RIGHT VENTRICULAR FUNCTION IN RESPIRATORY DISTRESS SYNDROME

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For Dad:

And when did you last see your father?

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DECLARATION

This thesis is the result of my own work. The material contained in this thesis has not been presented, nor is currently being presented, either wholly or in part for any other degree or other qualification.

Research performed at

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ABSTRACT

The right ventricle is the dominant ventricle in utero. It has a larger cardiac output, receives more of the venous return and has a larger volume than the left ventricle. Following birth the left ventricle enlarges and left ventricular output exceeds right ventricular output until closure of the ductus arteriosus. Corresponding changes in right ventricular dimensions and function during the transitional circulation remain uncertain.

Pulmonary hypertension is associated with increased morbidity and mortality in cardiorespiratory disorders such as persistent pulmonary hypertension of the newborn and respiratory distress syndrome. Right ventricular pathophysiology is potentially important in these conditions. The ability of the right ventricle to maintain adequate pulmonary blood flow despite increased pulmonary vascular resistance may be critical for optimal oxygenation. However, there is little published data on right ventricular volumes or function in healthy term newborn infants and none in preterm healthy infants.

Two dimensional echocardiography has been widely used to determine ventricular dimensions and function in infants and children with and without structural heart disease. Recent studies have successfully validated volume measurements made using echocardiography with magnetic resonance imaging, which is generally accepted as the "gold standard". The measured volumes can be used to calculate the stroke volume (diastolic volume - systolic volume). The right ventricular stroke volume can be used to assess function by calculating the ejection fraction

(stroke volume/diastolic volume) and the right ventricular output (stroke volume x heart rate).

The aim of this thesis was to investigate right ventricular performance and pathophysiology during the evolution of respiratory distress syndrome in neonates using two dimensional echocardiography. Base line measurements were recorded at six hours of age and these were compared to measurements made at 24 and 48 hours old (days 0,1 and 2 of life respectively).

Despite the validation, concerns still surround the use of ultrasound in multiple users, as there can be marked observer variation. Additionally, the validation with magnetic resonance angiography has been performed in young infants with a stable mature circulation. Therefore, the preliminary part of this thesis concerned establishing the intra observer repeatability of the technique and its agreement with Doppler calculated values. A coefficient of repeatability of 28% was demonstrated for the ellipsoid approximation method, this was better than the 52% for the Simpson's method. Additionally there was a systematic difference between the two different methods with the Simpson's method giving 30% smaller volume on average. Hence the ellipsoid approximation method was used to measure right ventricular performance in all subsequent studies. The ellipsoid method was then compared with the Doppler calculations with good correlation and acceptable agreement. It is important to note that because of the systematic difference with Doppler the ellipsoid method is therefore suitable for following trends rather than giving absolute values.

The establishment of the behaviour of the right ventricle in normal healthy and preterm term infants not requiring respiratory support was the next step in this investigation. In both these groups of infants right ventricular volumes decreased significantly over the three examinations, from day 0 to days 1 and 2 of life. Despite this there was little change in right ventricular function measurements. There was also no difference in right ventricular output between the two groups, or ejection fractions, despite the smaller volumes seen in the preterm infants.

The performance of the right ventricle in infants ventilated for respiratory distress syndrome was then compared with that from the healthy premature infants. The ventilated infants had smaller volumes but better right ventricular performance and a rise in right ventricular output by day two of life. Additionally the ejection fraction rose significantly with time and was higher in the ventilated infants on day two than in the healthy preterm group.

Amongst the ventilated preterm infants those with an oxygenation index of ten or more (severe respiratory disease) had worse right ventricular performance. In ventilated hypotensive infants commencement of a dopamine infusion caused a significant rise in right ventricular ejection fraction in all eight infants studied with no change in ductal flow characteristics. There was also a trend towards a rise in right ventricular output amongst these eight infants.

The involution of the right ventricle over the first two days of life is probably mediated by the fall in pulmonary vascular resistance and the increase in the end diastolic volume of the left ventricle. This was seen across healthy term and preterm infants and those with respiratory distress. The data in this thesis suggest that those infants with higher ventilatory requirements have a failure or retardation of this process. This may lead to both reduced pulmonary blood flow and therefore reduced left ventricular preload. The initiation of inotropic therapy caused a rise in right ventricular performance and output, therefore improving pulmonary blood flow and left ventricular preload. It may be that at earlier gestations the left ventricle is more reliant on the performance of the more dominant right ventricle to maintain cardiac output especially in the face of high mean airway pressures.

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CHAPTER ONE

INTRODUCTION

1.1 The Transitional Circulation

The transition from foetus to neonate is complex, involving alterations to most of the major organ systems. The cardiovascular system is no exception, with quite swift and profound alterations in haemodynamics. This causes difficulty in the assessment of neonatal cardiac function, as it has to be measured against an altering baseline.

1.2 Foetal Circulation

In the uterine environment the cardiovascular system is arranged in parallel, as opposed to the serial arrangement in mature infants. Figure 1.1 displays the foetal circulation in a schematic manner and figure 1.2 shows the distribution of the combined cardiac output of the foetus from ovine models.[1,2] Oxygenated blood from the placenta returns to the right side of the heart via the umbilical vein to the ductus venosus and then the inferior vena cava. This oxygenated blood does not fully mix with the deoxygenated blood returning from the lower body, as there is functional streaming in the inferior vena cava.[3] The Euclidean valves and crista of the right atrium preferentially stream the flow from the inferior vena cava towards the foramen ovale.[3] This further reduces the mixing with the deoxygenated blood returning from the upper body via the superior vena cava. These combined effects allow around 27% of the venous return to the heart to be redirected through the foramen ovale into the left atrium and thence the left ventricle.[2] The majority of this blood will be freshly oxygenated. This oxygenated blood has bypassed the pulmonary circulation and is ejected by the

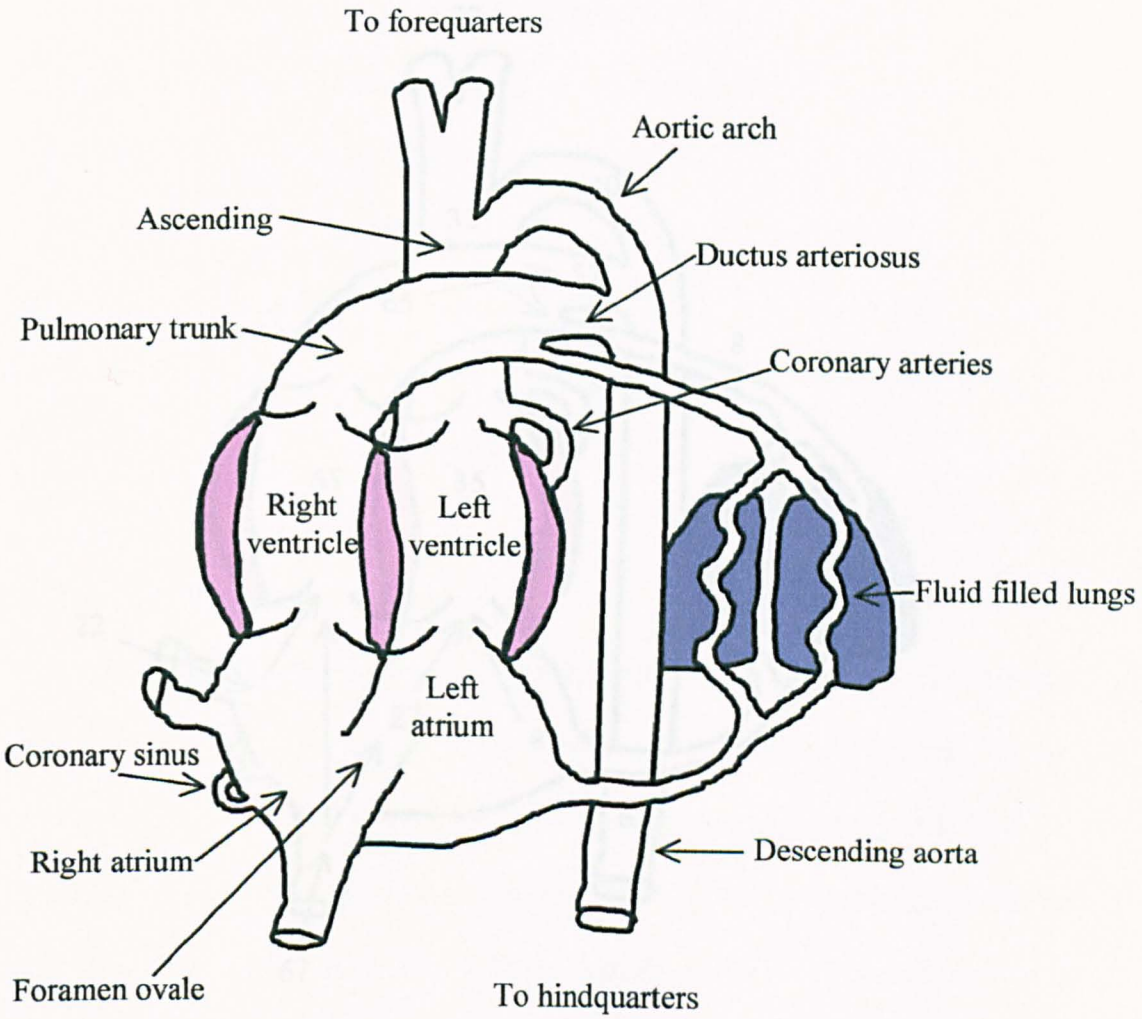

Figure 1.1: Representation of the foetal circulation.

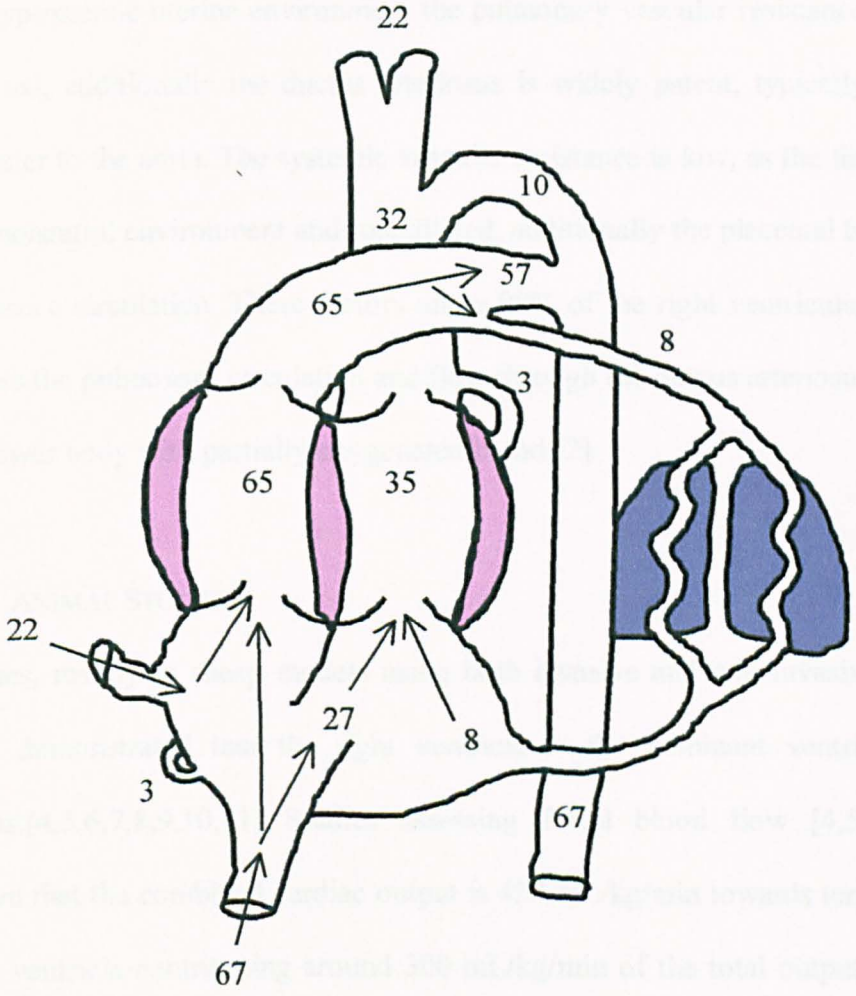

Figure 1.2: Blood flow in an ovine foetus, numbers represent the percentage of combined cardiac output. Refer to figure 1.1 for identification of chambers and vessels.

left ventricle to supply the upper body and critically the developing brain with oxygen rich blood. The blood that passes into the right ventricle, which is now mixed deoxygenated and oxygenated, is ejected into the pulmonary circulation. In the hypoxaemic uterine environment the pulmonary vascular resistance is greatly elevated, additionally the ductus arteriosus is widely patent, typically a similar diameter to the aorta. The systemic vascular resistance is low, as the foetus is in a thermoneutral environment and vasodilated, additionally the placental bed is a low resistance circulation. These factors allow 90% of the right ventricular output to bypass the pulmonary circulation and flow through the ductus arteriosus to supply the lower body with partially oxygenated blood.[2]

1.2.1 ANIMAL STUDIES

Studies, mainly in sheep models using both invasive and non invasive methods have demonstrated that the right ventricle is the dominant ventricle in the foetus.[4,5,6,7,8,9,10,11] Studies assessing foetal blood flow [4,5,6,7] have shown that the combined cardiac output is 450 mL/kg/min towards term, with the right ventricle contributing around 300 mL/kg/min of the total output, table 1.1, with a stroke volume in the near term ovine foetal right ventricle of around two mL/kg, compared with the one mL/kg in the left ventricle. Smolich et al [7] demonstrated that the ovine near term foetal right ventricle also has a higher myocardial blood flow and stroke work index than the left ventricle. Morphological studies of ventricular development have demonstrated that the ovine foetal right ventricle has a similar muscle mass to the left ventricle.[8,9] However, ultrastructure studies have shown that the ovine foetal right ventricle

	Combined foetal cardiac output, mL/kg/min	Heart rate, per minute	Ventricular output, mL/kg/min		Stroke volume, mL/kg	
			Left	Right	Left	Right
Foetus, at term	450	150	150	300	1	2
Newborn, at birth	-	200	400	400	2	2

Table 1.1: Ventricular performance during different ovine developmental stages.

near term has larger myocytes and a higher density of mitochondria and myofibrils than the left ventricle.[10] These data all suggest that the right ventricle is the dominant ventricle in the mammalian foetus.

1.2.2 HUMAN STUDIES

In humans there is some debate as to whether the right ventricle is still the dominant foetal ventricle. There is speculation that the left ventricle is nearly at parity with the right ventricle towards term and that this is essential to supply the higher metabolic demand of the developing human brain compared with lower mammals. However, there are few invasive studies that can be performed on human foetuses and therefore, conclusion must be drawn from non invasive assessments of cardiovascular function and post mortem studies. St John Sutton et al [12] used both two dimensional and M mode echocardiography from 20 weeks gestation to term to assess cardiac growth and performance. They found that the ratio of right to left ventricular dimensions was 0.96 and remained virtually constant throughout gestation. They reported fractional shortenings of 32% for the left ventricle at term and 36% for the right ventricle, but these were not significantly different from each other. In the same study they went on to measure the right and left ventricular free wall weights at post mortem in 24 foetuses from 16 to 38 weeks gestation. The right ventricle contributed 29% of total heart weight with the left ventricle contributing 30% of total heart weight. An ultrastructure and morphological study by Kim et al [13] in 44 post mortem specimens, ranging from 17 to 40 weeks showed no significant differences between left and right ventricular morphometric data. They demonstrated a progressive maturation of the

myocardium, but found no differences in myocytes, mitochondria or myofibrils between the ventricles. Veille et al [14] used M mode echocardiography on 80 foetuses between 17 to 42 weeks gestation. They found that the right ventricle was significantly larger in each case, but the ratio of right to left ventricle was only just greater than unity at 1.07. Doppler evaluations of cardiac output in 18 foetuses performed at 26 to 30 weeks gestation by Reed et al [15] gave right ventricular flow as 307 mL/kg/min compared with 232 mL/kg/min for the left ventricle. De Smedt et al [16] used Doppler to follow the ventricular output of 28 foetuses to term. At term they reported the combined cardiac output to be 550 mL/kg/min, with the left and right ventricles contributing 260 and 290 mL/kg/min respectively. They found that the ratio of right to left ventricular output fell from 1.3 at 15 weeks to 1.1 at term. This finding was reproduced by Schmidt et al [17] using two dimensional echocardiography in 50 foetuses from 18 to 40 weeks gestation. The right to left stroke volume ratio decreased from 1.36 to 1.10 during these examinations. These studies would seem to confirm that combined cardiac output in near term humans is therefore very similar to the ovine models of around 450mL/kg/min. The dominance of the right ventricle has been questioned in some studies in humans, however it is still likely to contribute more to the combined cardiac output of the foetus than the left ventricle, around 240 and 210 mL/kg/min respectively, table 1.2.

1.3 Transitional Phase

Birth, accompanied by the first breath and the transition from a warm liquid environment to the cold dry atmosphere, initiates dramatic changes to the

	Combined foetal cardiac output, mL/kg/min	Heart rate, per minute	Ventricular output, mL/kg/min		Stroke volume, mL/kg	
			Left	Right	Left	Right
Foetus, at term	450	150	210	240	1.4	1.6
Newborn, at birth	-	130	325	208	2.5	1.6
Newborn, at 5 days	-	120	216	216	1.8	1.8

Table 1.2: Overview of studies giving ventricular performance during different stages in the transitional circulation of humans.

circulation. These processes begin before delivery with a reduction in the circulating volume by 10 to 15% in infants delivered normally or operatively if labour is present.[18] Once the infant is delivered there is then an acute loss of venous return from the placental bed, as well as the loss of this low resistance peripheral circulation. The loss of this circulation also cuts the former oxygen supply from the mother, thus requiring a switch to breathing to accomplish gas exchange. To satisfy the demand for oxygen the pulmonary blood flow must rise rapidly, from 8% of combined cardiac output to around 50%.[2] This is assisted by the presence of oxygen in the lungs, which is a potent pulmonary vasodilator.[19] The pulmonary vascular resistance, therefore, drops rapidly within minutes of birth [7] and continues to fall over the first week of life. Until pulmonary artery pressures are around a third of the systemic pressure.[19] During this time the systemic vascular resistance rises steadily, mediated by the acute loss of the lower pressure placental circulation and the progressive peripheral vasoconstriction that occurs, as the infant becomes thermocompetent.[6] The changes in the pressures of the pulmonary and the systemic circulations affect the flow through the ductus arteriosus. Shortly after birth the flow becomes bi directional,[20,21] with the diastolic pressure in the aorta exceeding the diastolic pressure in the pulmonary arteries so that blood flows from the aorta into the pulmonary artery. The pressure difference is reversed during the systolic part of the cycle with blood flowing from the pulmonary artery into the aorta. As the pulmonary pressure continues to fall the systemic pressure rises. The aortic pressure then exceeds the pulmonary pressure throughout systole and diastole. This leads to constant aortic to pulmonary flow through the ductus

arteriosus.[20,21] These changes are usually manifest by the end of the first 24 hours in humans.[11] [20,22] Over this time period the increase in arterial oxygenation that is accompanied by the onset of air breathing causes a reduction in the size of the ductus arteriosus. These changes, mediated through local prostaglandin inhibition,[19] cause the unique spiral arrangement of smooth muscle in the wall of the ductus arteriosus to constrict.[19] Functional closure of the duct is usually complete within one hour in lambs [23] and by two days after birth in humans.[19] Anatomical closure by conversion into the ligamentum arteriosus occurs by around three months of age.[19] Catheter studies in healthy human infants have calculated that up to 35% of the left ventricular output, following birth, is shunted through the ductus arteriosus into the pulmonary circulation,[11] table 1.2, unlike in the lamb where the ventricles have equal outputs almost immediately.[1,2]

The vascular pressure changes brought about by birth affect the function of the foramen ovale. In the ovine foetus the right atrial pressure is higher than that of the left atrium,[2] allowing the right to left flow through this flap like valve. Following birth, with increased venous return to the left atrium, the pressure rises and pushes the foramen ovale closed.[2] This postnatal pressure difference has been demonstrated in humans with the right atrial pressure of two to six mmHg and the left atrial pressure of 5 to 14 mmHg.[11] [24] Postnatal ultrasonographic and Doppler studies have demonstrated both bi directional and left to right flow through the foramen ovale persisting for several days following birth.[20] Closure

of the foramen is usually complete within five days and anatomically sealed by three months.[19]

These structural alterations are mirrored by alteration in the functional performance of the heart. The left ventricle has an output of around 400 mL/kg/min in both the ovine models and in humans within the first few hours of life.[7] [11] [25,24] This is equivalent to the combined ventricular output of the foetus. This increase in left ventricular function is probably achieved by several mechanisms. Firstly around birth catecholamine levels rise to a lifetime maximum and remain elevated for the first week of life,[23] increasing contractility. The increase in pulmonary blood flow, mainly due to the fall in pulmonary vascular resistance and secondary to the closure of the ductus arteriosus, causes the left atrial pressure to rise.[2] [7] This increases left ventricular end diastolic volume [25,26] and hence increases stroke volume and cardiac output. Romero et al [8] showed that the rise in left atrial pressure does not fully explain the increase in left ventricular output. They demonstrated that the pressure volume curves of the ventricles following birth are shifted to distend more easily in the neonate than in the foetus.[8] This was also true of the right ventricle, which in that study was more compliant in both the foetus and the newborn. They also demonstrated ventricular interaction, as one ventricle was distended the volume of the other was compromised and this effect was more severe in the foetus than in the neonate. Grant et al [27] demonstrated in an ovine model that the function of the left ventricle improved with the release of the tamponade of the amniotic fluid and maternal tissues around the foetus. This tamponade was reduced even further with

the aeration of the lungs. These changes, the loss of tamponade, the increase in left ventricular compliance and the rise in left atrial pressure all allow the left ventricle to nearly double its output from foetal to neonatal life.[7] [25,26] Over the following days left ventricular output falls to lower levels of around 200 mL/kg/min.[23] [26]

The corresponding changes in the right ventricle in humans are less well documented. In ovine models the closure of foetal shunts is almost immediate and therefore left and right ventricular outputs in the neonate are equal, see table 1.1. Additionally, the functionally more dominant right ventricle has to only increase its output by 30%. This is mainly accommodated by the increase in the heart rate as right ventricular stroke volume is unchanged.[7] This is likely to be maintained, as there is little change in right atrial pressure [23] and the increased preload on the left ventricle, through ventricular interaction inhibits the loss of tamponade of maternal tissues and lung aeration.[8] [27] In humans the longer transitional phase means that right ventricular output and performance does not necessarily have to match that of the left ventricle, until the closure of the foetal shunts.

Emmanouilides et al [24] studied the cardiac output of 23 healthy newborn infants up to 35 hours of age, using the indicator dilution technique. The mean right ventricular output in these infants was 160 mL/kg/min with a stroke volume of 1.33 mL/kg and heart rate 124 beats per minute. Left ventricular stroke volume at this time was 25% higher at 1.66 mL/kg, hence the left ventricular cardiac output was 200 mL/kg/min. Gessner et al [11] using an indicator dye technique, found

similar values in 14 one hour old infants with a right ventricular output of around 165 mL/kg/min and stroke volume of 1.36 mL/kg. Again left ventricular output and stroke volumes were larger at 260 mL/kg/min and 2.15 mL/kg/min respectively. Both studies confirmed that around 30 to 35% of the left ventricular output went through the ductus arteriosus at this age. These early studies used highly invasive techniques, which have now been replaced by echocardiographic measurements, to assess cardiac performance in otherwise well infants. However they provide insight into the transitional circulation at delivery, but there are only measurements at the one time point in these studies.

Veille et al [28] and Wladimiroff et al [25] used M Mode echocardiography to follow the changes in the diameter of the right ventricle through gestation and the first 48 hours after birth. Right ventricular end diastolic diameter prior to birth was 17 mm. This fell to 11 mm by 10 minutes old and was 10 mm at 48 hours old, although the postnatal change was not significant. Right ventricular end systolic diameter prior to birth was 14 mm. This fell to nine mm by 10 minutes old and was eight mm at 48 hours old; again the postnatal change was not significant. Unfortunately unidimensional measurements of the right ventricle are not helpful in assessing ventricular performance because of its shape.[29,30,31,32,33,34,35]

Ichihashi et al [36] looked at the changes in the right ventricle from three days old to 35 days old in 25 healthy neonates using two dimensional echocardiography. They found no change in the right ventricular end systolic, end diastolic, or stroke volumes, 0.44, 1.00, 0.56 mL/kg respectively. The ejection fraction of the right

ventricle did not alter during this time period, 0.55, nor did the right ventricular output, 85 mL/kg/min. However, this study began at the end of the transitional circulation and therefore, does not reflect true adaptational changes.

Tamura et al [22] using two dimensional echocardiography followed the changes in right ventricular performance at 2, 24 and 120 hours (five days) old in 20 healthy term infants. They found that right ventricular end diastolic volume increased from 2.33 to 2.62 mL, stroke volume increased from 1.06 to 1.39 mL and right ventricular output rose from 144 to 174 mL/min from two to 24 hours, with no further change at 120 hours. End systolic volume remained unchanged, hence right ventricular ejection fraction rose from 0.45 to 0.53. They speculate that the closure of the ductus arteriosus is responsible for the rise in the right ventricular end diastolic volume and hence stroke volume. However, they state that this may not be the sole reason as there was no correlation between ductal diameter and end systolic volume. They also state that the volume reported may not be accurate as echocardiography may underestimate the true ventricular volume. It is worth noting that these volumes are reported in mL only and not corrected for birth weight. This would reduce to end systolic volume to around 0.4 mL/kg, the diastolic volume to 0.8 mL/kg making stroke volume around 0.4 mL/kg and the right ventricular output 55 mL/kg/min. The right ventricular stroke volume and ventricular output values in their study are quite a lot smaller than those from the invasive studies of Emmanouilides et al [24] and Gessner et al [11] and the authors state that further investigation into the behaviour of the right ventricle in the transitional circulation is required.

