REFERENCING ECHOCARDIOGRAPHIC MEASUREMENTS FOR PREMATURE AND LOW-BIRTH WEIGHT INFANTS

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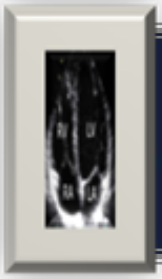

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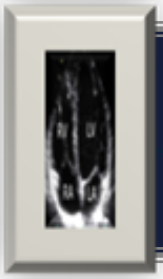
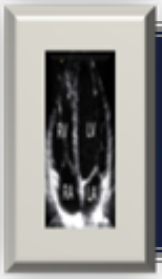


DECLARATION OF INDEPENDENT WORK

I, Salomi Jacobs, do hereby declare that this research project submitted to the Central University of Technology for the degree MAGISTER TECHNOLOGIAE: CLINICAL TECHNOLOGY is my own independent work that has not been submitted before to any institution by me or any other person in fulfillment of the requirements for the attainment of any qualification.

S Jacobs **Date**



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FIRSTLY OF ALL, I WISH TO DEDICATE THIS TO MY FATHER,

HENRI JACOBS, (05/02/1955- 29/07/2005),

AND THANK HIM FOR HIS LOVE FOR MEDICINE AND THIRST FOR KNOWLEDGE, THAT I PROUDLY INHERITED, AND HIS CONSTANT LOVE AND BELIEF, IN ME. I WOULD LIKE TO THANK HIM, WHO GAVE ME THE ABILITY AND THE OPPORTUNITY TO COMPLETE THIS DISSERTATION.

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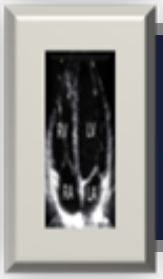


SUMMARY

Introduction: Reference ranges for cardiac measurement are available for adults, children and term infants but the same cannot be said for preterm or small for gestational age (SGA) infants surviving as a result of modern intensive care units.

No published data of reference ranges for preterm infants exists for the South African population. Infants with congenital heart disease are twice as likely to be small for their gestational age and these reference ranges may affect clinical management decisions, therapeutic response and prognosis of these neonates. The aim was thus to establish reference ranges for cardiac dimensions and functional values for preterm and low birth weight infants for central South Africa and compare them with international standards.

Methods: A total of 290 infants of less than 34 weeks of age and weighing less than 2500g at birth were examined during a twelve month period by echocardiography during the first 0-28 days of life. The study assessed normative cardiac measurements divided in M-Mode, 2-D and functional measurement for these infants in 3 weight groups.

Exclusion criteria were applied to any condition affecting the size and functionality of the cardiac system. The following dimensions were measured: Standard M-Mode values for the left ventricle, 2D measurements of valve mitral and tricuspid orifices, as well as functional assessments including Shortening fraction (SF %), Ejection fraction (EF %), and Muscle performance Index (MPI)-index of the Left and Right ventricle. Measurements were done by the leading edge methodology following the ASE recommendations.
A longitudinal study was also done to examine changes in these indices over the first month- on day 14 and day 28 of life. Interobserver differences were calculated for the variability between measurements of a single scan- 25 babies were re-measured and produced good repeatability.

Results: 290 infants were included to produce Referance ranges of measurements (means and standard deviations) for 3 weight groups namely: <0.999g, 1000-1499g, and 1500g – 2500g.

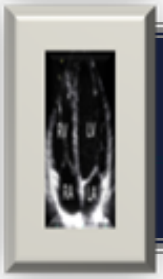
The gestational age's ranges between 26-38 weeks with a median of 31 weeks, gender distribution was almost equal with a slight female preponderance. Body surface area ranged from a minimum from 0.076 m^2 and a maximum of 0.184 m^2, the body weight ranged between a minimum of 690g and a maximum of 2500g with a median of 1360g.

Discussion: The left ventricular diastolic and systolic, interventricular septum, posterior wall, aortic and left atrium dimensions showed a proportionate increase in diameter with an increase in body weight There were no differences in cardiac dimensions between Small for Gestational age" (SGA) versus "Average for Gestational age" (AGA). Gender and race played no role in any functional measurements or with the cardiac sizes. Weight correlated well with BSA and the data suggest that weight only can be used to develop tables for clinical use.

Cardiac chambers increased with BSA and weight and functional measurements stayed the same throughout the weight groups. Systolic and global functions were remarkably similar and constant throughout weight categories. . The longitudinal study also confirmed that the values are applicable to all low birth weight infants up to 28 days of age.

