this group. The results for correlation of systolic pulmonary arterial pressure, and the arterial pressure ratio, with TPV and TPV/RVET are shown in table 15.8 (below), and graphically in figures 15.14, 15.15 and 15.16.

Table 15.8

<table>
<thead>
<tr>
<th></th>
<th>PA pressure (est)</th>
<th>PA:Ao ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>r</td>
</tr>
<tr>
<td>TPV</td>
<td>14</td>
<td>0.82</td>
</tr>
<tr>
<td>TPV/RVET</td>
<td>14</td>
<td>0.83</td>
</tr>
</tbody>
</table>

* TPV appeared to correlate in a manner best described by an exponential curve ($r^2=0.76$), seen in figure 15.15.

** TPV appeared to correlate in a manner best described by a logarithmic curve ($r^2=0.70$), seen in figure 15.16.
PEP v systolic pulmonary arterial pressure: Babies <33 weeks with closed arterial duct.

$y = 15.3 + 0.96x$

$R^2 = 0.72$

$R = 0.85$

TPV/RVET v systolic pulmonary arterial pressure: Term babies with a closed duct.

$R^2 = 0.69$

$R = 0.83$
**Figure 15.15**

TPV v systolic pulmonary arterial pressure:
Term babies with a closed duct

\[ y = 122 \times 10^{(-6.1e-3x)} \]

\[ R^2 = 0.76 \]

R = 0.82

**Figure 15.16**

TPV v pulmonary:systemic arterial pressure ratio:
Term babies with a closed duct

\[ y = 55 + 78 \times \text{LOG}(x) \]

\[ R^2 = 0.76 \]

R = 0.83
15.4 Discussion

(1) This analysis has been an attempt to identify factors which, by their elimination, may improve the weak correlation between systolic time intervals and their ratios with systolic pulmonary arterial pressure.

(2) Ductal patency in particular has a potent effect on the correlation, rendering the PEP/RVET ratio completely useless in determination of systolic pulmonary arterial pressure. This is not just the effect of turbulence interfering with measurement, because measurement of PEP is not altered by turbulence, and PEP did not correlate with systolic pulmonary arterial pressure when the duct was patent. PEP was relatively longer at a given systolic pulmonary arterial pressure in the presence of a patent duct. This could be explained if PEP is more closely related to diastolic or mean pulmonary arterial pressure than systolic pressure. Diastolic pressure may be raised by L-R ductal shunting as a result of left-to-right flow during diastole. When the duct is closed, pulmonary systolic arterial pressure may have a more consistent relationship to diastolic pressure, eg. as systolic pressure rises, so does diastolic, and therefore PEP (related to diastolic pressure) correlates with TR derived (systolic) pressures.

(3) The effect of ductal patency on the TPV/RVET ratio was not so clear, but certainly it worsened the correlation. A potential explanation could have been that the ratio reflects pulmonary vascular resistance more than systolic pressure, but this explanation seems unlikely because the values were not consistently lower (indicating a higher pulmonary vascular resistance) in babies with a patent duct. The difference is therefore probably due to increased error of measurement resulting from turbulence in the pulmonary artery. The accurate timing of the end of RVET can be very difficult in the presence of turbulence. It is also possible that, in cases of continuous left-to-right ductal flow, the forward pulmonary arterial flow is blunted by retrograde flow through the duct, leading to a shortened RVET.

(4) Gestational age had a marked effect on TPV. Babies of lower gestation have a shorter TPV at a given systolic pulmonary arterial pressure. These results are therefore consistent with the results of Evans and Archer (1990) who showed that healthy babies of lower gestation had lower TPV/RVET ratios (which would normally indicate a higher pulmonary arterial pressure), over the first three days of life.

(5) The TPV/RVET ratio appears to correlate less well with systolic pulmonary arterial pressure than the PEP/RVET ratio, when the duct is closed. TPV correlated as well with systolic pulmonary arterial pressure as the TPV/RVET ratio, particularly in the healthy preterm babies. This observation could be useful, because the measurement of a single systolic time interval is bound to be more repeatable than combining two into a ratio (see
chapter 16). Indeed, this may explain why TPV correlates as well as TPV/RVET with systolic pulmonary arterial pressure, despite the complicating influence of heart rate on TPV. Perhaps future studies of temporal variability, and the effect of therapeutic intervention, should include TPV alone rather than the TPV/RVET ratio, provided the heart rate does not fluctuate widely.

The final analysis showed that by careful selection of the population, the systolic time intervals and their ratios can provide a useful correlation with systolic pulmonary arterial pressure in the neonate. The regression line presented for PEP in preterm babies, derives from a particularly simple regression equation, such that an estimate of systolic pulmonary arterial pressure in mmHg can be made by subtracting 15 from PEP; eg. a PEP of 60 msec correlates approximately with a systolic pressure of 45 mmHg. Clearly this needs to be investigated further, in a prospective manner. The fact that PEP correlates as well as PEP/RVET is presumably due to the relatively small effect of heart rate on this time interval.

15.5

(1) In summary, TPV/RVET and PEP/RVET ratios are related to systolic pulmonary arterial pressure, but they are subject to other influences which include patency of the arterial duct, gestational age, and possibly other factors associated with respiratory distress.

(2) Within a limited gestational age range, and with a closed arterial duct, the PEP/RVET ratio, or PEP alone may be useful predictors of systolic pulmonary arterial pressure. The lack of correlation in the presence of a patent duct may be because PEP and PEP/RVET are more closely related to diastolic pressure or pulmonary vascular resistance.

(3) TPV and TPV/RVET have a close correlation with systolic pulmonary arterial pressure only in term babies with a closed duct, and in healthy preterm babies. These time intervals appear to be less useful in the sick preterm infant, particularly with a patent duct. The closer correlation seen in healthy babies suggests that factors such as myocardial dysfunction, or mechanical ventilation, may influence TPV and TPV/RVET.
Chapter 16:  Repeatability in measurement of Doppler ultrasound methods of pulmonary arterial pressure estimation.

16.1 Introduction

16.2 Repeatability between observers

1 Patients and methods
2 Results
   1 Subjective analysis
      1 TR
      2 TPV/RVET ratio
      3 PEP/RVET ratio
      4 PDAMAX
      5 PDAMEAN
   2 Statistical analysis
3 Discussion
4 Summary.

16.3 Temporal and within observer variability

1 Patients and methods
2 Results
3 Discussion

16.4 Summary

Figures
Bland-Altman plots of observations from two observers.
16.1 15 paired measurements of RV-RA pressure drop
16.2 15 paired measurements of peak TR jet velocity.

Tables

Tables 16.1 to 16.3- between observer study
16.1. Clinical details of patients.
16.2. Doppler measurements.
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Tables 16.4 to 16.7- within observer/temporal variability study
16.4. Clinical details of patients.
16.5. Paired Doppler measurements.
16.6. Coefficients of repeatability.
16.7. "Confidence steps" (inserted in text, section 16.3.3.)
Chapter 16: Repeatability in measurement of Doppler ultrasound methods of pulmonary arterial pressure estimation.

16.1 Introduction

(1) Preceding chapters have discussed the various different methods of estimating pulmonary arterial pressure in the neonate using Doppler ultrasound. All have their strengths, shortcomings and limitations. Because of this, and particularly because tricuspid regurgitation is frequently not present, even in the presence of pulmonary hypertension, it may be useful to combine these techniques. However, before there can be meaningful interpretation of individual measurements, the measurement error of each technique needs to be known.

(2) There are no reproducibility or repeatability studies of any of the Doppler methods for pulmonary arterial pressure determination in the neonate. A comparison of the four most frequently used methods is attempted in the present study, with some difficulty, because each method uses different units, and one is a ratio. Percentage variability of a ratio should probably not be directly compared with percentage variability of absolute values. Nevertheless, the method described by Bland and Altman, used in chapter 7 to compare Doppler and catheter derived RV-RA pressure drop, can also be used in repeatability studies, to produce a "coefficient of repeatability", representing 95% confidence limits, for each Doppler technique. The analysis is taken one stage further, producing a repeatability index, allowing some comparison between the techniques.

(3) Two aspects of repeatability were studied, namely interobserver (ie. between observer) variability, and intraobserver (within observer) variability. The study of within observer variability was designed to include a component of temporal variability, because most future studies using these Doppler techniques will be looking for change over a specified period. This time period is usually around one hour, eg after instigation of a specific therapy designed to lower pulmonary arterial pressure, so the same observer repeated the Doppler measurements one hour after the first measurements.

(4) The analysis of within observer repeatability was extended to include aortic and pulmonary stroke distances, as indices of pulmonary venous return and systemic venous return respectively.

(5) The Doppler methods to be studied were therefore in two categories, namely indices of pulmonary arterial pressure, and indices of blood flow.

(6) The indices of pulmonary arterial pressure were:
1. Application of the modified Bernoulli equation to the peak velocity of tricuspid regurgitation. Values were both analysed both in mmHg and metres/sec. No allowance was made for right atrial pressure.

2. Two systolic time interval ratios: the TPV/RVET and the PEP/RVET ratios obtained with pulsed Doppler at the pulmonary valve.

3. Maximal and mean left-to-right ductal flow velocities (in metres/sec.)

(7) Indices of blood flow were:

1. Aortic stroke distance and minute distance. These measurements are analogues of left ventricular output, which, in the absence of significant interatrial shunting, is a measure of pulmonary venous return (see methods chapter).

2. Pulmonary stroke distance and minute distance. These measurements are analogues of right ventricular output, and therefore reflect systemic venous return.

(7) Assuming that interatrial shunting is negligible, the extent to which left ventricular output exceeds right ventricular output indicates the proportion of blood passing L-R through the patent arterial duct. Since measurement of pulmonary arterial diameter is not reproducible, absolute values cannot reliably be compared, but relative changes in stroke distance over time will reflect relative change in the respective ventricular output. (Heart rate can be ignored in this context because it will be the same for left and right ventricular output).

16.2. Repeatability between observers

16.2.1 Patients and methods

(1) Two experienced neonatal Doppler echocardiographers, the author and a chief echocardiography technician, performed detailed echocardiographic studies on 26 neonates. There were 15 preterm babies and 4 term babies with structurally normal hearts, all of whom were clinically stable, (and 12 of whom had a patent duct) and 7 term babies with congenital heart disease (see table 16.1). The second examination was done immediately after the first. An attempt was usually made to record all of the Doppler measurements outlined above, though there were three exceptions to this. In addition to this, there were six babies in whom TR only was measured by three observers and, to avoid excessive handling, the other parameters were not measured. The babies with congenital heart disease also only had TR measured. Secondly, ECGs were not recorded in the well babies, so PEP could not
be measured in these. Thirdly, left-to-right ductal flow velocities were obviously only recordable when the duct was still patent.

(2) The third observer was an experienced echocardiographer, but with less practical experience in Doppler examination of the preterm neonate. This component was included in the study in an attempt to relate the results to the 'real-life' practical clinical setting. Each observer was unaware of the results of the other observers.

(3) The measured values were analysed by an independent statistician, who was asked to analyse the data to produce limits of accuracy for each technique, and to compare the relative repeatability between the techniques. This approach was used to avoid any bias in the interpretation of the results.

16.2.2 Results

(1) The subjects, and the measured Doppler values are listed in table 16.2. There were 16 paired measurements each of TR and TPV/RVET values, and 12 each of PEP/RVET and both PDA velocity measurements. For the TR measurements, the first two observers alone are included, to allow direct comparison with the reproducibility from the other methods. There are two useful ways of interpreting these results. The first is simply to look at the differences in measured values of each baby. The second is a more objective statistical analysis.

16.2.2.1 Subjective analysis

1. TR The RV-RA pressure drops determined by the TR technique are remarkably similar when comparing the results of the first two observers. The largest difference was in subject 20, of 6.5 mmHg. As discussed in chapter 7, larger errors can be expected at higher pressures. There were only two values above 60 mmHg, one was in subject 20 and the other was subject 26 in whom there was very close agreement. The fact that the agreement was this close is certainly a chance event; the value of the third observer was 14 mmHg lower. Nevertheless, even this largest discrepancy only represents a maximal difference of 0.34 metres/sec. between the highest and lowest values. Since most RV-RA pressure drops will be lower than this in the preterm baby, narrow margins of repeatability can be predicted.

2. TPV/RVET ratio Most of the paired values fall within 0.06 of each other, but there were four examples where the difference exceeded 0.08. The general impression is of worse agreement between observers than seen with the TR method.

3. PEP/RVET ratio In general there is close agreement, to within 0.05. On two occasions
however, the discrepancy was very large. In case 5 the second value was almost half the first value, and with case 18 the second value was almost double the first.

4. PDA MAX There was mostly close agreement between observers. The largest difference was 0.62 metres/sec. (subject 19); all the others were less than 0.4 metres/sec. The two measured velocities were 1.45 and 2.07 metres/sec. Applying the Bernoulli equation at these velocities, this represents a maximal difference in pressure drop across the duct of 8.8 mmHg: \((1.45^2 \times 4)=8.4 \text{ mmHg}, \) \((2.07^2 \times 4)=17.2 \text{ mmHg}\).

5. PDA MEAN Again there is mostly good agreement between observers. One subject (10) however, shows a large difference; 0.69 metres/sec., which (applying the modified Bernoulli equation, as done previously by Musewe et al (1990)) would represent a change in pressure drop across the duct of 8 mmHg \(((1.76^2 \times 4)-(1.07^2 \times 4) = 12.4-4.6 \text{ mmHg})\). This case also showed a large change in TPV/RVET ratio as well as PDA MAX suggesting that there may have been a genuine change in pressure between observers. In subject 1, the velocity almost doubled between observers, from 0.41 to 0.76 metres/sec. At such low velocities, very small changes in pressure gradient will produce large changes in velocity. This rise of 0.35 metres/sec. probably represents a true pressure change of less than 2 mmHg (although viscous friction may invalidate the modified Bernoulli equation at such a low velocity), which is surely to be expected from normal temporal variation: \((0.41^2 \times 4)=0.68 \text{ mmHg}, \) \((0.76^2 \times 4)=2.30 \text{ mmHg}\).

16.2.2.2 Statistical analysis

(1) The analysis used is described in detail by Bland and Altman (1986). Figures 16.1 and 16.2 are example plots of the difference between the two measurements against the mean value of the two measurements. Dotted lines indicate 2 standard deviations above and below zero difference. These lines represent the repeatability coefficient. Any change in the Doppler measurement larger than the repeatability coefficient represents a genuine difference, not attributable to between observer error (95% of the time). The coefficients for each method are shown in table 16.3 and confidence intervals for the coefficient are also shown. The wide confidence intervals reflect the small numbers.

(2) A repeatability index was designed to allow comparison of repeatability between the different Doppler techniques, since they are all in different units. The repeatability coefficient for each Doppler technique was divided by the overall mean measurement for that technique, and the ratio derived was then multiplied by 100 to produce a percentage. This index therefore represents the average percentage change required to reach significance. These values, also with their confidence intervals, shown in table 16.3.
Figure 16.1  
Difference between observers:  
RV-RA pressure drop

Figure 16.2  
Difference between observers  
for velocity of TR jet
Taking PDAMAX as an example, the average velocity was 1.98 metres/sec. The coefficient of repeatability was 0.56; 0.56/1.98 = 0.28. Therefore the repeatability index is 28%.