Although much understanding has been gained of the function of perinatal cardiac function there is no clear view of the performance of the right ventricle during this period.

1.4 Neonatal Morbidity and Cardiovascular Function

Neonatal morbidity is most commonly associated with respiratory distress and up to 60% of premature infants less than 32 weeks gestation develop respiratory distress syndrome.[37] In this condition there is pulmonary immaturity and often surfactant deficiency.[37] Infants may also have concomitant pulmonary hypertension and this is associated with increased mortality and the development of chronic lung disease.[38,39] Respiratory failure may cause up to 80% of deaths in such infants.[40] In this condition elements of the foetal circulation remain,[20] [38,39] with pulmonary hypertension, persisting foetal shunts and right to left shunting. In such conditions delivery of deoxygenated blood to the gas exchange interface for oxygenation is critical. This is the role of the right ventricle. Therefore, response of the right ventricle to this increased load may underpin the recovery from these conditions.

Investigation of cardiovascular function in premature human neonates has firstly used invasive blood pressure monitoring. Miall Allen et al [41] showed that systemic hypotension in ventilated infants is associated with worse neurological outcomes, secondary to intraventricular haemorrhage and cystic periventricular leukomalacia. Further work by Gill and Weindling, using M Mode echocardiography has investigated whether the systemic hypotension was

secondary to hypovolaemia or cardiogenic in origin.[42] Their study demonstrated that poor myocardial contractility is a major cause of systemic hypotension in premature ventilated hypotensive infants, as opposed to hypovolaemia. Evans & Klucklow,[20] using Doppler studies over four days in ventilated premature infants have shown that both left ventricular and right ventricular outputs are lower with more severe respiratory disease. This may be a result of reduced venous return as a result of the higher mean airway pressures [43] used to ventilate infants with severe respiratory distress syndrome, and/or to the increased afterload seen in these infants [39] that reduces the right ventricular stroke volume.[44] Evans & Klucklow,[20] found that left and right ventricular outputs were closely related to each other and to the presence of persisting foetal shunts and that low biventricular output, less than 150 mL/kg/min, was common in infants who went on to die. In the infants studied right ventricular output increased from 200 mL/kg/min on day one to 290 mL/kg/min on day four and the left ventricular output in these infants went from 230 to 280 mL/kg/min. The rise in right ventricular output was significant, but not so the left. No comment is made on stroke volume for each ventricle or the heart rate. The outputs of each ventricle were not reported to be significantly different from each other. Therefore it is not clear whether the rise in right ventricular output is secondary to ductal closure (35% were closed on day one and 65% on day four) or due to a change in stroke volume, or due to an increase in heart rate. Additionally, measurements were recorded by several individuals on multiple infants and therefore these changes were not recorded in the same infants at serial time points.

Unlike systemic blood pressure, measurement of pulmonary artery pressure is not available by direct invasive methods.[45,46] Echocardiography has been used in ventilated infants to demonstrate that elevated pulmonary pressures in these infants are independently predictive of the development of chronic lung disease.[38,39] The effect of this increased afterload on the right ventricle has not been established and there is only one report [22] on the volumes and changes in performance of the right ventricle in the neonatal period, with none in infants with cardiorespiratory distress. Alteration in the behaviour of the right ventricle when exposed to increased afterload and medical interventions has also not yet been reported.

1.5 Aim of the Study

To test the hypothesis that right ventricular dysfunction is associated with more severe respiratory disease in infants with respiratory distress syndrome.

1.6 Objectives

To assess the reproducibility of echocardiography when used as a tool for measurement of right ventricular function.

To establish the functional changes in the right ventricle of healthy term infants during the transitional circulation.

To compare the functional changes in the right ventricle during transitional circulation of healthy preterm infants to their term counterparts.

To measure right ventricular function in infants with respiratory failure and compare these with the data from the term and preterm infants.

To assess the effect of positive inotropes on the performance of the right ventricle.

CHAPTER TWO

MEASUREMENT OF RIGHT VENTRICULAR FUNCTION AND STUDY METHODS

2.1 Indices of Ventricular Function

Echocardiography has been widely used to study diastolic,[47] systolic [48] and global ventricular [49] function in neonates. There is no single modality of ventricular function that is independent of the others.[19] Moreover, each measure is often interdependent on one or more of the others, so a range of measurements has developed to assess the components of ventricular function.[19] These have been assessed in the left ventricle and the right ventricle, as the same physiological principles apply to both.[43,44] The most important factors determining ventricular function are preload, contractility and afterload,[19] [23] but these can not be considered without the effect that heart rate has on cardiac performance.

2.1.1 PRELOAD

Preload is the stress in the wall of the ventricle before systole begins. This reflects the venous return to the heart and the compliance of the ventricle. It is commonly assessed invasively using the atrial pressure, using the assumption that the pressure volume curve of the ventricle is constant. However, Pinson et al [9] and Romero et al [8] have shown that the pressure volume curves of the left and right ventricle change with gestation and is dependent on the volume loading of the other ventricle.

Increased filling pressure and therefore preload, via the Frank Starling mechanism, will increase cardiac output.[19] However, beyond a certain filling pressure the ventricle over distends reducing the output and the ejection

fraction.[19] Foetal ventricles are poorly compliant partly due to inherent immaturity,[8] [16] but mainly secondary to the tamponade of surrounding structures.[27] This appears to effectively negate the Frank Starling mechanism in the ovine foetus [8]. In human foetuses Kenny et al [50] demonstrated that an increase in heart rate caused by auditory stimuli was not associated with an increase in cardiac output. They concluded that the Frank Starling mechanism must therefore be intact, although attenuated, as stroke volume was reduced in these healthy foetuses. They did not volume load the foetuses to demonstrate this change and therefore it may have been a physiological response to maintain cardiac output, as there was no change in foetal state to require a higher cardiac output.

The loss of tamponade at birth increases the compliance of both ventricles [27] however; they are still less compliant than more mature ventricles.[8] The poor compliance serves to reduce preload as for any given filling pressure the ventricle will distend less, potentially reducing the stroke volume and the ejection fraction.

The only measurement that accounts for the filling pressure, the ventricular compliance and the volume loading in the other ventricle is the end diastolic volume. Therefore, this is a better index of preload than just atrial pressures alone.

2.1.2 AFTERLOAD

Afterload is the stress in the wall of the ventricle during the contraction phase.[6] It is the force against which the ventricle has to work, which is the blood pressure

in the arteries, systemic or pulmonary. Again this is dependent on several factors; peripheral vascular resistance and vascular capacitance have dramatic effects on afterload, as does cardiac output itself. In the systemic circulation the arterial pressure is usually taken as the marker of afterload. Non invasive measurement of pulmonary artery pressure is possible,[45] using tricuspid regurgitation,[46] ductal flow velocities [38] and systolic ratios.[39] However, Reller et al [51] and Pinson et al [52] showed that the right ventricle in the perinatal period is acutely pressure sensitive and rises in the afterload reduce stroke volume by increasing end systolic volume. Therefore in the right ventricle both stroke volume and end systolic volume are indices of afterload,[23] as well as the pulmonary artery pressure.

2.1.3 CONTRACTILITY

This is the intrinsic ability of the ventricle to shorten its fibres.[53] This can be assessed with the ejection fraction,[23] [53] which is end diastolic volume minus end systolic volume divided by the end diastolic volume, table 2.1. However, the end diastolic volume as discussed in the previous section is directly related to preload. The end systolic volume, especially in the right ventricle may be affected by afterload, as discussed in the above section. Invasive measures of contractility can be performed during cardiac catheterisation, for example the pressure rise in the ventricle at initial systole. These have been used to validate the pressure rise calculated from tricuspid regurgitation [54] as a non invasive measure of contractility. However it is not always possible to detect tricuspid regurgitation with colour flow mapping and therefore it is not possible to obtain a usable

Doppler signal for this technique, leaving ejection fraction as the most available measure for contractility.

2.1.4 HEART RATE

This reflects the time interval for one heart cycle. As heart rate increases so the filling time decreases and at extreme heart rates this may adversely affect preload.[19] [23] During foetal life, in ovine models the main control of cardiac output is the heart rate and contractility.[23] However, two studies in healthy foetuses, both human and ovine, showed that an increase in heart rate, not associated with some other positively inotropic stimulus, was not associated with an increase in cardiac output.[50] [55] As the heart rate increased there was a reduction in the stroke volume in both studies.[50] [55]

2.2 Measurements Possible with Echocardiography

It is not possible to obtain independent measurements of preload, afterload, and contractility. Therefore, several overlapping measures are used to provide this information. It is possible to derive an assessment of preload, afterload and contractility from the volume of the ventricle at end systole and at end diastole.[6] [56] In the right ventricle these reflect afterload and preload, respectively and can be used to calculate stroke volume, ejection fraction and ventricular output,[56] table 2.1.

Stoke volume	end diastolic volume - end systolic volume
Ejection fraction	stroke volume / end diastolic volume
Ventricular output	stroke volume x heart rate

Table 2.1: Equations to calculate ventricular function and performance from end systolic and end diastolic volumes.

2.2.1 End Diastolic Volume

End diastolic volume is the volume of the ventricle just before the beginning of systole. It is a reflection of the compliance of the ventricle at any given pressure and the amount of venous return to that ventricle.[23] Impaired ventricular relaxation, that is a stiff ventricle, will reduce end diastolic volume. Reduced venous return, either secondary to peripheral venous pooling or poor cardiac output will also diminish end diastolic volume, as ventricular filling is diminished.

2.2.2 End Systolic Volume

This is the volume of the ventricle just before the beginning of diastole. It is a reflection of the contractility of the ventricle and the afterload. Increasing afterload will reduce the volume of blood that the ventricle can eject and therefore increase end systolic volume. Increased contractility, via catecholamines or other positive inotropes, will reduce end systolic volume. Adverse biochemical factors, such as acidosis and hypoxia will reduce contractility and thereby increase end systolic volume.[19] [23]

2.2.3 Stroke Volume

This is the volume of blood ejected in each heart cycle. It is the difference between the end diastolic volume and the end systolic volume, table 2.1. As such preload, contractility and afterload affect it. Changes in ventricular volumes may not lead to changes in stroke volume. If both end systolic and end diastolic volumes fall stroke volume may be maintained or even increase, as long as the difference between the volumes is constant or rises. Again there may be no

change or a fall in stroke volume despite increases in ventricular volumes as long, as the difference between the volumes is constant or falls.

2.2.4 Ejection Fraction

This is the ratio of stroke volume to end diastolic volume, table 2.1. It is the percentage of blood ejected from the heart in each cycle. It can be affected by preload, afterload and contractility.[23] Ejection fraction is widely used to monitor ventricular performance.[23] [56]

2.2.5 Ventricular Output

This is the volume of blood ejected by the heart per minute. It is the stroke volume multiplied by the heart rate, table 2.1. So again it reflects preload, afterload, contractility as well as the chronotropic state of the heart.

2.3 Validation of Echocardiographic Right Ventricular Measurements

Echocardiography is widely used in children and infants to assess both cardiac structure and function. Its non invasive character and mobility make it an ideal tool for the cardiovascular assessment of sick neonates. However, the widespread use of a measure because of ease does not make the results accurate, reliable or repeatable. The use of echocardiography has been generally accepted for the assessment of left ventricular function and this has been validated against more invasive methods of assessing cardiac function.[57,58]

The right ventricle, because of its crescenteric geometry and non circumferential contraction,[56] has made non invasive assessment of its function difficult to perform and validate. The advent of fast magnetic resonance angiography that can be gated to the electrocardiogram has enabled the accurate determination of the volume of the right ventricle in vivo. This has allowed comparison of the highly accurate technique of magnetic resonance angiography with the readily available bedside technique of echocardiography. Several groups have now compared magnetic resonance angiography measurements, the current accepted gold standard of assessment of cardiac volumes (and therefore performance), with two dimensional echocardiography in children and found acceptable agreement and correlation of values.[33,34,35]

2.3.1 Mathematical Models for Right Ventricular Volume Measurement

Several mathematical models are available for the calculation of right ventricular volumes. Helbing et al [33] used right ventricular magnetic resonance angiography to determine the reliability of five echocardiographic techniques for measuring right ventricular volumes and function measurements in 17 healthy children. The mean age of their subjects was 11 years with a standard deviation of 2.5 years. Three were methods that required images in two planes and two were monoplane techniques. All five techniques used the apical four chamber view, with two of the bi plane techniques using the parasternal short axis view and the third bi plane technique used the subcostal right ventricular outflow view, see figure 2.1. The volumes were calculated using three different formulae, the

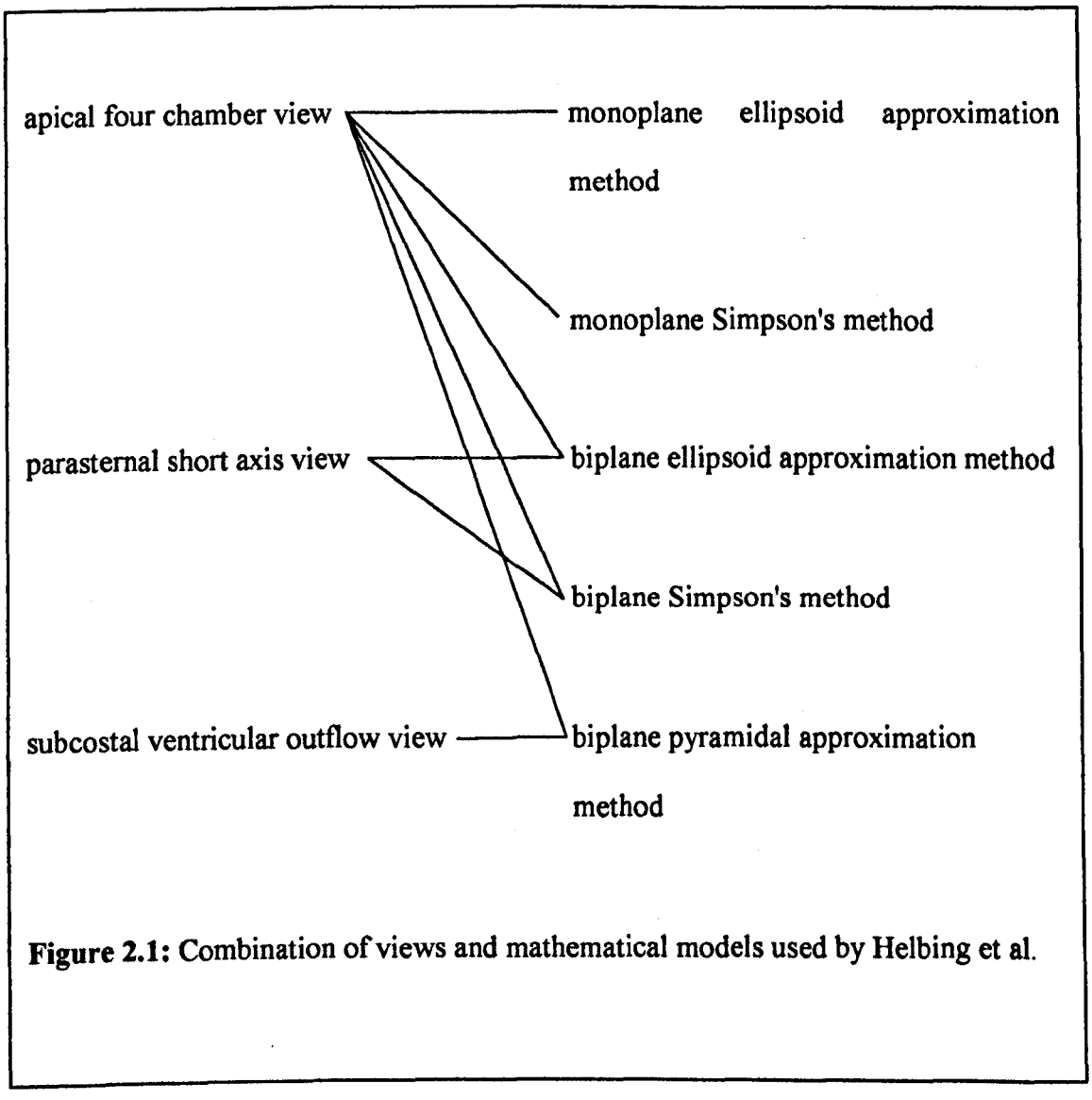

Figure 2.1: Combination of views and mathematical models used by Helbing et al.

ellipsoid approximation method, the Simpson's multiple slice method and the pyramidal approximation method.

2.3.2 Volumetric Measurements

In their study mean (standard deviation) right ventricular end diastolic volume calculated using magnetic resonance angiography was 92 (27) mL. Mean (standard deviation) right ventricular end systolic volume calculated using magnetic resonance angiography was 33 (13) mL. Table 2.2 summaries the mean differences between the magnetic resonance angiography and the echocardiographic calculated right ventricular volume data from the paper. All five methods gave volumes at end systole and at end diastole that correlated significantly ($p<0.005$) with the volumes from magnetic resonance angiography.

All five methods demonstrated an acceptable mean difference in the end systolic volume and acceptable limits of agreement, table 2.2. This would make each echocardiographic method suitable for trend measurements in individual patients, but not for estimating absolute values for ventricular volumes.

2.3.3 Functional Measurements

These volumes were then used to calculate the ejection fraction of the right ventricle. In their study mean (standard deviation) right ventricular ejection fraction calculated using magnetic resonance angiography was 65 (8)%. Both the monoplane views gave as good functional results as the biplane views. The correlation between echocardiographic ejection fractions compared with magnetic

	Systolic r Diastolic r	End systole mean difference (limits of agreement)	End diastole mean difference (limits of agreement)
Mononplane ellipsoid approximation method	0.67 0.77	14 (-6 to 34)	46 (13 to 79)
Mononplane Simpson's method	0.69 0.75	15 (-5 to 35)	52 (19 to 85)
Biplane ellipsoid approximation method	0.78 0.57	9 (-9 to 27)	37 (-8 to 82)
Biplane Simpson's method	0.81 0.66	8 (-8 to 24)	37 (2 to 72)
Biplane pyramidal approximation method	0.82 0.86	-4 (-18 to 10)	14 (-17 to 45)

Table 2.2: Correlation and limits of agreement between five echocardiographic methods of right ventricular volume measurement and magnetic resonance angiography, volumes give in mL. Mean difference is magnetic resonance angiographic measurement minus echocardiographic measurement.

resonance angiography were strongly significant, with $p<0.005$ for all five techniques.

Table 2.3 shows the correlation coefficients and the level of agreement between the ejection fractions measured by the five echocardiographic methods and magnetic resonance angiography. The monoplane ellipsoid approximation method, the monoplane Simpson's method, the biplane ellipsoid approximation and the biplane Simpson's method had a small mean difference with magnetic resonance angiography. However, as the confidence intervals for these four methods cross 0% difference there is no systematic difference between them and the gold standard measurement. Additionally the limits of agreement are acceptably narrow for clinical use.

All these methods showed acceptable limits of agreement with magnetic resonance imaging and would therefore be suitable for following the trends in a patient. However, all echocardiographic measures generally gave smaller volumes and ejection fractions than the magnetic resonance angiography.

2.3.4 Other Considerations

The complex geometry of the right ventricle makes simple unidimensional M Mode assessment of function inappropriate, unlike in the left ventricle.[56] Additionally the function of the right ventricle can be affected by the respiratory cycle. Venous return to the right side of the heart is augmented by the inspiratory phase and inhibited by the expiratory phase of breathing.[19] Helbing et al [33]

	r	Percentage mean difference (limits of agreement)
Mononplane ellipsoid approximation method	0.72	5 (-9 to 19)
Mononplane Simpson's method	0.75	10 (-2 to 22)
Biplane ellipsoid approximation method	0.76	9 (-3 to 21)
Biplane Simpson's method	0.69	11 (-1 to 23)
Biplane pyramidal approximation method	0.66	11 (1 to 21)

Table 2.3: Correlation and limits of agreement between five echocardiographic methods of right ventricular ejection fraction measurement and magnetic resonance angiography. Mean difference is magnetic resonance angiographic measurement minus echocardiographic measurement.

therefore, averaged over four heart cycles to account for this variation. Other authors working in neonates have found that five consecutive heart cycles is the minimum required to account for this variation.[59,60]

Helbing et al found that the biplane views gave more accurate volume measurements. All of these required an apical four chamber view, which was suitable for analysis in all cases. However, only 70% of the second plane images were good enough quality from the parasternal short axis view and only 52% of the subcostal views were of sufficient quality to allow analysis. Only the monoplane volume estimates could be performed in all patients.

2.3.5 CONCLUSIONS

Several mathematical models for measurement of right ventricular volumes have now been validated against the gold standard of magnetic resonance imaging. These display good correlation, close limits of agreement, and in some cases no systematic difference.[33]

The aim of this thesis is to study right ventricular function in sick neonates. It is, therefore, important to use methods that are quick, reliable and that show good correlation and close agreement with the gold standard. The presence of a systematic difference is not problematic when following trends in individual patients, as the long as the limits of agreement are within acceptable values.

The monoplane ellipsoid approximation and the monoplane Simpson's methods in Helbing et al's study both used the apical four chamber view. This gave suitable images in every case. There was good correlation in both systole and diastole with magnetic resonance angiography. There was no systematic difference and close limits of agreement in the systolic measurements with magnetic resonance angiography. In the diastolic measurements there was a systematic difference in both methods but the limits of agreement were acceptable. The ejection fraction for each method also showed good correlation and close limits of agreement, with no systematic error for the ellipsoid approximation method and a small systematic difference for the Simpson's method when compared with magnetic resonance angiography. Therefore, these two methods are probably the most suitable for use in sick neonates and will be used in this thesis to measure right ventricular volumes and performance.

2.4 Study Methods

2.4.1 Subjects and Ethical Considerations

All infants were studied during the first two days of extra uterine life once informed written parental consent was given. The local research ethics committee had reviewed the protocol and had approved it.

All infants were born and recruited at Liverpool Women's Hospital.

2.4.2 ECHOCARDIOGRAPHY

I conducted all examinations with the infants at rest or asleep and performed all the subsequent analyses. The first examination was detailed to exclude any cardiac malformations.

2.4.3 EQUIPMENT

Echocardiography was performed using the General Electric Colour Flow Mapping 800 series, figure 2.2. This incorporated a multifrequency 5 to 7.5 MHz imaging transducer, colour flow mapping, high frequency pulse wave Doppler and continuous wave Doppler. The images from the examinations were digitally stored in an integrated digital archiving system, an Apple Macintosh computer using the Echopac software version 5.3 (General Electric Ultrasound, Bedford UK).

2.4.4 EXAMINATIONS

Two dimensional images of the right ventricle were recorded from the apical four chamber view (figure 2.3) with the septum as vertical as possible and the tricuspid value as horizontal as possible, as described by Helbing et al.[33] [60]

Colour flow maps of flow of the ductus arteriosus and the foramen ovale were recorded.[61,62]

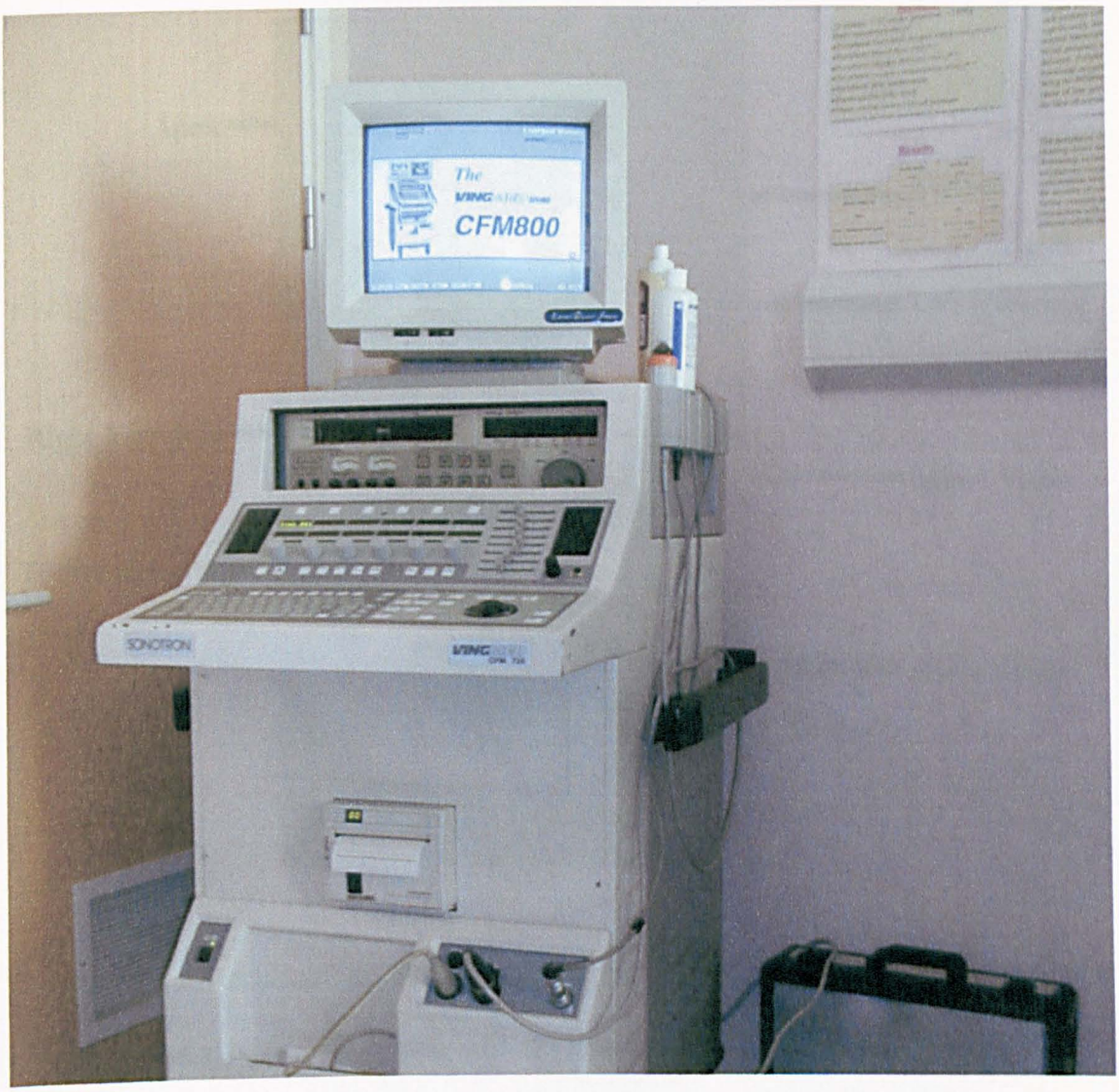

Figure 2.2: General Electric Colour Flow Mapping 800 series, incorporating a multifrequency 5 to 7.5 MHz imaging transducer, colour flow mapping, high frequency pulse wave Doppler and continuous wave Doppler and an integrated digital archiving system, an Apple Macintosh computer using the Echopac software version 5.3 (General Electric Ultrasound, Bedford UK).