Differences existed between some of the average South African infant's cardiac chambers and international values. The Inter Ventricular Septum (IVS) and Posterior Wall (PW) measured thicker and the Left Atrium larger. This could be due to numerous factors that should be investigated further.

Conclusion: The study emphasized the profound effect of growth and weight gain on the cardiac structure and that population specific reference values should therefore be developed and used.



OPSOMMING

Inleiding: Kardiale verwysings waardes vir kardiale metings is beskikbaar vir volwassenes, kinders en volterm babas. Dieselfde kan nie gesê word vir vroeggebore of klein vir swangerskapsduur babas wat oorleef as gevolg van moderne intensiewe sorg eenhede nie. Geen gepubliseerde data vir hierdie groep babas bestaan vir die Suid-Afrikaanse bevolking nie. Babas met kongenitale hartsiektes is twee keer meer geneig om klein te wees vir hulle gestasie-ouderdom. Hartgroottes beinvloed kliniese besluitneming t.o.v. terapeutiese beplanning asook prognose van hierdie groep babas.

Die doel van hierdie studie was die daarstelling van verwysingswaardes vir hartgroottes en fuksies vir vroeggebore en lae geboortegewig babas woonagtig in sentraal Suid-Afrika en dit te vergelyk met internasionale verwysingswaardes.

Metodes: 'n Totaal van 290 babas jonger as 34 weke met ‘n gewig van minder as 2500g by geboorte is gedurende 'n tydperk van twaalf maande met behulp van eggokardiografie ondersoek gedurende die eerste 0-28 lewensdae.

Die studie het normale kardiale en funksionele afmetings vir babas in 3 verskillende gewigs groepe bepaal. Enige veranderlike wat die grootte en die funksie van die kardiale stelsel kon beinvloed is as uitsluitings kriteria toegepas. Die volgende afmetings is bepaal: Standard M-mode van die linker ventrikel, 2D-mates van die mitraal en trikuspidale klep openinge, sowel as funksionele assessering, bestaande uit verkortings fraksie (SF%), uitwerpfraksie (EF%), asook globale miokard werksverigtings indeks(MPI) van die linker en regter ventrikels.

Metings het voldoen aan ASE aanbevelings.'n Longitudinale studie is ook gedoen om die veranderinge in hierdie waardes te ondersoek oor die eerste maand van lewe. Interondersoeker variasie is ook bereken ten einde herhaalbaarheid van resultate te bevestig.

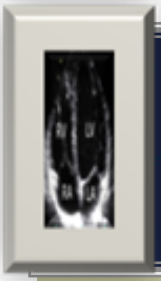
Resultate: 290 babas is ingesluit om verwysings waardes van metings (gemiddeldes en standaardafwykings) vir die volgende drie gewigsgroepe te bepaal naamlik: <0.999g, 1000-1499g, en 1500g - 2500g.

Die gestasie-ouderdom het gewissel tussen 26-38 weke met 'n mediaan van 31 weke. Geslag verspreiding was byna gelyk met effens meer vroulike babas. Liggaams oppervlak het gewissel vanaf 'n minimum van 0,076 m^2 tot 'n maksimum van 0,184 m^2, liggaams gewig het gewissel van 690g tot 2500g met 'n mediaan van 1360g.

Bespreking: Die M-mode hart afmetings het 'n proporsionele toename in deursnee met 'n toename in liggaamsmassa getoon. Sistoliese en globale funksies was merkwaardig konstant oor al die gewigs kategorieë. Daar was geen verskille in die hart afmetings vir klein vir gestasie-ouderdom teenoor normaal vir gestasie-ouderdom nie. Geslag en ras het geen rol gespeel in die funksionele metings of met hart groottes nie. Gewig het byna ‘n perfekte korrelasie met liggaams massa oppervlak getoon wat daarop dui dat enige een van die twee gebruik kan word.

Die longitudinale studie het ook bevestig dat hierdie afmetings van toepassing is op alle lae geboortegewig babas vanaf dag een tot en met ouderdom van 28 dae. Subtiele verskille is gevind tussen sommige Suid-Afrikaanse babas se hart kamer afmetings en internasionale waardes. Die inter ventrikulêre septum en posterior wand het dikker gemeet en die linker atrium asook aorta groter. Verskeie faktore kan hiertoe lei en moet verder ondersoek word.