16.2.3 Discussion

(1) It is unfortunate that it was not possible to measure all five parameters in every baby. Nevertheless, the differences in between observer repeatability of the techniques were large and unequivocal. In particular, both systolic time interval ratios were not reproduced accurately by two experienced observers. Comparing the repeatability indices, it is clear that, in terms of percentage change required to detect a significant difference, the TR technique is the best. Using the TR velocity in metres/sec., a difference of over 8% can be detected with confidence whereas using the TPV/RVET ratio, the difference must be over 35% to be detected with confidence.

(2) It is interesting that the index is lower for the TR velocity when it is expressed in metres/sec. (8%), than when it is expressed in mmHg (15%). This difference can only be due, in some way, to transformation from velocity to pressure, and therefore presumably is due to the multiplication factor, $4v^2$. This situation is clarified when figures 16.1 and 16.2 are compared. The difference between observers becomes much larger at higher values, but this is not so marked with values expressed in metres/sec. The largest difference between observers is 6.6 mmHg, (86.9-80.3 mmHg) for subject 20, but the difference in metres/sec. is 0.18 metres/sec. (4.66-4.48 metres/sec.). The percentage error in mmHg for this subject is $(6.6/83.3) \times 100 = 8\%$ and in metres/sec. is $(0.18/4.57) \times 100 = 4\%$. Therefore larger percentage errors can be expected at higher pulmonary arterial pressures, when the results are expressed in mmHg. Since subjects with pulmonary hypertension are likely to have higher temporal variability anyway, due to the nature of this condition, it would seem especially prudent in these subjects to express the velocity in metres/sec. rather than mmHg when values from two separate observers are to be compared.

(3) As mentioned at the start of this section, there are problems comparing percentage change like this. In particular, to use the repeatability index in the context of ductal flow velocities is probably unwise, because some of the values were very low; and only small changes in velocity can produce large percentage differences. For example, in subject 11, the maximal ductal velocity changes from 0.48 to 0.60 m/sec., a change of only 0.12 m/sec., yet this represents a difference of 25%. If the Bernoulli equation is applied to the ductal flow velocity, this 25% difference indicates a calculated change in pressure drop of less than 1 mmHg! Nevertheless, ductal flow velocities and the TR jet are both recorded in metres/sec., and a significantly larger interobserver error was found for ductal flow velocity, even when they were in the same range (between 2.4 and 3.5 metres/sec.). This larger
difference could be explained either by genuine between observer error or by temporal variability. Ductal flow depends on the balance of systemic and pulmonary arterial pressures, and each of these pressures has its own inherent variability, therefore it would be surprising if ductal flow were not more variable than tricuspid regurgitation, which reflects pulmonary arterial pressure alone.

(4) What does a repeatability coefficient of 0.13 for the TPV/RVET ratio actually mean in terms of the estimated pulmonary arterial pressure? An idea of the effect of these wide confidence intervals can be obtained by referring to the data of Kosturakis et al (1984), who correlated the TPV/RVET ratio obtained from the distal main pulmonary artery with directly measured mean pulmonary arterial pressure in 17 children with congenital heart disease. Their data have been redrawn in figure 16.3. The original data show enormous variability, with a weak correlation, and large standard error of the estimate. A TPV/RVET ratio of 0.25 could imply a mean pulmonary arterial pressure of between 22 and 60 mmHg, even before applying the repeatability coefficient for determination of this ratio. However, if the scatter from this data is ignored, and a perfect correlation line is drawn, the effect of actual observed differences in the present study can be examined. The average difference between observers for the TPV/RVET ratio was 0.06 (range 0 to 0.11). Subject 18 is therefore an average example. The two ratios, 0.34 and 0.29 are indicated in figure 16.3. The resulting average difference in mean pulmonary arterial pressure is 8 mmHg, higher than the largest error of the TR flow measurements.

(5) However these results are analysed, the between observer variability of the TPV/RVET ratio is very high, and the same is true of the PEP/RVET ratio. Such poor repeatability is unacceptable in the clinical setting, where values may be generated by a number of different observers. This evidence, and the evidence from simultaneous Doppler-catheterisation studies, suggest that systolic time intervals, including the TPV/RVET ratio, cannot be relied upon to follow the course of changes in pulmonary arterial pressure in the newborn when the observations are made by more than one observer.

(6) Why is the reproducibility so poor? When the difference between the PEP, TPV, and RVET measurements of the two observers are expressed as percentage error, the average mean error (mean interobserver error) was highest for TPV (17%). Mean error was 9% for RVET and 13% for PEP. Therefore it is the determination of TPV which, on average, caused the most difficulty. Since, as previously discussed, the principle effect of movement of the pulsed Doppler sample around the pulmonary artery is to alter TPV (Pandis et al, 1986), it may be that subtle differences in positioning of the sample around these small main pulmonary arteries are to blame for this error. Turbulence within the pulmonary artery sometimes disturbs the contour of the pulmonary waveform, making accurate location of the point of peak velocity, as well as the end of the ejection time, rather difficult and prone to
Figure 16.3

Mean pulmonary arterial pressure v TPV/RVET ratio (Kosturakis et al, 1984)

"Average difference" between two TPV/RVET values (subject 10)
subjective variability.

(7) All time intervals were therefore difficult to repeat accurately. Are these results inconsistent with results from other studies of repeatability in older children? Most publications validating the TPV/RVET ratio against direct measurement do not report variability between observers, but Dabestani et al (1987) reported a mean interobserver error for TPV of 6.8% among 39 adults. This is half the mean error in the present study. This difference could be due to a number of factors. Adults usually lie still, and have much larger pulmonary arteries. Babies tend not to lie motionless, have very narrow pulmonary arteries, and turbulence from ductal flow can disturb the signal. Furthermore, there may also be more genuine temporal variability occurring between examinations, particularly in the ventilated babies. Nevertheless, if we assume that Dabestani et al had a similar mean error for RVET as for TPV (9%), the expected error for the TPV/RVET ratio can be estimated from these figures. Thus, when a TPV of 70 msec and a RVET of 200 msec is measured by the first observer, and TPV is overestimated by 9% and RVET underestimated by 9% by the second observer, the TPV/RVET ratio will change from 70/200=0.35 to 76.3/182=0.42, representing an increase of 20%. Therefore, even applying these more modest margins of error, differences greater than 20% are to be expected frequently due to interobserver error alone.

(8) This analysis suggests that our results are broadly consistent with those of Dabestani et al; high interobserver error for the TPV/RVET ratio is to be expected.

16.2.3. In summary, this section has defined limits of between observer variability, by producing a repeatability coefficient for each Doppler technique for determining pulmonary arterial pressure in the neonate. A comparison of these techniques using a repeatability index shows that TR velocity measurement carries the least interobserver error, particularly when results are expressed in metres/ sec. rather than mmHg. Measurement of maximal ductal flow is less repeatable than TR velocity, possibly because ductal flow is dependent on the balance of systemic and pulmonary arterial pressures, whereas TR reflects only pulmonary arterial pressure. The repeatability index may unfairly discriminate against the ductal flow technique because small changes at low velocities are interpreted as high percentage errors.

16.3. Variability due to within observer error and temporal variability.

16.3.1. Introduction

(1) During haemodynamic assessment in neonatal intensive care, two measurements are
usually made by a single observer before and after some kind of therapeutic intervention. It would therefore be useful to define the confidence limits for the degree of change in a measurement over a given time period. For example, if a baby with a TR velocity of 3.2 metres/sec. is given tolazoline, and at re-examination half an hour later, the TR velocity is 3.05 metres/sec., can we be 95% confident that there has been a genuine change due to the drug, or could this change be due to random, temporal or within observer variability?

(2) The study was extended to include indices of blood flow, including aortic stroke distance and pulmonary stroke distance. Systolic blood pressure and heart rate were also recorded as easily recognisable clinical parameters of haemodynamic temporal variability. (It would have been better to have had between observer data for these measurements as well, but this was not done.)

16.3.2 Patients and methods

(1) Eleven babies receiving intensive care underwent two detailed Doppler-echocardiographic examinations separated by approximately one hour. They were aged between 12 and 64 hours. The first 12 hours were avoided because of the potential for rapid haemodynamic change over this time, and to avoid excessive handling during this critical period. Five babies were receiving 100% oxygen. Birth weight was between 785 g and 3545 g (mean 1840 g) and gestational age was between 26 and 40 weeks (mean 32.3 weeks). Further clinical details are given in table 16.4.

(2) Each examination was performed by the same observer, recording the first and second scans on separate tapes to be analysed subsequently on different occasions. This was done to avoid the examiner remembering the results of the first scan and generating bias in the interpretation of the Doppler signals.

(3) Care was taken to include only babies who were clinically stable, and in particular, not having large swings in oximetry readings. Pulse oximetry was used in all babies and readings at the second examination were always within 3% of the first.

(4) Systemic arterial pressure was recorded with oscillometry (Dinamap) to avoid the handling necessary for Doppler sphygmomanometry. The RV-RA : BP ratio was also calculated.

(5) Aortic minute distance was calculated by multiplying aortic stroke distance by the heart rate. This is an index of left ventricular output, (as described earlier in chapter 6) avoiding the error introduced by repeated measurement of the cross-sectional area of the aorta. Temporal variability of aortic minute distance are comparable to that of left ventricular
output in studies where a single measurement (rather than paired measurements) of the aortic root was made. Similarly, pulmonary stroke and minute distance was also calculated.

16.3.3. Results

(1) The paired measurements are shown in table 16.5. The same analysis as described for between observer variability was done here, and a repeatability coefficient and repeatability index were calculated and presented in table 16.6. These are small numbers, and the confidence intervals are wide. Nevertheless, the results for the indices of pulmonary arterial pressure are strikingly similar to those of the interobserver study. Measurement of the velocity of tricuspid regurgitation was very repeatable, with little temporal variability (under these stable conditions). It can be deduced that within observer variability is low. Once again, the repeatability is better when values are expressed in metres/sec. rather than mmHg (9% versus 17%). (It needs to be remembered that a high repeatability index is associated with poor repeatability). The RV-RA:BF ratio, has a higher repeatability index (23%), indicating that this measurement was less repeatable, presumably due to the fact that two measurements are combined, each with its own inherent variability and error, into a ratio. The TPV/RVET ratio has a narrower repeatability coefficient (0.10) than with the interobserver study, demonstrating the importance of using a single observer with this method.

(2) Aortic stroke distance had a low repeatability index, of 10%, of the same order as heart rate (11%). Combing these two values, the minute distance had a repeatability index of 17%. Therefore to confidently detect a change in left ventricular output using Doppler echocardiography, there must be a change of over 17%. Pulmonary stroke distance had a significantly higher repeatability index (26%).

(3) As mentioned in the previous section (16.2.3.), the repeatability index may sometimes be an unfair means of comparison for the parameters of pulmonary arterial pressure. To test the value of each of these Doppler measurements further, the repeatability coefficient was divided by the total range of values which are likely to be seen in the sick neonate. In effect this analysis shows how many “confidence steps” there are from lowest to highest values, and is an indication of how useful the test may be in distinguishing low pulmonary arterial pressures from high ones. For example, the vast majority of RV-RA pressure drop values encountered in this thesis lie between 12 mmHg and 65 mmHg, a range of 53 mmHg. The repeatability coefficient is 6.5 mmHg. The number of ‘confidence steps’ over this range is 53/6.5 = 8.2. The other values are presented overleaf.
Table 16.7

<table>
<thead>
<tr>
<th>Doppler Measurement</th>
<th>Lowest expected value</th>
<th>Highest expected value</th>
<th>Expected range</th>
<th>Repeatability coefficient</th>
<th>Number of &quot;confidence steps&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR velocity (m/s)</td>
<td>1.8</td>
<td>4.0</td>
<td>2.2</td>
<td>0.26</td>
<td>8.5</td>
</tr>
<tr>
<td>TPV/RVET</td>
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<td>0.50</td>
<td>0.32</td>
<td>0.10</td>
<td>3.2</td>
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<td>0.50</td>
<td>0.38</td>
<td>0.12</td>
<td>3.2</td>
</tr>
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<td>PDAMAX (m/s)</td>
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<td>3.50</td>
<td>3.10</td>
<td>0.48</td>
<td>6.5</td>
</tr>
<tr>
<td>Ao Stroke Dist</td>
<td>5.0</td>
<td>16.0</td>
<td>11.0</td>
<td>1.1</td>
<td>10.0</td>
</tr>
<tr>
<td>Pa Stroke Dist</td>
<td>2.5</td>
<td>14.0</td>
<td>11.5</td>
<td>1.9</td>
<td>6.1</td>
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</table>

16.3.4 Discussion

(1) When any new measurement technique is introduced into clinical practice, it is essential to evaluate the error inherent in the technique. The 'acceptable' error, for a technique to be clinically useful, alters according to the degree of change in a given variable that can occur. A technique detecting a 20% change will be of little value if a parameter never varies by more than 20%. On the other hand, a technique detecting a 20% change could be very useful if variation of 100% is anticipated. This aspect of the 'usefulness' of a technique, with a known range of error of measurement, is most important in comparing different techniques. Thus, although the ductal flow velocities and systolic time intervals have similar indices of repeatability, the ductal flow velocities may be more useful because the range of potential change is larger. This was summarised by using the concept of "confidence steps" above. Systolic time intervals are therefore likely to be of less use than ductal flow velocities, when following the effect of therapeutic intervention to lower pulmonary arterial pressure. Nevertheless, an index of pulmonary arterial pressure may often be needed when there is neither a measurable TR jet, nor a patent arterial duct, and systolic time intervals can be used in the context of serial measurement by the same observer, provided the limits of repeatability are borne in mind.

(2) Aortic stroke distance was the most reproducible measure of flow, with the same average percent variability (approximately 10%) over one hour as heart rate and the velocity
of tricuspid regurgitation. There have been other reports of repeatability of this measurement. Mellander et al (1987), in a study of ten children from six weeks to 13 years of age, found a mean coefficient of repeatability for aortic velocity measurements of between 2.5 and 10.9% (each patient underwent six consecutive examinations). The values suggest similar limits of repeatability to the present study. However, Robson et al (1988), in their study of eight healthy adults, showed a lower repeatability coefficient for both aortic stroke distance (6.4%), and left ventricular output (9%). The figure of 9% compares rather favourably with that of 17% for aortic minute distance in the present study. However, it is hardly surprising that sick preterm babies should have a greater degree of temporal haemodynamic variability than healthy adults, and the fact that left ventricular output can vary so much (by more than 300% in some babies in chapter 14), suggest that the confidence interval of 17%, would provide a useful confidence step in assessing change.

(3) The most thorough evaluation of repeatability of left ventricular output measurements in neonates was done by Hudson et al in 1990. They studied 12 healthy neonates, using the same method as the present study, (using continuous wave Doppler from the suprasternal notch), and found within observer variance of 16.5% for aortic minute distance- remarkably similar to our findings.