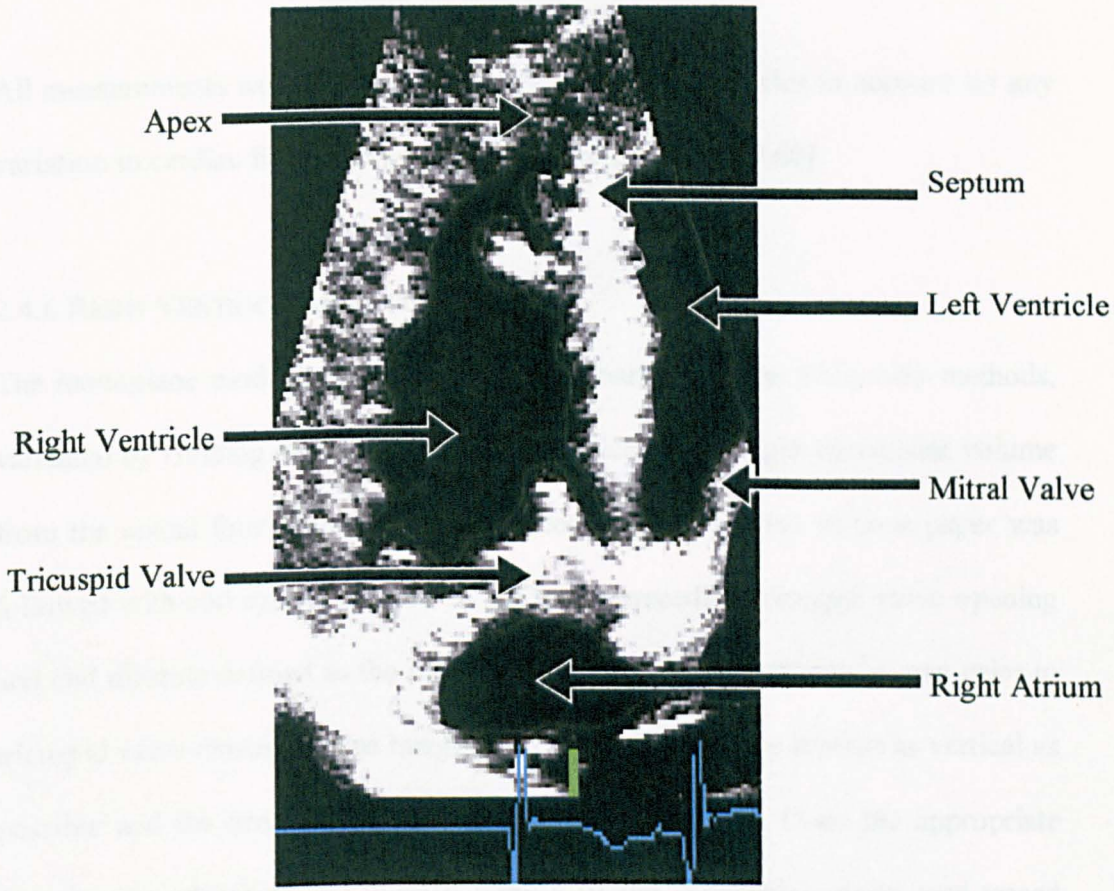

Figure 2.3: An echocardiographic image of the right ventricle from the apical four chamber view, taken at mid systole with the tricuspid valve closed.

2.4.5 IMAGE ANALYSIS

This was conducted using the integrated Echopac software, specifically designed for this purpose.

All measurements were averaged over at least five heart cycles to account for any variation in cardiac function that occurs with respiration.[59,60]

2.4.6 RIGHT VENTRICULAR VOLUMES

The monoplane models, the ellipsoid approximation and the Simpson's methods, validated by Helbing et al [33] were used to calculate the right ventricular volume from the apical four chamber view. The technique described in their paper was followed with end systole defined as the frame preceding tricuspid valve opening and end diastole defined as the frame with the maximum ventricular area prior to tricuspid valve closure. These images were recorded with the septum as vertical as possible and the tricuspid valve as horizontal as possible. Once the appropriate frames were identified the internal margin of the ventricular cavity was traced using the integrated software package, figure 2.4. For the ellipsoid approximation method the area within the tracing was calculated and the distance from the centre of the tricuspid valve to the apex was measured and the formula in table 2.4 was used to calculate the volume at end systole and at end diastole. At least five consecutive heart cycles were analysed and the average end systolic and average end diastolic volume for each was recorded. For the Simpson's method the traced cavity was divided, by the integrated software, into 20 slices, figure 2.4. The diameter and the height of the slice are known and these are used to calculate a

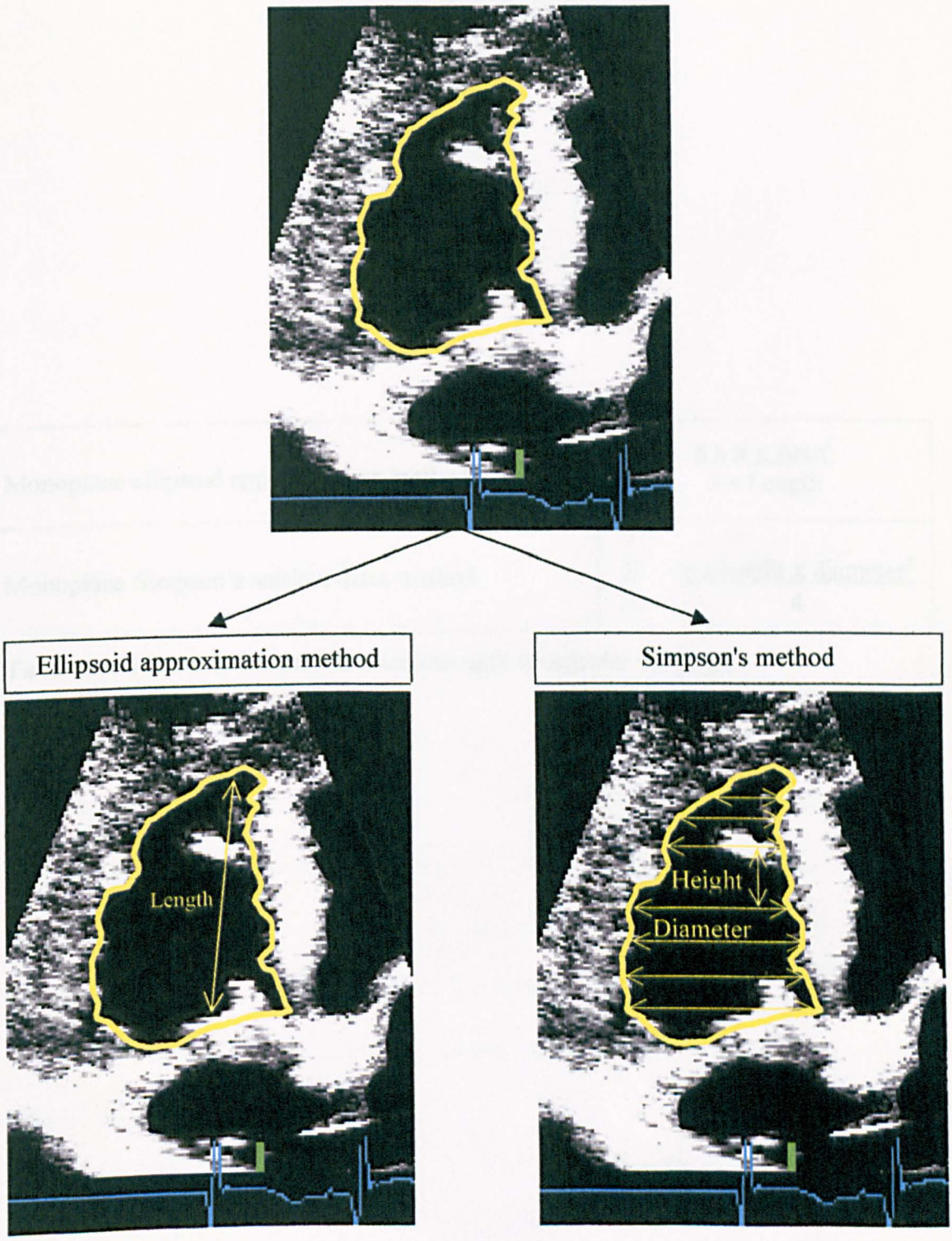

Figure 2.4: Top panel shows the internal ventricular margin delineated. For the ellipsoid approximation method the area within this is calculated and the length of the ventricle is measured. For the Simpson's method the ventricle is sliced into 20 equal discs, distorted here for demonstration purposes, of known height and diameter.

Monoplane ellipsoid approximation method	$\frac{8 \times \pi \times \text{Area}^2}{3 \times \text{Length}}$
Monoplane Simpson's stacked discs method	$\sum_{20}^{1} \frac{\pi \times \text{height} \times \text{diameter}^2}{4}$

Table 2.4: The formulae used to calculate right ventricular volumes.

volume as though this slice was a disc. The 20 volumes from the slices or discs are summed to give a total volume at end systole and at end diastole, as in the formula in table 2.4. Again this was repeated over a minimum of five heart cycles to account for respiratory variation. From colour flow maps and Doppler recordings the change in ductal flow characteristics were recorded at each examination and the minimum ductal diameter measured.[62]

2.4.7 Doppler Right Ventricular Output

This was performed using the method described by Evans and Klucklow.[20] The pulmonary valve was visualised and the diameter measured at the point of insertion into the artery walls. The diameter of the valve was used to calculate the area of the valve orifice. The Doppler signal of blood flow velocity was recorded with the angle of incidence as close to zero as possible, but at most within 20 degrees, negating the need for angle correction.[5] [53] The integral of this signal was measured using the software, giving the distance the blood has moved with each heart beat. This was combined with the pulmonary valve area to give the volume of blood ejected per heart beat. The heart rate was used to then produce the right ventricular output. This was averaged over five cycles to account for any respiratory variation.

2.4.8 Data Storage

Patient data was recorded from the notes and nursing charts. This along with echocardiographic data was stored in a Microsoft Access database in accordance with the Data Protection Act.

CHAPTER THREE

REPEATABILITY AND DOPPLER COMPARISON

3.1 Introduction

The assessment of repeatability is critical to ensure that changes in measurements are real and not due to observer error.[63] The measurement of intra observer repeatability and the limits of agreement between two different methods use the technique described by Bland and Altman.[63] They described the British Standards Institution's coefficient of repeatability. This is a measure of the spread of the differences between repeated measurements. This is not a measure of accuracy, however if a test has an acceptable coefficient of repeatability, or two methods display close limits of agreement, then when a change in measurement is detected this can be taken to represent a true change in the measured parameter.[63]

The validation studies discussed in Chapter 2 were performed in older infants with stable mature circulations. However, it is possible that the correlation coefficients and limits of agreement are not applicable to the transitional circulation. Therefore, Doppler echocardiography, which is widely used in neonates to assess volume flow,[20] [57,58] [61] [64] was used to assess the right ventricular output independently of the volume calculations.

3.2 Aims

1) To assess the intra observer repeatability of each of the two methods of right ventricular volume measurement.
2) To assess the agreement between the ellipsoid approximation method and Simpson's method.

3) To compare the calculated right ventricular output from the volume measurements with the best repeatability and Doppler calculated right ventricular output.

3.3 Methods

3.3.1 PATIENTS

23 healthy infants were recruited from the postnatal wards at Liverpool Women's Hospital, having obtained informed parental consent. In all 23 patients both the ellipsoid approximation method and Simpson's method volume calculations were performed. In 19 of the infants a repeat set of images to measure the repeatability for each method was obtained and in 17 of the infants the right ventricular Doppler output was recorded. All examinations occurred with the infants at rest or asleep.

3.3.2 IMAGING AND ANALYSIS

The images of the right ventricle were recorded as previously described using the technique in section 2.4.4.[33] All 23 examinations yielded images suitable for analysis and during 19 of the examinations a second set of paired images were recorded five minutes later. To ensure that a true measure of repeatability was made the ultrasound probe was taken off the chest between each set of paired images. Then using the technique described in section 2.4.7 [20] the right ventricular output was recorded using the pulmonary valve Doppler signal. These images were analyzed once all 23 examinations had been completed. Heart rate

was measured simultaneously throughout the examination using electrocardiogram electrodes.

3.3.3 Statistical Analysis

Repeatability studies used the British Standards Institution's coefficient of repeatability.[63] The smaller the coefficient of repeatability the better the repeatability of the test.

Data analysis was performed using SPSS for Windows, Arcus Quickstat and Microsoft Excel. All probability values were calculated with two tailed tests in either SPSS or Arcus. Correlation was assessed using the Spearman rank correlation coefficient and differences between paired measurements assessed by the Wilcoxon Signed Ranks Test.

3.4 Results

3.4.1 Repeatability

Table 3.1 shows the volumes from the 19 repeated examinations for both the ellipsoid approximation method and Simpson's method, along with the heart rate at the beginning and end of the examinations for all 23 examinations.

3.4.1.1 Ellipsoid Approximation Method

The mean difference (limits of agreement) between repeated measurements for the right ventricular end systolic volume was 8% (-17 to 33). The mean (limits of agreement) for right ventricular end diastolic volume was 6% (-21 to 32). The

		First Measurement	Second Measurement
Ellipsoid Approximation Method, mL	Systole	3.29 (2.82 to 3.72)	2.91 (2.59 to 3.35)
	Diastole	6.82 (6.16 to 7.84)	6.34 (5.76 to 8.03)
Simpson's Method, mL	Systole	2.24 (1.93 to 2.59)	2.01 (1.87 to 2.66)
	Diastole	5.25 (4.07 to 5.72)	4.87 (4.26 to 5.72)
Heart Rate		115 (109 to 122)	119 (113 to 124)

Table 3.1: Median (interquartile range) volumes for the repeated measurements.

mean difference (limits of agreement) between repeated measurements overall was 3% (-24 to 31) see figure 3.1. The coefficient of repeatability for systole was 26%, 28% for diastole and 27% overall.

3.4.1.2 Simpson's Method

The mean difference (limits of agreement) between repeated measurements for the right ventricular end systolic volume was 9% (-36 to 53). The mean (limits of agreement) for right ventricular end diastolic volume measurements was 2% (-33 to 37). The mean difference (limits of agreement) between repeated measurements overall was 5% (-35 to 45) see figure 3.2. The coefficient of repeatability for systole was 45%, 36% for diastole and 41% overall.

3.4.1.3 Heart Rate

In the 23 infants the mean difference (limits of agreement) for heart rate at the beginning and end of the examinations was -2% (-21 to 17), figure 3.3. The coefficient of repeatability for this electronically recorded measurement was 19%.

3.4.2 Comparison between the Ellipsoid Approximation method and the Simpson's Method

The volumes measured in the 23 infants using both methods are shown in table 3.2. The end systolic and end diastolic volumes measured using the Simpson's methods were statistically significantly smaller when compared with those measured by the ellipsoid approximation method ($p<0.0001$). There was good correlation between the ellipsoid approximation method and the Simpson's

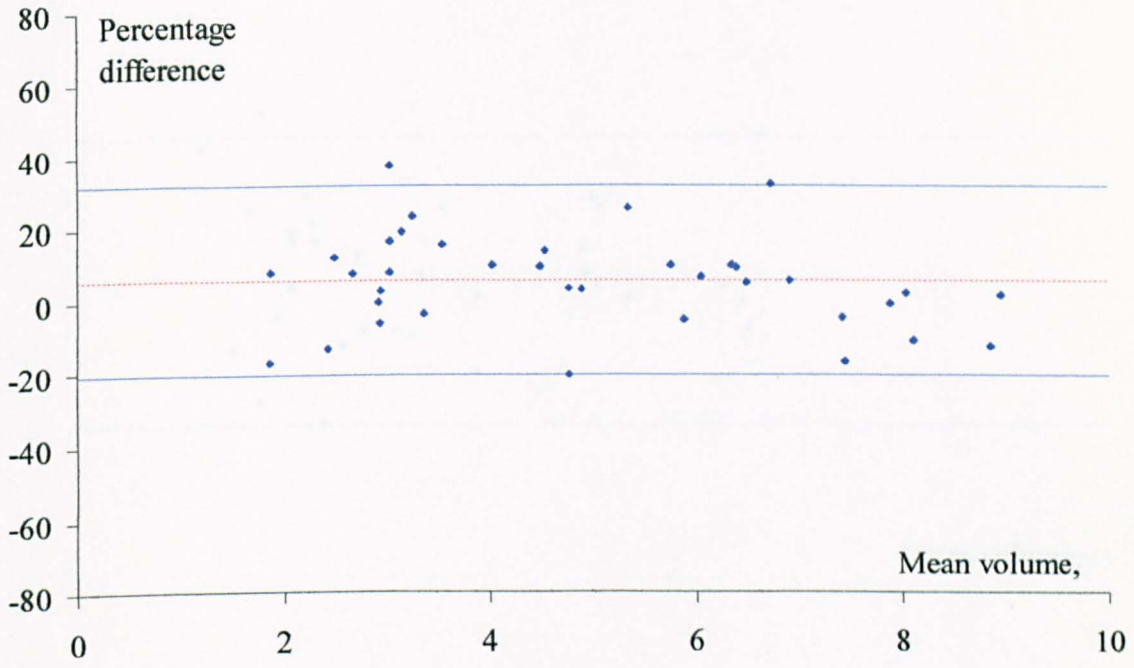

Figure 3.1: Intra observer repeatability for the ellipsoid approximation method. The x axis shows the mean volume of the paired measurements and the y axis shows the difference between the paired measurements expressed as a percentage of their mean volume. Also shown are the overall mean difference (red dashed line) and limits of agreement around this (blue solid lines).

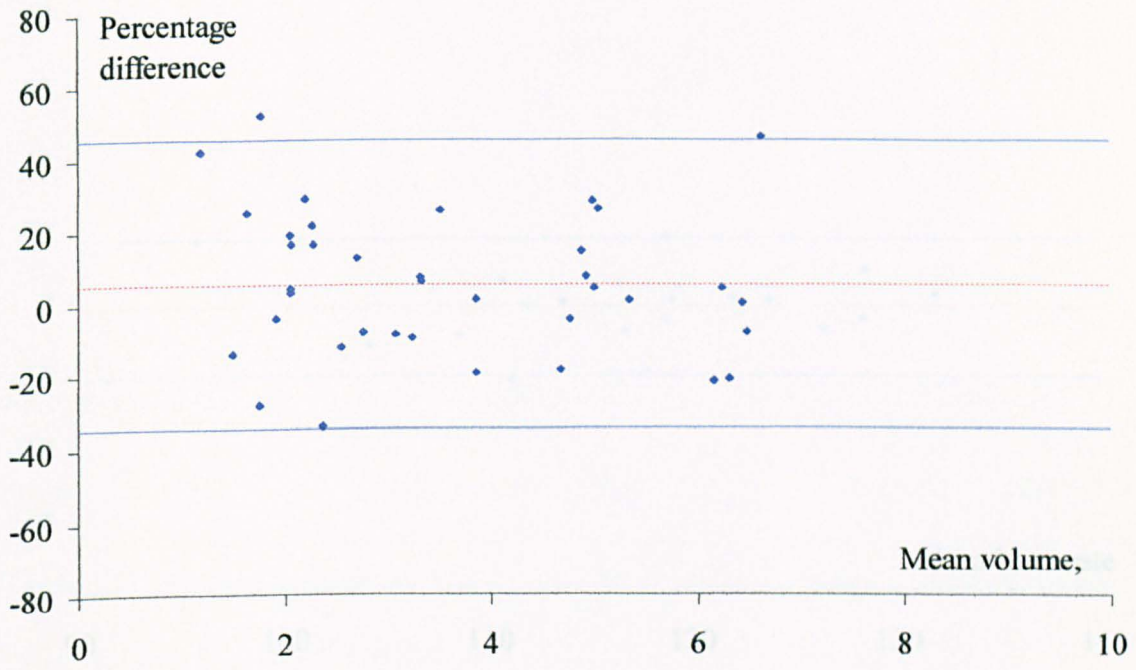

Figure 3.2: Intra observer repeatability for the Simpson's method. The x axis shows the mean volume of the paired measurements and the y axis shows the difference between the paired measurements expressed as a percentage of their mean. Also shown are the overall mean difference (red dashed line) and the limits of agreement (blue solid lines).

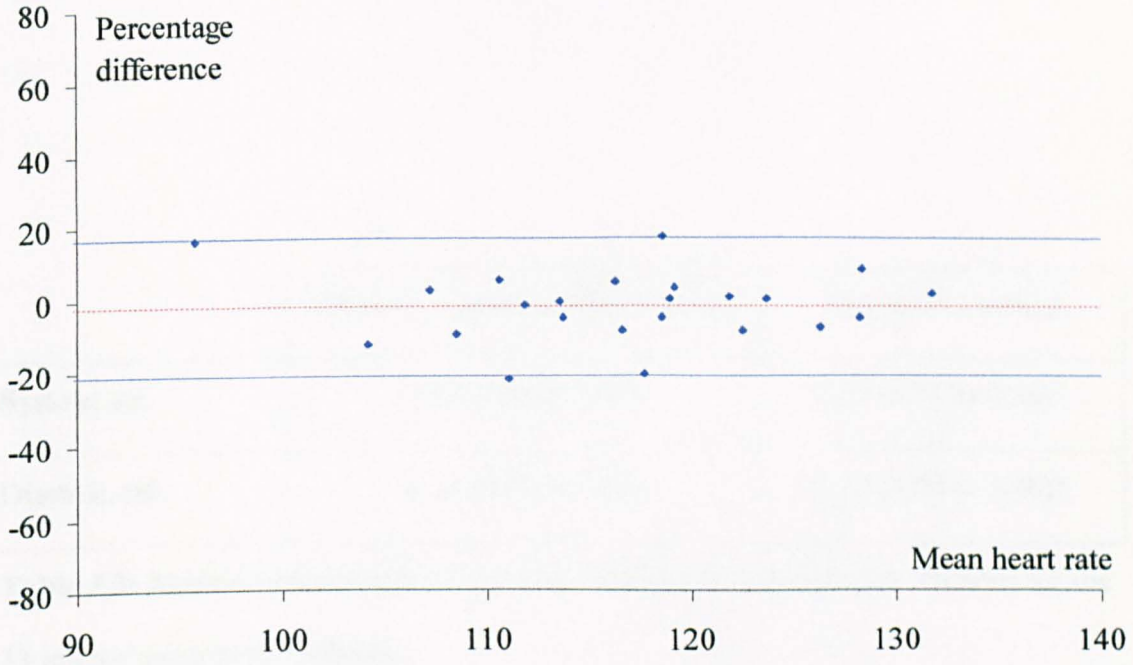

Figure 3.3: Intra observer repeatability for the heart rate measured at the beginning and at the end of the examination. The x axis shows the mean heart rate and the y axis shows the difference between the heart rates expressed as a percentage of their mean. Also shown are the overall mean difference (red dashed line) and limits of agreement around this (blue solid lines).

	Ellipsoid Approximation Method	Simpson's Method
Systole, mL	2.99 (2.60 to 3.83)	2.27 (2.01 to 2.55)*
Diastole, mL	6.73 (6.41 to 7.63)	5.11 (4.80 to 5.40)*

Table 3.2: Median (interquartile range) end systolic and end diastolic volumes for the 23 infants using both methods.

**p<0.0001compared with ellipsoid approximation method.*

method, rho = 0.96, p<0.0001, figure 3.4. The mean difference (limits of agreement) between these two methods for end systolic volume was 34% (2 to 66). The mean difference (limits of agreement) between right ventricular end diastolic volume was 34% (10 to 58). The overall mean difference (limits of agreement) between the ellipsoid approximation method and the Simpson's method was 34% (6 to 62), figure 3.5.