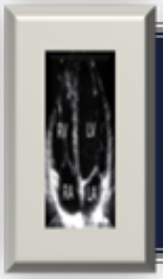
Gevolgtrekking: Ten slotte beklemtoon hierdie studie die diepgaande effek van groei en gewigstoename op die hart grootte en funksies asook die feit en belang dat bevolking spesifieke verwysing waardes ontwikkel moet word.



LIST OF DEFINITIONS

Ejection Fraction (EF)	**"The volume of blood ejected from the ventricle during each systole can be expressed as a percentage of the end- diastolic volume. This gives the ejection fraction of the heart. The normal range for the left ventricle ejection fraction is between 52% - 75% (Silverman, 1993).**
Shortening fraction (SF)	**"Represents the transverse diameter fractional shortening of the left ventricle at the level of the mitral valve and are generally considered as a very reliable index of left ventricular systolic performance (Silverman, 1993).**
Left ventricle end- diastolic diameter (LVEDD)	**"Left ventricle internal diameter at end – diastole" (Silverman, 1993).**
Left ventricle end systolic diameter (LVESD)	**"Left ventricle internal diameter at the end – systole" (Silverman, 1993).**
M-mode Echocardiography	**"In the M-mode format, the B- Line sweeps across the face of a cathode ray tube. Because of the persistence of the phosphor of the tube, the B-mode dots leave a trail as they move. This trail depicts the motion of the intra cardiac structure relative to time, also known as time- motion presentation" (Silverman, 1993).**
Hemodynamic	**"Hemodynamic refers to the investigation of the physical principles of blood flow and the circulation" (Silverman, 1993).**
Premature birth	**"Refers to the birth of an infant that haven't yet reached gestational maturity" (Godfrey & Baum 1979; Subramanian, 2009).**
Low birth weight (LBW) infants	**"Infants (less than 2500g) who are mostly but not exclusively, preterm babies" (Godfrey & Baum 1979; Subramanian, 2009).**

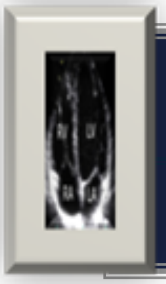
Very Low Birth Weight (VLBW) infants	**"Infants (less than 1500g) who are mostly but not exclusively, preterm babies" (Godfrey & Baum 1979; Subramanian, 2009).**
Extremely Low Birth Weight (ELBW) infants	**"Infants (less than 1000g) who are mostly but not exclusively, preterm babies" (Godfrey & Baum 1979; Subramanian, 2009).**
Small for Gestational Age (SGA)	**"Defined as babies whose birth weight lies below the 10th percentile for a specific gestational age, they may be full term or preterm infants" (Goldenberg *et al.*, 2008) and who are classified as infants with a low birth weight.**
Myocardial Performance Index (MPI)	**"Is a non-invasive, quantitative, Doppler-based measurement of global cardiac function, which integrates systolic and diastolic function (Tei, Ling, Hodge, Bailey, Oh, Rodeheffer, Tajik & Seward, 1995).**
Intrauterine Growth Retardation (IUGR)	**When fetal size is less than expected, the condition is known as intrauterine growth retardation (IUGR) or also known as fetal growth restriction (FGR) (Godfrey & Baum 1979).**
Ballard Score	**Gestational age is determined by the Ballard Score (Ballard, Khoury, Wedig, Wang, Eilers-Walsman & Lipp, 1991). The method uses both neurological and external features to determine gestational age. Each feature is given a score and these scores are added up to give a final score (Appendix E).**
Average for gestational age (AGA)	**"Defined as babies whose birth weight is within the normal percentiles for a specific gestational age, they may be full term or preterm infants" (Godfrey & Baum 1979).**