(4) In chapter 14 it was shown that the neonate regulates left ventricular output primarily by alteration in stroke volume rather than heart rate, at least with regard to left-to-right ductal shunting, (this was also shown by Walther et al in 1989 and Lindner et al, in 1990) so serial measurement of stroke distance may be a useful, and a highly reproducible way to observe changes in left ventricular output. Pulmonary stroke distance showed greater variability. This of course, may be due to genuine temporal variation, rather than measurement error, but a measurement error might result from the phenomenon described by Lighty et al (1986), where the velocity measured by pulsed Doppler varies considerably with position of the Doppler sample in the main pulmonary artery. Care was taken to minimise this effect, but, as discussed with regard to the measurement of TPV, small movements can produce big changes in the relative position of the sample within the small pulmonary artery.

16.4.

(1) In summary, this second section has evaluated the cumulative temporal, random and within observer variability of Doppler indices of flow and pulmonary arterial pressure, over a one hour period in babies undergoing intensive care in the first three days of life (excluding the first 12 hours). These limits of repeatability can have practical application for all of the techniques in evaluating therapeutic intervention designed to alter pulmonary vascular resistance. The techniques that were most reproducible were the velocity of
tricuspid regurgitation and aortic stroke distance.

(2) A new technique for evaluating the "usefulness" of a measurement technique has been described, by calculating the number of "confidence steps" for the technique, by dividing the expected range of values within the population to be studied by the repeatability coefficient.
Table 16.1. Patient details for between observer study

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<tr>
<th>id</th>
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<th>FiO2 %</th>
<th>age hours</th>
<th>diagnosis</th>
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</tr>
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<td>3250</td>
<td>21</td>
<td>212</td>
<td>COARCTION post op</td>
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HMD, hyaline membrane disease, all ventilated.
Table 16.2. Repeatability study. Doppler values from different observers on the same babies.
Table 16.3. Between observer variability: Coefficient of repeatability and repeatability index for Doppler measurements of pulmonary arterial pressure.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>No. pairs</th>
<th>Repeatability coefficient</th>
<th>95% confidence limits (%)</th>
<th>Repeatability index (%)</th>
<th>95% confidence limits (%)</th>
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</thead>
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<tr>
<td>TR velocity</td>
<td>16</td>
<td>0.24</td>
<td>0.18 - 0.37</td>
<td>8</td>
<td>6 - 12</td>
</tr>
<tr>
<td>(metres/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV-RA</td>
<td>16</td>
<td>6.3</td>
<td>4.7 - 9.5</td>
<td>15</td>
<td>11 - 22</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPVET</td>
<td>16</td>
<td>0.13</td>
<td>0.10 - 0.20</td>
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<td>26 - 54</td>
</tr>
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<td>PEPET</td>
<td>12</td>
<td>0.12</td>
<td>0.09 - 0.20</td>
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<td>32 - 74</td>
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<td>PDA max</td>
<td>12</td>
<td>0.56</td>
<td>0.40 - 0.92</td>
<td>28</td>
<td>20 - 47</td>
</tr>
<tr>
<td>(metres/sec)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PDA mean</td>
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<td>0.41 - 0.95</td>
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<td>26 - 60</td>
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<td>(metres/sec)</td>
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Table 16.4. Subjects for temporal/within observer variability study

<table>
<thead>
<tr>
<th>ID</th>
<th>Gestation (weeks)</th>
<th>Bwt (g)</th>
<th>Diagnosis</th>
<th>Age (hours)</th>
<th>FIO2 %</th>
<th>Oximetry %</th>
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<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>1640</td>
<td>HMD (surf)</td>
<td>64</td>
<td>24</td>
<td>85</td>
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<tr>
<td>2</td>
<td>36</td>
<td>2800</td>
<td>HMD (surf)</td>
<td>28</td>
<td>65</td>
<td>85</td>
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<td>3</td>
<td>29</td>
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<td>Immaturity</td>
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<td>4</td>
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<td>5</td>
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<td>HMD, PTC</td>
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<td>90</td>
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<td>6</td>
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<td>2535</td>
<td>HMD, PTC</td>
<td>17</td>
<td>100</td>
<td>89</td>
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<tr>
<td>7</td>
<td>32</td>
<td>1610</td>
<td>Pulm H’age</td>
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<td>100</td>
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<td>935</td>
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<td>2000</td>
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<td>HMD, asphyxia</td>
<td>14</td>
<td>100</td>
<td>81</td>
</tr>
</tbody>
</table>

Immaturity, baby was ventilated because of respiratory centre immaturity (recurrent apnoea) and wet lungs. Pulm H’age, pulmonary haemorrhage. surf, baby has received surfactant therapy. PTC, persistent transitional circulation.
Table 16.5. Temporal/within observer variability.
Doppler values from the start of the study (1) to one hour later (2).

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Table 16.6. Temporal variability: Coefficient of repeatability and repeatability index for Doppler measurements of pulmonary arterial pressure and flow.

<table>
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<th>Measurement</th>
<th>No.pairs</th>
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<th>95% confidence limits</th>
<th>Repeatability index (%)</th>
<th>95% confidence limits (%)</th>
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<td>6 - 17</td>
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<td>RV-RA (mmHg)</td>
<td>8</td>
<td>6.45</td>
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<td>PDA max (meters/sec)</td>
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<td>Aortic minute distance (cm)</td>
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<td>Pulmonary stroke distance (cm)</td>
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<td>Systolic BP (mmHg)</td>
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<td>8</td>
<td>5 - 15</td>
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<td>Heart rate (beats/min)</td>
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<td>17</td>
<td>12 - 30</td>
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<td>8 - 20</td>
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<td>RV-RA : BP ratio</td>
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<td>0.18</td>
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<td>23</td>
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</tr>
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</table>
Chapter 17: The haemodynamic effects of different levels of inspired and blood oxygen in neonatal respiratory failure

17.1 Introduction

17.2 Study group

17.3 Methods

17.4 Statistical analysis

17.5 Results

1. 84-88% to 95-97% SaO2
2. 95-97% to 100% SaO2
3. 84-88% to 100% SaO2

17.6 Discussion

1. Doppler echocardiographic methods and "confidence step" analysis
2. Interpretation and significance of the findings

17.7 Summary

Tables
17.1 Details of subjects and clinical status
17.2 Haemodynamic measurements at 84-88% SaO2

Figures
17.1 Direction of change in SaO2 within each subject.
17.2 Serial values for RV-RA pressure drop with increasing SaO2

Figures 17.3 to 17.5 display "confidence steps" in pulmonary arterial pressure evaluation
17.3 84-88% to 95-97% SaO2
17.4 95-97% to 100% SaO2
17.5 84-88% to 100% SaO2

There are two photographs relevant to this chapter, demonstrating change in ductal flow with increasing arterial oxygen saturation: 24 - At 85% SaO2 there is bidirectional ductal flow. 25 - At 100% SaO2 there is pure left-to-right ductal flow.
Chapter 17: The haemodynamic effects of different levels of inspired and blood oxygen in neonatal respiratory failure

17.1 Introduction

(1) Careful control of arterial oxygenation is crucial to the management of babies with neonatal respiratory failure. Hyperoxia is associated with retinal damage, and for this reason, most units try to avoid high blood oxygen levels, particularly in extreme prematurity. The longitudinal study presented earlier in chapter 10 showed that hyaline membrane disease is associated with pulmonary hypertension, systemic hypotension and prolonged ductal patency. From physiological studies in both animals and humans, (discussed in chapter 1), it can be predicted that, in the presence of respiratory disease, the attainment of normal oxygen levels by the adjustment of supplemental oxygen could lead to a beneficial reduction in pulmonary arterial pressure, an increase in systemic pressure, and ductal constriction or closure (Saling et al, 1960; Cook et al, 1963; Cassin et al, 1964; Moss et al, 1964). Thus increasing inspired oxygen levels might ameliorate some of the major haemodynamic features of neonatal respiratory failure. Healthy preterm infants normally have arterial oxygen saturation levels of above 95%, as assessed by a pulse oximeter validated against arterial line measurements (Poets et al, 1992). Therefore, it could be argued that maintaining oxygen saturations below this level is not physiologically appropriate, particularly since with this instrument SaO2 values below 97%, are not associated with hyperoxaemia defined as PaO2 values greater than 100 mmHg.

(2) The Doppler echocardiographic techniques evaluated in this thesis now permit detailed assessment of the haemodynamic effects of different levels of inspired oxygen. This study uses four of these Doppler echocardiographic methods of pulmonary arterial pressure estimation combined with Doppler indices of blood flow and with systemic arterial pressure.

(3) There were two main aims to this study:

1. To study the haemodynamic effects of a temporary increase in arterial oxygen saturation (SaO2) from 84-88%, to 95-97% for 10-15 minutes in preterm babies with respiratory failure.

2. To study the effect of ten minutes of hyperoxia (FiO2 and SaO2 100%, or as high as possible when unventilated) in babies over 30 weeks gestation with respiratory failure.
17.2 Study group

Eighteen preterm infants undergoing intensive care were studied. Clinical details are summarised in table 17.1. In subjects 1-3 the arterial duct had closed. The other 15 had patent ducts and are listed in order of gestational age from 28 to 36 weeks, (mean 31.2 weeks). Birth weights were 800-2990 g (mean 1721 g). They were aged between 9 and 76 hours. One baby receiving positive pressure ventilation (IPPV) was breathing air (subject 15), and another 24% oxygen (subject 14). The rest were breathing between 40 and 65% oxygen. All but two were receiving IPPV (subjects 17 and 18).

17.3 Methods

(1) All echocardiographic examinations were performed by the same observer and recorded on tape for subsequent analysis. The results for different values of inspired oxygen and therefore different SaO₂ levels were recorded on different tapes to avoid subjective bias in interpretation of the Doppler signals. Patients were selected only if they were clinically stable. None had undergone any other therapeutic intervention over the previous hour, such as administration of inotropes or surfactant or alteration of ventilator settings. Each baby had already been positioned in a supine position after their last period of nursing care. No additional sedation was given for the examination. Prior to echocardiography, the SaO₂ level was controlled by a Nellcor N200 pulse oximeter in the beat to beat mode, and, when necessary, the FiO₂ was adjusted to achieve an SaO₂ level between 84 and 88%. This particular oximeter was used because it has been calibrated against arterial line measurement for use in the neonate (Southall et al, 1987; Bucher et al, 1989). The SaO₂ was stable for at least 15 minutes before the start of the investigation.

(2) Following the first echocardiographic examination, the FiO₂ was elevated to achieve 95-97% saturation, and the level was maintained for ten minutes before the second examination. The final measurement was done after increasing the FiO₂ to 100% to achieve 100% saturation for ten minutes.

(3) On applying the Nellcor N200 pulse oximeter, some babies were found to have 100% arterial saturation at the beginning of the study. In these cases, the procedure was performed in reverse, allowing the inclusion of some babies of less than 30 weeks gestation in the hyperoxia stage, although they were not breathing 100% oxygen. Figure 17.1 summarises the examinations performed at each level, and the order in which they were done in each baby.
Figure 17.1 to show direction of arterial oxygen saturation change in each baby

OXIMETRY RECORDING

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<td>18-</td>
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</table>
The Doppler measurements taken were as follows.

a) Indices of pulmonary arterial pressure.
   1. PEP/RVET ratio.
   2. TPV/RVET ratio.
   3. PDA max (metres/sec) - This measurement is determined by the pressure gradient between the aorta and pulmonary artery, and hence can change due to either (or both) systemic and pulmonary arterial pressure changes.
   4. TR. (metres/sec)

b) Indices of pulmonary and systemic flow.
   1. Aortic stroke distance. (Reflecting serial change in left ventricular stroke volume, which is influenced primarily by pulmonary venous return, and hence is an index of pulmonary blood flow)
   2. Pulmonary stroke distance. (Reflecting serial change in right ventricular stroke volume, and therefore an index of systemic venous return)

Normal values for these measurements have not been published. Amongst the 17 healthy preterm neonates (the same babies as in chapter 8 on pulmonary arterial pressure determination in healthy neonates), the values between 12 and 72 hours were, mean (SD): aortic stroke distance 9.6 (1.6) cm, range 7.0 to 12.9 cm; pulmonary stroke distance 7.8 (2.2) cm, range 4.7 to 12.5 cm.

Ductal size was graded visually from 0-3 as described in the methods chapter (6).

Also recorded was heart rate and systolic blood pressure by oscillometry (Dynamap), or by indwelling arterial line.

17.4 Statistical analysis

Limits of repeatability for the Doppler measurements were established in the previous chapter, and were used in the analysis of results in this section. Each of the Doppler measurements is in different units, so to allow meaningful comparison of the results from all of the babies and all of the techniques, the values have been expressed as changes from the initial value in "confidence steps". One confidence step is equal to the repeatability coefficient of that measurement or the change required to reach significance, larger than the expected limits of within observer, random or temporal variability. Taking tricuspid regurgitation as an example, the repeatability coefficient is 0.26 m/s. A change of 0.26 m/s from the initial value indicates a significant change, and represents one confident step. A change of 0.52 m/s is two confident steps etc. Changes in each Doppler index are presented...
as confidence steps from the baseline value. The other repeatability coefficients were:
PEP/RVET, 0.12; TPV/RVET, 0.10; PDA max 0.48 m/s; aortic stroke distance 1.1 cm, and
pulmonary stroke distance 1.9 cm.

17.5 Results

(1) The baseline values for the Doppler measurements are shown in table 17.2. The first
three subjects had closed arterial ducts, and subjects 3 and 6 did not have tricuspid
regurgitation. In subjects 3, 8 and 16, there was interference on the ECG signal, so that PEP
could not be accurately determined. Therefore, in these babies some indices of pulmonary
arterial pressure were not measured.

(2) Figure 17.2 shows serial measurements of the right ventricle to right atrial (RV-RA)
pressure drop calculated using the modified Bernoulli equation in babies in whom the peak
velocity of tricuspid regurgitation was measurable.

(3) Figures 17.3, 17.4 and 17.5 summarise the changes in each index of pulmonary arterial
pressure between different saturations. Leftward deflection from zero indicates a fall in
pulmonary arterial pressure (ie a decrease in TR and PEP/RVET, and an increase in
TPV/RVET and PDAMAX), and rightward deflection indicates a rise. Figure 17.5 shows
examples of the change in the Doppler indices with a fall in pulmonary arterial pressure.

17.5.1. Change between 84-88% and 95-97% SaO₂ (Figure 17.3)

(1) There were no consistent changes, only two of the fifteen babies (13%), included in this
stage showed clear evidence of falling pulmonary arterial pressure (subjects 4 and 17). In
some babies, the Doppler indices seem to indicate change in opposing directions, though
they never reach a confidence step in opposite directions. The duct closed completely in
one baby (subject 14). The duct constricted slightly in another two (subjects 8 and 12)
associated with an increase in ductal flow velocity, and in baby 12, with a rise in mean
blood pressure (7 mmHg). There were no significant changes in aortic or pulmonary stroke
distance.