3.4.3 Correlation and Agreement Between the Ellipsoid Approximation Method with Doppler Measurements

Seventeen infants had both ellipsoid approximation method and pulmonary artery Doppler derived estimations of right ventricular output. Median (interquartile range) right ventricular output was 135 (102 to 162) and 230 (168 to 322) mL/kg/min, respectively. Right ventricular output was significantly smaller when calculated by the right ventricular volume technique when compared with the Doppler measurements, (p<0.001). There was significant correlation between the two methods, rho = 0.75, p < 0.001. The mean difference (limits of agreement) between the two measurements was 181% (-2 to 365).

3.5 Discussion

3.5.1 Repeatability

The ellipsoid approximation method was the more repeatable of these two measures with an overall coefficient of repeatability of 27%. The coefficient of repeatability for the Simpson's method was worse at 41% overall. A coefficient of repeatability of less than 30% is in keeping with other cardiorespiratory research

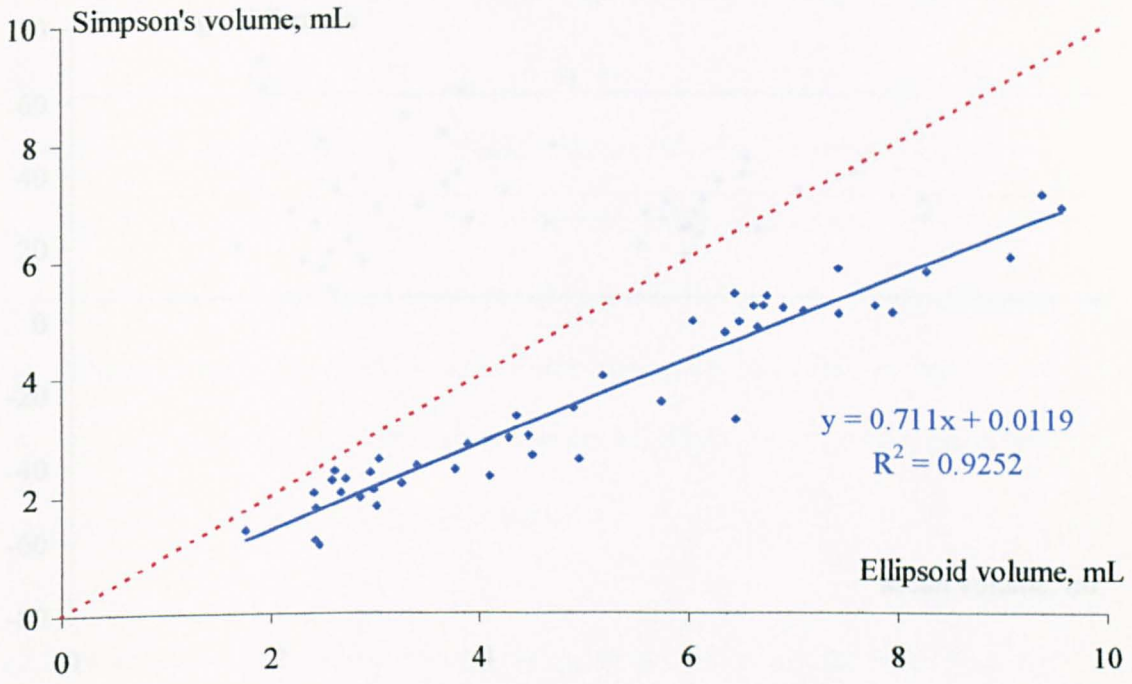

Figure 3.4: Showing the correlation between the ellipsoid approximation method on the x axis and the Simpson's method on the y axis. The regression line is shown along with its equation and the R squared value. The line of unity is shown as the red dashed line.

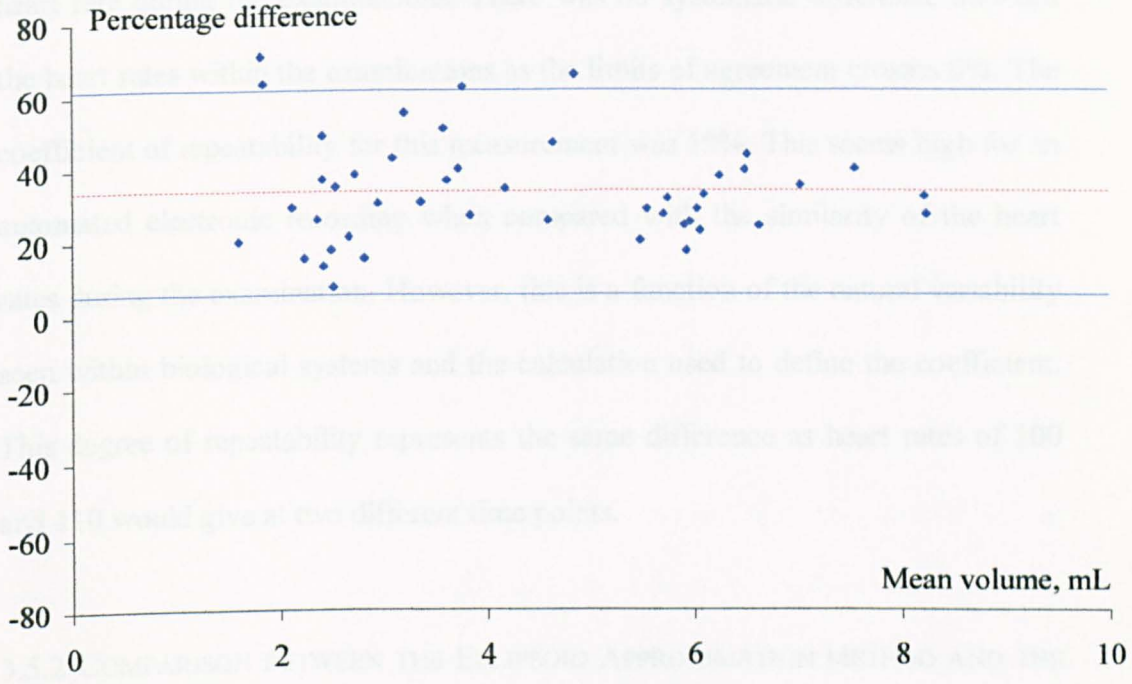

Figure 3.5: The limits of agreement between the ellipsoid approximation method and the Simpson's method. The x axis shows the mean volume of the measurements and the y axis shows the difference between the measurements (ellipsoid approximation result minus Simpson's method result) expressed as a percentage of their mean volume. Also shown are the overall mean difference (red dashed line) and 95% confidence intervals around this (blue solid lines).

tools, such as measurement of functional residual capacity and estimation of effective pulmonary blood flow.[65] It is a function of biological variables to produce a high coefficient of repeatability. Figure 3.3 shows the repeatability of heart rate during the examinations. There was no systematic difference between the heart rates within the examinations as the limits of agreement crosses 0%. The coefficient of repeatability for this measurement was 19%. This seems high for an automated electronic recording when compared with the similarity of the heart rates during the examination. However, this is a function of the natural variability seen within biological systems and the calculation used to define the coefficient. This degree of repeatability represents the same difference as heart rates of 100 and 110 would give at two different time points.

3.5.2 Comparison between the Ellipsoid Approximation method and the Simpson's Method

Figure 3.4 shows the correlation between the two different methods. There is a strong and significant correlation between these variables, from these data it is not possible to comment on which technique is superior, unlike in figures 3.1 and 3.2. The mean difference between paired measurements made by the two methods was 34% with limits of agreement of 6% to 62%. This does not include 0% difference, therefore there is a systematic difference in the volumes calculated by the two methods, with the ellipsoid approximation method recording a 34% larger volume than the Simpson's method on average. The poor performance of the Simpson's method may be because it relies upon dividing the ventricle into 20 slices of a known height. These then have their volume calculated as though they are discs.

The twenty volumes are then summed to give a total volume for the ventricle. It is likely the irregularity of the right ventricular cavity, see figure 3.6, causes the diameter of the discs to alter across their height, possibly giving rise to D or D' to calculate the volume. This would be accentuated especially at end systole. The software takes no account of this difference, unlike in the ellipsoid approximation method, where the area of the cavity is calculated accurately. Therefore, it might be expected that there would be greater variability in the results using the Simpson's model in an irregular cavity. If the Simpson's method was to always use the smaller of D or D' then this would explain the statistically significantly smaller volumes seen with the Simpson's method. Again one would expect this to be more pronounced at end systole, which is demonstrated in figure 3.5. It is important to note that in the validation of both of these methods against magnetic resonance angiography a systematically smaller volume was calculated by echocardiography.[33] Although, there was no formal comparison between the two echocardiographic techniques, the reported volumes at end systole and end diastole were similar.

3.5.3 Correlation and Agreement Between the Ellipsoid Approximation Method with Doppler Measurements

The ellipsoid approximation method was the most repeatable of the volumetric methods and gave larger volumes than the Simpson's method. The right ventricular output calculated from the ellipsoid approximation method was compared with Doppler derived right ventricular output. There was satisfactory correlation between the two methods, however the limits of agreement were quite

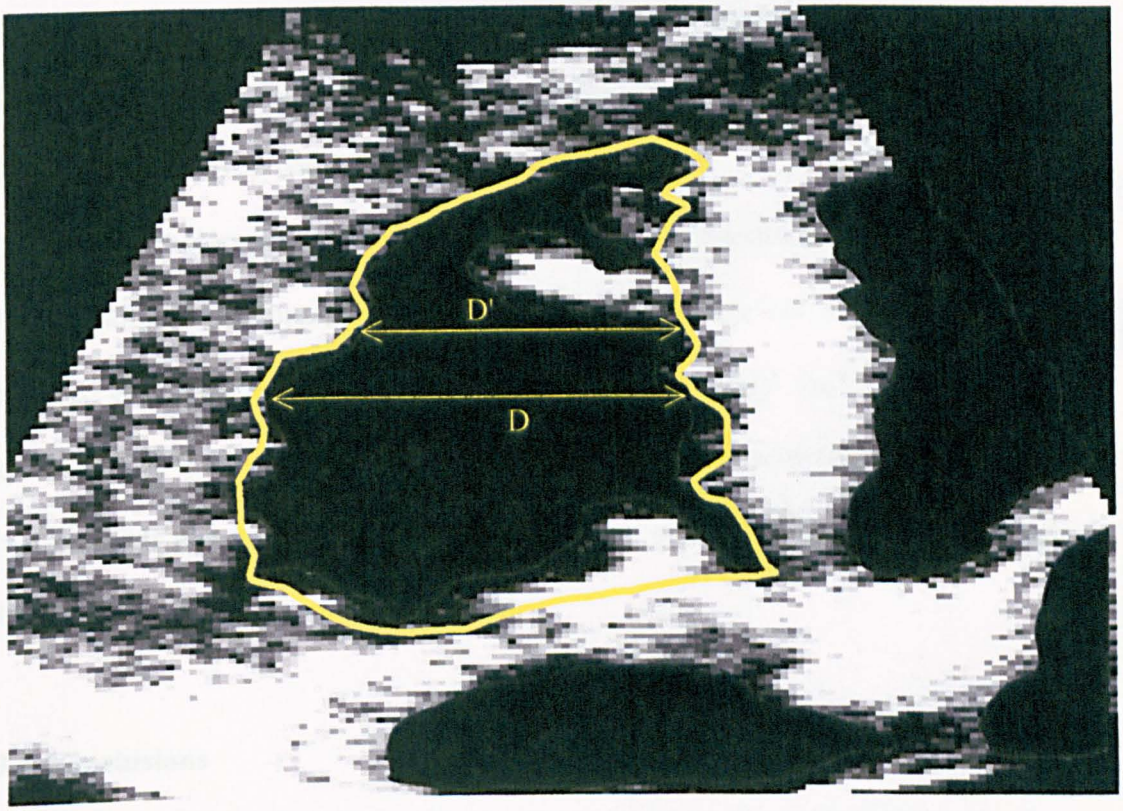

Figure 3.6: Apical four chamber view of the right ventricle, showing variation in the diameter within a slice. The image is distorted to emphasise the possible source of error.

wide. The Doppler calculated values were significantly larger than the volumetric calculations. This may be a function of the ductal flow characteristics, which if open were all left to right in all these infants and therefore would increase pulmonary blood flow. The presence of ductal flow may be one of the reasons that the limits of agreement between the two methods are large, as in the infants where the ductus arteriosus was widely patent there would be much larger pulmonary flow detect by Doppler but no additional volume from the volumetric calculations. Additionally, such Doppler measurements themselves are not the gold standard method of measurement,[66] although they are widely accepted as being useful.[20] [64] However, the fact that there is acceptable correlation between the two methods gives further reassurance that these physiological variables can be followed using this type of measurement.

3.6 Conclusions

The ellipsoid approximation method gave the most repeatable measurements. Overall it had a coefficient of repeatability of 27%. This was much lower than the coefficient of repeatability for the Simpson's method, which was 41% overall. Additionally, in this study the Simpson's method gave systematically smaller volumes than the ellipsoid approximation method by 34% on average. Validation studies of echocardiography against magnetic resonance angiography have demonstrated that echocardiography, whichever method is used, gives smaller systolic and diastolic volumes.[33] These three factors strongly suggest that the ellipsoid approximation method should be the preferred technique for right ventricular volume estimation in neonates. As a double check and although

recognizing it is not a gold standard technique comparison of the ellipsoid approximation method with Doppler derived measurements demonstrated satisfactory correlation and agreement. This additional factor, along with the coefficient of repeatability, suggests that the ellipsoid approximation method should be the preferred measure of right ventricular volumes in future studies. Therefore, all further measurements of right ventricular volume in this thesis will use the ellipsoid approximation method.

CHAPTER FOUR

RIGHT VENTRICULAR VOLUMES IN HEALTHY TERM AND HEALTHY PREMATURE INFANTS

4.1 Introduction

The right ventricle is the dominant ventricle in utero.[2] [7] [50] It has a larger cardiac output, receives more of the venous return and has a larger volume than the left ventricle.[2] [7] [17] [50] Following birth the left ventricle enlarges [28] and left ventricular output exceeds right ventricular output [11] [24] until closure of the ductus arteriosus.[24] Corresponding changes in right ventricular dimensions and function during the transitional circulation remain uncertain.

Pulmonary hypertension is associated with increased morbidity and mortality in cardiorespiratory disorders such as persistent pulmonary hypertension of the newborn and respiratory distress syndrome.[21] Right ventricular pathophysiology is potentially important in these conditions. The ability of the right ventricle to maintain adequate pulmonary blood flow despite increased pulmonary vascular resistance may be critical for optimal oxygenation.

Two dimensional echocardiography has been widely used to determine ventricular dimensions and function in infants and children with and without structural heart disease.[53] Recent studies have successfully validated volume measurements made using echocardiography with magnetic resonance imaging, which is generally accepted as the "gold standard".[33]

4.2 Aim

Prior to measuring right ventricular function in premature neonates with respiratory distress it is necessary to demonstrate the normal changes that occur in

healthy air breathing neonates. Therefore, the aims of this study were to follow the changes in right ventricular volumes during the first two days of life in healthy term and preterm infants using two dimensional echocardiography.

4.3 Methods

4.3.1 PATIENTS

Healthy term infants were recruited from the postnatal wards at Liverpool Women's Hospital. Premature infants, who did not require any respiratory support beyond initial resuscitation, were recruited from the neonatal unit at Liverpool Women's Hospital. Three echocardiographic examinations were performed on each infant on days 0, 1 and 2 respectively. All infants were examined during quiet respiration or whilst asleep. Patient demographic data including birth weight, gestational age, mode of delivery, Apgar scores and cord acid base status were recorded from maternal and infant case notes. The local research ethics committee approved the study and prospective written parental consent was obtained.

4.3.2 ECHOCARDIOGRAPHIC IMAGING

The GE Ultrasound CFM 800 (GE Ultrasound, Bedford UK) was used for all examinations as described in section 2.4.3 following the technique described in section 2.4.4.

4.3.3 Image Analysis

Stored images were analysed over a minimum of five consecutive cardiac cycles, to allow for respiratory variation in ventricular filling,[59] once recruitment was complete, as described in section 2.4.5. The ellipsoid monoplane calculation was used to measure the end systolic and end diastolic volumes as described in section 2.4.6.

4.3.4 Statistical Analysis

Numerical data are presented as median (interquartile ranges). Serial measurements at different time points in individuals were compared using Friedman's two way analysis of variance.[67] Comparison between groups used the Mann Whitney U test at a given time point. A p value of less than 0.05 was taken as being significant.

A sample size of 16 infants in each group would allow the detection of a change in volume of one standard deviation from the baseline value (80% power at a 5% significance level).

4.4 Results

Eighteen healthy term infants were recruited and seventeen healthy premature infants. All of the 105 completed examinations produced images of sufficient quality for analysis. None of the infants had a congenital heart defect identified. Demographic and birth details are shown in table 4.1. Seven out of the 18 term infants and 10 out of the 17 preterm infants were male. Median (interquartile

	Term		Preterm	
Total infants	18		17	
Males	7	(39%)	10	(59%)
Gestation, weeks	39	(38 to 41)	33	(31 to 34)
Birth weight, kg	3.35	(3.00 to 3.45)	1.74	(1.44 to 2.00)
Caesarean section	9	(50%)	15	(88%)
Apgar at 5 minutes	10	(10 to 10)	9	(9 to 10)
Cord pH	7.33	(7.28 to 7.35)	7.36	(7.32 to 7.38)
Cord base excess	-3.8	(-1.6 to -5.1)	-1.4	(-0.5 to -2.6)

Table 4.1: Population characteristics, values expressed as number (percent) or median (interquartile range).

range) age at each examination for all 35 infants was 5 (4 to 6), 26 (24 to 29) and 49 (47 to 51) hours on days 0, 1 and 2 respectively. Ages at examination are shown in table 4.2 for each group with no significant difference between the groups, $p = 0.99$, $p = 0.43$ and $p = 0.32$ for days 0, 1 and 2 respectively. There was no significant difference in the heart rates between examinations in the term infants, $p = 0.80$, table 4.2. The premature infants had a significantly faster heart rate at each examination compared with the same examination in the term infants, $p < 0.001$, table 4.2. The premature infants had a significantly slower heart rate at the third examination when compared with the previous two, $p = 0.002$, table 4.2.

There was a strong positive correlation between the infant's birth weight and the calculated ventricular volumes at the first examination, rho = 0.86 for systole and rho = 0.87 for diastole, $p < 0.0001$ for both, figure 4.1. There was a strong positive correlation between the infant's gestation and the ventricular volumes at the first examination, rho = 0.76 for systole and rho = 0.77 for diastole, $p < 0.0001$ for both, figure 4.2. Once corrected for birth weight there was no correlation between the infant's ventricular volumes and gestation, rho = 0.03 for systole, $p = 0.87$ and rho = 0.07 for diastole, $p = 0.70$, figure 4.3. Therefore all right ventricular volumes were corrected for birth weight and are presented as mL/kg.

All infants had a reducing arterial duct diameter over the three examinations (table 4.2). Twelve infants had an open duct with pure left to right flow on day one, of whom five were preterm. Three infants from each group had residual left to right

		Day 0	Day 1	Day 2
Age, hours	Terms	5 (3 to 8)	26 (24 to 31)	50 (48 to 54)
	Prems	5 (5 to 6)	26 (24 to 28)	49 (47 to 50)
Heart rate, per minute	Terms	112 (107 to 120)	119 (111 to 125)	115 (104 to 122)
	Prems	141 (133 to 149)*	140 (132 to 143)*	128 (122 to 141)*†
Ductus arteriosus diameter, cm	Terms	0.39 (0.27 to 0.42)	0 (0 to 0.25)	0 (0 to 0)
	Prems	0.36 (0.26 to 0.41)	0 (0 to 0.09)	0 (0 to 0)
Ductus arteriosus detected	Terms	16/18 (89%)	7/18 (39%)	3/18 (17%)
	Prems	17/17 (100%)	5/17 (29%)	3/17 (18%)

Table 4.2: Age, heart rate and ductus arteriosus' characteristics for each group across the three examinations, values are median (interquartile ranges), or number (percent).

**p < 0.001, compared with term infants at the same time point*

†p = 0.002 compared with previous measurements

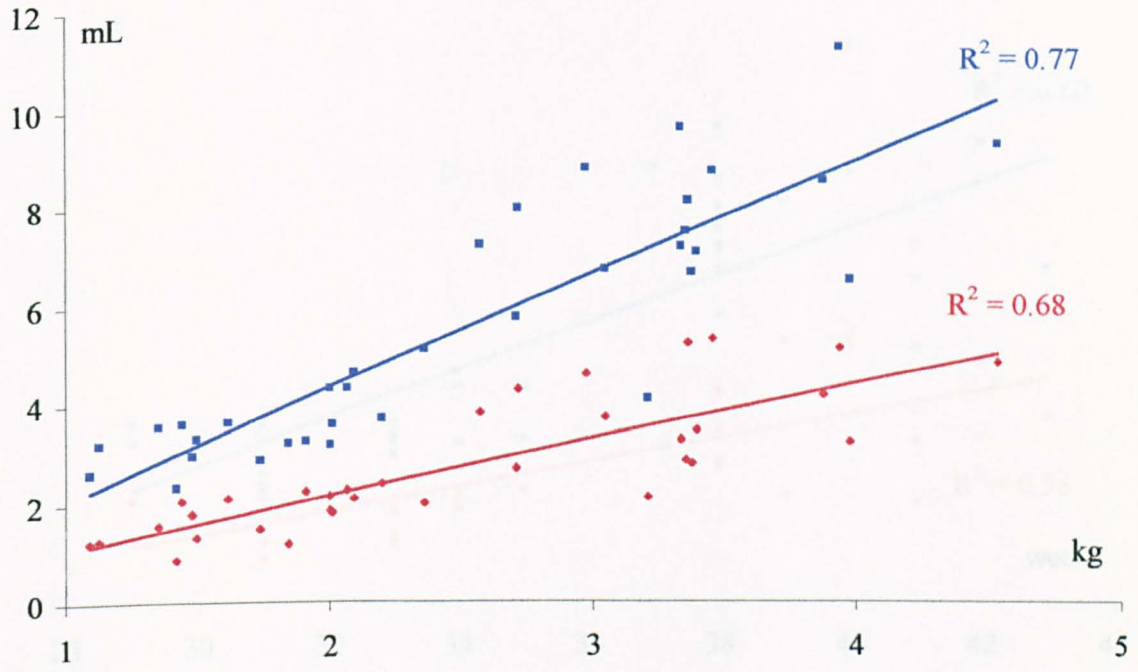

Figure 4.1: Correlation between right ventricular end diastolic volume (blue data points) and right ventricular end systolic volume (red data points) both in mL with birth weight in kg. Regression lines and the R^2 value are shown for each.

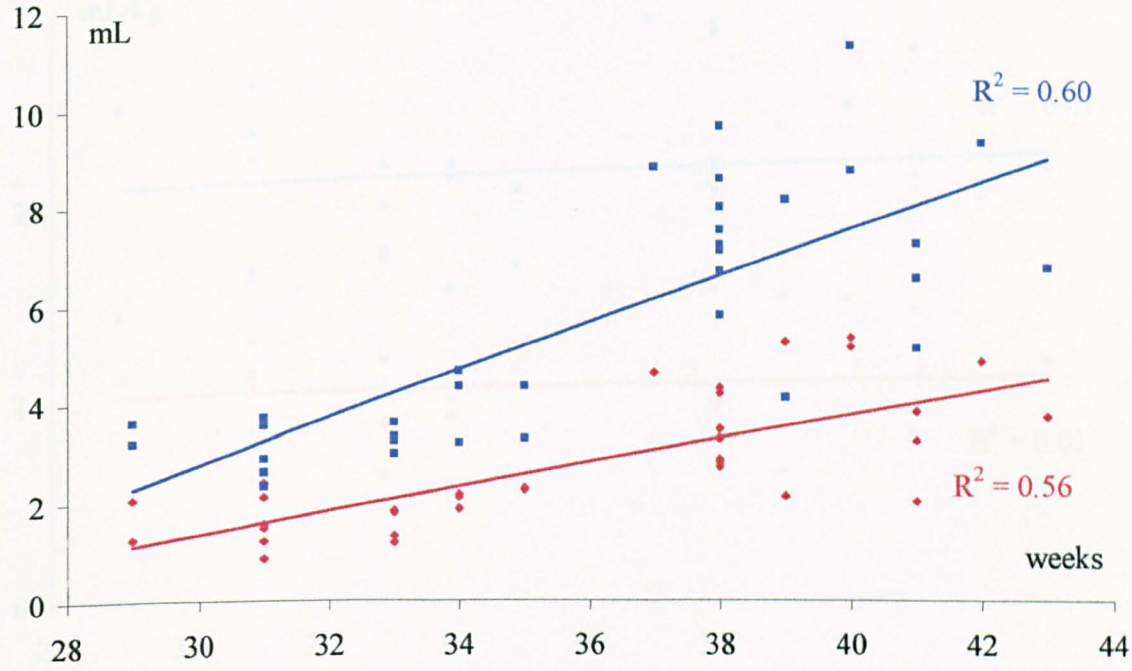

Figure 4.2: Correlation between right ventricular end diastolic volume (blue data points) and right ventricular end systolic volume (red data points) both in mL with gestation in weeks. Regression lines and the R^2 value are shown for each.