LIST OF ACRONYMS

%	Percentage
=	Equals
>	More than
2D	Two – dimensional
AGA	Average for gestational age
ASE	American Society of Echocardiography
BMI	Body Mass Index
BSA	Body surface area
Cm	Centimeters
CO^2	Carbon dioxide
ECG	Electro cardio graph
ELBW	Extremely low birth weight
et al.	et alii (and others)
g	Gram
h	Hour
HMD	Hyaline membrane disease
IUGR	Intra uterine growth restriction
IVC	Inferior vena cava
IVS	Interventricular Septum
kg	Kilogram
LA	Left atrium
LBW	Low birth weight
LV	Left ventricle
LVEDD	Left ventricle end diastolic diameter
LVEF	Left ventricle Ejection fraction
LVESD	Left ventricle end systolic diameter
m^2	square meter

mm	**Millimeter**
M-mode	**Motion mode**
N	**Number of Samples Analyzed**
P	**Statistical significance**
PB	**Preterm birth**
PDA	**Patent ductus arteriosus**
PW	**Posterior Wall**
RDS	**Respiratory distress**
RV	**Right ventricle**
SF	**Shortening fraction**
SGA	**Small for gestational age**
SVC	**Superior vena cava**
UFS	**University of the Free State**
VLBW	**Very low birth weight**



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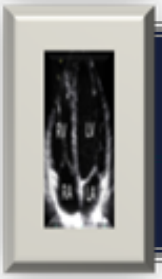

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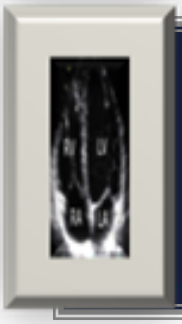


CHAPTER 1

INTRODUCTION

The recognition and identification of serious cardiac diseases in the newborn is challenging (Godfrey & Baum 1979; Moss & Adams 1968). Major structural heart and pulmonary diseases may have profound effects on cardiac chambers and sizes. The availability and usefulness of echocardiography has fostered its popularity as a diagnostic test. A major advantage of echocardiography in the assessment of fragile, unstable premature or low birth weight infants is the fact that it's non-invasive, easy to use and has no known risks or side effects (Silverman, 1993). Linear measurements from M-Mode and 2D images have proven to be reproducible with low intra-observer and inter-observer variability (Godfrey & Baum 1979).

The assessment of cardiac chamber dimensions, great arteries and veins are important to distinguish abnormal dimensions from normal, especially in children with dysfunction where the heart chambers may be hypoplastic or enlarged (Moss & Adams 1968).

The importance of echocardiography, to provide hemodynamic information has markedly increased. Doppler flow studies provide direct assessment of blood flow in the cardiovascular system, and this can provide useful information concerning intra cardiac pressures and pressure gradients (Godfrey & Baum 1979; Moss & Adams 1968).

An understanding of fetal hemodynamic as well as the acute and chronic changes that occur with transition to the newborn circulation are important for the care of normal newborns and are crucial for the recognition, diagnosis, and management of a newborn with significant congenital heart disease (Lundstrom, 1974; Moss & Adams 1968). The premature cardiovascular system in preterm infants often seems unstable and fragile, especially in the early neonatal period. The myocardium of preterm infants can easily be influenced by hypoxia and ischemia, resulting in systemic and pulmonary hypo-perfusion. In the critically ill, very low birth weight infants, reduced left ventricular function, decreased left ventricular output and persistence of pulmonary hypertension have been reported (Lundstrom, 1974; Moss & Adams 1968).

Fetal right ventricular function differs markedly from that of the adult in several important aspects. Before birth, the ductus arteriosus allows the fetal heart to function as two pumps in parallel, with the dominant right ventricle (RV) pumping double the volume of blood than the left ventricle (LV). Only a small portion of

RV output passes into the pulmonary vascular bed (8-10%), whereas the majority of RV output bypasses the fetal lung and flows into the aorta via the ductus arteriosus in the near term fetus (Moss & Adams 1968).

Pulmonary blood flow increases up to 10 fold within minutes of birth as pulmonary vasculature resistance decreases to 10% of the fetal level. Failure of the newborn to progress naturally through these transitions, as may occur with premature birth or persistent pulmonary hypertension, may result in ventricular vascular interactions that may be detrimental (Godfrey & Baum 1979; Moss & Adams 1968).

Infants with congenital heart disease are approximately twice as likely to be small for gestational age and this may affect clinical management decisions, therapeutic response and prognosis of these neonates (Godfrey & Baum 1979; Chesler, 1986;). Reference echocardiographic values for full term infants have been well established [Roge, Silverman, Hart & Ray (1978); Walther, Siassi, King & Wupy (1986); Tan, Silverman, Hoffman, Legas & Schmidt (1992); Skelton, Gill & Parsons (1998)] but the same cannot be said for preterm or small for gestational age (SGA) infants. Internationally, some series exists [Roge *et al*., (1978); Walther *et al*.,(1986); Tan *et al*.,(1992) and Skelton *et al*., (1998], but they are usually small, and none exist for SGA babies. Of note, no published data of reference ranges for preterm infants exists for the South African population.