17.5.2. Change between 95-97% and 100% SaO₂ (figure 17.4)

(1) Five of the ten babies show clear evidence of a fall in pulmonary arterial pressure, and
in two this fall was large (subjects 12 and 13). When the modified Bernoulli equation was
applied to the TR velocity, the fall in RV-RA pressure drop in these two babies was
12 mmHg and 17 mmHg respectively. Ductal constriction was seen in four babies (subjects
Figure 17.2

Serial values for right ventricle-right atrial pressure drop.

RV-PA pressure drop (mmHg)

ID

1
2
4
5
7
8
9
10
11
12
13
14
15
16
17
18

SaO2

86% 96% 100%
12,13,15,17), and this was associated with a slight rise in mean blood pressure (4-6 mmHg) in three and a significant fall in aortic stroke distance (2.2-3.1 cm) in three. Babies 7 and 18 also had a rise in blood pressure (5 and 8 mmHg respectively) without obvious ductal constriction.

17.5.3 Change between 84-88% and 100% SaO\textsubscript{2} (figure 17.5)

(1) Of the 11 babies who passed from the lowest saturation to the highest saturation, 7 experienced a definite fall in pulmonary arterial pressure (64%). The change in pattern and velocity of ductal flow was sometimes very striking (plates 24 and 25). Subject 18 had an increase in ductal flow velocity only which was associated with an increase in mean blood pressure of 7 mmHg; both systolic time intervals were unchanged. Pulmonary arterial pressure did not fall at all in two babies (subjects 7 and 14); baby 7 had very poor ventricular function, (reflected in the low aortic and pulmonary stroke distances), and hyaline membrane disease complicated by pneumonia, while baby 14 was the only baby not to have pulmonary hypertension in the first place (the initial RV-RA pressure drop was only 14 mmHg).

(2) Aortic stroke distance fell significantly in only one baby (subject 12), by 3.7 cm (30%) associated with the only significant rise in blood pressure (9 mmHg systolic and 13 mmHg mean). Between 96 and 100% SaO\textsubscript{2}, the aortic stroke distance had risen slightly in subjects 15 and 17. These babies had a significant fall in stroke distance during ductal constriction between 86% and 96% saturation. Overall, between 96 and 100% SaO\textsubscript{2}, the fall in aortic stroke distance was not to one confidence step in these babies.

(3) Pulmonary stroke distance rose in only one baby (subject 18) by one confident step.

17.6. Discussion

17.6.1 Doppler echocardiographic methods and "Confidence step" analysis

(1) Previous non-invasive evaluations of pulmonary arterial pressure in hyaline membrane disease have concentrated on only one echocardiographic technique. However, there may be merits in combining a number of techniques, because each has its own advantages and disadvantages. The peak velocity of tricuspid regurgitation reflects systolic pulmonary arterial pressure, whereas flow velocity through the arterial duct is related to the balance of pulmonary and systemic arterial pressures throughout the cardiac cycle (Musewe et al 1987; Houston et al, 1989). The PEP/RVET ratio is probably most closely related to pulmonary vascular resistance or diastolic pulmonary arterial pressure, and probably also to right
Legend for figures 17.3, 17.4 and 17.5

These three figures summarise the changes in all of the Doppler echocardiographic indices of pulmonary arterial pressure at the three levels of arterial oxygen saturation; 86%, 96% and 100%. To allow the measurements, each with different units, to be displayed simultaneously, the results are expressed as multiples of coefficient of repeatability ('confidence steps') for each measurement. The coefficients of repeatability for each method were derived earlier in chapter 16 from the temporal/within observer variability study.

A leftward deflection from zero would indicate a fall in pulmonary arterial pressure. This represents a fall in peak velocity of tricuspid regurgitation (TR), or right ventricular pre-ejection period/ejection time ratio (PEP/RVET), and a rise in time to peak velocity/ejection time ratio (TPV/RVET) or ductal flow velocity (PDAMAX). A rightward deflection would indicate a rise in pulmonary arterial pressure.

The figures are discussed further in the text (17.5.1.-3.)
Change in pulmonary arterial pressure

Figure 17.3

86-96 %

- PEP/RVET
- TPV/RVET
- PDAMAX
- peak TR jet
Change in pulmonary arterial pressure

Figure 17.4

ID 96-100 %

- PEP/RVET
- TPV/RVET
- PDAMAX
- peak TR jet

CONFIDENCE STEPS
Change in pulmonary arterial pressure

Figure 17.5
86-100 %

- PEP/RVET
- TPV/RVET
- PDAMAX
peak TR jet

CONFIDENCE STEPS
Confidence steps in non-invasive indices of pulmonary arterial pressure with changing arterial oxygen levels.
ventricular performance (Hirschfeld et al, 1975b; Riggs et al, 1977b), while the TPV/RVET ratio is probably most closely related to systolic or mean pulmonary arterial pressure (Kosturakis et al, 1984; Stevenson, 1989). The previous chapter has shown that these two systolic time ratios, and the ductal flow velocities, are prone to wide observer error in the premature neonate. The changes in ductal flow, however, were sometimes dramatic (as shown in plates 24 and 25 showing the change in ductal flow in a baby with alteration in \( \text{SaO}_2 \) from 85% to 100%), and were qualitatively the most convincing evidence of haemodynamic change. This study shows that these various techniques can be usefully combined in serial study with the more reproducible measurement of tricuspid regurgitation, when the units of measurement are expressed in terms of confident steps. Each step represents the coefficient of repeatability for that technique, or the change in measurement reaching the limits of observer, random and temporal variability.

(2) There are other advantages to using 'confidence step' analysis. Absolute values of systolic time intervals do not accurately reflect the same pulmonary arterial pressure in different children (Dabestani et al, 1987) and several studies have shown that they cannot reliably differentiate children with pulmonary hypertension from those without (Kosturakis et al, 1984; Newth et al, 1984; Friedman et al, 1986). Nevertheless, they may be useful in serial analysis within the same baby. The confident steps of change can be used regardless of the particular relationship of pulmonary arterial pressure to the time interval ratio in each baby.

(3) The TPV/RVET ratio was shown by Vogel et al (1991) to be insensitive in the detection of oxygen induced pulmonary vasodilation in children with congenital heart disease, but this does not necessarily imply that the ratio is of no value in children with structurally normal hearts, provided limits of repeatability are observed. However, in the present study, two observed changes in the TPV/RVET ratio were against the trend of the other observations, suggesting observer error (subject 15 at 96-100% and subject 18 at 86-96%). Combining these two pieces of evidence, it would seem prudent not to rely on the TPV/RVET ratio alone in following changes in pulmonary arterial pressure.

17.6.2. Interpretation and significance of the findings

(1) Between 86% and 96% \( \text{SaO}_2 \) pulmonary arterial pressure, did not change significantly in most babies. Ductal constriction occurred in three babies. Haemodynamic changes were more universal and more significant when saturations oxygen rose from 96 to 100%, and the overall effect of a change from 86 to 100% \( \text{SaO}_2 \) was a fall in pulmonary arterial pressure in 7 (possibly 8) of the 11 babies studied. In this latter group, some of the variation in response between babies will have been in part be due to differences in arterial \( \text{pO}_2 \) at 100%
SaO₂, which can vary enormously. It would have been better to record arterial pO₂ as well as SaO₂. Nevertheless, the effect on pulmonary arterial pressure is clear, but what of the effect on pulmonary blood flow?

(2) Oxygen can theoretically increase or decrease pulmonary blood flow in the presence of an arterial duct with a left-to-right shunt and high pulmonary vascular resistance, because ductal constriction will decrease pulmonary flow, and pulmonary vasodilation will increase it. The index of pulmonary blood flow in the present study, aortic stroke distance, was therefore influenced by the net effect of these two opposing factors. The only detectable change in the present study was a fall in association with ductal constriction, suggesting that, in these babies, ductal patency was a more important determinant of pulmonary flow than pulmonary vascular resistance. Why should this be so when high pulmonary vascular resistance is thought to be an important component of hyaline membrane disease? The answer may lie in the patient selection. All of the babies were clinically stable, and they did not have severe disease; receiving less than 65% inspired oxygen. Some babies were already over the worst stage of their disease and some had received artificial surfactant. The babies in whom aortic stroke distance fell also had relatively high starting values, suggesting that pulmonary arterial flow was not low in these babies, despite high pulmonary arterial pressures. Further studies are required of babies with more severe disease.

(3) The haemodynamic changes were particularly striking given the short time periods over which SaO₂ was altered. Further studies could also study the effect of altering arterial oxygenation over longer periods.

(4) There is continuing debate about the most appropriate arterial blood oxygen levels at which to nurse the sick premature neonate, because of the potential complications of hyperoxia and hypoxia. Yet the haemodynamic effects of varying inspired and blood oxygen levels have not previously been investigated in babies with neonatal respiratory failure. The longitudinal study of Evans and Archer (1991a), and the study presented in chapter 10 of this thesis, failed to show a convincing link between pulmonary arterial pressure and arterial oxygenation. This is surprising because studies using direct measurement of pulmonary arterial pressure in healthy human babies have demonstrated that oxygen is a potent pulmonary vasodilator (Saling et al, 1960; Moss et al 1964). Halliday et al (1980), using serial values for the PEP/RV ET ratio, showed a fall in pulmonary arterial pressure with increasing SaO₂ in babies with bronchopulmonary dysplasia. It must be concluded that it is only by such serial measurements within the same baby, rather than cross-sectional studies, that the influence of SaO₂ and FiO₂ on vascular tone can be studied effectively.
There is currently a good deal of interest in the haemodynamic effects of administering artificial surfactant. The results of this paper suggest that such studies need to take the effects of arterial blood and inspired oxygen levels into account because observed haemodynamic changes could be a consequence of altered oxygenation rather than surfactant per se.

(1) In summary, this study demonstrates the important influence of inspired and arterial blood oxygen levels in the sick premature neonate upon ductal patency and upon pulmonary arterial pressure, and has demonstrated the potential use of "confidence steps" in haemodynamic assessment.

(2) The study has not established an "optimal" arterial oxygen saturation, because this is a complex issue involving more than just haemodynamics and ductal patency. Moreover most neonatal units would rely on both PaO₂ and SaO₂ levels to guide blood oxygenation. However, most of the concepts surrounding "adequacy" of oxygenation revolve around providing sufficient oxygen delivery to the tissues and the varying effects of different P₅₀ levels and the shape of the oxygen dissociation curves. This chapter illustrates that the effects of airway and blood oxygen level may also have major haemodynamic effects which themselves influence oxygen uptake in the lungs and oxygen delivery to the tissues. It is probably only through the process of a randomised controlled trial that the optimal levels of oxygenation can be established.
Table 17.1. Details of patients undergoing study of the haemodynamic effect of changing arterial oxygen saturation.

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MAP, mean airway pressure. PDA, patent arterial duct. TR, pansystolic (measurable) tricuspid regurgitation.

* The arterial duct closed between 86 and 96% SaO₂.
Table 17.2. Haemodynamic measurements at 84-88% oximetry values.

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* lowest oximetry reading was 95% in air. ^ ductal flow, pattern of flow through the arterial duct, bidirectional, L-R=pure left-to-right, int="intermediate" with left-to-right flow, zero flow in mid systole.

AoSD, Aortic stroke distance. BPsys, systolic systemic arterial pressure. ^ arterial line. HR, heart rate in beats per minute. PASD, stroke distance at the pulmonary valve. PDA max, maximal left-to-right velocity in the arterial duct.
Addendum—Chapter 18: Doppler echocardiographic evaluation of persistent transitional circulation

18.1 Introduction

18.2 Patients and methods

18.3 Results - initial examination

1. Determination of pulmonary arterial pressure
   1. Using peak velocity of tricuspid regurgitation
   2. Ductal flow
   3. Systolic time intervals

2. Other Doppler echocardiographic features
   1. Interatrial shunting
   2. Fractional shortening of the left ventricle
   3. Pulmonary stroke distance
   4. Left ventricular output
   5. Left atrial and left ventricular dimensions


18.4 Results - Monitoring recovery and the effect of intervention

1. "Haemodynamic profile"
2. Tolazoline
3. Clinical improvement
   1. Pulmonary and aortic stroke distance
   2. Systolic pulmonary : systemic arterial pressure ratio
   3. "PDAMAX"
   4. Systolic time intervals

18.5 Discussion

The figures are listed on the next page

Tables

18.1 Clinical details of 33 babies presenting with persistent transitional circulation and, taken from the initial examination of these babies:

18.2 Doppler echocardiographic indices of pulmonary and systemic arterial pressure and ductal size

18.3 Doppler echocardiographic indices of pulmonary and systemic blood flow and myocardial performance
Addendum-Chapter 18: Doppler echocardiographic evaluation of persistent transitional circulation

Figures

These graphs present the haemodynamic data of 30 babies with persistent transitional circulation at presentation, and are compared to normal values 10th and 90th centiles from healthy babies over the first three days of life. Plots distinguish premature babies from term babies and survivors from non-survivors.

18.1 Pulmonary-systemic arterial pressure ratio (term and preterm babies)
18.2 Maximal left-to-right ductal flow velocity in term babies
18.3 Maximal left-to-right ductal flow velocity in preterm babies
18.4 TPV/RVET ratio (term and preterm babies)
18.5 Fractional shortening of the left ventricle
18.6 Pulmonary stroke distance in term babies
18.7 Pulmonary stroke distance in preterm babies
18.8 Left ventricular output
18.9 Left ventricular stroke volume index
18.10 Systolic systemic arterial pressure

These graphs represent the haemodynamic profiles of patients receiving therapy to reduce pulmonary arterial pressure.

18.11 A subject who deteriorated with tolazoline, as pulse oximetry values fell, the pulmonary-systemic arterial pressure ratio increased due to a larger fall in systemic rather than pulmonary arterial pressure.
18.12 This subject benefitted from tolazoline. The pulmonary-systemic arterial pressure fell, ductal flow changed from pure right-to-left to bidirectional and pulse oximetry values rose.
18.13 Increased ventilation reduced pCO2 in this subject, and bidirectional ductal flow changed to pure left-to-right flow.
18.14 A profile from a baby who did not recover; pulmonary arterial pressure remains at or above systemic pressure, and pulmonary and aortic stroke distances remain low.

These graphs use "confidence step" analysis of haemodynamic change in groups of babies, using the confidence steps for expected temporal variability form chapter 16.

18.15 Six babies who received tolazoline.
18.16 Pulmonary and aortic stroke distance during clinical improvement in 15 babies.
18.17 Pulmonary-systemic arterial pressure ratio during clinical improvement in ten babies.
18.18 Maximal left-to-right ductal flow velocity during clinical improvement in ten babies.
Addendum-Chapter 18: Doppler echocardiographic evaluation of persistent transitional circulation

During the three year period of the research, the author carried out echocardiographic examination of most of the babies presenting to the Newcastle neonatal units with persistent transitional circulation. There were no formal entry criteria for inclusion, except that the supervising neonatologist felt that persistent transitional circulation was contributing significantly to the babies' illness. Some babies were examined at the specific request of the neonatologists to exclude congenital heart disease. This chapter is a pilot study of the data which were collected from these babies.