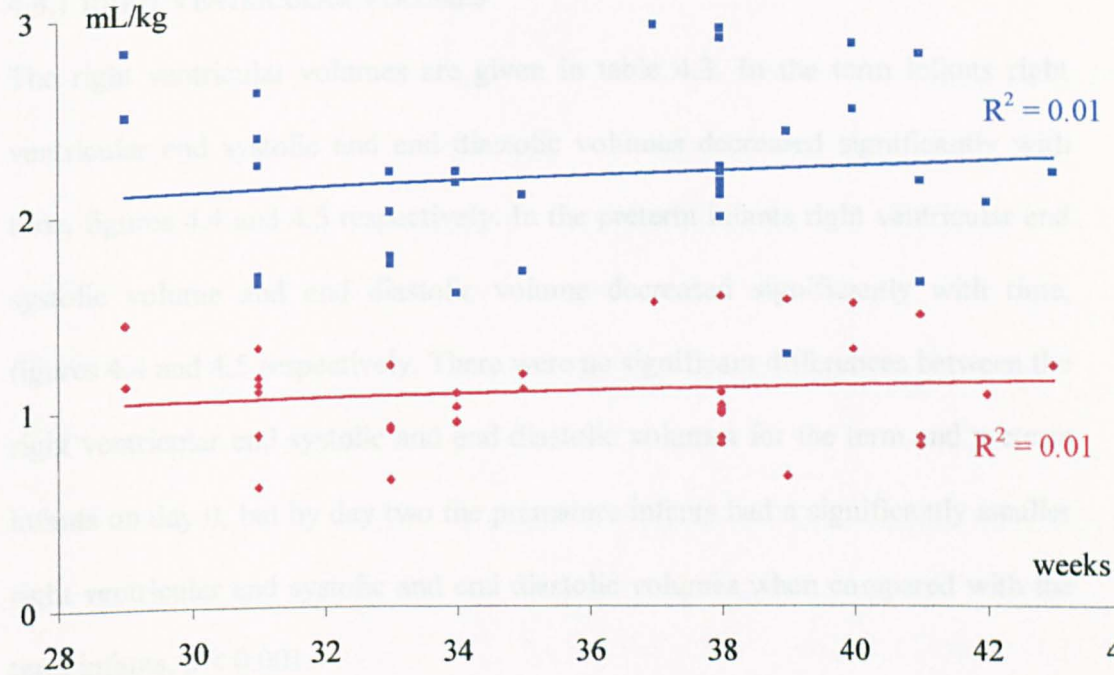

Figure 4.3: Correlation between right ventricular end diastolic volume (blue data points) and right ventricular end systolic volume (red data points) both corrected for birth weight in mL/kg with gestation in weeks. Regression lines and the R^2 value are shown for each.

flow detectable on colour flow mapping on day two, with a median diameter 0.21 cm (range 0.06 to 0.27) in those six infants.

4.4.1 Right Ventricular Volumes

The right ventricular volumes are given in table 4.3. In the term infants right ventricular end systolic and end diastolic volumes decreased significantly with time, figures 4.4 and 4.5 respectively. In the preterm infants right ventricular end systolic volume and end diastolic volume decreased significantly with time, figures 4.4 and 4.5 respectively. There were no significant differences between the right ventricular end systolic and end diastolic volumes for the term and preterm infants on day 0, but by day two the premature infants had a significantly smaller right ventricular end systolic and end diastolic volumes when compared with the term infants, $p < 0.001$.

4.4.2 Right Ventricular Stroke Volume

In the term and preterm infants' right ventricular stroke volume did not significantly alter over the study period. The right ventricular stroke volume was not significantly different between the term and preterm infants on day 0. In the preterm infants the right ventricular stroke volume when compared with the term infants on day one and two was significantly smaller, table 4.3.

4.4.3 Right Ventricular Ejection Fraction

There was no significant difference in the right ventricular ejection fraction between the term and the preterm infants. In the term infants right ventricular

		Day 0	Day 1	Day 2
End systolic volume, mL/kg	Terms	1.04 (0.88 to 1.44)	0.82 (0.70 to 1.03)	0.92 (0.72 to 0.97)
	Prems	1.09 (0.91 to 1.16)	0.72 (0.54 to 0.91)	0.61 (0.54 to 0.76)*
End diastolic volume, mL/kg	Terms	2.21 (2.10 to 2.75)	2.05 (1.81 to 2.38)	1.91 (1.81 to 2.13)
	Prems	2.09 (1.71 to 2.25)	1.47 (1.23 to 1.98)*	1.43 (1.22 to 1.78)*
Stroke volume, mL/kg	Terms	1.15 (0.99 to 1.36)	1.11 (0.98 to 1.35)	1.08 (0.92 to 1.30)
	Prems	1.04 (0.79 to 1.21)	0.84 (0.72 to 0.98)*	0.82 (0.67 to 0.92)†
Ejection fraction	Terms	0.51 (0.48 to 0.55)	0.59 (0.53 to 0.65)‡	0.57 (0.49 to 0.59)
	Prems	0.49 (0.41 to 0.56)	0.53 (0.49 to 0.59)	0.57 (0.51 to 0.61)§
Right ventricular output, mL/kg/min	Terms	138 (103 to 165)	134 (117 to 175)	115 (100 to 138)
	Prems	154 (115 to 171)	112 (95 to 145)	107 (85 to 147)

Table 4.3: Right ventricular measurements, expressed as median (interquartile range).

**p<0.001, †p=0.035 compared with term infants at the same time point.*

‡p=0.01, §p=0.06 compared with measurement on day 0.

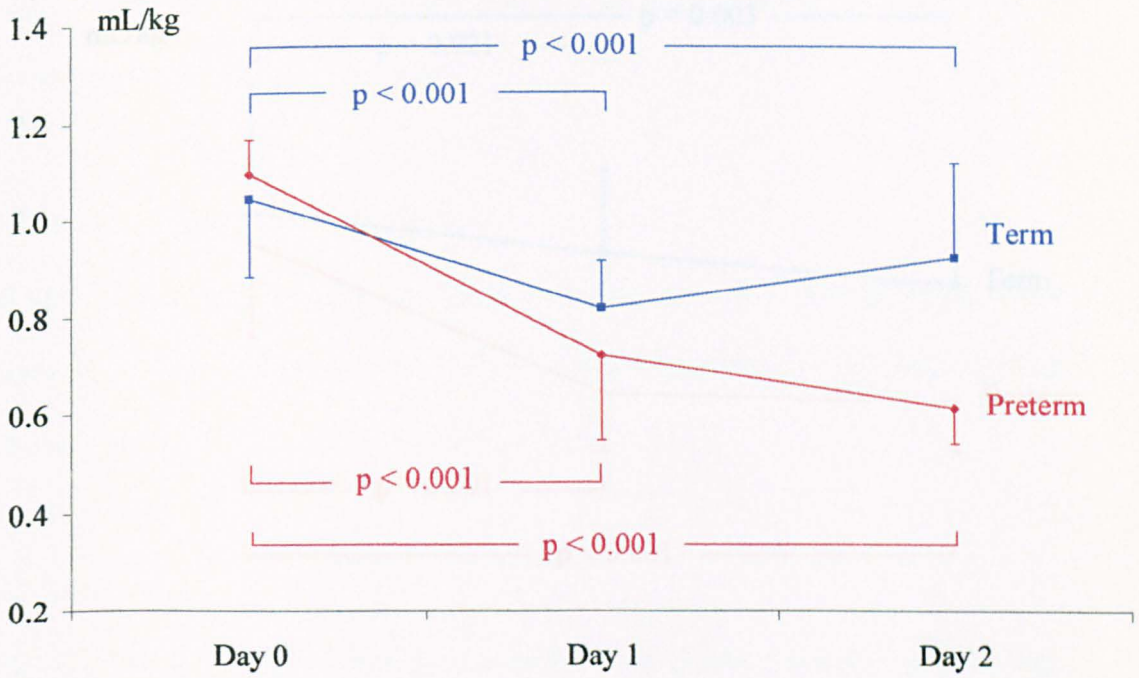

Figure 4.4: Change in right ventricular end systolic volume with time, with volume in mL/kg on the y axis. The graph shows medians and interquartile ranges for the healthy term infants (blue data) and the healthy preterm infants (red data).

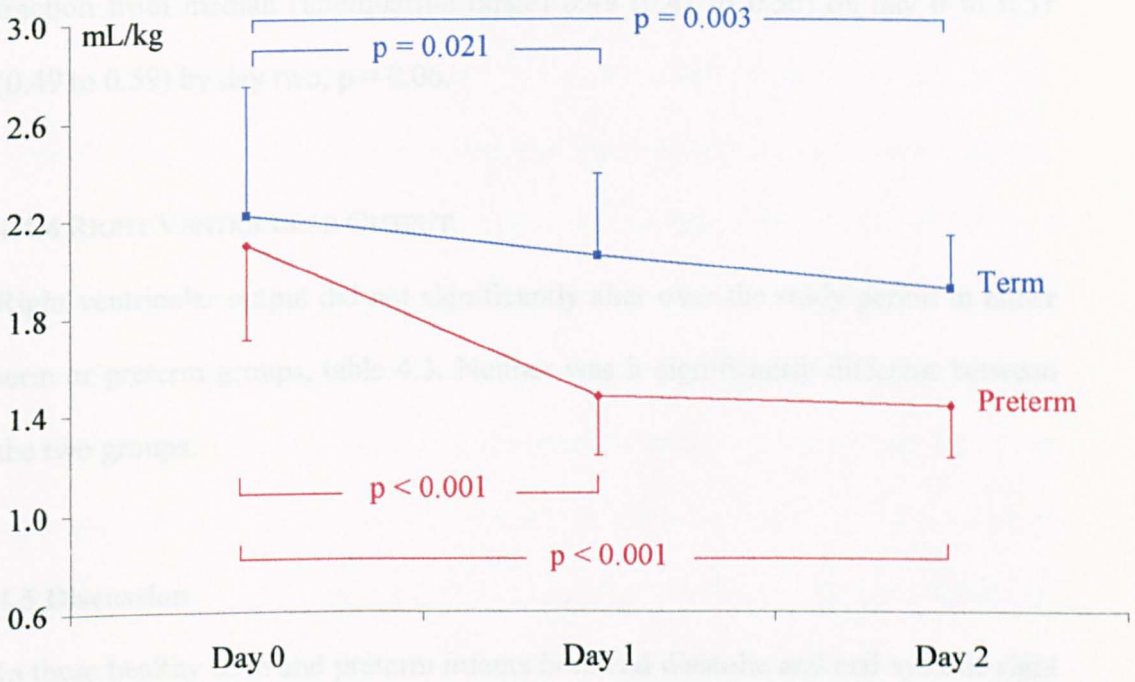

Figure 4.5: Change in right ventricular end diastolic volume with time, with volume in mL/kg on the y axis. The graph shows medians and interquartile ranges for the healthy term infants (blue data) and the healthy preterm infants (red data).

ejection fraction increased significantly from a median (interquartile range) of 0.51 (0.48 to 0.55) on day 0 to 0.59 (0.53 to 0.65) by day one, $p = 0.01$. In the preterm infants there was a tendency towards a rise in right ventricular ejection fraction from median (interquartile range) 0.49 (0.41 to 0.56) on day 0 to 0.57 (0.49 to 0.59) by day two, $p = 0.06$.

4.4.4 Right Ventricular Output

Right ventricular output did not significantly alter over the study period in either term or preterm groups, table 4.3. Neither was it significantly different between the two groups.

4.5 Discussion

In these healthy term and preterm infants both end diastolic and end systolic right ventricular volumes decreased over the first two days of extra uterine life. There was no difference between the end systolic, end diastolic and stroke volume in the term and preterm infants when corrected for birth weight on day 0. There was no evidence of a significant change in the stroke volume or cardiac output of the right ventricle over time in each group. Stroke volume was significantly smaller in the preterm infants compared with the term infants on day one and two, although right ventricular outputs were similar. This is probably a consequence of the significantly higher heart rate in the preterm group. There was a trend toward an increase in right ventricular ejection fraction with time, although this only reached statistical significance in the term infants.

Previous studies in human and animal foetuses have demonstrated that the right ventricle is the dominant ventricle in utero, both in terms of stroke volume and cardiac output.[2] [50] At early gestations the right ventricle has thicker free muscular wall, with similar mass to the left ventricle [12] and is stiffer than at later gestations.[8] At term the right ventricle is less compliant than the left ventricle.[59] Following birth left ventricular stroke volume and output increase dramatically.[28] [50] This increase in left ventricular stroke volume is achieved predominantly through an increase in left ventricular end diastolic volume secondary to an increased pulmonary venous return.[26] Pressure volume characteristics of the two ventricles are related through ventricular interaction in such a way that the volume of one ventricle is inversely related to the pressure in the other ventricle, because of the restraining effects of the pericardium.[9] Therefore, the likely result of an increase in left ventricular dimensions and pressure will be a reduction in right ventricular volumes. Although left ventricular volumes were not specifically measured in this study; the findings of a decrease in right ventricular end systolic and diastolic volume over the first two days of life are consistent with this hypothesis.

In these infants there was no significant change in right ventricular output or stroke volume despite a reduction in right ventricular end diastolic volume over the first two days of life. The right ventricular stroke volume and output may remain unchanged because there is a concomitant decrease in right ventricular end systolic volume. Right ventricular stroke volume is sensitive to afterload changes. [8,9] So with a higher afterload there is a larger the right ventricular end systolic

volume. [52] Although this can be mitigated by development of right ventricular hypertrophy with time. [9] The work of the right ventricle falls dramatically following birth because of the fall in pulmonary vascular resistance. [52] The right ventricle then has a much reduced afterload than it is used to, leading to improved contractility and a smaller right ventricular end systolic volume. [52] After correction for birth weight there were no significant differences between the preterm and term infants' right ventricular volumes on day 0. Over the next two examinations the preterm right ventricle was significantly smaller in both systole and diastole compared with the term infants, despite the weight correction. The morphology of the foetal and therefore preterm heart may accentuate the changes seen following delivery in the term infants. Romero et al [8] demonstrated in postmortem ovine foetal hearts that the right ventricle was less compliant than the left ventricle for the same filling pressure. Saint John Sutton et al [12] demonstrated in human foetuses using M mode echocardiography and post mortem specimens that the right ventricular free wall was as thick as the left ventricular free wall. Kenny et al [50] and Reed et al [15] used Doppler ultrasound serially in human foetuses to demonstrate that both foetal ventricles rely on atrial systole to fill the ventricle, rather than early passive filling that is dominant in older children and adults.[53] At term following delivery the left ventricle becomes more compliant and the early diastolic phase is the dominant component of ventricular filling.[59] This increase in compliance does not occur in the right ventricle as the atrial component remains dominant.[47] [59,60] The above studies suggest that the relative functional hypertrophy of the right ventricle in more premature infants coupled with the decreased compliance, especially in the right

ventricle, at earlier gestations contribute to the more rapid involution of the right ventricle that was seen in the premature infants.

There was a large proportion of infants born by caesarean section, (50%) in the term group. This occurred as a reflection of the discharge policy in the study hospital. The mothers of infants born operatively would automatically stay for four days and therefore the infants would be available for all three examinations. Some infants born vaginally are discharged as early as six hours old and often before 36 hours after delivery. Therefore, it would not be possible to recruit these infants. Originally 23 healthy term infants were recruited, of these five were discharged after the second examination and therefore only 18 infants completed the study. In the preterm infants more were born by caesarean section than in the term group. The operative delivery was reason for the prematurity for most of these infants as there was four sets of triplets in this group.

A recent study by Tamura et al,[22] of similar design in term infants has produced conflicting results. They demonstrated an increase in right ventricular end diastolic volume, with no change in end systolic volume, leading to an increase in right ventricular stroke volume and output from two hours old compared with 24 hours and 120 hours of age. Tamura et al used the Simpson's biplane model, requiring both the apical four chamber and parasternal short axis views. The same model was used by Schmidt et al,[17] but the volumes reported by Tamura et al are three to four fold smaller, table 4.4. Using a different mathematical model, right ventricular volumes measured in this study are much closer to estimates in

	Gessner et al [11]	Emmanouil-ides et al [24]	DeSmedt et al [16]	Schmidt et al [17]	Tamura et al [22]	This thesis
Subjects	14 term infants	23 term infants	28 term foetuses	50 term foetuses	20 term infants	18 term infants
Age	0 to 120 minutes	6 to 34 hours	36 to 40 weeks	40 weeks†	2 hours†	5 hours*
Method	Dye dilution		Doppler	2D ultrasound		
Diastolic volume	-	-	-	7.8 mL†	2.3 mL†	7.4 mL*
Systolic volume	-	-	-	2.7 mL†	1.3 mL†	3.6 mL*
Stroke volume	-	5.2 mL*	6.4 mL†	5.1 mL†	1.1 mL†	3.7 mL*
Output, mL/min	505*	643*	915†	720†	144†	444*

Table 4.4: Comparison of human right ventricular output and volumes from different studies; values are *medians or †means & expressed in mL or mL/min.

near term human foetuses, table 4.4. Furthermore, previous studies of human foetuses and newborns using M mode echocardiography have shown a decrease in the right ventricular dimensions after birth.[25] [28,29] Several studies have validated ultrasound assessment of cardiac volumes against invasive angiography, magnetic resonance imaging and ventricular cast formation in both infant humans and animals.[30,31,32,33] [35] Ultrasound does tend to produce lower volume estimates than magnetic resonance imaging.[33] However, studies have shown this to be a systematic difference and therefore applicable for the assessment of trends.[33] [35] Assessment of changes in ventricular volume is likely to be preferable to measurements of changes in a single dimension, for example transverse diameter, because of the complex geometry of the right ventricle.[29]

Failure of normal cardiovascular adaptation, with persistently elevated pulmonary vascular resistance and pulmonary hypertension, is important in the pathophysiology of persistent pulmonary hypertension of the newborn and respiratory distress syndrome.[21] [69] Right ventricular dysfunction in the face of increased afterload may compromise pulmonary blood flow. Information about changes in right ventricular volumes at birth and in the early neonatal period may give valuable insights into the pathophysiological mechanism of hypoxaemic respiratory failure in these conditions. Although a number of studies have been performed to investigate left ventricular function in newborn infants with respiratory failure,[42] [70] there is little published work on right ventricular performance. Low right ventricular output (as a component of a biventricular low output state) is associated with severe respiratory distress syndrome and is almost

universal in infants who subsequently die.[20] The relative importance and contribution of right ventricular dysfunction in determining low right ventricular output in such infants remains unknown.

This study provides reference values for right ventricular volumes in healthy term and preterm infants. These are essential prior to assessment of right ventricular function in neonates with respiratory disorders. Right ventricular systolic and diastolic volumes decreased within the first two days following birth, but right ventricular output remained unchanged.

CHAPTER FIVE

RIGHT VENTRICULAR VOLUMES IN INFANTS VENTILATED FOR RESPIRATORY DISTRESS SYNDROME

5.1 Introduction

The ability of the right ventricle to respond to the increased afterload associated respiratory distress syndrome [69] may affect the course and severity of the illness. However, there is no published work looking at the function of the right ventricle during the evolution of respiratory distress syndrome in premature infants, nor are there any data on the change in right ventricular performance with institution of cardiotropic drugs such as positive inotropes.

5.2 Aims

5.2.1 Study One

The aim of this study was to measure right ventricular indices in premature infants ventilated for respiratory distress syndrome over the first two days of life. These data were then compared with the right ventricular indices measured in healthy premature infants. Additionally ventilated infants with more severe respiratory disease were compared with those with more mild disease.

5.2.2 Study Two

The aim of this study was to assess the change, if any, in performance of the right ventricle after the commencement of inotropic therapy.

5.3 Methods

5.3.1 PATIENTS

5.3.1.1 Study One

Premature infants ventilated for respiratory distress syndrome were recruited from the neonatal unit. Three echocardiographic examinations were performed on days 0, 1 and 2 on each infant. Patient demographic data including birth weight, gestational age, mode of delivery, Apgar scores, cord acid base status, arterial blood gases at time of examination and oxygenation index were recorded prospectively from maternal and infant case notes. Outcome data such as death and the incidence of chronic lung disease were also prospectively recorded. The local research ethics committee approved the study and prospective written parental consent was obtained. The results from these ventilated infants were compared with the results obtained from the healthy premature infants in chapter four, who acted as controls.

5.3.1.2 Study Two

Premature infants ventilated for respiratory distress syndrome were recruited from the neonatal unit. Two echocardiographic examinations were performed; one prior to the commencement of and another one hour after a dopamine infusion was started. Patient demographic data including birth weight, gestational age, mode of delivery, Apgar scores, cord acid base status, arterial blood gas at time of examination and oxygenation index were recorded from maternal and infant case notes. Outcome data such as death and the incidence of chronic lung disease were

also recorded. The local research ethics committee approved the study and prospective written parental consent was obtained.

5.3.2 Echocardiographic Imaging and Analysis

The GE Ultrasound CFM 800 (GE Ultrasound, Bedford UK) was again used for all examinations and examinations were stored using the integrated digital archiving system (Echopac, version 5.3, GE Ultrasound). In study one a complete examination was completed and the right ventricle was imaged as described in the methods section in section 2.4.4. Stored images were analysed by the method as in section 4.3.3. The instability of the infants in study two only allowed for the examination of the right ventricular function and ductal flow characteristics.

5.3.3 Statistical Analysis

Data analysis was performed as described in section 4.3.4.

5.3.3.1 Sub Groups for Analysis in Study One

Those infants who developed chronic lung disease of prematurity, that is an persisting requirement for oxygen supplementation at 36 weeks corrected gestational age, and/or died were compared with those who survived without long term oxygen requirements.

All infants less than one kg birth weight born at Liverpool Women's Hospital are treated with three doses of prophylactic indomethacin.[71] As this would affect

the rate of ductal patency ventilated infants less than one kg were compared with those over one kg.

In order to investigate the effect of more severe respiratory disease the ventilated infants were stratified into those with an oxygenation index of less than 10 and those of 10 and more [72] at the time of first examination.

5.4 Results

5.4.1 STUDY ONE

Seventeen premature infants ventilated for respiratory distress were recruited; none of these infants dropped out of the study. All of the 51 completed examinations produced images of sufficient quality for analysis. None of the ventilated infants had a congenital heart defect identified. Demographic and birth details for the ventilated infants are shown in table 5.1, along with the same data from the healthy premature infants from chapter four. All but two infants received antenatal steroids and all were intubated and given surfactant in delivery suite.

Total respiratory support and other outcome measures for the ventilated infants are shown in table 5.2. Three infants died, one at a week of age from necrotising entercolitis, one at four days old from pulmonary hypoplasia and one at three days old from an accidental iatrogenic overdose unrelated to this study. Intraventricular haemorrhage was graded using the Papile [73] classification. Four infants had a grade one intraventricular haemorrhage, one had a grade two intraventricular haemorrhage and three infants had a grade four intraventricular haemorrhage.

	Healthy Preterm	Ventilated Preterm
Total infants	17	17
Males	10 (59%)	9 (52%)
Gestation, weeks	33 (31 to 34)	27 (27 to 28)
Birth weight, kg	1.74 (1.44 to 2.00)	0.97 (0.91 to 1.11)
Caesarean section	15 (88%)	12 (71%)
Apgar at 5 minutes	9 (9 to 10)	9 (7 to 9)
Cord pH	7.36 (7.32 to 7.38)	7.33 (7.27 to 7.37)
Cord base excess	-3.8 (-1.6 to -5.1)	-3.6 (-3.0 to -4.5)

Table 5.1: Population characteristics, values expressed as number (percent) or median (interquartile range).

Days of ventilation	3 (2 to 4)
Days of nasal continuous positive airways pressure	0 (0 to 1)
Days of supplemental oxygen	4 (0 to 47)
Days requiring respiratory support	8 (4 to 65)
Oxygenation index at time of first examination	4 (2 to 10)
Inotropic support	5/17 (29%)
Intraventricular haemorrhage	8/17 (47%)
Death	3/17 (18%)
Chronic lung disease	6/17 (35%)
Chronic lung disease and/or death	9/17 (53%)
Home in supplemental oxygen	4/17 (24%)

Table 5.2: Morbidity and mortality amongst the ventilated premature infants, values expressed as median (interquartile range) or as number (percent).

Ages at examination, for both the ventilated and the healthy premature groups, are shown in table 5.3 as are heart rate and ductal characteristics. All but one ventilated infant had a reducing arterial duct diameter over the three examinations. Two ventilated infants had residual left to right flow detectable on colour flow mapping on day two, with diameters 0.25 and 0.11 cm in those infants. The ventilated infant with a residual diameter of 0.11 cm required treatment for a patent ductus arteriosus at six days of age. The other residual shunt was the only one that remained unchanged from day 0 but required no further treatment in the longer term. Blood flow through the ductus arteriosus was pure left to right or bi directional in all except one ventilated infant. This infant with pulmonary hypoplasia had pure right to left shunting on day 0 and on day one. However, this ductal shunt was closed by the time of the third examination. There was no significant difference between the ductal diameters or rate of closure in those infants less than one kg (n = 10), median (interquartile range) on day 0 0.18 (0.16 to 0.21) cm, when compared with those over one kg (n = 7), median (interquartile range) on day 0 0.18 (0.13 to 0.24) cm, p = 0.90.

5.4.1.1 Right Ventricular Volumes and Function

In the ventilated infants there were significant falls in both end systolic and end diastolic right ventricular volume with time, figures 5.1 and 5.2. The stroke volume did not alter significantly in the ventilated infants across the three examinations, table 5.4. Right ventricular ejection fraction increased significantly by day two as did right ventricular output and heart rate, table 5.4.