The aim of this study was to establish reference echocardiographic values for premature & low birth weight infants, based on cross sectional echocardiographic measurements.

CHAPTER 2

LITERATURE REVIEW

2.1 EPIDEMIOLOGY AND CLASSIFICATION OF PREMATURE AND LOW-BIRTH WEIGHT INFANTS

A "premature" infant can be defined as one that has not yet reached the level of mature development, and is born before 37 weeks gestational age (Matthew & MacDorman 2006). Gestational age is determined by the Ballard Score (Ballard, Khoury, Wedig, Wang, Eilers-Walsman & Lipp, 1991). The method uses both neurological and external features to determine gestational age. Each feature is given a score and these scores are added up to give a final score (Appendix E). Premature birth, commonly used as a synonym for preterm birth, refers to the birth of an infant that haven't yet reached gestational maturity (Godfrey & Baum 1979; Subramanian, 2009). Premature infants are at greater risk for short and long term complications, including disabilities and impediments in growth and mental development. Significant progress has been made in the care of premature infants, but not in reducing the prevalence of preterm birth (Goldenberg, Hauth & Andrews 2000; Subramanian, 2009).

Preterm birth is still a major cause of neonatal mortality in developed countries. Internationally, it is estimated that in 2005, 9.6% of all births were preterm which translates to about 12.9million preterm births (Bulletin of the World Health Organization 2010).

No data have been published on the global incidence of preterm birth. Preterm birth rates from developed countries, such as the United Kingdom, the United States and Scandinavian countries, have shown a dramatic rise over the past 20 years (Bulletin of the World Health Organization, 2010).

Factors possibly contributing to but not completely explaining this upward trend, include increased rates of multiple births, greater use of assisted reproduction techniques, increases in the proportion of births among women over 34 years of age and changes in clinical practices, such as greater use of elective Caesarean section (Bulletin of the World Health Organization, 2010).

About 0.5 million preterm births occurred in Europe and the same number in North America, while 0.9 million occurred in Latin America and the Caribbean. The highest rates occurred in Africa and North

America, where 11.9% and 10.6%, respectively, of the births were preterm. Europe, where 6.2% of the births were preterm, had the lowest rate (Bulletin of the World Health Organization, 2010).

Approximately 85% of this burden is concentrated in Africa and Asia, where 10.9 million births are preterm. The analysis shows that the burden of preterm birth is disproportionately concentrated in Africa and Asia (31% and 54%, respectively; Bulletin of the World Health Organization, 2010).

Clearly, different risk factors play a role in the high rates of preterm births indifferent regions. In North America, the increasing age of women giving birth, leads to more maternal complications and Caesarean sections, and explain the high preterm birth rates. An increase in multiple pregnancies may be the other contributing factor (Bulletin of the World Health Organization, 2010).

In Africa, the high prevalence of preterm births can probably be attributed to intrauterine infection, suboptimal maternal care, or inadequate drug availability and distribution. Due to the devastating effects of preterm births the identification of preventable causes, should be a top priority in the developing world (Bulletin of the World Health Organization, 2010).

According to United Nations International Children's Emergency fund (UNICEF), 22% of all low- birth weight infants born in developing countries are born in Africa. They state that the number of low-birth weight infants is more than double the number born in developed regions (UNICEF, 2009: Online).

South Africa is rated at a level of 14.6 % for the private sector and the percentage may increase to as much as 25% affecting dominantly the lower income group of the public sector (Statistics South Africa, 2011: Online).

2.2 REASONS CONTRIBUTING TO PRETERM BIRTH (PB)

The cause for PB is in many situations elusive and unknown. Numerous factors appear to be associated with the development of PB, making the reduction of PB a challenging proposition (Goldenberg *et al*., 2008).

a) **Spontaneous**

About forty to forty–five percent of premature infants are due to spontaneous PBs that follows preterm labour and 25-30% premature infants are born due to premature rupture of membranes (Krupa, Faltin, Cecatti & Souza, 1994).

b) **Natural response to infections**

The exact causes of spontaneous premature membrane rupture are not fully understood. Literature suggests that many cases are triggered by the body's natural response to certain infections including those involving amniotic fluid and fetal membranes. However, in about half of all cases of premature births, no causes can be demonstrated (Krupa *et al*., 1994).

c) **Obstetrical**

The remaining 30-35% are PBs induced for obstetrical reasons (obstetricians may have to deliver the baby preterm because of a deteriorating intrauterine environment (i.e. infection, intrauterine growth retardation) or significant endangerment of maternal health (e.g. pre-eclampsia; Goldenberg *et al*., 2008).