18.1 Introduction

(1) While there have been previous echocardiographic studies of persistent transitional circulation, they have generally concentrated on the use of one particular measurement, such as the PEP/RVET ratio (Riggs et al, 1977). This chapter firstly explores the feasibility of pulmonary arterial pressure estimation by both the tricuspid regurgitation and ductal flow techniques in persistent transitional circulation. In addition, echocardiographic measurements of flow and myocardial performance are analysed, to see which indices of flow or pressure most usefully quantify severity of the disease, monitor its progress, or predict outcome.

(2) The results are compared with values from normal babies, and some serial values during therapeutic intervention or recovery are reported.

18.2 Patients and methods

(1) Over a three year period, 34 babies with clinical evidence of PTC were referred for echocardiographic evaluation. There were no strictly defined clinical criteria for echocardiography; each baby was considered by the attending clinicians to have hypoxaemia disproportionate to lung disease, and specific therapy of PTC had already been started or was being considered.

(2) Each baby underwent detailed Doppler echocardiographic examination as described in the methods chapter (chapter 6.).

(3) Four babies were excluded from detailed analysis because their diagnosis rendered meaningful interpretation of results difficult: One baby had transposed great arteries. Two babies had generalised severe skeletal myopathy of unknown cause (subjects 31 and 32), and both died, one from pneumonia and the other from multi-organ failure. One baby of 32
weeks gestation with hyaline membrane disease and pulmonary interstitial emphysema (subject 33) had echocardiographic evidence of very high pulmonary blood flow, despite hypoxaemia. In all the other 30 babies, features consistent with persistent transitional circulation were present, ie evidence of right-to-left inter-atrial or ductal shunting (including bidirectional shunting), and left atrial and left ventricular dimensions did not suggest high pulmonary venous return. These 30 babies are therefore the subjects of this study. There were 14 term babies (birth weight 2585g-4390g), and 16 preterm babies (gestation 26-36 weeks, birth weight 855-4615g). Only three babies had pure “pfc syndrome” as described by Gersony et al (1969); there being no obvious precipitating cause for the problem. Many of the babies had a history of perinatal asphyxia and most of the premature babies had underlying hyaline membrane disease. A list of the principle underlying diagnoses are shown in table 18.1, along with clinical status at the first examination, and the main underlying diagnoses.

(4) Simultaneous pre-ductal pulsed oximetry and transcutaneous oxygen readings were recorded. Recent blood gas result (within 2 hours of the examination) was also recorded including arterial pCO2 when this was available.

(5) The clinical condition of these 30 babies fluctuated rapidly, and consequently some were not hypoxaemic at the time of the examination (see table 18.1); eight babies had an oximetry reading > 90% saturation, sixteen babies (53%) had a blood pH >7.34 and 11 were acidic; six had a pH below 7.30. Four babies had a pCO2 > 6.5 kPa, indicating respiratory failure. Twelve of the thirty babies subsequently died (42%). However, two very low birth weight babies died early of respiratory failure due to pulmonary interstitial emphysema such that death was not directly related to the PTC. Results of 18 survivors are compared later with 10 non-survivors who died as a consequence of PTC.

(6) The findings of the initial echocardiographic assessment are presented. In most cases (23 of 30) a number of serial examinations were performed (between 2 and 11), either around the time of a therapeutic intervention, or over a number of days. Some pertinent features of these serial examinations are reported.

(7) Normal values, taken from the normal healthy term and preterm babies described earlier in chapter 8, are used for comparison. 10th, 50th and 90th percentiles were calculated for each Doppler echocardiographic measurement in three age bands over the first 72 hours. The results are tabulated in appendix E. Some of the measurements did not alter noticeably over the first three days (LA:Ao ratio, fractional shortening, heart rate, and stroke volume index); percentiles for these values were calculated including all measurements taken over the first three days of life.
18.3. Results

Each of the Doppler echocardiographic features are considered separately, and compared against normal values. The figures are designed to establish any link with subsequent outcome, and therefore only show values taken from 28 babies, excluding the two babies who died early from pulmonary interstitial emphysema.

18.3.1. Determination of pulmonary arterial pressure

18.3.1.1. Tricuspid regurgitation

(1) Tricuspid regurgitation was measurable in 9 of the 15 term babies (60%), and in 12 of the 15 preterm babies (80%). There was a particularly strong Doppler signal (grade 4' as described in the methods chapter, with a clear velocity profile with every beat), in 13 of the 21 babies with measurable tricuspid regurgitation (62%). Therefore, 9 babies in total (30%) did not have tricuspid regurgitation sufficient to generate a measurable signal, although 8 of these 9 had a patent duct, and flow patterns all indicated high pulmonary arterial pressures, including 3 babies with suprasystemic pulmonary arterial pressure indicated by pure right-to-left ductal flow.

(2) Derived pulmonary and systemic arterial pressure values are shown in table 18.2. The estimated systolic pulmonary arterial pressure (allowing 5 mmHg for right atrial pressure in ventilated babies) was less than 30 mmHg in four of the preterm babies. However, these low values were accompanied by low systemic pressure, such that the lowest pulmonary:systemic (systolic) arterial pressure ratio was 0.7:1. The mean Pa:Ao systolic pressure ratio was 1.02:1 (range 0.7:1 to 1.83:1). The ratio was over 1.0:1 in 10 of the 21 babies with measurable tricuspid regurgitation (48%).

(3) Values for the pulmonary:systemic arterial pressure ratio are compared to normal values in figure 18.1.

(4) The initial pulmonary : systemic arterial pressure ratio was not different in babies who died and in those who recovered, but in babies who recovered the ratio fell with increasing age. Pulmonary arterial systolic pressure did not always fall precisely at the same time as clinical improvement was seen (vide infra). Rising systemic arterial pressure contributed to the fall in the ratio during recovery.

18.3.1.2. Ductal flow

(1) Details of ductal size, flow pattern and flow velocity are shown in table 18.2.
Figure 18.1

Pulmonary:systemic arterial pressure ratio in babies with PTC compared with healthy babies.
(2) 5 babies had a closed arterial duct, and in a further 4 babies the duct was small. Therefore significant ductal shunting could not have been present in 9 babies (30%), all of whom were over 35 weeks gestation.

(3) 4 babies (13%) had pure right-to-left flow (type 1), 19 (63%) had bidirectional flow (type 2), and 2 (7%) had pure left-to-right flow with very low velocity (less than 0.2 m/s) in systole (type 4). Therefore all of the babies with a patent arterial duct had a pulmonary arterial pressure approaching or above systemic levels.

(4) Figures 18.2 and 18.3 plot values for the maximal left-to-right ductal flow, in term and preterm babies respectively. Babies with pure right-to-left ductal flow are indicated as zero left-to-right velocity. The 10th and 90th percentiles for the healthy term and preterm babies are also shown. All but two babies had velocities below the 10th percentile.

18.3.1.3. Systolic time intervals

(1) The TPV/RVET ratio was measured in 28/30 babies. There is a wide spread of values (0.20 to 0.52), and little relationship between these and TR determined pulmonary arterial systolic pressure values. High values in particular would not have been expected.

(2) In figure 18.4, the initial TPV/RVET ratios, divided into those from babies who survived and from those who did not, are plotted with 10th and 90th percentiles from healthy babies. Nine of these 26 values (35%) lie below the 10th percentile, indicating pulmonary hypertension, but the rest are within the normal range. There was no relationship to subsequent survival.

(3) The PEP/RVET ratio was measured in only 14/30 babies, because the ultrasound machine was not linked to the ECG monitor in the early part of this study. The two highest values (0.86 in subject 1 and 0.88 in subject 14) occurred in two babies who had particularly poor right ventricular function by subjective assessment (by cross-sectional echocardiography). One value in (0.24 in subject 4) is surprisingly low because of the high estimated pulmonary arterial systolic pressure from tricuspid regurgitation and bidirectional ductal flow.
Figure 18.2
Maximal L-R ductal flow velocity in term babies with PTC

- --- 90 %
- --- 50 %
- --- 10 %
- ○ term survived
- ● term died

Figure 18.3
Maximal L-R ductal flow velocity in preterm babies with PTC

- --- 90 %
- --- 50 %
- --- 10 %
- △ preterm survived
- ▲ preterm died
Figure 18.4

TPV/RVET ratio in term and preterm babies with PTC

Figure 18.5

Fractional shortening of the left ventricle in babies with PTC
18.3.2. Other Doppler echocardiographic features

18.3.2.1. Inter-atrial shunting

(1) The oval foramen was patent in every baby, and pulsed Doppler interrogation of the pattern of flow during the cardiac cycle revealed pure right-to-left flow in four babies (subjects 13, 14, 18 and 20). Flow was bidirectional in all of the rest, although right-to-left flow was noticeably longer during hypoxaemic episodes, and became predominantly left-to-right with recovery.

18.3.2.2. Fractional shortening (of the left ventricle)

(1) The initial values of this index of myocardial performance are shown in figure 18.5. 22 of the 27 values (81%) lie within the expected normal range. Two of the three values lying well below the 10th percentile (fractional shortening 20% or less) occurred in babies who subsequently died; left ventricular stroke volume was also very low. Two values were very high. One was in subject 2 (fractional shortening of 54%), who was an unventilated term baby receiving inotropic support who did well. The stroke volume index was low in this baby despite the brisk myocardial performance (1.12 ml/kg); low pulmonary venous return rather than poor ventricular function must have been the cause of this low stroke volume in this baby. The other, subject 19 (fractional shortening 61%) had a grossly hypertrophied myocardium which was assumed to be secondary to maternal diabetes; this baby was extremely unwell with hypotension and poor peripheral perfusion, and died a few hours after the examination.

18.3.2.3. Pulmonary stroke distance

(1) Pulmonary stroke distance is an index of right ventricular stroke volume, which in turn is dependant on systemic venous return. (Pulmonary stroke volume is not reported due to the unreliability of measurement of pulmonary valve or artery diameter). Results are reported in table 18.3 and figures 18.6 and 18.7, which separate babies who survived from those who did not. 6 of the 14 values from term babies (43%) and 4 of the 12 values from the preterm babies (33%) had values below the 10th centile. Across the group, there seemed to be no consistent relationship to outcome or to concurrent arterial oxygenation. However, the two values below 2 cm both occurred in very sick term babies who did not recover. The Doppler trace was remarkable in these two babies in that there was no forward flow through the pulmonary valve with every second or third beat. In babies with low initial values (only), pulmonary stroke distance rose during recovery.
Figure 18.6  
**Pulmonary stroke distance in term babies with PTC**

- 90%
- 50%
- 10%
- term survived
- term died

Figure 18.7  
**Pulmonary stroke distance in preterm babies with PTC**

- 90%
- 50%
- 10%
- preterm survived
- preterm died
18.3.2.4. Left ventricular output

(1) In figure 18.8, 27 left ventricular output values (from 28 babies) are presented, comparing survivors and non-survivors. Eleven of the twenty seven (41%) lie below the 10th centile. Four babies had very low values, below 100 mls/kg/min (subjects 4, 13, 18 and 19), and all four subsequently died. In several babies, (particularly subjects 5, 6, 7, 22 and 26) the output was maintained over 100 mls/kg by profound tachycardia (>180 beats per minute) in the presence of a low stroke volume index. The left ventricular stroke volume index (stroke volume/body weight) is shown against normal percentiles in figure 18.9. 18 of the 27 values (66%) lie below the 10th percentile. Six of the seven lowest values (<1ml/kg) were in babies who did not recover. The relationship of low values to subsequent death is stronger than that for systemic arterial pressure (figure 18.10).

18.3.2.5. Left atrial and left ventricular dimensions

(1) These were recorded as crude indices of pulmonary venous return and left ventricular filling. End diastolic dimensions are represented as a ratio of aortic root dimension (LA:Ao and LVEDD:Ao ratios), in table 18.3. Most of the LA:Ao ratios lie in the low normal range; nine values (30%) lay below the 10th percentile (0.95:1 in term babies, 0.84:1 in preterms). LVEDD:Ao ratio lay below the 10th centile (1.53:1 in term babies, 1.56:1 in preterms) in 12 babies (40%). There was no consistent relationship between these measurements and eventual outcome.

18.3.3.

(1) In summary, in the initial echocardiogram, an estimate of pulmonary arterial pressure was possible by analysing ductal flow or measuring the peak velocity of tricuspid regurgitation in all but one of the 30 babies with persistent transitional circulation. Tricuspid regurgitation was not present in a quarter of the group, which is surprising considering that it has been considered to be one of the important clinical features of PTC (Gersony, 1984). The fact that the arterial duct was closed or very small in a third of the babies demonstrates that right-to-left shunting must have occurred only at the oval foramen or within the lungs in these babies, and not at ductal level. The TPV/RVET ratio did not add useful information in this study. None of these three indices of pulmonary arterial pressure was a useful predictor of eventual outcome.

(2) Most of the babies had normal left ventricular function. However, low left ventricular output and stroke volume index was frequent, reflecting either poor left ventricular filling as a consequence of low pulmonary venous return, or poor ventricular function. The lowest values occurred in babies who did not recover, such that these measurements may prove to
Figure 18.8
Left ventricular output and subsequent survival in PTC

Figure 18.9
LV stroke volume index and subsequent survival in PTC
Systolic, systemic arterial pressure in babies with PTC.

Figure 18.10

- Term 90%
- Term 10%
- Preterm 90%
- Preterm 10%

- \(\Delta\) preterm survived
- \(\blacksquare\) preterm died
- \(\circ\) term survived
- \(\bullet\) term died

Systolic upper limb BP (mmHg)

age hours
be useful predictors of eventual outcome, in future prospective studies.

(3) Echocardiographic assessment of the 34 babies initially examined, who were all felt clinically to have persistent transitional circulation, demonstrated diverse haemodynamic features, to the extent that one baby did not have significant right-to-left intracardiac or ductal shunting, and therefore did not truly have persistent transitional circulation, despite the clinical presentation. Another baby had unsuspected cyanotic congenital heart disease.

18.4 Monitoring recovery and the effect of intervention

The above analysis looked at the initial assessment only, but the assessment of therapy in babies with PTC can be difficult and serial measurements might be useful in the detection of response to therapy. This section aims to discover which Doppler echocardiographic measurements provide the most useful means of assessment during recovery.