		Day 0	Day 1	Day 2
Age, hours	Healthy	5 (5 to 6)	26 (24 to 28)	49 (47 to 50)
	Ventilated	5 (4 to 6)	26 (23 to 27)	49 (48 to 50)
Heart rate, per minute	Healthy	141 (133 to 149)	140 (132 to 143)	128 (122 to 141)
	Ventilated	143 (134 to 155)	144 (136 to 164)	164 (152 to 165)*†
Ductus arteriosus diameter, cm	Healthy	0.36 (0.26 to 0.41)	0.00 (0.00 to 0.09)	0.00 (0.00 to 0.00)
	Ventilated	0.18 (0.15 to 0.22)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
Ductus arteriosus detected	Healthy	17/17 (100%)	5/17 (29%)	3/17 (18%)
	Ventilated	17/17 (100%)	4/17 (24%)	2/17 (12%)

Table 5.3: Age, heart rate and characteristics of the ductus arteriosus of infants in each group across the three examinations, values are median (interquartile ranges), or number (percent).

**p<0.001, compared with healthy preterm infants at the same time point.*

†p=0.015, compared with measurement on day 0.

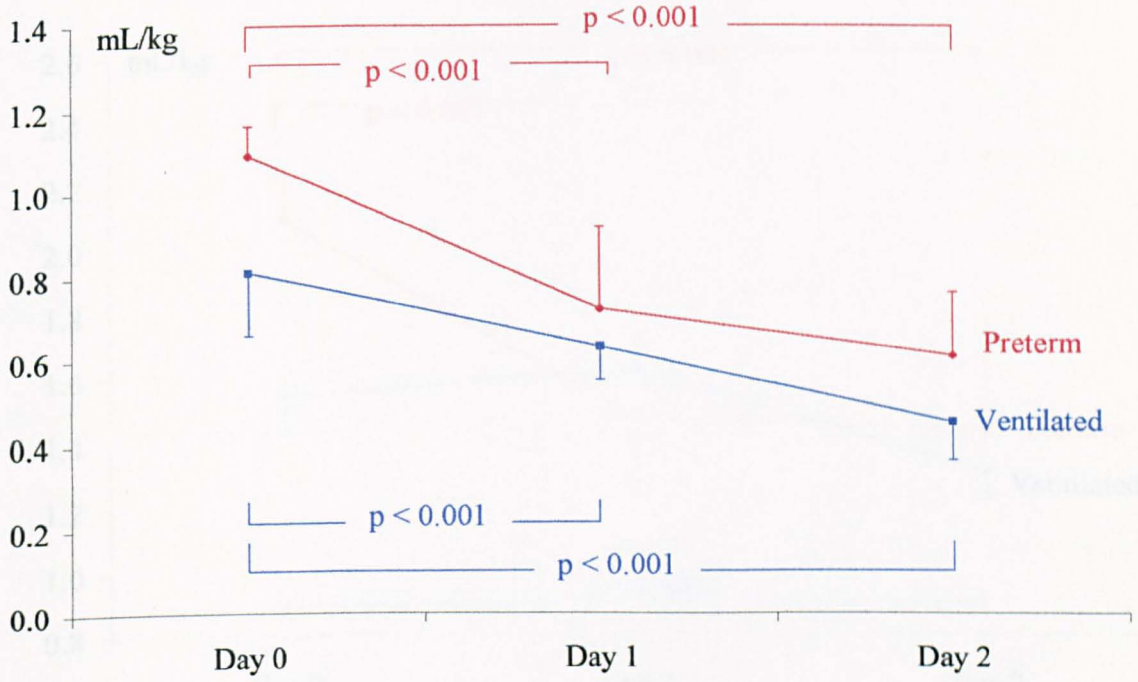

Figure 5.1: Change in right ventricular end systolic volume with time, with volume in mL/kg on the y axis. The graph shows medians and interquartile ranges for the healthy preterm infants (red data) and the ventilated preterm infants (blue data).

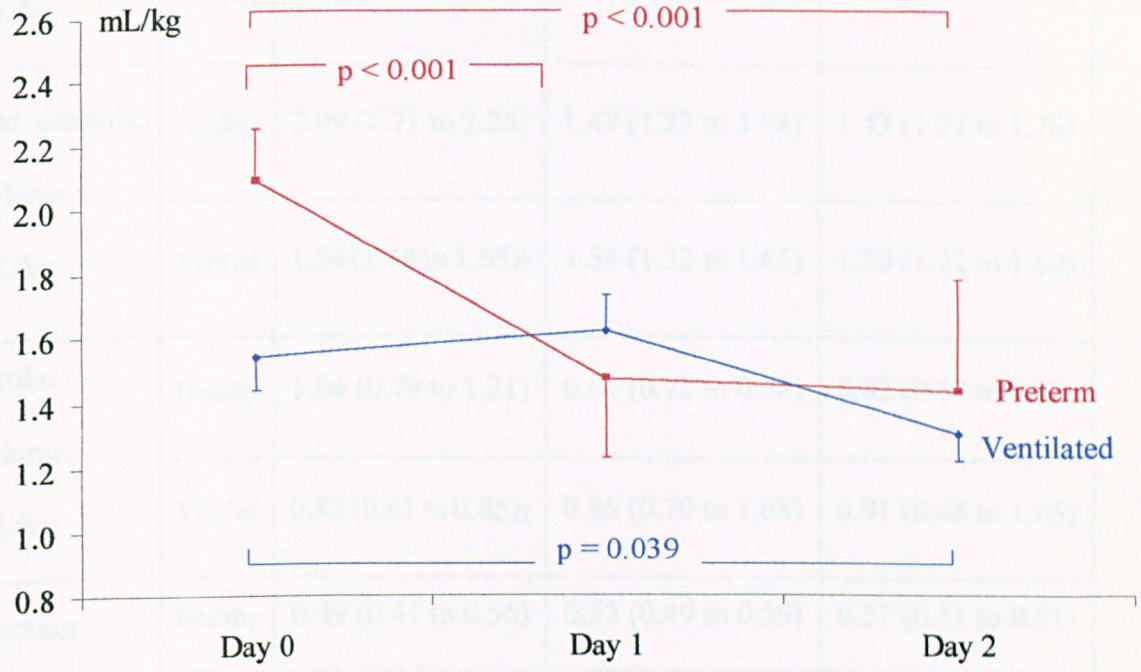

Figure 5.2: Change in right ventricular end diastolic volume with time, with volume in mL/kg on the y axis. The graph shows medians and interquartile ranges for the healthy preterm infants (red data) and the ventilated preterm infants (blue data).

		Day 0	Day 1	Day 2
End systolic volume, mL/kg	Healthy	1.09 (0.91 to 1.16)	0.72 (0.54 to 0.91)	0.61 (0.54 to 0.76)
	Vent'ed	0.80 (0.66 to 0.91)*	0.60 (0.53 to 0.72)	0.45 (0.39 to 0.54)†
End diastolic volume, mL/kg	Healthy	2.09 (1.71 to 2.25)	1.47 (1.23 to 1.98)	1.43 (1.22 to 1.78)
	Vent'ed	1.54 (1.44 to 1.65)*	1.54 (1.32 to 1.65)	1.30 (1.22 to 1.60)
Stroke volume, mL/kg	Healthy	1.04 (0.79 to 1.21)	0.84 (0.72 to 0.98)	0.82 (0.67 to 0.92)
	Vent'ed	0.82 (0.61 to 0.85)‡	0.85 (0.70 to 1.08)	0.91 (0.68 to 1.05)
Ejection fraction	Healthy	0.49 (0.41 to 0.56)	0.53 (0.49 to 0.59)	0.57 (0.51 to 0.61)
	Vent'ed	0.48 (0.44 to 0.56)	0.56 (0.52 to 0.65)	0.62 (0.58 to 0.71)‡Δ
Right ventricular output, mL/kg/min	Healthy	154 (115 to 171)	112 (95 to 145)	107 (85 to 147)
	Vent'ed	120 (96 to 125)‡	119 (99 to 145)	140 (113 to 168)∞

Table 5.4: Right ventricular volume measurements, expressed as median (interquartile range).

**p<0.001, †p<0.01, ‡p<0.05 compared with healthy preterm infants at the same time point.*

Δp<0.001, ∞p<0.05 compared with measurement on day 0.

5.4.1.2 Comparison with Healthy Premature Infants

The indices of right ventricular volume and function are shown in table 5.4 for the ventilated infants. The data from the healthy premature infants from chapter four are also shown for comparison. The ventilated infants had a significantly smaller right ventricular end systolic volume on day 0 and on day two when compared with the healthy premature infants. The right ventricular end diastolic volume, stroke volume and right ventricular output were all significantly smaller on day 0 in the ventilated infants, but not on day one and two. The ejection fraction in the ventilated infants was significantly higher on day two, as was the heart rate, when compared with the healthy preterm infants.

5.4.1.3 Sub Group Analysis in the Ventilated Infants

5.4.1.3.1 Respiratory Morbidity and Death

Those infants that developed chronic lung disease and/or death had no significant differences in right ventricular values or function when compared with those that did not.

5.4.1.3.2 Extremely Low Birth Weight Infants

There were no significant differences between the right ventricular indices for those infants above and below one kg.

5.4.1.3.3 Mild versus More Severe Respiratory Distress

There were six infants with an oxygenation index of 10 or more at the time of the first examination and compared with the infants with lower oxygenation indices

these infants tended to have smaller right ventricular end diastolic volumes on day one, median (interquartile range) 1.27 (0.99 to 1.49) mL/kg versus 1.62 (1.38 to 1.73) mL/kg, p = 0.048. The stroke volume in these infants tended to be smaller on day one of life, median (interquartile range) 0.74 (0.53 to 0.85) mL/kg versus 0.88 (0.72 to 1.16) mL/kg, p = 0.048. Right ventricular output was also lower in these infants on day one, median (interquartile range) 97 (94 to 125) mL/kg/min versus median (interquartile range) 141 (110 to 159) mL/kg/min, p = 0.048. There were no significant differences in heart rate, systolic volume, ejection fraction and ductal patency between these two sub groups.

5.4.2 Study Two

Eight hypotensive premature infants ventilated with respiratory distress were recruited; none of these infants dropped out of the study. All of the 16 completed examinations produced images of sufficient quality for analysis. None of the infants had a congenital heart defect identified. All had received a 20mL/kg bolus of 0.9% saline prior to the initiation of dopamine for inotropic support at 5 μg/kg/min. Demographic and birth details are shown in table 5.5. The infants were ventilated for a median (interquartile range) of 4 (3 to 8) days. Three infants died from extreme prematurity. Two infants had a grade one intraventricular haemorrhage, two had a grade two intraventricular haemorrhage and one had a grade four intraventricular haemorrhage. The ductus arteriosus was restrictive in all infants with pure left to right or bi directional flow present, with no changes in flow characteristics between the two scans. Table 5.6 shows the measurements made before and after the initiation of inotropes. After the commencement of

Total infants	8
Males	4 (50%)
Gestation, weeks	27 (26 to 27)
Birth weight, kg	0.95 (0.77 to 1.12)
Caesarean section	4 (50%)
Apgar at 5 minutes	7 (6 to 7)
Cord pH	7.30 (7.24 to 7.34)
Cord base excess	-3.0 (-1.3 to -4.6)
Oxygenation index	8 (5 to 15)
Age at first examination, hours	9 (4 to 16)

Table 5.5: Population characteristics of study two infants, values expressed as number (percent) or median (interquartile range).

	Pre dopamine infusion	One hour post dopamine initiation
End systolic volume, mL/kg	1.06 (0.81 to 1.5)	0.73 (0.51 to 0.99)*
End diastolic volume, mL/kg	1.65 (1.33 to 2.43)	1.52 (1.01 to 1.72)
Heart rate	146 (132 to 159)	167 (150 to 179)
Stroke volume, mL/kg	0.57 (0.47 to 0.79)	0.69 (0.46 to 0.87)
Ejection fraction	0.36 (0.29 to 0.46)	0.51 (0.43 to 0.53)*
Right ventricular output, mL/kg/min	90 (67 to 115)	112 (86 to 143)†
Mean arterial blood pressure, mmHg	23 (21 to 26)	33 (30 to 37)*

Table 5.6: Right ventricular volume measurements, pre and post commencement of inotropic support in study two infants, expressed as median (interquartile range).

**$p<0.01$, †$p=0.07$ compared with pre dopamine measurement*

inotropes there was a significant decrease in right ventricular end systolic volume from a median (interquartile range) of 1.06 (0.81 to 1.50) mL/kg to 0.73 (0.51 to 0.99), figure 5.3. Right ventricular ejection fraction rose significantly with inotropic therapy, from a median (interquartile range) of 0.36 (0.29 to 0.46) to 0.51 (0.43 to 0.53), figure 5.4. Heart rate rose significantly as well from a median (interquartile range) of 146 (132 to 159) to 167 (150 to 179), $p = 0.008$. There was a trend for right ventricular output to increase from a median (interquartile range) of 90 (67 to 115) to 112 (86 to 143) mL/kg/min, although this was not significant, $p = 0.07$, figure 5.5. Mean arterial blood pressure increased significantly from a median (interquartile range) of 23 (21 to 26) to 33 (30 to 37) mmHg.

5.5 Discussion

5.5.1 Study One

In healthy term and healthy preterm infants both end diastolic and end systolic right ventricular volumes decreased over the first two days of extra uterine life. A similar change was observed in the ventilated infants, but again there was no evidence of a significant change in the stroke volume with time. However, the right ventricular output in these ventilated infants had risen significantly by day two, as had the ejection fraction and heart rate. Compared with the healthy premature infants, right ventricular end systolic, end diastolic and stroke volume was significantly smaller in the ventilated preterm infants on day 0, but only remained so for right ventricular end systolic volume by the third examination. Despite this right ventricular outputs were similar in the two groups. The ventilated infants had a significantly higher right ventricular ejection fraction than

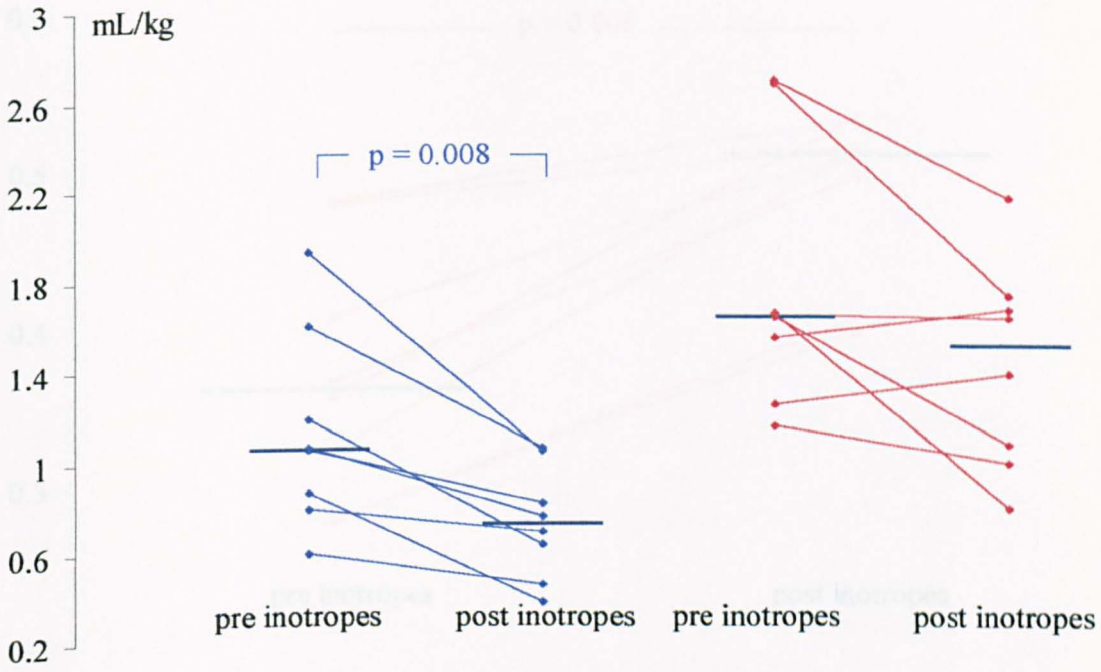

Figure 5.3: Change in right ventricular systolic (in blue) and diastolic (in red) volume in mL/kg pre and one hour post commencement of inotropes in study two infants, with horizontal bars showing median value.

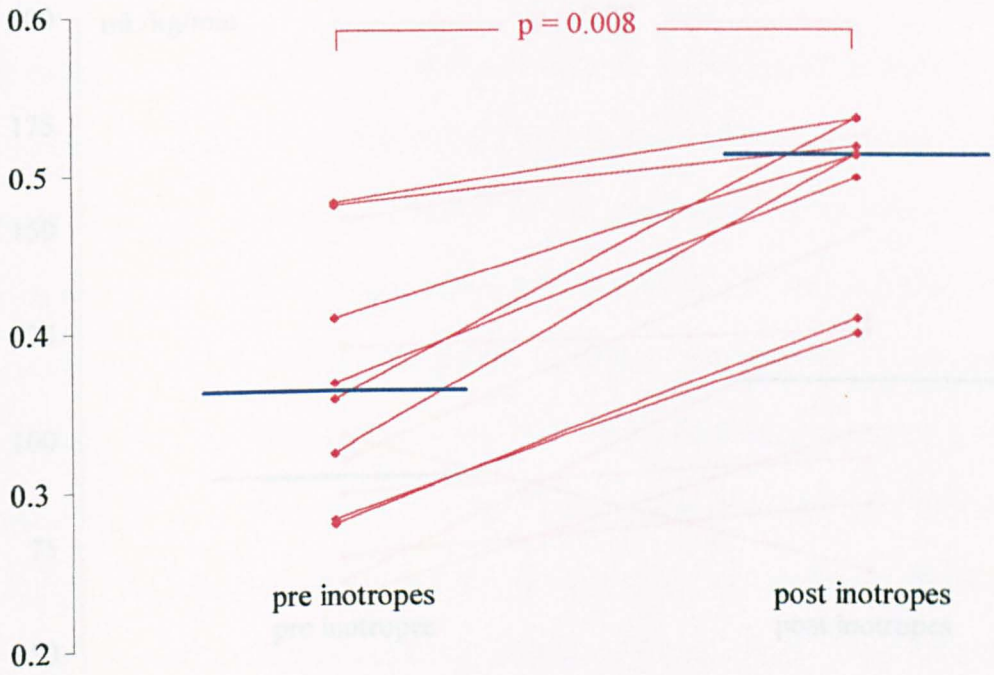

Figure 5.4: Change in right ventricular ejection fraction pre and one hour post commencement of inotropes in study two infants, with horizontal bars showing median value.

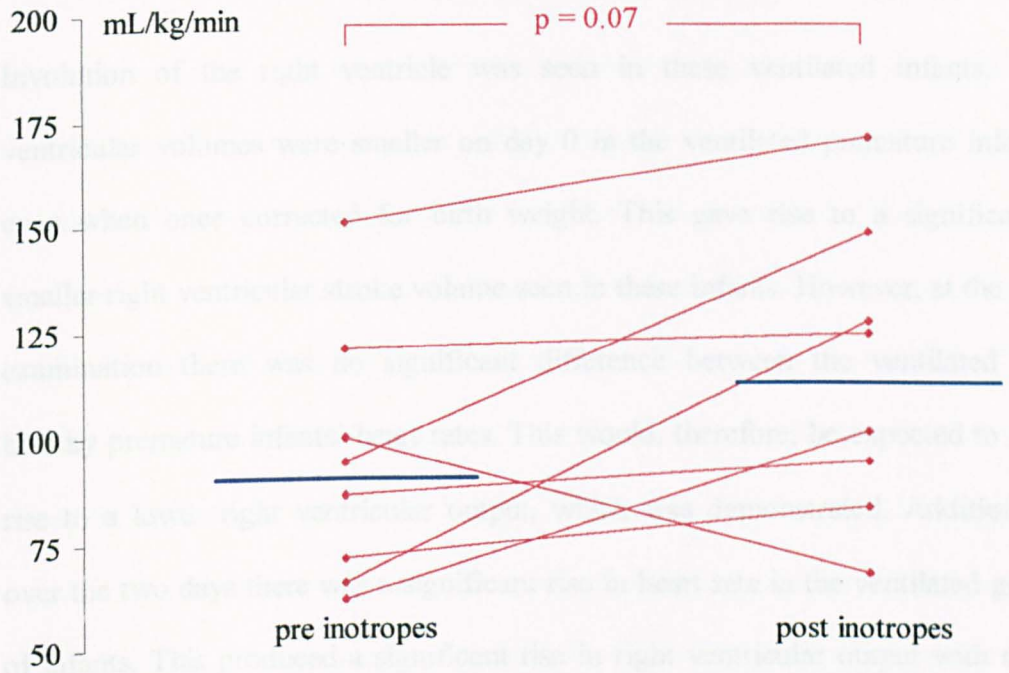

Figure 5.5: Change in right ventricular output in mL/kg/min pre and one hour post commencement of inotropes in study two infants, with horizontal bars showing median value.

the healthy premature infants by day two. In infants with more severe respiratory distress compared to those with mild disease the right ventricular end diastolic volume, stroke volume and output were significantly smaller.

Involution of the right ventricle was seen in these ventilated infants. The ventricular volumes were smaller on day 0 in the ventilated premature infants, even when once corrected for birth weight. This gave rise to a significantly smaller right ventricular stroke volume seen in these infants. However, at the first examination there was no significant difference between the ventilated and healthy premature infants' heart rates. This would, therefore, be expected to give rise to a lower right ventricular output, which was demonstrated. Additionally over the two days there was a significant rise in heart rate in the ventilated group of infants. This produced a significant rise in right ventricular output with time, despite no significant change in the right ventricular stroke volume of the ventilated infants. It has been suggested that there is linear growth of the ventricular cavity throughout gestation.[12] [74] However, these were unidimensional studies of the right ventricle. More recent studies [16,17] of both right ventricular volume and output have demonstrated an exponential rise in both left and right ventricular volumes during mid-gestation, when corrected for estimated foetal weight. This is a possible explanation for the significantly smaller right ventricular volumes in the ventilated preterm infants, who were around six weeks more immature than the healthy preterm infants, despite having corrected the volumes for birth weight. Additionally the right ventricle is stiffer at earlier gestations [15,16] [50] and this would exacerbate any hypovolaemia that

commonly occurs due to immediate cord clamping [75] that is routine in the more premature infants.

On day 0 the ventilated infants had significantly lower right ventricular output compared with the unventilated infants. Again this may be due in part to the 10 fold rise seen in both left and right ventricular output through mid to late gestation,[16,17] even allowing for correction using estimated foetal weight. Additionally, studies in ventilated infants have demonstrated the negative effect of ventilation on right and left ventricular output.[20] [61] This is thought to be mediated through impaired venous return with the level of impairment related to the mean airway pressure.[61] This effect was seen in the subgroup of infants with higher oxygenation indices, who had significantly lower right ventricular outputs. There was no difference in heart rates between those with higher or lower oxygenation indices, and therefore the lower output may be mediated by the significantly smaller right ventricular stroke volumes in the infants with higher oxygenation indices. This diminished stroke volume may reflect the smaller right ventricular end diastolic volume, as there was no difference in the end systolic volumes of these infants. This may be the result of poor venous return seen in infants treated with higher mean airway pressures. [61]

Unlike the healthy term and preterm infants, in the ventilated preterm infants the right ventricular output increased significantly during the study. Evans and Klucklow [20] demonstrated a rise in both left and right ventricular output using Doppler echocardiography in a population of ventilated premature infants. It

would appear that this rise in output was accomplished through a significant increase in the heart rate of the ventilated infants that was not seen in the healthy premature infants. The rise in the right ventricular output could be due to closure of the ductus arteriosus leading to an increase in venous return. However, this is unlikely as the rate of ductal patency was similar in the ventilated and non ventilated groups, unlike most other studies in neonates. [20] [61,62] [76] This may reflect the practice in the study centre of giving three doses of indomethacin to all infants under one kg at birth. Therefore, ductal closure is unlikely to be the source of the rise in right ventricular output in these ventilated infants. Once the ductus arteriosus has closed the only source of extra pulmonary shunting is the foramen ovale. Previous studies [20] [77] have demonstrated this to be usually bidirectional and even right to left in infants with severe lung disease. Therefore, it is unlikely to be a source of high volume flow and increased right ventricular output. This rise in right ventricular output therefore seems to be mediated by a sustained rise in the heart rate in these infants.

The increased right ventricular output was accompanied by a rise in the ejection fraction of the right ventricle. There was also a trend towards a rise in right ventricular ejection fraction in the non ventilated term and preterm infants. However, the ejection fraction in the ventilated infants was significantly higher than in the healthy premature infants. The improved ejection fraction may account for the rise in the right ventricular output seen in these infants along with the rise in heart rate. This increase in function may be due to a combination of effects alluded to in section 4.5. Studies have demonstrated that at earlier gestation the

right ventricle is more muscular and end systolic volume is after load dependent.[12] [15] [50] [53] In ovine models [7] it has been demonstrated that the work of the right ventricle falls following birth. It could be argued that a premature reduction in the work of the right ventricle, at a time when there is comparative functional right ventricular hypertrophy (that is mid gestation), would lead to a rise in the ventricular performance as measured by ejection fraction. The acute loss of high pulmonary vascular resistance that occurs with exposure to oxygen and transition to gaseous ventilation could, therefore, account for the significantly smaller right ventricular systolic volumes in the ventilated premature infants compared with the slightly more mature unventilated healthy preterm infants. This may further explain the rise in the right ventricular output seen at this time.