2.2.1 GLOBAL PERCENTAGES OF PREMATURE INFANTS CLASSIFIED ACCORDING TO GESTATIONAL SIZE:

- 5% of PBs occur at less than 28 weeks (extreme prematurity),
- 15% at 28-31 weeks (severe prematurity),
- 20% at 32-33 weeks (moderate prematurity) and
- 60-70% at 34-36 weeks (near term) (Subramanian, 2009).

2.2.2 CLASSIFICATION BY GESTATIONAL AGE AND WEIGHT

Since weight is easier to determine than gestational age, and weight generally correlates with gestational age, infants may be underweight for other reasons than a preterm delivery.

Low birth weight (LBW) infants (less than 2500g) are mostly but not exclusively, preterm babies. Very Low Birth Weight (VLBW) infants have a birth weight of less than 1500g and Extremely Low Birth Weight (ELBW) infants weigh less than 1000g. Almost all neonates in these latter two groups are born prematurely (Goldenberg *et al*., 2008; Subramanian 2009: Online).

2.2.3 SMALL FOR GESTATIONAL AGE (SGA)

Small for Gestational Age (SGA) infants are classified as infants with a low birth weight, although they may be full term or preterm infants (Lundstrom, 1974; Larsen William, 2001). Therefore, these infants do not fall into the reference categories specified for the premature infant. SGA infants may have a low weight, but are older according to gestational age (they are thus more mature). They can neither be evaluated on their gestational age, nor weight, because they are smaller in the weight categories compared to their peers (Lundstrom, 1974; Larsen William, 2001).

2.2.3.1 CHARACTERISTICS OF SGA INFANTS

(a) The infant appears thin and wasted; their skin is loose and dry.

(b) There is little subcutaneous fat; their face appears shrunken and wrinkled.

(c) The length and head size may be normal but the head looks really big in comparison to the rest of the body (Lundstrom, 1974)

2.2.3.2 CONDITIONS THAT OCCUR MORE FREQUENTLY IN THE SGA INFANT

(a) **Asphyxia** (a condition arising when the body is deprived of oxygen, causing unconsciousness or death, suffocation). They tolerate labour poorly due to the decreased metabolic stores of carbohydrates and often needs resuscitation at birth (Lundstrom, 1974; Godfrey & Baum, 1979; Larsen William, 2001).

(b) **Meconium aspiration** (when a newborn inhales fecal discharge during labour or delivery).
The fetus inhales amniotic fluid containing meconium, or it occurs when the neonate takes his first breath and can lead to atelectasis, pneumothorax, or pneumonitis (Lundstrom, 1974; Godfrey & Baum, 1979; Larsen William, 2001).

(c) **Hypoglycaemia** (abnormally low blood glucose usually resulting from excessive insulin or a poor diet). This most likely occurs 12 to 48 hours after birth but may also be noted within 6 hours if the infant is severely hypoxic and may lead to neurological damage (Lundstrom, 1974; Godfrey & Baum, 1979; Larsen William, 2001).

(d) **Hypothermia** (a condition in which the core temperature of the body drops below that required for normal metabolism and body functions). The development of hypothermia in the SGA infant can be attributed to the lack of subcutaneous fat (Lundstrom, 1974; Godfrey & Baum, 1979; Larsen William, 2001).

(e) **Polycythemia** (an abnormal increase of haemoglobin in the blood either through reduction of plasma volume or the increase in red cell numbers. It may be a primary disease of unknown cause or a secondary condition linked to respiratory or circulatory disorder). This is frequently seen when the reason for SGA is placental insufficiency (Lundstrom, 1974; Godfrey & Baum, 1979; Larsen William, 2001).

(f) **Congenital anomalies** (involves defects on or damage to a developing fetus, it may be the result of genetic abnormalities, the intrauterine environment, errors of morphogenesis, or a chromosomal abnormality). The genitourinary and cardiovascular systems are most commonly affected in these SGA infants (Lundstrom, 1974; Godfrey & Baum, 1979; Larsen William, 2001).