18.4.1. The 'haemodynamic profile'

(1) Analysing combined serial Doppler echocardiographic measurements within a subject, it is possible to graphically display the results to allow easy visual interpretation. An example of such a haemodynamic profile obtained from a detailed study is shown in figure 18.11. Subject 29 showed no beneficial effect from tolazoline and was examined before the injection, and 5 and 30 minutes later. There was a sharp fall in oximetry readings, with the post-ductal saturation becoming lower than preductal, signifying right-to-left ductal shunting. This was associated with a fall in systemic arterial pressure (37 mmHg) and also of pulmonary arterial pressure (19 mmHg), such that the pulmonary:systemic arterial pressure ratio increased. Ductal flow changed from bidirectional, (with a maximal left-to-right velocity of 0.9 m/s), to pure right-to-left flow. Pulmonary stroke distance changed little, and aortic stroke distance fell marginally. In response to this dramatic deterioration, he was given a 15 mls/kg bolus of plasma. Systemic arterial pressure rose more than pulmonary arterial pressure, and oximetry values returned towards the starting point as ductal flow became bidirectional again. There was a marked rise in aortic stroke distance while pulmonary stroke distance remained unchanged, suggesting that most of the increased left ventricular output went via the arterial duct into the pulmonary circulation. Systolic time intervals changed little initially, but TPV (and the TPV/RVET ratio) rose markedly after the administration of the plasma. The rise in TPV might reflect a fall in pulmonary vascular resistance, while pulmonary flow increased (through a rise in left ventricular output and some L-R ductal shunting) and pulmonary arterial pressure remained the same.

(2) Tolazoline presumably reduced systemic vascular resistance more than pulmonary vascular resistance, leading to right-to-left ductal shunting. This was rectified when the systemic vascular compartment was filled by injected plasma, resulting in a rise in systemic
Figure 18.11 Detrimental effect of a bolus of tolazoline

Subject 29:
31 weeks, 2290g.
blood pressure, a reduction in right-to-left ductal shunting and an increase in left ventricular stroke volume.

(3) Figure 18.12 shows a similar profile in subject 2, in whom tolazoline induced an improvement. After a tolazoline bolus, arterial oxygen saturation rose and pulmonary arterial pressure fell from suprasystemic to subsystemic levels. This was accompanied by a change in ductal flow pattern from pure right-to-left to bidirectional flow, and a rise in both pulmonary and aortic stroke distances. Right ventricular TPV rose during further recovery, but changed little at the time of the initial improvement.

(4) Figure 18.13 demonstrates improvement following increased ventilation in subject 20. Arterial PCO2 fell from 8.3 to 5.8 kPa and arterial oxygen saturation rose from 81% to 93%. The pulmonary:systemic arterial pressure ratio fell and bidirectional ductal flow changed from bidirectional to pure left-to-right flow. In this case, aortic and pulmonary stroke distances changed little. Plates 15 to 17 show sequential change in ductal flow in another baby (subject 16) during a similar period of improved ventilation and increase in systemic arterial oxygen saturation. Ductal flow changes from pure right-to-left through bidirectional to a pattern alternating between bidirectional and pure left-to-right flow.

(5) Figure 18.14 shows a haemodynamic profile from a baby who did not recover. Systolic pulmonary arterial pressure remains at or above systemic levels throughout, and pulmonary and aortic stroke distances remain low.

18.4.2. Tolazoline

(1) A haemodynamic profile was obtained from six babies who were examined before and 10 minutes to one hour after a test dose of intravenous tolazoline (1-2mg/kg). A sustained rise in oximetry of more than 5% was accepted as evidence of beneficial effect. 3 babies had no beneficial effect, and three had a rise in saturation of 8%,14%, and 14% respectively.

(2) There were no measurements from the initial scan which differentiated babies who responded to tolazoline from those who did not, although all had features of PTC.

(3) The haemodynamic changes induced by tolazoline are summarised graphically in figure 18.15, using the 'confidence step' approach, first used in the preceding chapter. The same repeatability coefficients are employed here, to compare values before and after treatment. 'Beneficial effects' are displayed as a shift to the right. These were a fall in TR jet velocity, a rise in the TPV/RVET ratio, and a rise in ductal flow velocity, systemic arterial systolic pressure, pulmonary and aortic stroke distances. The opposite ('detrimental') changes are displayed as a shift to the left.
Figure 18.12. Subject 2. Treatment with tolazoline and progress afterwards.

Subject 2:
42 weeks, 4390g
Figure 18.13. Improvement in saturation with fall in arterial pCO2 (8.3-5.8 kPa).

Subject 28: 31 weeks, 1600g.
Figure 18.14 Serial haemodynamic data from a baby who did not recover from PTC

Subject 7: 40 weeks, 3335g, (closed arterial duct)
Figure 18.15

The haemodynamic effects of tolazoline

-7%

+3%

+4%

+8%

+14%

NOTE: Subject 7 did not have a patent arterial duct.
Subjects 11 & 18 had no TR.
Subject 18 TPV/RVET not done.

Confidence steps
Figure 18.15 demonstrates that there was a wide variation in response to tolazoline. Subjects 26 and 2, for example, are seen to be opposites; the former got worse and the latter got better. However, pulmonary arterial pressure fell in both babies. The important difference is that in subject 26 systemic pressure also fell markedly and ductal flow changed from bidirectional to right-to-left, whilst in subject 2 it did not, and ductal flow changed from right-to-left to bidirectional.

Aortic stroke distance rose in one baby who showed little benefit in terms of arterial oxygenation (subject 12). This increase in left ventricular stroke volume might have been due to a fall in systemic vascular resistance rather than an increase in left-to-right ductal shunting. In subject 7 saturation increased despite a fall in systemic pressure and static pulmonary arterial systolic pressure. The lack of harmful effect is probably because the arterial duct was closed in this baby, and the balance of systemic pressures was therefore less critical. The clinical improvement in this case was therefore probably due to decrease in right-to-left interatrial shunting, and/or a decrease in pulmonary vascular resistance leading to improved right ventricular performance. It may be important that left and right ventricular stroke volumes showed a small increase rather than a decrease in this baby.

18.4.3. Echocardiographic features during improvement in clinical state

Babies with PTC frequently recover in a stepwise fashion as effective pulmonary blood flow increases. To see what haemodynamic events were associated with such improvement, serial values were analysed, in those babies in whom they were available, and a stage when arterial saturation showed a sustained increase was identified. The scan during improvement is compared with that immediately before. In some babies this represented the first noticeable improvement leading to eventual recovery, but in others it was only temporary.

It was possible to identify such an improvement in 19 of the 33 babies and the results are presented in the 'confidence step' manner. It should be noted however, that the original repeatability studies were based on temporal variability over one hour, and the present study compares paired values a mean of 30 hours apart, and temporal variability is certainly greater than that over one hour. Nevertheless, this type of analysis allows different measurements to be reviewed together in a simple graphical manner and is thus (probably) the best technique available.

The baby who appeared not to truly have PTC after the first analysis (subject 33) is not included in this section, but 5 serial scans were available in subject 31, including a period of improvement, so this is included here. Subject 25 had two clear episodes of improvement and is thus represented twice.
Figure 18.16  Haemodynamic changes during improvement in PTC: Pulmonary and aortic stroke distance

"detrimental change"  "beneficial change"

ID

-4 -3 -2 -1 0 1 2 3 4

Confidence steps

babies with a closed duct

duct closed between scans

ductal constriction

patent duct

[Graph showing changes in stroke distance with confidence steps for different IDs]
18.4.3.1. Pulmonary and aortic stroke distance

(1) Figure 18.16 shows the values for 15 paired measurements of pulmonary stroke distance and 18 of aortic stroke distance. During improvement in PTC, when increased pulmonary blood flow is to be expected, one or both stroke distances should increase. With an increase in pulmonary blood flow, when the duct is closed, pulmonary stroke distance must increase, and when patent either or both could increase. Because of this the babies in figure 18.16 are divided into three groups according to ductal patency. At the top are three babies who had a closed arterial duct on both examinations. The next 7 are babies in whom the duct closed between the two examinations, and the remaining 10 babies at the bottom had a patent duct throughout. The duct also constricted noticeably between scans in subjects 11 and 17.

(2) One or both of the stroke distances increased in all but one baby in whom both were measured. Both stroke distances fell in one baby (subject 15); the improvement in this baby was therefore not associated with increased pulmonary blood flow. Four other babies had some fall in aortic stroke distance but they all had a closing arterial duct, so that pulmonary blood flow was less dependant on left ventricular output. Three of these babies had pulmonary stroke distance measurements, which rose as aortic stroke distance fell. For this to occur, either left-to-right interatrial shunting, or systemic venous return must have increased as the duct constricted, raising right ventricular output as left ventricular output fell. In three babies with a patent duct, pulmonary stroke distance fell marginally, but in each case there was a rise in aortic stroke distance. Presumably left-to-right ductal flow was important in maintaining pulmonary blood flow in these babies.

18.4.3.2. Systolic pulmonary:systemic arterial pressure ratio

(1) Paired estimates of pulmonary arterial systolic pressure were made in 10 of the babies, and the changes, expressed as the pulmonary:systemic arterial pressure ratio are shown in figure 18.17. Two went up and two went down. Clearly, significant clinical improvement can occur without a fall in the systolic pulmonary:systemic arterial pressure ratio.

18.4.3.3. PDAMAX

(1) The changes are shown in figure 18.18. Of the 10 babies with a patent duct at both studies, 6 had a rise in maximal left-to-right flow velocity, 1 had a fall and 3 did not change significantly. Of particular interest is subject 10, who had a rise in PDAMAX but also had a rise in the systolic pulmonary : systemic arterial pressure ratio. Ductal flow changed from pure right-to-left to bidirectional flow, and the maximal left-to-right flow changed from zero to 0.5 m/s in diastole. In this case, clinical improvement was therefore associated with the balance of pulmonary and systemic arterial pressures changing to give left-to-right flow
Haemodynamic changes during improvement in PTC:
Systolic pulmonary: systemic arterial pressure ratio

Confidence steps (1 step=0.18:1)
Haemodynamic changes during improvement in PTC:

PDA MAX (maximal L-R ductal flow)

Confidence steps (1 step=0.48m/s)
during diastole with right-to-left flow continuing only during systole.

18.4.3.4 Systolic time intervals

(1) Both the TPV/RVET ratio and the PEP/RVET ratio results were analysed as above, but neither changed reliably with clinical improvement. They frequently changed in the opposite direction than would be expected from changes in ductal flow and tricuspid regurgitant velocity.

18.4.4

(1) In summary, Doppler indices of pulmonary arterial pressure can be combined usefully with other measurements to give insight into complex haemodynamic events in babies with persistent transitional circulation. It is important to stress that although the observations were recorded in association with clinical improvement, cause and effect are not clearly established in every case.

(2) Changes in ductal flow velocity were often striking, and were sensitive indicators of alterations in the balance of pulmonary and systemic arterial pressures. Tricuspid regurgitation was often measurable and useful in the diagnosis of pulmonary hypertension, but was not as sensitive as ductal flow as an indicator of haemodynamic change, and was frequently more time consuming to measure, particularly in the larger babies.

(3) Serial measurement of aortic and pulmonary stroke distances seem to be useful in detecting therapeutic benefit, but the important influence of the arterial duct (and the pattern of flow through it) needs to be borne in mind when interpreting results. With a closed duct, the aim of therapy, to increase pulmonary blood flow, can be easily monitored by serial measurement of pulmonary stroke distance because the right ventricle is the only source of pulmonary blood flow. With a patent duct the situation is more complex, because both ventricles can supply pulmonary blood flow, and the balance of supply from each may change.

18.5. Discussion

(1) Previous echocardiographic studies of persistent transitional circulation have concentrated on the use of one measurement alone, such as the PEP/RVET ratio (Riggs et al, 1977a, Johnson et al, 1980). The results of Johnson et al were particularly important, because they suggested that the PEP/RVET ratio could differentiate babies who would respond to tolazoline. An alternative interpretation of their results, is that the test merely differentiated those with PTC and those without. Clinical experience, and the few
examples in this chapter, suggests that merely having PTC does not indicate that tolazoline will actually be of clinical benefit. While the measurement of a single systolic time interval is attractive, because it is simple, the problem with such an approach is that the variety within the population being studied can easily be missed. For example, a quarter of the babies in this study did not have tricuspid regurgitation, and a fifth had a closed arterial duct at the initial examination. Both tricuspid regurgitation and patent duct are features usually considered to be an integral part of PTC. PTC obviously varies markedly between babies and the findings in this study are therefore broadly in keeping with those of Reimenschneider et al (1976) as discussed in chapter 10. Nevertheless, I regret not measuring the PEP/RVET ratio in more of the babies with PTC; it would have been interesting to compare results with those of Johnson et al, and since they do not all have a patent duct or tricuspid regurgitation, an alternative method of assessment is frequently required. The fact that the PEP/RVET ratio is prolonged by right ventricular dysfunction in some ways makes the measurement more useful; a fall in the ratio is likely to be associated with clinical improvement even if pulmonary arterial pressure does not fall. The TPV/RVET ratio does not appear to be of much clinical value.

(2) Presumably those babies with the worst right ventricular dysfunction secondary to perinatal ischaemia are most likely to have tricuspid regurgitation and more right-to-left interatrial shunting as a consequence of both the tricuspid regurgitation and poor right ventricular diastolic function. More of the preterm babies had tricuspid regurgitation than the term babies, and therefore the findings of this study, and of the studies in chapters 8 and 10 (in healthy babies and those with hyaline membrane disease) are in keeping with the observations of Setzer et al (1980) who showed that papillary muscle necrosis in an autopsy series, was found only in term babies with a history of perinatal asphyxia, but was frequent, and unrelated to asphyxia, in preterm babies. Perhaps the papillary muscles of preterm babies are more vulnerable to ischaemia than term babies, leading to a higher prevalence of tricuspid regurgitation in preterms.

(3) In other babies the main problem may be high pulmonary vascular resistance combined with right-to-left ductal shunting. Therapeutic intervention can be tailored to the individual according to echocardiographic findings; with significant right-to-left shunting for example, raising systemic arterial pressure may be particularly helpful by reversing the pressure gradient across the duct.

(4) Evidently some babies can appear to have PTC clinically, but on echocardiographic assessment they do not. Two striking examples occurred in this study. In one baby the main haemodynamic finding was a significant left-to-right ductal shunt with high pulmonary blood flow rather than too little - it is hard to know how frequent this is; clearly such babies would not be helped by tolazoline. Perhaps there were babies like this in Johnson et al's
study in the non-responder group. The echocardiographic diagnosis of transposed great arteries in a baby who was receiving treatment for PTC was only made because of this research project. A number of structural heart diseases can present with persistent transitional circulation (Long et al, 1984) and this case serves as a reminder that all such babies should have at least one echocardiographic assessment to exclude congenital heart disease, as proposed by Lindsay et al in 1983.

(5) A problem with this study is the lack of good information about interatrial shunting. Colour flow mapping can provide useful qualitative information, but this was not available, and detailed pulsed Doppler interrogation of interatrial flow is very time consuming and involves subcostal scanning which is frequently tolerated less well in the critically ill neonate. Some of the results of this study might have been more easy to interpret if interatrial flow had been more carefully evaluated, perhaps by using contrast echocardiography (van Hare et al, 1989). However, to avoid excessive disturbance of these fragile babies this was not done. Hiraishi et al (1991) recorded interatrial flow in six babies with PTC. The flow was predominantly right-to-left, and became evenly balanced between right-to-left and left-to-right with improvement and ductal closure, whereas in healthy babies flow was always predominantly left-to-right.