There was no difference between the right ventricular function of those infants who developed chronic lung disease and/or died when compared with those that survived without chronic lung disease. The development of chronic lung disease is multifactorial and not solely dependent on being ventilated.[37] Only one infant in this study, born with pulmonary hypoplasia, had supra systemic pulmonary artery pressure. The right ventricular end systolic volumes in this infant were 0.98, 0.81 and 0.80 mL/kg on days 0, 1 and 2 respectively. The stroke volumes were 0.61, 0.13 and 0.45 mL/kg respectively. The right ventricular ejection fractions were 0.38, 0.14 and 0.36, respectively. The poor ventricular performance and low stroke volume in this infant lead to the right ventricular outputs of 97, 22 and 70 mL/kg/min over the three examinations. This infant's right ventricular

measurements were very different from the remainder of the group's, table 5.4. One possible explanation is that the large end systolic volumes and hence poor ventricular performance on each day may be a direct result of the high pulmonary vascular resistance seen in this infant. Although with only one infant with such severely elevated pulmonary vascular resistance this remains speculation. In this infant pulmonary vascular resistance was suprasystemic, as this was the only infant with pure right to left shunting through the ductus arteriosus in the whole group. In all other infants pulmonary artery pressure was exceeded by systemic pressure. More formal measurements of pulmonary pressures were not available as not all infants had detectable tricuspid regurgitation [46] nor did the ductus arteriosus [69] remain open in all infants for all three examinations.

The small number of infants with severe respiratory distress syndrome in this study may reflect the high use of antenatal steroids and the use of natural surfactants. These both have led to a reduction in the numbers of infants with severe acute respiratory distress and to an increase in survival.[40]

This study provides insights into the pathophysiology of the right ventricle in respiratory distress syndrome. Right ventricular systolic and diastolic volumes decreased over the first two days following birth and right ventricular output increased. Infants with more severe lung disease have worse right ventricular function and reduced pulmonary blood flow. This failure of normal cardiovascular adaptation may prolong the course of the disease and predispose infants to increased hypoxaemia.

5.5.2 STUDY TWO

Several studies have demonstrated an improvement in arterial blood pressure and left ventricular function following administration of inotropes or fluid boluses.[61] [76] [78] We have shown that there is a mirrored effect on the right ventricle with a reduction in end systolic volume, an improvement in contractility and a rise in right ventricular output.

These changes, although not previously reported, are in keeping with expected alterations in haemodynamics. Inotropes improve left ventricular function and therefore increase systemic blood flow. This should result in more venous return to the right ventricle, despite the presence of a restricting ductus arteriosus, which in isolation should cause a rise in right ventricular end diastolic volume. All infants received a dopamine infusion, which is a potent vasoconstrictor, this would produce a further increase in the right ventricular preload, which has to be accommodated. There are only two possible physiological responses to these changes, an increase in stroke volume and/or heart rate, as these are the determinants of cardiac output. However, a change in stroke volume can be accommodated by several permutational changes in the difference in volume between end systole and end diastole. The absolute values or the direction of movement of the end systolic or end diastolic volumes are less important that the change in the difference between them. In this study there was no alteration in right ventricular end diastolic volume, probably because the same increase in preload was also affecting the left ventricle and through the restraining effects of the pericardium [9] both ventricles were limited in the increase in end diastolic

volume available. Additionally the left ventricle is more compliant in comparison with the right ventricle at earlier gestations and would probably distend more easily.[8] [15] [27] [50] [59] There was a trend towards increase for both right ventricular stroke volume and output. The small sample size in this study may have prevented detection of a statistically significant rise between the two examinations. It is possible that the small difference between the median stroke volumes and right ventricular outputs may have been significant if larger numbers of infants were studied. Indeed using this as pilot data for a sample size calculation with an 80% probability of detecting this degree of difference at the 5% level of significance for the right ventricular output data would require paired measurements in 25 infants. However, for the alpha and beta 33 infants would be need to detect the difference seen in the right ventricular stroke volume data. There was a significant increase in the heart rate following the inotropic infusion. The higher heart rate gives less time for ventricular filling, and therefore the rise in ejection fraction accommodates for this. The time between the decision to start inotropic support and the initiation of the infusion is a small time window leading to the limited number of infants recruited into this study. Hence, only eight paired examinations were available for analysis.

There are many proposed mechanisms for the hypotension seen in preterm infants. Hypovolaemia,[76] poor cardiac function [42] and hypocortisolism.[79] It is likely that in any infant there may be more than one factor predisposing to the development of hypotension.[37] It is possible that a poorly functioning right ventricle, with low output in the face of high pulmonary vascular resistance, may

have a marked impact on the preload of the left ventricle. In the foetus the right ventricle is the dominant ventricle at early gestations, with a thicker wall, a larger output, and a bigger stroke volume.[2] [7,8] [50] Through the later stages of gestation the ultra structure of the ventricles matures to cope with the adaptation that occurs following birth.[13] However, given the discordance in ventricular maturity, it is possible to speculate that in a newly born preterm infant the left ventricle may well depend on the adequate preload supplied by the relatively hypertrophied right ventricle to maintain adequate systemic blood flow.

In these hypotensive infants an infusion of dopamine resulted in an increase in heart rate, right ventricular ejection fraction and right ventricular output and a decrease in right ventricular end systolic volume.

5.6 Conclusions

These studies have demonstrated that the right ventricle does undergo involution in ventilated infants in a similar manner to more mature infants. There was a significant rise in the right ventricular output with time, probably mediated by a rise in heart rate. Dopamine enhances right ventricular performance in hypotensive ventilated neonates.

CHAPTER SIX

CONCLUSIONS

6.1 Summary

The aim of this thesis was to investigate right ventricular performance and pathophysiology in the evolution of respiratory distress syndrome, of the neonate, using two dimensional echocardiography.

The use of echocardiography is widely accepted in children and infants to delineate cardiac anatomy and function. However, the quantification of function has been difficult, as there have been only other non gold standard measurements available for comparisons, such as cine angiography from catheter studies, and dye dilution techniques.[66] The advent of magnetic resonance angiography has allowed the validation of echocardiography as a valuable technique for the quantification of cardiac performance.[33] In neonates echocardiography is a readily available technique that can be performed quickly at the cot side. Despite the validation, concerns still surround the use of ultrasound by multiple users, as there can be marked inter observer variation. Additionally, the validation with magnetic resonance angiography has been performed in young infants with a stable mature circulation. Therefore, the preliminary part of this thesis concerned establishing the intra observer repeatability of two of the validated volume estimation methods. A coefficient of repeatability of 28% was demonstrated for the ellipsoid approximation method, this was better than the 52% for the Simpson's method. Additionally there was a systematic difference between the two different methods with the Simpson's method giving around 30% smaller volumes on average. Hence the ellipsoid approximation method was used to measure right ventricular performance in all subsequent studies. The ellipsoid

method was then compared with the Doppler calculations with good correlation and acceptable agreement. It is important to note that this method is therefore suitable for following trends rather than giving absolute values.

The establishment of the behaviour of the right ventricle, over the first two days of life, in normal healthy and preterm term infants not requiring respiratory support was the next step in this investigation. In both these groups of infants right ventricular volumes decreased significantly over the three examinations. There was also no difference in right ventricular output between the two groups, or ejection fractions, despite the smaller volumes seen in the preterm infants.

The performance of the right ventricle in infants ventilated for respiratory distress syndrome was then investigated. These infants had smaller right ventricular volumes but better right ventricular performance, with a rise in right ventricular output by 48 hours compared with the healthy infants. The rise in right ventricular output has previously been demonstrated with Doppler studies.[20] Additionally the ejection fraction rose significantly with time and was higher in the ventilated infants on day two than in the healthy preterm group. This may suggest that the functionally more effective preterm right ventricle is better able to cope with the increased work in respiratory distress syndrome. Amongst the ventilated infants those with the more severe respiratory disease had worse right ventricular performance. Although not enough infants died from respiratory causes to demonstrate a significant relationship with outcome.

The use of a dopamine infusion was associated with a significant improvement in right ventricular performance with no change in ductal flow characteristics. There was also a trend toward enlarged right ventricular stroke volume and improved right ventricular output.

6.2 Study Limitations

Echocardiography is the only cot side cardiac imaging technique available for unstable neonates. The validation of the technique used has been performed in older infants outside of the transitional circulation. It is possible that the measured changes in ventricular performance are mediated by a conformational changes in the ventricular shape following delivery [29] that would not be detected as only one plane of visualisation was used. However, most of the infants studied had completed the change from foetal to mature circulation by the third examination. Therefore, they had similar circulations to those infants in the validation study by Helbing et al [33] who found that single plane assessment was as accurate as bi plane measurements. The advantage of single plane examinations is speed with which they can be performed and in this study all examinations yielded suitable images. Although not an accepted gold standard the right ventricular output measured by two dimensional methods and by pulmonary artery Doppler showed good correlation, despite the expected wide limits of agreement.

The numbers of infants studied was small. However, the sample size estimate was for 16 infants in each group and this was achieved. There was no difficulty in recruiting infants except in the hypotensive study where the window of

opportunity for recruitment was extremely short. It is possible to speculate that if more infants had been recruited more subtle differences between the groups may have become apparent. Despite the small sample size all of the infants had an improvement in ejection fraction as shown in figure 5.4.

There were only a few infants with very severe lung disease. This may be a reflection of the change in local practice from using an artificial surfactant to a natural one and a high rate of antenatal steroid usage. Ideally a larger number of infants with severe lung disease could have been studied, but this was not possible within the study time frame.

The recording of simultaneous biventricular data may have given additional insights into the functional interdependence of the right and left ventricle.

6.3 Implications of Findings

The involution of the right ventricle over the first 48 hours of life is probably mediated by the fall in pulmonary vascular resistance [7] and the increase in the end diastolic volume of the left ventricle.[25,26] This was seen across healthy term and preterm infants and those with respiratory distress. The data in this thesis might lead to a suggestion that those infants with higher ventilatory requirements have a failure or retardation of this process. This is likely to lead to both reduced pulmonary blood flow and therefore reduced left ventricular preload. The initiation of inotropic therapy caused a rise in right ventricular performance and output, therefore improving pulmonary blood flow and left ventricular preload. It

may be that at earlier gestations the less dominant left ventricle is more reliant on the performance of the functionally hypertrophied right ventricle to maintain cardiac output especially in the face of high mean airway pressures. This could be exacerbated by the relative hypovolaemia seen in the most premature infants because of the immediate cord clamping that occurs in this situations.[75]

6.4 Further Study

Advances in neonatal care have changed the course of neonatal respiratory distress syndrome. Administration of antenatal steroids and postnatal surfactant has profoundly changed the outcomes for many infants.[40] One of the limitations of this thesis was the sole focus on the right ventricle and future studies should include both right and left ventricular function measurements. This will help to elucidate the interaction between the ventricles.

This thesis addressed respiratory distress in premature infants and focused on right ventricular performance. Isolated right ventricular diastolic function studies such as Doppler velocities for right ventricular filling were not performed. Using this technique several authors have demonstrated increase reliance on active filling rather than passive filling,[15] [50] [60] [80] as is found in stiffer ventricles. It has been demonstrated that delayed cord clamping in premature infants [75] reduces oligovolaemia and enhances post natal lung adaptation. The effect of this auto transfusion is in marked contrast to the findings that higher fluid volumes [37] and multiple postnatal blood transfusions [37] are associated with an increased incidence of chronic lung disease. It may be that placental auto

transfusion aids the stiffer premature ventricle, as it will require higher distending pressures to ensure adequate preload, without the possibility of extraneous iron overload and fluid shifts associated with donor transfusions and fluid resuscitation respectively. It would be interesting to investigate right ventricular diastolic filling patterns particularly in infants were there is delayed cord clamping to attempt to demonstrate higher right ventricular volumes and improved diastolic function.

None of the infants studied in this thesis received high frequency oscillation ventilation and the rate of nasal continuous positive airways pressure use was low. This reflects the local practice in the unit where the studies were conducted. However, given the suggestion found in this thesis and elsewhere that higher ventilatory pressures lead to a reduction in right ventricular preload,[20] [61] it may be possible to demonstrate differences in right ventricular performance between infants receiving these different modes of ventilation. Exponents of high frequency oscillation ventilation claim that the continuous distending airways pressure used is markedly attenuated down the respiratory tract,[81,82] leading to a marked reduction in potential barotrauma. This may minimize the reduction in preload and therefore allows cardiorespiratory adaptation to progress more readily.

Studies looking at inhaled nitric oxide, a potent pulmonary vasodilator, have found that pulmonary artery pressure has been reduced and oxygenation is improved.[83] However, in preterm infants these changes have been only short lived and not translated into longer term improvements in outcome.[83] The acute

reduction of pulmonary artery pressure seen may lead to an off loading of the right ventricle. It may be possible to study changes in the performance of the right ventricle following the administration of inhaled nitric oxide in a similar design to the second study in chapter five.

Echocardiography is widely used in neonates and can be used to establish the presence of poor myocardial function.[21] [42] [84] There are now biochemical markers that can detect even minimal myocardial damage, such as cardiac troponin T.[85] This has been used in preterm ventilated infants [86,87,88] and seems to have none of the disadvantages of creatine kinase and its isoforms. It may now be possible to relate ventricular performance, using echocardiographic measures with a direct marker of myocardial damage in ventilated preterm infants.

6.6 Conclusion

This thesis has demonstrated, over the first two days after birth, that there is an involution of the right ventricle. This is seen regardless of the gestation at the time of delivery. However, the more premature the infant the smaller the right ventricular cavity was, despite the correction for birth weight. Amongst infants with respiratory distress syndrome right ventricular performance was worse in those exposed to higher mean airway pressures. The performance of the right ventricle in this situation can be enhanced by the use of a dopamine infusion.

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APPENDIX ONE

EHTICAL APPROVAL

DOCUMENTATION

Alder Hey

Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP
Telephone: 0151-228 4811

ROYAL LIVERPOOL CHILDREN'S N.H.S. TRUST

Our ref: 1/E/35/98

21 September 1998

Dr N V Subhedar
Neonatal Unit
Liverpool Women's Hospital
Crown Street
Liverpool
L8 7SS

Dear Nim

RE: APPLICATION E/35/98: RIGHT VENTRICULAR FUNCTION IN NEONATES

Thank you for having attended the recent Ethics Committee meeting to discuss the methodology, parent information document and other issues.

In summary the Committee is able to approve this study, pending the receipt of a revised parent information document. I am enclosing a copy of your original document with some marked suggestions/ideas. Importantly, bullet points should be avoided and the format should include more prose, rather than 'bulleted' statements.

The Committee would strongly recommend that this study be conducted in at least two phases. The first should be undertaken in healthy term and pre-term infants to establish reliability and reproducibility (intra and inter-observer) and only then to proceed to the second phase if reliability is found. The second phase could then evaluate right ventricular function in two groups - infants with RDS, and infants with RDS and some intervention as outlined in your original application.

I hope that these comments/suggestions are felt to be helpful and we look forward to receiving a revised parent information document.

Yours sincerely

Richard E Appleton
Chairman
Paediatrics Research Ethics Committee

Enc

Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP
Telephone: 0151-228 4811

Alder Hey
ROYAL LIVERPOOL CHILDREN'S N.H.S. TRUST

Our ref: 2/E/35/98

28 September 1998

Dr N V Subhedar
Neonatal Unit
Liverpool Women's Hospital
Crown Street
Liverpool
L8 7SS

Dear Nim

RE: APPLICATION E/35/98: RIGHT VENTRICULAR FUNCTION IN NEONATES

Thank you for the amended parent information document. The Committee have noted and approved the changes.

Approval for the study was given.

We would like to wish you well with the study and look forward to seeing a preliminary report in 12 months

Yours sincerely

Richard E. L

Richard E Appleton
Chairman
Paediatrics Research Ethics Committee

APPENDIX TWO

PARENT INFORMATION

SHEETS AND CONSENT FORM

Liverpool
Women's
Hospital

NEONATAL UNIT

Liverpool Women's Hospital
Crown Street
Liverpool L8 7SS
Tel: 0151 708 9988
Fax: 0151 702 4028

Your ref:
Our ref:
If telephoning please ask for:

.....
Direct Line: 0151 702 4093

Fax Line: 0151 702 4082

PARENT INFORMATION

RIGHT VENTRICULAR FUNCTION IN NEONATES

Dr SJ Clark, Dr NV Subhedar, Dr CW Yoxall,

What is the Study about?

The right ventricle is the part of the heart which pumps blood to the lungs. We wish to measure how well the right ventricle is working using ultrasound scanning (similar to the antenatal scans done in pregnancy). We hope to get a better understanding of how lung disease can affect the workings of the right ventricle.

Which babies will be studied?

Healthy full term babies and healthy premature babies will be scanned. This will show us how well the right ventricle works in healthy new born babies. Some new born babies with breathing difficulties will also be scanned. This may show us how the right ventricle is affected by the lungs, when they are not working properly.

What will this involve for my/our child?

An ultrasound scan of the baby's heart will be performed at 6 hours, 24 hours and 48 hours after birth.

Are there any side effects?

None are known.

Can I/We change our mind about being in the study?

Yes. At any time you may decide not to continue. This will not affect any other care which your baby receives.

If you have any other questions please feel free to ask. We will be happy to discuss any queries with you. Please contact any of the above doctors for more details on 0151-702-4093.

An NHS Trust

Liverpool
Women's
Hospital

NEONATAL UNIT

Liverpool Women's Hospital
Crown Street
Liverpool L8 7SS
Tel: 0151 708 9988
Fax: 0151 702 4028

Your ref:
Our ref:
If telephoning please ask for:

.....
Direct Line: 0151 702 4093

Fax Line: 0151 702 4082

PARENT INFORMATION

RIGHT VENTRICULAR FUNCTION IN HYPOTENSIVE NEONATES

Dr SJ Clark, Dr NV Subhedar, Dr CW Yoxall,

What is the Study about?
The right ventricle is the part of the heart which pumps blood to the lungs. We wish to measure how well the right ventricle is working using ultrasound scanning (similar to the antenatal scans done in pregnancy). We hope to get a better understanding of how lung disease can affect the workings of the right ventricle.

Which babies will be studied?
New born babies with breathing difficulties and low blood pressure will be scanned. A scan will be performed when the blood pressure is low and one will be performed once medicine has been started to treat the blood pressure. This may show us how the right ventricle is affected by the medicine used to treat low blood pressure in babies.

What will this involve for my/our child?
An ultrasound scan of the baby's heart will be performed when the blood pressure is low, while the medicine is being prepared. Another scan will be performed one hour after the medicine has bee started. Your baby's medicine will not be delayed by the examination.

Are there any side effects?
None are known.

Can I/We change our mind about being in the study?
Yes. At any time you may decide not to continue. This will not affect any other care which your baby receives.

If you have any other questions please feel free to ask. We will be happy to discuss any queries with you. Please contact any of the above doctors for more details on 0151-702-4093.

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Women's
Hospital

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Crown Street
Liverpool L8 7SS
Tel: 0151 708 9988
Fax: 0151 702 4028

Your ref:
Our ref:
If telephoning please ask for:

.....
Direct Line: 0151 702 4093

Fax Line: 0151 702 4082

CONSENT FORM

RIGHT VENTRICULAR FUNCTION IN NEONATES

Dr SJ Clark, Dr NV Subhedar, Dr CW Yoxall,
Neonatal Intensive Care Unit, Liverpool Women's Hospital.
0151-709-1000 ext. 2360

I/we give permission for my/our child ..... to be included in the above study. The purpose is to measure how the heart functions differently in premature & full term babies. The nature of the study requires the use of ultrasound to scan the heart.

This has been explained to me by .....
(print name)

I understand that my child's participation in the study is entirely voluntary on my/our part and that I/we have the right to withdraw our/my child at any time without stating a reason and without prejudice to his/her treatment. I/we have also read the explanatory document for parents for this study and I/we understand that I/we have the right to request further information both in relation to my/our child or to the study from the supervising doctor.

Signature of parent/guardian .....

Please print name .....

Date .....

Signature of investigator .....

An NHS Trust

APPENDIX THREE

DATA FROM THE REPEATABILITY AND DOPPLER COMPARISON STUDY

Volumes for the repeatability measurements: the ellipsoid approximation method, mL				
Patient	Systole	Repeated Systole	Diastole	Repeated Diastole
1	4.97	4.82	8.30	9.41
2	4.22	3.83	11.67	9.11
3	3.62	2.87	8.13	7.97
4	2.85	3.03	6.05	5.48
5	3.16	2.92	7.67	8.56
6	4.71	4.28	7.85	7.92
7	2.99	2.91	6.67	6.04
8	2.27	2.59	6.66	6.34
9	2.64	2.34	7.83	5.65
10	1.95	1.80	4.85	4.69
11	3.60	2.47	6.03	4.66
12	4.86	4.22	9.03	8.90
13	2.78	2.58	6.69	6.11
14	3.45	2.85	7.11	6.72
15	3.82	3.27	7.26	7.60
16	3.30	3.42	6.82	8.08
17	2.92	2.93	5.74	6.05
18	3.29	2.79	6.26	5.86
19	1.70	2.02	4.28	5.27

Volumes for the repeatability measurements: the Simpson's method, mL				
Patient	Systole	Repeated Systole	Diastole	Repeated Diastole
1	3.08	3.39	5.65	6.98
2	2.95	3.21	8.17	5.10
3	1.97	2.77	6.39	6.11
4	2.88	2.54	5.12	4.75
5	2.47	2.09	6.24	6.75
6	2.51	2.02	5.71	4.29
7	1.88	1.96	4.67	4.87
8	2.24	1.90	5.25	4.53
9	2.52	1.88	5.72	4.40
10	1.84	1.43	3.88	3.84
11	2.24	1.31	3.44	3.20
12	3.98	3.07	6.46	6.44
13	2.08	2.02	5.37	5.32
14	2.10	2.01	4.25	5.11
15	1.50	1.99	3.48	4.23
16	2.65	2.87	5.50	6.84
17	2.25	1.86	5.12	4.90
18	1.44	0.94	3.44	3.23
19	1.39	1.60	2.40	2.71

Volumes from the comparison of the two different methods, mL				
	Ellipsoid Approximation Method		Simpson's Method	
Patient	Systole	Diastole	Systole	Diastole
1	2.47	6.47	1.17	3.26
2	2.43	4.96	1.25	2.59
3	1.76	4.48	1.44	2.98
4	2.43	5.19	1.81	4.00
5	3.02	6.73	1.82	5.21
6	2.87	6.05	1.97	4.94
7	2.68	6.50	2.05	4.93
8	2.41	7.45	2.06	5.84
9	2.99	5.76	2.10	3.55
10	3.26	6.92	2.20	5.17
11	2.59	6.37	2.26	4.76
12	2.72	6.46	2.27	5.42
13	4.11	8.29	2.32	5.79
14	2.96	7.80	2.38	5.20
15	2.61	6.77	2.42	5.38
16	3.77	9.09	2.43	6.04
17	3.41	6.68	2.50	4.84
18	3.05	6.65	2.60	5.20
19	4.51	7.45	2.67	5.07
20	3.89	7.12	2.85	5.11
21	4.29	9.58	2.95	6.89
22	4.37	7.97	3.32	5.09
23	4.91	9.39	3.46	7.11

Heart rate at the recording of the two different volume measurements, beats per minute		
Patient	During ellipsoid measurement	During Simpson's measurement
1	111	113
2	97	111
3	103	88
4	120	113
5	111	123
6	110	117
7	135	122
8	120	132
9	114	107
10	122	122
11	131	107
12	121	117
13	97	125
14	103	114
15	103	132
16	115	122
17	113	114
18	119	119
19	133	130
20	124	133
21	124	124
22	116	129
23	109	106

Right ventricular output calculated by the ellipsoid approximation method and pulmonary artery Doppler derived methods, mL/kg/min		
Patient	Ellipsoid approximation method	Pulmonary valve Doppler
1	97	230
2	102	263
3	66	158
4	90	166
5	146	228
6	171	332
7	135	244
8	143	186
9	166	381
10	108	204
11	99	152
12	170	269
13	135	166
14	140	399
15	205	405
16	162	322
17	118	168

APPENDIX FOUR

DATA FROM THE HEALTHY TERM AND HEALTHY PREMATURE INFANTS STUDY

Term Infants				
Patient	Sex	Gestation, weeks	Birth Weight, kg	Mode of Delivery
1	male	41	2.36	Vaginal
2	male	41	3.98	Caesarean
3	female	43	3.05	Vaginal
4	male	40	3.94	Vaginal
5	male	39	3.21	Vaginal
6	male	42	4.54	Vaginal
7	female	38	3.36	Caesarean
8	female	41	2.58	Vaginal
9	male	38	3.40	Caesarean
10	female	38	2.72	Caesarean
11	female	40	3.46	Caesarean
12	female	37	2.98	Caesarean
13	female	38	3.34	Caesarean
14	female	38	3.38	Caesarean
15	female	38	3.88	Caesarean
16	female	39	3.37	Vaginal
17	male	38	3.34	Vaginal
18	female	38	2.71	Vaginal

Term Infants				
Patient	Cord pH	Cord BE	Apgar@1	Apgar@5
1	7.21	-4.1	9	10
2	7.23	-3.8	10	10
3	7.33	-4.6	9	10
4	7.18	-6.2	7	10
5	7.33	-4.6	8	10
6	7.43	1.5	9	10
7	7.20	-7.4	7	10
8	7.28	-1.6	9	10
9	7.35	-0.3	9	10
10	7.35	-6.4	9	10
11	7.28	-5.1	9	9
12	7.33	-3.8	9	10
13	7.35	-1.3	9	10
14	7.28	-1.9	9	10
15	7.33	-2.5	9	10
16	7.34	3.1	9	10
17	7.31	-6.7	9	10
18	7.41	-2.6	9	10

Term Infants						
Patient	Heart Rate			Age in Hours		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	130	124	127	12	36	58
2	116	126	105	9	36	53
3	100	139	120	5	24	48
4	109	106	108	3	23	45
5	107	111	114	8	31	54
6	103	94	91	12	34	58
7	122	116	123	2	24	47
8	109	123	90	11	34	57
9	110	109	100	4	27	46
10	122	105	103	2	29	47
11	108	112	116	7	29	55
12	114	122	125	4	24	49
13	121	115	90	4	24	49
14	117	115	118	3	25	50
15	124	141	127	5	24	50
16	104	124	111	5	28	52
17	107	131	138	3	25	49
18	119	140	120	7	25	49

Term Infants						
Patient	Systolic Volume, mL			Diastolic Volume, mL		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	2.01	1.57	1.7	5.12	4.04	4.28
2	3.23	4.22	3.87	6.55	11.67	9.05
3	3.72	1.96	2.92	6.75	5.67	5.74
4	5.15	3.62	4.09	11.32	8.13	9.28
5	2.11	1.88	3.29	4.1	4.52	6.26
6	4.85	5.7	4.18	9.35	9.82	9.01
7	2.85	2.64	2.35	7.53	7.83	4.94
8	3.82	1.85	1.73	7.26	6.73	5.41
9	3.45	2.16	2.42	7.11	6.45	5.95
10	4.29	2.99	2.5	8.01	6.67	6.08
11	5.33	4.97	3.24	8.77	8.3	5.29
12	4.6	2.85	2.77	8.83	6.05	5.16
13	3.27	2.4	2.5	7.22	5.93	6.22
14	2.78	2.44	2.02	6.69	8.51	7.15
15	4.19	4.71	3.42	8.59	7.85	8.43
16	5.25	2.85	3.57	8.16	5.99	7.2
17	3.25	3.16	2.47	9.67	7.67	6.06
18	2.69	1.95	2.66	5.78	4.85	4.95

Term Infants						
Patient	Systolic Volume, mL/kg			Diastolic Volume, mL/kg		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	0.85	0.66	0.72	2.17	1.71	1.81
2	0.81	1.06	0.97	1.65	2.93	2.27
3	1.22	0.64	0.96	2.21	1.86	1.88
4	1.31	0.92	1.04	2.87	2.06	2.35
5	0.66	0.59	1.02	1.28	1.41	1.95
6	1.07	1.26	0.92	2.06	2.16	1.98
7	0.85	0.79	0.70	2.24	2.33	1.47
8	1.48	0.72	0.67	2.82	2.61	2.10
9	1.01	0.64	0.71	2.09	1.90	1.75
10	1.58	1.10	0.92	2.94	2.45	2.24
11	1.54	1.44	0.94	2.53	2.40	1.53
12	1.54	0.96	0.93	2.96	2.03	1.73
13	0.98	0.72	0.75	2.16	1.78	1.86
14	0.82	0.72	0.60	1.98	2.52	2.12
15	1.08	1.21	0.88	2.21	2.02	2.17
16	1.56	0.85	1.06	2.42	1.78	2.14
17	0.97	0.95	0.74	2.89	2.30	1.81
18	0.99	0.72	0.98	2.13	1.79	1.83

Term Infants						
Patient	Stroke Volume, mL/kg			Ejection Fraction		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	1.32	1.05	1.09	0.61	0.61	0.60
2	0.83	1.87	1.30	0.51	0.64	0.57
3	0.99	1.22	0.92	0.45	0.65	0.49
4	1.56	1.14	1.32	0.55	0.55	0.56
5	0.62	0.82	0.92	0.49	0.58	0.47
6	0.99	0.91	1.06	0.48	0.42	0.54
7	1.39	1.54	0.77	0.62	0.66	0.52
8	1.34	1.89	1.43	0.47	0.73	0.68
9	1.08	1.26	1.04	0.51	0.67	0.59
10	1.37	1.35	1.32	0.46	0.55	0.59
11	0.99	0.96	0.59	0.39	0.40	0.39
12	1.42	1.07	0.80	0.48	0.53	0.46
13	1.18	1.06	1.11	0.55	0.60	0.60
14	1.16	1.80	1.52	0.58	0.71	0.72
15	1.13	0.81	1.29	0.51	0.40	0.59
16	0.86	0.93	1.08	0.36	0.52	0.50
17	1.92	1.35	1.07	0.66	0.59	0.59
18	1.14	1.07	0.84	0.53	0.60	0.46

Term Infants						
Patient	Right Ventricular Output, mL/kg/min			Diameter of Ductus Arteriosus, cm		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	171	129	138	0.00	0.00	0.00
2	97	235	137	0.00	0.00	0.00
3	99	169	111	0.20	0.00	0.00
4	170	121	142	0.24	0.18	0.12
5	66	91	106	0.27	0.00	0.00
6	102	86	97	0.27	0.00	0.00
7	170	179	94	0.28	0.00	0.00
8	146	233	129	0.33	0.00	0.00
9	118	137	104	0.38	0.24	0.00
10	166	142	136	0.39	0.00	0.00
11	108	107	69	0.39	0.31	0.00
12	162	132	100	0.41	0.00	0.00
13	143	121	100	0.42	0.29	0.24
14	135	207	178	0.42	0.00	0.00
15	140	114	164	0.44	0.25	0.00
16	90	116	119	0.45	0.25	0.21
17	205	177	149	0.49	0.00	0.00
18	135	150	101	0.56	0.29	0.00

Healthy Premature Infants				
Patient	Sex	Gestation, weeks	Birth Weight, kg	Mode of Delivery
1	male	31	1.74	Caesarean
2	female	31	1.62	Caesarean
3	female	34	2.00	Caesarean
4	male	31	1.09	Caesarean
5	female	31	1.35	Vaginal
6	male	31	2.20	Vaginal
7	male	35	1.91	Caesarean
8	male	31	1.42	Caesarean
9	male	33	1.85	Caesarean
10	female	33	2.01	Caesarean
11	female	35	2.07	Caesarean
12	male	29	1.13	Caesarean
13	male	34	2.00	Caesarean
14	male	29	1.44	Caesarean
15	female	33	1.49	Caesarean
16	male	34	2.10	Caesarean
17	female	33	1.48	Caesarean

Healthy Premature Infants				
Patient	Cord pH	Cord BE	Apgar@1	Apgar@5
1	7.38	-0.6	9	9
2	7.36	-1.4	7	9
3	7.34	-2.2	10	9
4	7.35	-0.8	7	7
5	7.38	-1.2	10	10
6	7.39	2.4	8	9
7	7.32	-3.7	8	9
8	7.35	0.2	5	10
9	7.38	-2.5	9	10
10	7.42	-1.3	9	10
11	7.30	-1.4	5	9
12	7.38	-0.1	5	9
13	7.31	-4.1	9	10
14	7.38	-0.1	9	10
15	7.29	-2.9	9	9
16	7.38	-2.2	9	9
17	7.33	-3.6	9	10

Healthy Premature Infants						
Patient	Heart Rate			Age in Hours		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	127	146	114	6	26	50
2	159	141	134	6	26	50
3	144	135	130	3	23	47
4	138	143	147	6	26	50
5	143	163	141	6	30	53
6	141	141	131	5	26	50
7	128	110	122	5	26	49
8	149	135	128	5	24	49
9	150	126	124	8	30	51
10	136	140	141	5	23	47
11	130	132	126	4	25	47
12	172	164	159	3	24	46
13	133	130	117	5	28	49
14	179	158	172	3	21	45
15	129	128	116	5	26	50
16	139	132	110	6	29	50
17	147	140	126	6	28	49

Healthy Premature Infants						
Patient	Systolic Volume, mL			Diastolic Volume, mL		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	1.51	0.91	0.98	2.88	2.4	1.9
2	2.13	0.88	1.08	3.64	1.8	2.37
3	2.16	2.05	1.57	4.32	3.51	3.27
4	1.23	0.77	0.46	2.62	2.24	1.95
5	1.57	1.46	1.27	3.55	3.09	3.1
6	2.4	0.86	1.01	3.71	2.96	2.43
7	2.25	1.05	1.03	3.26	2.35	2.67
8	0.87	0.69	0.77	2.34	1.71	1.33
9	1.19	1.45	1.17	3.22	3.1	2.41
10	1.83	1.84	1.23	3.59	3.54	2.88
11	2.27	1.49	1.06	4.33	2.98	2.45
12	1.27	1.13	1	3.2	2.23	2.04
13	1.87	1.46	0.99	3.19	2.94	2.83
14	2.08	0.93	0.98	3.61	1.57	2.95
15	1.33	1.87	1.14	3.31	3.57	2.31
16	2.11	1.12	1.24	4.64	2.4	2.56
17	1.81	1.29	1.13	2.97	3.18	2.92

Healthy Premature Infants						
Patient	Systolic Volume, mL/kg			Diastolic Volume, mL/kg		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	0.87	0.52	0.56	1.66	1.38	1.09
2	1.32	0.54	0.67	2.25	1.11	1.47
3	1.08	1.02	0.78	2.16	1.75	1.63
4	1.12	0.70	0.42	2.39	2.05	1.78
5	1.16	1.08	0.94	2.63	2.29	2.30
6	1.09	0.39	0.46	1.69	1.35	1.10
7	1.18	0.55	0.54	1.71	1.23	1.40
8	0.61	0.49	0.54	1.65	1.20	0.94
9	0.64	0.79	0.63	1.75	1.68	1.31
10	0.91	0.91	0.61	1.78	1.76	1.43
11	1.10	0.72	0.51	2.09	1.44	1.18
12	1.13	1.00	0.89	2.84	1.98	1.81
13	0.93	0.73	0.49	1.59	1.47	1.41
14	1.44	0.65	0.68	2.51	1.09	2.05
15	0.89	1.25	0.76	2.22	2.39	1.55
16	1.01	0.53	0.59	2.21	1.15	1.22
17	1.22	0.87	0.76	2.01	2.15	1.98

Healthy Premature Infants						
Patient	Stroke Volume, mL/kg			Ejection Fraction		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	0.79	0.86	0.53	0.48	0.62	0.48
2	0.93	0.57	0.80	0.41	0.51	0.54
3	1.08	0.73	0.85	0.50	0.42	0.52
4	1.27	1.34	1.36	0.53	0.66	0.76
5	1.47	1.21	1.36	0.56	0.53	0.59
6	0.60	0.95	0.65	0.35	0.71	0.58
7	0.53	0.68	0.86	0.31	0.55	0.61
8	1.04	0.72	0.39	0.63	0.60	0.42
9	1.10	0.89	0.67	0.63	0.53	0.51
10	0.87	0.84	0.82	0.49	0.48	0.57
11	1.00	0.72	0.67	0.48	0.50	0.57
12	1.71	0.98	0.92	0.60	0.49	0.51
13	0.66	0.74	0.92	0.41	0.50	0.65
14	1.06	0.44	1.37	0.42	0.41	0.67
15	1.33	1.14	0.78	0.60	0.48	0.51
16	1.21	0.61	0.63	0.55	0.53	0.52
17	0.78	1.28	1.21	0.39	0.59	0.61

Healthy Premature Infants						
Patient	Right Ventricular Output, mL/kg/min			Diameter of Ductus Arteriosus, cm		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	100	125	60	0.14	0.00	0.00
2	149	80	107	0.16	0.09	0.06
3	155	98	110	0.22	0.00	0.00
4	175	192	200	0.23	0.00	0.00
5	210	196	192	0.26	0.00	0.00
6	84	135	85	0.28	0.22	0.00
7	68	75	105	0.29	0.00	0.00
8	154	97	51	0.32	0.00	0.00
9	165	112	84	0.36	0.28	0.21
10	119	119	115	0.38	0.00	0.00
11	130	95	85	0.38	0.00	0.00
12	293	160	147	0.41	0.00	0.00
13	87	96	108	0.41	0.00	0.00
14	191	70	236	0.45	0.43	0.27
15	171	145	91	0.46	0.00	0.00
16	168	81	69	0.48	0.00	0.00
17	115	179	152	0.53	0.23	0.00

APPENDIX FIVE

DATA FROM THE VENTILATED PREMATURE INFANT STUDY

Ventilated Premature Infants				
Patient	Sex	Gestation, weeks	Birth Weight, kg	Mode of Delivery
1	male	27	0.99	caesarean
2	female	24	0.47	caesarean
3	female	28	0.97	caesarean
4	male	28	1.13	caesarean
5	male	28	1.28	vaginal
6	male	28	1.11	caesarean
7	male	26	0.84	caesarean
8	female	29	0.97	caesarean
9	female	29	0.97	caesarean
10	male	29	0.95	caesarean
11	male	25	0.91	vaginal
12	female	27	0.67	caesarean
13	female	24	0.65	caesarean
14	female	27	1.02	caesarean
15	female	27	1.24	vaginal
16	male	27	1.23	vaginal
17	male	27	1.08	vaginal

Ventilated Premature Infants				
Patient	Cord pH	Cord BE	Apgar@1	Apgar@5
1	7.35	-3.7	9	9
2	7.38	-1.2	6	9
3	7.31	-3.4	8	10
4	7.32	-3.5	7	9
5	7.13	-3.0	6	9
6	7.35	-4.5	9	9
7	7.38	-0.2	2	1
8	7.24	-8.4	6	8
9	7.06	-15.7	4	7
10	7.23	-7.7	5	10
11	7.39	-4.0	6	10
12	7.34	-3.6	7	7
13	7.33	-3.6	2	7
14	7.27	-3.1	1	1
15	7.39	-0.1	3	7
16	7.31	-9.8	9	9
17	7.37	-3.0	5	8

Ventilated Premature Infants						
Patient	Heart Rate			Age in Hours		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	160	170	155	8	27	50
2	157	137	141	4	26	48
3	139	126	164	5	23	46
4	134	129	153	2	19	44
5	169	166	170	6	29	53
6	155	139	137	3	25	47
7	126	136	165	8	30	54
8	143	150	151	6	27	49
9	134	164	152	4	26	48
10	141	144	174	6	27	50
11	146	144	164	5	24	44
12	148	153	169	8	26	50
13	131	165	171	4	28	52
14	122	129	160	3	3	50
15	142	125	165	4	25	49
16	146	148	144	7	23	50
17	155	177	164	4	22	48

Ventilated Premature Infants			
Patient	Day 0 Oxygenation index	Days of ventilation	Days of Nasal CPAP
1	67	4	0
2	2	27	0
3	2	1	8
4	2	3	1
5	4	2	0
6	10	3	1
7	4	3	0
8	3	1	1
9	2	1	0
10	3	1	0
11	10	21	0
12	2	8	0
13	6	17	0
14	3	2	1
15	10	3	0
16	25	4	0
17	26	4	0

Ventilated Premature Infants			
Patient	Days of supplemental oxygen	Discharged in Supplemental oxygen	Total days of respiratory support
1	4	No	8
2	47	Yes	74
3	61	Yes	70
4	61	Yes	65
5	44	Yes	46
6	0	No	4
7	1	No	4
8	0	No	2
9	0	No	1
10	0	No	1
11	70	Yes	91
12	80	Yes	88
13	15	No	32
14	0	No	3
15	30	No	33
16	0	No	4
17	3	No	7

Ventilated Premature Infants				
Patient	Chronic lung disease and/or death	Required Inotropic support	Worst Grade of intraventricular haemorrhage	Died before discharge
1	Yes	Yes	4	yes
2	Yes	No	0	no
3	Yes	No	1	no
4	Yes	No	1	no
5	Yes	Yes	1	no
6	No	No	0	no
7	No	No	4	no
8	No	No	2	no
9	No	No	0	no
10	Yes	No	0	yes
11	Yes	No	1	no
12	Yes	No	0	no
13	Yes	Yes	4	yes
14	No	No	0	no
15	No	Yes	0	no
16	No	No	0	no
17	No	Yes	0	no

Ventilated Premature Infants						
Patient	Systolic Volume, mL/kg			Diastolic Volume, mL/kg		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	0.98	0.81	0.80	1.59	0.94	1.25
2	1.10	0.72	0.72	1.92	1.54	1.71
3	0.81	0.72	0.45	1.65	1.60	1.30
4	0.83	0.70	0.67	1.48	1.38	1.58
5	1.06	0.77	0.47	1.65	1.64	1.22
6	0.48	0.53	0.54	1.25	1.21	1.51
7	0.86	0.56	0.33	1.62	1.73	0.79
8	0.51	0.55	0.36	1.46	1.25	1.29
9	0.66	0.60	0.39	1.92	1.32	1.83
10	0.55	0.54	0.37	1.44	1.62	1.27
11	0.80	0.53	0.40	1.76	1.49	1.60
12	0.71	0.49	0.52	1.54	1.65	1.19
13	0.91	0.63	0.82	1.34	2.06	1.89
14	0.77	0.71	0.30	1.37	1.81	1.35
15	0.67	0.87	0.39	1.51	1.66	0.80
16	1.01	0.48	0.44	1.86	1.33	1.12
17	0.60	0.46	0.48	1.16	0.99	1.65

Ventilated Premature Infants						
Patient	Stroke Volume, mL/kg			Ejection Fraction		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	0.61	0.13	0.45	0.38	0.14	0.36
2	0.82	0.82	0.99	0.43	0.53	0.58
3	0.84	0.88	0.86	0.51	0.55	0.66
4	0.65	0.68	0.91	0.44	0.49	0.58
5	0.59	0.88	0.75	0.36	0.53	0.62
6	0.78	0.68	0.97	0.62	0.56	0.64
7	0.76	1.17	0.45	0.47	0.68	0.58
8	0.96	0.70	0.93	0.65	0.56	0.72
9	1.26	0.72	1.44	0.66	0.55	0.79
10	0.89	1.08	0.90	0.62	0.67	0.71
11	0.96	0.97	1.21	0.54	0.65	0.75
12	0.83	1.16	0.67	0.54	0.70	0.56
13	0.43	1.43	1.08	0.32	0.69	0.57
14	0.60	1.10	1.05	0.44	0.61	0.78
15	0.84	0.80	0.41	0.56	0.48	0.52
16	0.85	0.85	0.68	0.46	0.64	0.61
17	0.56	0.53	1.17	0.48	0.53	0.71

Ventilated Premature Infants						
	Right Ventricular Output, mL/kg/min			Diameter of Ductus Arteriosus, cm		
Patient	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
1	97	22	70	0.18	0.11	0
2	129	113	140	0.3	0	0
3	117	111	141	0.19	0	0
4	87	88	139	0.25	0.14	0.25
5	99	145	128	0.12	0	0
6	120	94	132	0.14	0	0
7	96	159	75	0.22	0	0
8	137	105	140	0.17	0	0
9	169	119	218	0.22	0	0
10	125	155	156	0.13	0	0
11	140	139	198	0.16	0	0
12	123	177	113	0.15	0	0
13	56	236	184	0.16	0	0
14	73	141	168	0.25	0	0
15	120	99	68	0.09	0	0
16	125	125	98	0.23	0.19	0.11
17	86	94	192	0.18	0.15	0

Hypotensive Ventilated Premature Infants				
Patient	Sex	Gestation, weeks	Birth Weight, kg	Mode of Delivery
1	male	28	1.278	vaginal
2	female	24	0.560	caesarean
3	female	26	0.984	caesarean
4	female	27	1.244	vaginal
5	male	27	1.078	vaginal
6	male	26	0.910	vaginal
7	male	27	0.828	caesarean
8	female	24	0.610	caesarean

Hypotensive Ventilated Premature Infants				
Patient	Cord pH	Cord BE	Apgar@1	Apgar@5
1	7.13	-3.0	6	9
2	7.33	-3.6	2	7
3	7.29	-1.4	2	4
4	7.39	-0.1	3	7
5	7.37	-3.0	5	8
6	7.32	-9.9	3	7
7	7.27	-7.5	1	6
8	7.14	-1.0	2	3

Hypotensive Ventilated Premature Infants			
Patient	Oxygenation index	Days of ventilation	Days of Nasal CPAP
1	4	2	0
2	6	17	0
3	11	34	1
4	10	3	0
5	26	4	0
6	4	5	1
7	6	4	0
8	28	1	0

Hypotensive Ventilated Premature Infants			
Patient	Days of supplemental Oxygen	Discharged in Supplemental oxygen	Total days of respiratory support
1	44	Yes	46
2	15	No	32
3	42	Yes	77
4	30	No	33
5	3	No	7
6	10	No	16
7	0	No	1
8	0	No	2

Hypotensive Ventilated Premature Infants				
Patient	Chronic lung disease and/or death	Required Inotropic support	Worst Grade of intraventricular haemorrhage	Died before discharge
1	Yes	Yes	1	no
2	Yes	Yes	4	yes
3	Yes	Yes	1	no
4	No	Yes	0	no
5	No	Yes	0	no
6	No	Yes	2	no
7	Yes	Yes	0	yes
8	Yes	Yes	2	yes

Hypotensive Ventilated Premature Infants					
Patient	Age in Hours	Heart Rate		Mean Arterial Blood Pressure, mmHg	
		Pre	Post	Pre	Post
1	6	160	169	24	43
2	4	131	148	21	35
3	24	156	190	21	30
4	4	125	165	30	35
5	4	155	177	39	72
6	14	137	154	23	28
7	22	134	146	16	21
8	12	160	180	22	30

Hypotensive Ventilated Premature Infants						
	Systolic Volume, mL/kg		Diastolic Volume, mL/kg		Stroke Volume, mL/kg	
Patient	Pre	Post	Pre	Post	Pre	Post
1	1.06	0.77	1.65	1.64	0.59	0.88
2	1.05	0.82	1.55	1.68	0.50	0.86
3	1.19	0.64	1.65	1.08	0.46	0.44
4	0.87	0.39	1.66	0.80	0.80	0.41
5	0.60	0.46	1.16	0.99	0.56	0.53
6	1.60	1.07	2.70	2.18	1.10	1.11
7	0.80	0.70	1.26	1.39	0.46	0.69
8	1.93	1.05	2.69	1.74	0.75	0.69

Hypotensive Ventilated Premature Infants				
	Ejection Fraction		Right Ventricular Output, mL/kg/min	
Patient	Pre	Post	Pre	Post
1	0.36	0.53	94	148
2	0.32	0.51	66	127
3	0.28	0.41	71	83
4	0.48	0.52	99	68
5	0.48	0.53	86	94
6	0.41	0.51	151	171
7	0.37	0.50	61	101
8	0.28	0.40	121	124

APPENDIX SIX

PUBLICATIONS

Clark, S.J., Yoxall, C.W., Subhedar, N.V. Right Ventricular Performance in Hypotensive Preterm Neonates Treated with Dopamine. *Pediatric Cardiology* 2001 **In Press**

Abstract

Introduction: Systemic hypotension with left ventricular dysfunction is a common complication of neonatal respiratory distress syndrome and is often treated with inotropic agents. Although pulmonary hypertension with elevated pulmonary vascular resistance is also an important pathophysiological finding in respiratory distress syndrome, the effect of inotropes on the right ventricle has not been studied. The aim of this study was to assess changes in right ventricular dimensions and function with inotropic therapy in hypotensive preterm infants.

Methods: Hypotensive neonates with respiratory distress syndrome were studied before and one hour after the initiation of a dopamine infusion. Right ventricular performance was assessed by two dimensional echocardiography using the ellipsoid approximation method.

Results: Eight hypotensive neonates were recruited with a median (interquartile range) gestation of 27 (26 to 27) weeks. Right ventricular end systolic volume fell significantly from a median (interquartile range) of 1.06 (0.81 to 1.50) to 0.73 (0.51 to 0.99) mL/kg, $p<0.01$ one hour following dopamine therapy. Right ventricular end diastolic volume did not change significantly. Right ventricular ejection fraction increased significantly from 0.36 (0.29 to 0.46) to 0.51 (0.43 to 0.53), $p<0.01$. There was a trend toward an increase in right ventricular output from 90 (67 to 115) to 112 (86 to 143) mL/kg/min, $p=0.07$.

Conclusions: Dopamine increases right ventricular ejection fraction through a reduction in right ventricular end systolic volume.

Keywords: right ventricle, ventricular volume, neonate, newborn infant, human, dopamine, hypotension

Clark, S.J., Yoxall, C.W., Subhedar, N.V. Right Ventricular Volume Measurements in Healthy Term and Preterm Neonates. *Archives of Disease in Childhood* 2001 **In Press**

Abstract

Objective: Pulmonary hypertension is associated with worse perinatal outcomes in infants with respiratory disorders. In these infants right ventricular dysfunction may result in poor pulmonary blood flow. The objective of this study was to evaluate the practicability and repeatability of echocardiographic measurements of right ventricular volume in healthy term and preterm neonates, and to follow changes in right ventricular volumes over the first two days of life.

Methods: Serial echocardiographic examinations were performed on day 0, 1 and 2 on healthy term and preterm neonates. Two methods of estimating right ventricular volumes were assessed: the ellipsoid approximation and Simpson's stacked discs methods. Systolic and diastolic volumes on days 1 and 2 were compared with baseline values on day 0. Term and preterm volumes were compared at the same time points.

Results: 35 infants were recruited, 18 term and 17 preterm. Right ventricular volumes were significantly lower on day 1 and day 2 compared with baseline in both term and preterm infants. Median (interquartile range) end systolic and diastolic volumes for term infants on days 0, 1 and 2 were 1.04 (0.88-1.44), 0.82 (0.70-1.03), 0.92 (0.72-0.97) mL/kg and 2.21 (2.10-2.75), 2.05 (1.81-2.38), 1.91 (1.81-2.13) mL/kg, respectively. In preterm infants the values were 1.09 (0.91-1.16), 0.72 (0.54-0.91), 0.61 (0.54-0.76) mL/kg and 2.09 (1.71-2.25), 1.47 (1.23-1.98), 1.43 (1.22-1.78) mL/kg, respectively.

Conclusions: Right ventricular volume decreases over the first two days of life in healthy term and preterm infants.