(6) The fact that low left ventricular stroke volume is found in the most severe disease is not surprising, since it is reduced both by poor left ventricular performance, and by low pulmonary venous return. On the other hand, right-to-left shunting at atrial level must contribute to left ventricular filling and this might be expected to increase left ventricular output in babies with a large shunt. However, as this contribution increases, systemic venous flow destined for the right ventricle decreases, causing reduced flow into the pulmonary artery, and hence a reduction in effective pulmonary blood flow, pulmonary venous return and left ventricular filling. Thus a right-to-left atrial shunt may not result in a significant rise in left ventricular output. If there is, in addition, right-to-left ductal shunting, left ventricular stroke volume decreases further due to decreased pulmonary venous return. The net result of the worst haemodynamic scenario in PTC is thus a reduction in left ventricular stroke volume, whether or not the arterial duct is patent. It is, of course, this low output which supplies the already hypoxic brain. A further study seems to be worth while to evaluate the predictive power of low left ventricular output and stroke volume index in determining eventual outcome in critically ill babies with PTC. None of the assessments of pulmonary arterial pressure appeared to be related to outcome in this study, in contrast to Musewe et al (1990) who found that babies with pure right-to-left ductal flow were more likely to die subsequently.

(7) This final chapter has used the Doppler indices of pulmonary arterial pressure that were investigated for their validity and reproducibility in earlier chapters, and combined...
them with indices of pulmonary and systemic blood flow to study babies with persistent transitional circulation. The complex interaction of ventricular function, arterial pressures, blood flow and atrial and ductal shunts makes any such analysis very difficult. However, this chapter, and the preceding chapter investigating the haemodynamic influence of arterial oxygenation, demonstrate the enormous potential that Doppler echocardiography has in haemodynamic assessment in the sick newborn baby. Careful Doppler echocardiographic evaluation may help to eradicate the "therapeutic cookbook" approach to the management of babies with persistent transitional circulation which has been heavily criticised (Philips JB, 1984). Instead, using a combination of qualitative and quantitative measurements, invasive and non-invasive methods, a haemodynamic profile can be drawn for each baby, such that a therapy can be "tailor made" for the individual, and the response then monitored serially.
Chapter 19: Discussion and closing remarks

Which method?

(1) The initial aim of this thesis was to study the potential of measuring the peak velocity of tricuspid regurgitation in the non-invasive determination of pulmonary arterial pressure in the newborn. The method was found to be accurate and repeatable, but feasibility of measurement was limited; in many babies, even those with high pulmonary arterial pressure, peak tricuspid regurgitation could not be measured. It became clear early on therefore, that other non-invasive means of pulmonary arterial pressure estimation would still be needed in this population. So when should the other techniques be used, and how should the results be interpreted?

(2) Some of the main characteristics of the four techniques explored in this thesis are summarised in table 19.1.

(3) Systolic time intervals have the important advantage of being measurable in virtually every baby. The fact that there is now considerable evidence that systolic time intervals are unreliable in the estimation of pulmonary arterial pressure in babies with a left-to-right intracardiac shunt need not mean that they are useless in babies with a structurally normal heart. However, the TPV/RVET ratio in particular seems to be unreliable, both in terms of repeatability of measurement and in its relationship to pulmonary arterial pressure. The results in this thesis are in accord with data correlating this ratio with direct pressure measurement. This ratio will be of limited value in the clinical setting, even in monitoring the course of pulmonary arterial pressure in the individual, but the ratio might have a research role in the comparison of two populations, because individual variation is less important. TPV and TPV/RVET only correlated with TR-derived pulmonary arterial pressure closely enough to be of value in healthy babies of restricted gestation and in babies with a closed duct. Therefore, when two populations are being compared, they must be of similar gestation, and the arterial duct should probably be closed in both groups. Even under these circumstances conclusions must be cautious because the effect of ventricular dysfunction and tricuspid regurgitation are unknown.

(4) The PEP/RVET ratio is a somewhat more attractive measurement, because both pulmonary arterial hypertension and right ventricular dysfunction increase the ratio. During persistent transitional circulation, and severe hyaline membrane disease, a fall in the ratio can be expected, and has been shown by others, to indicate clinical improvement. The large error in repeatability was disappointing, but in serial measurement it might be improved by using only PEP, provided that there are not large fluctuations in heart rate. PEP and the PEP/RVET ratio were incompletely evaluated in this thesis, and deserve further evaluation.
particularly amongst babies with persistent transitional circulation.

(5) Recording ductal flow was usually very simple, and required less time and dexterity than the measurement of tricuspid regurgitation. Even though the modified Bernoulli equation should probably not be applied to the measured velocities to derive pulmonary arterial pressure values, the alteration in flow with clinical change is frequently obvious without measurement of velocities, allowing rapid, qualitative detection of haemodynamic change. Confidence step analysis showed that the velocity measurements can also be useful in quantitative assessment of serial haemodynamic change within a baby. This method seems to be the best way to detect subtle changes in the balance of systemic and pulmonary arterial pressure, provided of course that the duct is patent. If ductal flow could in some way be recorded continuously, continuous evaluation of the balance between systemic and pulmonary arterial pressures would be possible. A prototype Doppler probe, attachable to the skin, has been designed for this purpose and is already under construction. This method of monitoring could be extremely useful, not only in the assessment of babies with pulmonary hypertension, but also in the assessment of quantity of left-to-right ductal shunting. This thesis has shown that with ductal constriction end-diastolic left-to-right ductal flow velocity rises, and the systolic:diastolic velocity ratio falls. Furthermore, the haemodynamic effect of inspired and blood oxygen levels in newborns with respiratory failure (and a patent duct) could potentially be re-studied using such a device without repeated handling of very ill babies.

**Combining estimates of pressure and flow**

(1) The potential of detailed Doppler echocardiographic examination was shown in the evaluation of babies with persistent transitional circulation. Doppler assessment of pulmonary arterial pressure should only be one part (although a very important part!) of the haemodynamic assessment of these babies. While the measurement of ductal flow velocity showed the closest correlation to clinical improvement, it was left ventricular output that was most closely related to eventual outcome. Future studies of neonatal haemodynamic events should probably combine Doppler echocardiographic measurements in this way. Although there is, as yet, no non-invasive measurement of pulmonary vascular resistance, it is now possible to produce serial estimates of systemic and pulmonary blood flow at the same time as estimates of systemic and pulmonary arterial pressure. When these factors are combined with indices of ventricular function, it is feasible to evaluate therapeutic intervention, such as inotropes, surfactant or vasodilators, in a much more meaningful way than by measuring blood pressure and blood gas tensions in isolation. In effect, haemodynamic information that once could only be obtained by cardiac catheterisation can now be obtained repeatedly and non-invasively.
The next logical step is to aim for continuous non-invasive haemodynamic evaluation, such as is already available from indwelling arterial pressure lines and pulse-oximetry. The balance of systemic and pulmonary arterial pressure has been found repeatedly to be central to perinatal circulatory adaptation, in health and disease. A practical way to monitor this continuously is a logical progression and a worthwhile goal following the work of this thesis.
### Table 19.1

Features of four non-invasive methods of pulmonary arterial pressure estimation in the newborn

<table>
<thead>
<tr>
<th>Method</th>
<th>Repeatability Index*</th>
<th>Relation to systolic PA pressure</th>
<th>Complicating factors</th>
<th>Strongest points</th>
<th>Weakest points</th>
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</thead>
<tbody>
<tr>
<td>TR (m/sec)</td>
<td>8-9%</td>
<td>Direct relationship, Accurate.</td>
<td>Assumption of right atrial pressure</td>
<td>Accurate, Repeatable, Many &quot;confidence steps&quot; (^{\text{**}})</td>
<td>Not feasible to measure in many babies. Technically demanding.</td>
</tr>
<tr>
<td>TPV/RVET ratio</td>
<td>34-36%</td>
<td>Inverse relationship, Accuracy unpredictable.</td>
<td>Not all known; heart rate, gestation, ductal patency.</td>
<td>Usually easy to measure</td>
<td>Poor repeatability. Many complicating factors. Few &quot;confidence steps&quot;.</td>
</tr>
<tr>
<td>PEP/RVET ratio</td>
<td>36-45%</td>
<td>Direct relationship. Accuracy unpredictable, good in restricted groups with closed duct.</td>
<td>Ventricular dysfunction, ductal patency.</td>
<td>Usually easy to measure. Link to RV dysfunction can be an advantage.</td>
<td>Poor repeatability. Few &quot;confidence steps&quot;.</td>
</tr>
<tr>
<td>PDA max (m/sec)</td>
<td>28-47%</td>
<td>Inverse relationship. Accuracy variable.</td>
<td>Affected by systemic pressure &amp; ductal constriction.</td>
<td>Usually easy to measure. Many &quot;confidence steps&quot; Reflects balance of Ao and PA pressures.</td>
<td>Need patent duct. Uncertain whether modified Bernoulli equation can be applied.</td>
</tr>
</tbody>
</table>

* Repeatability index from between and within observer studies

\(^{\text{**}}\) The number of confidence steps within the expected range of values in the neonatal population
Appendix contents

pages
A. 353 Advice sheet for parents.
B. 354-360 Data collection sheets.
C. 361-362 Explanation of abbreviations on data sheets.
D. 363 Data collection sheets for repeatability and oxygenation studies.
E. 364-369 Percentiles of Doppler echocardiographic measurements in healthy babies over the first three days of life.
Appendix A.  INFORMATION FOR VOLUNTEERS

Throughout the World, the care of sick Newborn babies is advancing very quickly indeed. The Princess Mary Maternity Hospital has an advanced intensive care baby unit, at the forefront of quality care and research. The Maternity Hospital also has close ties with the Heart Unit at Freeman Hospital.

The hearts and circulation of very small premature babies, especially those with immature lungs, and perhaps in oxygen or on a ventilator undergo terrific stress.

This stress can lower the amount of blood getting into the lungs, and hence the babies easily become short of oxygen which is obviously potentially harmful.

We are currently studying the heart and the circulation through the lung in these small ill babies using the most modern ultrasound equipment. (Using a machine very much like the one you yourself will have been scanned with during pregnancy). As you know this technique is completely pain free and harmless.

As well as looking at unwell babies to try and help in their treatment we need to know more about well, normal babies of all sizes during the first few days of life, since we know that the circulation changes a lot over this time. Hence we are looking for healthy babies to examine over the first week of life, and asking for volunteers. This, of course, would not imply an extended stay in hospital, but we may ask you to return for one outpatient visit.

Each baby in the study will have about 3 examinations in the first week of life. For practical reasons, not all volunteers will be examined, but those that are will have a small bonus in that they would have this further evidence to show that their baby's heart is completely normal.

Your help in this important research would be very much appreciated.

Many thanks in advance,

Dr Jonathan Skinner MRCP (UK)
RESEARCH REGISTRAR IN PAEDIATRICS

CONSENT FORM

I consent to my newborn baby having a series of echocardiographic examinations in the first week of life.

The procedure has been explained to me by Dr Skinner and I understand that this is for research purposes and is unlikely to be of direct benefit to my child.

I may withdraw from the study simply by informing my midwife or Dr Skinner.

Signed ---------------- Date ----------------

Name ---------------- Hosp. No. ----------------
**Appendix B**

**Data collection sheets**

<table>
<thead>
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<th>BASIC DATA</th>
<th>ICH STUDY</th>
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**MOTHER**

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**SMOKER**

- Y = 1 N = 0

**DIABETIC**

- Y = 1 N = 0

**OTHER MED PROB**

- Y = 1 N = 0

**SPECIFY**

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<tr>
<th>PREGNANCY [0=No prob 1=FET 2=APH 3=PRM 4=RL/Ab 5=TRIM 6=TRIP 7=HYDRAM 8=OLIGOM YEL 9=IUE 10=BP(above) 11=OTHER]</th>
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</thead>
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</tbody>
</table>

**INDUCED**

- Y = 1 N = 0

**ACCELERATED**

- Y = 1 N = 0
Baby

Basic ICN Study Data

Study ID No.

Study Group No.
[A=1 B=2 C=3 DUCT=4 BPD=5 Vent PN=6 OTHER=7]

Birth

Baby

Surname

Forename

Hospital No.

Gestation (Completed Weeks)

Birth Wt (g)

< 10th centile Y = 1 N = 0

Sex M = 1 F = 2

DOB

Time of Birth

Time to 1st gasp

Time to reg. resps.

Intubated Y = 1 N = 0

Ventilated Y = 1 N = 0

Congenital abnormality Y = 1 N = 0

Specify

Delivery [0=VND 1=EmSu 2=EISk 3=Forc 4=PH 5=Br 6=GhDis 7=Other]

Evidence of fetal distress Y = 1 N = 0

Place of birth 0=Inbn 1=UT 2=NT

CORD pH 6.60

Place 1st pH 6.60

---

355
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<table>
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<th>NUTRITION [Bott=1 Brst=2 Tube=3 IV=4] S=5</th>
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<tr>
<th>CAFFEINE</th>
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<th>CURRENT WT (g)</th>
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<tr>
<th>RESP [0=Well 1-RDS 2-Pneum 3=Mec Asp 4=Cong pneum 5=Acq pneum 6=Hyplp lungs 7=TN 8=Other]</th>
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<th>Fungochothorax</th>
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<thead>
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<th>Sepsis (0=0 1=General 2=UTI 3=Mening 4=Skin 5=Other)</th>
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<table>
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<tr>
<th>Perinatal asphyxia Y=1 N=0</th>
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<table>
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<tr>
<th>CIRCULATION [0=0 CLPDA=1 PFC=2 ?Poor LVF=3 Low BP=4 PreExtx=5 PostExtx=6 Hydrops=7 Other=8]</th>
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<tr>
<th>Abdo [0=0 1=Hypglyc 2=Low Na 3=High Na 4=Renal failure 5=Other]</th>
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<th>Other diagnosis Y=1 N=0 (UNCLASSIFIED)</th>
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<table>
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<tr>
<th>Recent Collapse 0=N Y=1 Severe=2 (Critical=3, Others=4, PH&lt;7-20)</th>
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<table>
<thead>
<tr>
<th>Cerebral U/S Right H (0-3) + Left</th>
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<table>
<thead>
<tr>
<th>Heart murmur Y=1 N=0</th>
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<table>
<thead>
<tr>
<th>PDA suspected N=0 Pos=1 Prob=2</th>
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<table>
<thead>
<tr>
<th>Indomethacin [N=0 To start=1 Had 1st dose=2 Had 2nd dose=3 3rd dose=4]</th>
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<table>
<thead>
<tr>
<th>CIVS</th>
<th>O=Not Asperible L=Normal</th>
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<tbody>
<tr>
<td></td>
<td>2=Mild AG+ (95-JT+AG+)</td>
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<td></td>
<td>3=Severe AG+ (59+)</td>
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<th>Recent Transfusion Y=1 N=0</th>
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| PCV | |
|-----|---|---|---|---|---|---|---|---|
|     | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|     |   |   |   |   |   |   |   |   |

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<tr>
<td>OTHER DRUGS</td>
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<tr>
<td>----------------------------</td>
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<tr>
<td>TOLAZ (0=0 1=To start 2=Post Dose 3=Infus 4=Post Infus)</td>
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<tr>
<td>DOBUTAMINE N=0 To start=1 Omit=2 Time omit (hours) Dose (mcg/kg/min)</td>
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<tr>
<td>DOPAMINE N=0 Start=1 Omit=2 Time / Dose</td>
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<td>ANTIBIOTICS Y=1 N=0</td>
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<th>METAB (Blank = Missing value)</th>
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<tr>
<td>Ca^{2+}</td>
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<tr>
<td>Mg^{2+}</td>
<td>*</td>
</tr>
<tr>
<td>BSL</td>
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<tr>
<td>Albumen</td>
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<tr>
<th>VENTILATION N=0 PEEP=1 INV=2 FULL=3</th>
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<tbody>
<tr>
<td>% O2</td>
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<tr>
<td>Resp rate</td>
<td>*</td>
</tr>
<tr>
<td>PAP</td>
<td>*</td>
</tr>
<tr>
<td>PEEP</td>
<td>*</td>
</tr>
<tr>
<td>MAP</td>
<td>*</td>
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<tr>
<td>I:E</td>
<td>*</td>
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<tr>
<td>Insp time</td>
<td>*</td>
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<td>HR</td>
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| Paralysed Y=1 N=0 Nortphine Y=1 N=0 |    |

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<th>RECENT Gas 0=DONE CAP=1 ART=2</th>
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<tr>
<td>O₂</td>
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<th>SAT Meter % TcO₂ TcCO₂</th>
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357
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<tr>
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<td>PDA VISUALISED</td>
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<tr>
<td>A° DIM</td>
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<tr>
<td>LA DIM</td>
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<td>IVS thickness</td>
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<td>LVEDD</td>
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<tr>
<td>LV POST WALL</td>
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<td>LVESD</td>
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<tr>
<td>*SHORT FRACT (%)</td>
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<tr>
<td>RV Dimen$^m$</td>
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<tr>
<td>SECTOR</td>
</tr>
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<td>A° DIM$^p$</td>
</tr>
<tr>
<td>*A° CSA</td>
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<td>PA DIM</td>
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<tr>
<td>*PA CSA</td>
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<td>A° INT DIM</td>
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<tr>
<td>BIDIRECTIONAL PLEX IN PDA</td>
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<td>TRUE MEAN DUCT PLEX</td>
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<td>(from curve)</td>
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<td>(bounded only)</td>
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<td>END SYST</td>
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<td>END DIAST</td>
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<tr>
<td>RATIO RIGHT</td>
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358
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**Doppler**

- **Ao Stroke Distance**
- **Ao Velocity**
  - Signal Used (CW=1 PW=2)
- **Pa Stroke Distance**
- **Pa Velocity**
  - Signal Used (CW=1 PW=2)

**Tr Jet**

- **Grade (0-4)**
- **Max T.R. Jet (m/s)**
- **RV - RA Press Drop**
- **Elevated RA Suspected Clinically? Y=1 N=0**

**PDA Jet**

- **Cw**
  - Not present 1=R-L 2=BID 3=L-R
- **Cw Max PDA Jet (L-R)**
- **Cw Min PDA Jet (L-R)**
- **Pul Max PDA Jet (L-R)**
- **Pul Min PDA Jet (L-R)**
- **Mean Ductal Flow**

**Lpa Ductal Antegrade Flow?**

Blank = No search 0 = None 1 = Short 2 = Pan diastole

**Mr Jet**

- **Grade (0-4)**
- **Max Jet**

**Pr Jet**

- **0 = No 1 = Early Diast 2 = Mid Diast 3 = Late**
- **Max Jet**

**Arch A/V Flow** 359
### Ultrasound Data

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<td></td>
<td>GSF</td>
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<tr>
<td>PFO M-W</td>
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<td>A/P Timing</td>
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### Inlet Valves

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<th>a Height</th>
<th>e/a</th>
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<th>Time Q-W to Onset</th>
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### Timing

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<th>AT</th>
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<th>Heart Rate</th>
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</table>
Appendix C- Abbreviations on data collection sheet.

Basic Data Sheet 1 (mother)

Pregnancy: PET=preeclampsia, APH=antepartum haemorrhage PRM=prolonged rupture of membranes, Rh/Ab=isoimmunisation, rhesus or other, hydr=hydramnios, olig=oligihydramnios, IU=intruterine growth retardation, BP=hypertension, not PET.

Basic Data Sheet 2 (baby)

Delivery: 0=normal vaginal delivery, 1=emergency section, 2=elective section, 3=forceps, 4=ventouse, 5=breech, 6=shoulder dystocia.

place of birth: 0=inborn, 1 intrauterine transfer, 2=neonatal transfer.

Patient Status 1

RESP=dominant respiratory disease- 1, RDS=HMD, 2=not used 3=meconium aspiration, 4=congenital pneumonia, 5=acquired pneumonia, 6=hypoplastic lungs, 7=transient tachypnoea, 8=BD or other, 9=lung disease of extreme prematurity.

Circulation (clinically evident circulatory problem) 0=no problem, 1=clinically evident & 'symptomatic' L-R ductal shunt, 2=persistent fetal circulation, 3=suspected poor left ventricular function, 4=hypotension, 5=pre-exchange transfusion, 6=post exchange, 7=hydrptic, 8=other.

Heartmurmur detected by attending clinicians 1=yes, 0=no

PDA suspected= clinical suspicion of left-to-right ductal shunt 0=unlikely, 1=possible, 2=probable.

Clinical CNS= neurological state.

PCV=packed cell volume

Fluids= daily fluid allowance in mls/kg/day.

Patient Status 2

Ventilation PAP=peak airway pressure (cm H$_2$O), PEEP=positive end expiratory pressure, IMV=intermittent mandatory ventilation, FULL=positive pressure ventilation, MAP=mean airway pressure.
### Appendix C - Abbreviations on data collection sheet (cont.).

#### Ultrasound Data 1

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Ao DIM</td>
<td>Aortic root dimension (leading edge method)</td>
</tr>
<tr>
<td>LA DIM</td>
<td>Left atrial dimension (at end atrial diastole)</td>
</tr>
<tr>
<td>IVS thickness</td>
<td>Interventricular septal thickness</td>
</tr>
<tr>
<td>LVEDD</td>
<td>Left ventricular end diastolic dimension</td>
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<td>LV post wall</td>
<td>Left ventricular posterior wall thickness</td>
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<td>LVESD</td>
<td>Left ventricular end systolic dimension</td>
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<td>RV Dimension</td>
<td>Right ventricular end diastolic dimension</td>
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#### Sector

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<tr>
<td>AoDIM</td>
<td>Aortic root dimension (cross-sectional echo, measured at base of aortic valve)</td>
</tr>
<tr>
<td>PA DIM</td>
<td>Pulmonary artery dimension at pulmonary valve, measured at base of pulmonary valve</td>
</tr>
<tr>
<td>Ao INT DIM</td>
<td>Internal diameter of aortic root measure on M-mode</td>
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</tbody>
</table>

#### Ultrasound sheet 2

Final five boxes are the +/- ductal flow velocity in metres per second at 30% of the R-R interval, (corresponding approximately to mid systole).

#### Ultrasound sheet 3

- **PFO**: patent foramen ovale. 0 = not patent. 1 = bidirectional flow 2 = left-to-right flow 3 = high velocity left-to-right flow (maximally >0.6 metres/sec)

#### Inlet valves

- 'e' height = mean peak velocity of the early, passive, diastolic inflow velocity.
- 'a' height = velocity of second phase (atrial contraction)

#### Timing

= systolic time intervals at the aortic (left) and pulmonary (right) valves. (AT = TPV)
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<th>ATC</th>
<th>PTP</th>
<th>PO2</th>
<th>PCO2</th>
<th>ETCO2</th>
<th>VCO2</th>
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Data Collection Sheet for Oxygeneation Studies

Appendix D
Appendix E  Normal haemodynamic values from healthy babies

1. Preterm babies

<table>
<thead>
<tr>
<th>Systolic systemic arterial pressure (mmHg)</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
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<table>
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<tr>
<th>Aortic stroke distance (cm)</th>
<th>10th centile</th>
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<th>90th centile</th>
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<th>PDAMAX (metres/second)</th>
<th>10th centile</th>
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<td>Age group (hrs) number</td>
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<td>Age group (hrs) number</td>
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Appendix E  Normal haemodynamic values from healthy babies

1. Preterm babies

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<thead>
<tr>
<th>Age group (hrs)</th>
<th>number</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
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<td>13-36</td>
<td>All together, 60</td>
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<td>37-72</td>
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<td>mean 1.82</td>
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<tr>
<td>73-144</td>
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Heart rate (beats/minute)

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<th>Age group (hrs)</th>
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<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
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<tbody>
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<td>0-12</td>
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<td>123</td>
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<td>73-144</td>
<td>mean 140</td>
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LV stroke vol. index (mIs/kg)

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<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
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</table>

LV output (mIs/kg/min)

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<th>Age group (hrs)</th>
<th>number</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
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<tbody>
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<td>0-12</td>
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<td>10</td>
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<td>All together, 56</td>
<td>166</td>
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Appendix E  Normal haemodynamic values from healthy babies

1. Preterm babies

<table>
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<th>Age group (hrs)</th>
<th>PA stroke distance (cm)</th>
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<th>TPV/RVET ratio</th>
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<th>Fractional shortening (%)</th>
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<td>All together, 54</td>
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<td>37-72</td>
<td>mean 31</td>
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<td>(SD 6.3)</td>
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### Appendix E  Normal haemodynamic values from healthy babies in the first three days of life

#### 2. Term babies

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<th>Systolic systemic arterial pressure</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
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<td>Age group (hrs)</td>
<td>number</td>
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<th>90th centile</th>
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<table>
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<th>PDAMIN (metres/second)</th>
<th>10th centile</th>
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<th>90th centile</th>
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<td>Age group (hrs)</td>
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<td>0</td>
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<th>PDAMEAN (metres/second)</th>
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Appendix E  Normal haemodynamic values from healthy babies  
in the first four days of life

2. Term babies

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<th>LA:Ao ratio</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (hrs)</td>
<td>number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-36</td>
<td>All together, 76</td>
<td>0.95</td>
<td>1.15</td>
</tr>
<tr>
<td>37-72</td>
<td></td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>LVEDD:Ao ratio</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (hrs)</td>
<td>number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-36</td>
<td>All together, 66</td>
<td>1.53</td>
<td>1.77</td>
</tr>
<tr>
<td>37-72</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart rate (beats/minute)</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (hrs)</td>
<td>number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td></td>
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</tr>
<tr>
<td>13-36</td>
<td>37</td>
<td>104</td>
<td>120</td>
</tr>
<tr>
<td>37-72</td>
<td>28</td>
<td>108</td>
<td>122</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>LV stroke vol. index (mls/kg)</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (hrs)</td>
<td>number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-36</td>
<td>All together, 77</td>
<td>1.26</td>
<td>1.63</td>
</tr>
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<td>37-72</td>
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</table>

<table>
<thead>
<tr>
<th>LV output (mls/kg/min)</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
</tr>
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<tbody>
<tr>
<td>Age group (hrs)</td>
<td>number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-36</td>
<td>34</td>
<td>154</td>
<td>196</td>
</tr>
<tr>
<td>37-72</td>
<td>27</td>
<td>149</td>
<td>192</td>
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</table>

| 37-72       | 18           | 131          | 172          | 214          |
Appendix E  Normal haemodynamic values from healthy babies in the first four days of life

2. Term babies

<table>
<thead>
<tr>
<th>PA stroke distance</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (hrs)</td>
<td>number</td>
<td>(cm)</td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td>17</td>
<td>5</td>
<td>8.2</td>
</tr>
<tr>
<td>13-36</td>
<td>16</td>
<td>7</td>
<td>8.8</td>
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<tr>
<td>37-72</td>
<td>14</td>
<td>6.6</td>
<td>8.6</td>
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</table>

<table>
<thead>
<tr>
<th>TPV/RVET ratio</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (hrs)</td>
<td>number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td>19</td>
<td>0.22</td>
<td>0.31</td>
</tr>
<tr>
<td>13-36</td>
<td>15</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>37-72</td>
<td>13</td>
<td>0.3</td>
<td>0.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fractional shortening</th>
<th>10th centile</th>
<th>50th centile</th>
<th>90th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (hrs)</td>
<td>number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td>All together, 64</td>
<td>25</td>
<td>34</td>
</tr>
</tbody>
</table>

mean 33.5 (SD 7.0)
Publications from this thesis

Full publications

1. Skinner JR, Boys RJ, Hunter S, Hey EN.
"Non-invasive determination of pulmonary arterial pressure in healthy neonates".

2. Skinner JR, Boys RJ, Hunter S, Hey EN.
"Pulmonary and systemic arterial pressure in hyaline membrane disease"
Archives of Disease in Childhood 1992;67:366-373

3. Skinner JR, Milligan DWA, Hunter S, Hey EN.
"Central venous pressure in the ventilated neonate"
Archives of Disease in Childhood 1992;67:374-377

"Validation of right heart pressure determination by Doppler in infants with tricuspid regurgitation"
Archives of Disease in Childhood 1993;69:216-220

Published abstracts

1. Skinner JR, Hunter S, Hey EN
"Tricuspid regurgitation in the newborn: Doppler estimation of pulmonary artery pressure"

2. Skinner J, Boys RJ, Hunter S, Hey EN.
"Non-invasive determination of pulmonary arterial pressure in healthy neonates".
Pediatrics Digest 1992;2:4-5, (Invited abstract)

3. Skinner JR, Hunter S, Hey EN
"Tricuspid regurgitation and pulmonary artery pressure in hyaline membrane disease"

4. Skinner JR, Hunter S, Hey EN.
"Pulmonary artery pressure in hyaline membrane disease".

continued overleaf.
Published abstracts (continued)

5. Skinner JR, Hunter S, Hey EN
"Cardiac Output in the Premature Neonate: The Influence of Ductus Arteriosus"
Br J Radiol, 1991:64;660 (Abstr)

"A new method to assess ductal shunting"

7. Skinner JR, Hunter S, Hey EN.
"Regulation of cardiac output in the premature neonate: stroke volume or heart rate?"
Peditr Cardiol 1991:12 (4);258 (Abstr)

8. Skinner JR, Stuart AGS, O'Sullivan J, Hunter S
"Validation of right heart pressure determination by Doppler in infants with tricuspid regurgitation"
Paediah' Cardiol 1992:13 (4);272-3 (Abstr)

10. Skinner J, Hunter S, Hey EN
"Evaluation of the TPV/RVET ratio in determining pulmonary arterial pressure in the neonate"

11. Skinner J, Hunter S, Hey EN
"Pulmonary arterial pressure in the newborn and the time to peak velocity/right ventricular ejection time ratio - influence of gestation and ductal patency"
Cardiol Young 1993: 3 (Supp 1), Abstract 410.
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Tsuda E. Transient left pulmonary artery stenosis in the neonatal period. Cardiol Young 1993; 3:120.(abstract)


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