2.3 THE CIRCULATORY SYSTEM

2.3.1 THE HUMAN FETAL CIRCULATORY SYSTEM

Fetal circulation differs from neonatal, mainly because the lungs are not in use and the fetus obtains oxygen and nutrients from the mother through the placenta and the umbilical cord (Chesler, 1986; Agata, Hiraishi, Oguchi, Misawa, Horiguchi, Fujino, Yashiro & Shimada, 1991; Klabunde, 2005).

The placenta at term carries about 40% of the combined ventricular output (Moss & Adams, 1968; Chesler, 1986). This is augmented by venous return from the lower half of the body to 69% returning via the Inferior Vena Cava (IVC), in contrast to 21% returning via the Superior Vena Cava (SVC) and 3% coronary venous return. At most, 2% of the SVC return crosses the foramen ovale to enter the left atrium which therefore receives 27% of the total output through the IVC and foramen ovale and 7% of the total output as pulmonary venous return. Thus 34% of total cardiac output comes to pass through the left ventricle, whereas, 66% passes through the right ventricle: one third of this originates from the SVC and the remainder from the IVC and coronary sinus. The high fetal pulmonary vascular resistance ensures that only 8 - 10% of the total right ventricle output passes to the lungs, the rest traverses the widened patent ductus arteriosus (Moss & Adams, 1968; Godfrey & Baum, 1979; Chesler, 1986).

Blood from the placenta is carried to the fetus via the umbilical vein. About half of this enters the fetal ductus venosus and is carried to the inferior vena cava, while the other half enters the liver. The branch of the umbilical vein that supplies the right lobe of the liver first joins with the portal vein. The blood then moves to the right atrium of the heart. In the fetus, blood passes from the right atrium to the left atrium through the foramen ovale, thus bypassing pulmonary circulation. The blood flows into the left ventricle from where it is pumped through the aorta into the body. Some of the blood flows from the aorta through the internal iliac arteries to the umbilical arteries, and re-enters the placenta, where carbon dioxide (CO_2) and other waste products from the fetus are taken up and enter the maternal circulation (Moss & Adams, 1968; Chesler, 1986; Klabunde, 2005;).

The ductus is an important structure during fetal life as it allows unloading of the RV and joins the pulmonary trunk to the aorta with a diameter equivalent to the pulmonary artery and larger than the aorta. Premature closure of the fetal ductus will result in an immediate increase in afterload of the RV with resultant hypertrophy, dysfunction, dilation, tricuspid valve regurgitation, papillary muscle stress, and ischemia, sometimes resulting in papillary muscle rupture with flail valve. An increase in pulmonary trunk pressure may change blood flow in the high resistance, fluid filled lungs, this pressure leads to hypertrophy of the media, causing pulmonary hypertension and post natal persistent pulmonary hypertension of the neonate (Gewillig, Brown, De Catte, Debeer, Eyskens, Cossey, Van Schoubroeck, Van Hole & Devlieger, 2009).

Right ventricular function plays a critical role in a number of congenital and acquired cardiac conditions. Accurate measurements of RV function are important in planning treatment and predicting prognosis. Until recently, RV function has attracted less attention than LV function. The main reasons have been due to the lack of understanding of its important role in the circulation and difficulties in assessing its function due to its complex anatomy. The RV has a greater geometrical complexity than the LV, and the RV free wall is heavily trabeculated making edge recognition difficult. Overlap between the RV and other cardiac chambers in some imaging modalities makes reliable volume measurement difficult (Gewillig *et al*., 2009). Compared to the LV, the RV is a thin walled structure under normal conditions. The normal RV is accustomed to a low pulmonary resistance and, hence, low afterload; thus, normal RV pressure is low and RV compliance high. The RV is therefore, sensitive to changes in afterload and alterations in RV size and function are indicators of increased pulmonary vascular resistance and load transmitted from the left sided chambers. Elevations in RV afterload are manifested acutely by RV dilatation and chronically by concentric RV hypertrophy (Lundstrom, 1974; Godfrey & Baum, 1979;).

2.3.2 POSTNATAL CIRCULATORY DEVELOPMENT

An understanding of fetal hemodynamics and the acute and chronic changes that occur with transition to the newborn circulation are important for the care of normal newborns and are crucial to the recognition, diagnosis, and management of the newborn with significant congenital heart disease (Moss & Adams, 1968; Godfrey & Baum, 1979; Silverman, 1993; Goldenberg *et al*., 2008).

a) **Function**

The primary function of the circulatory system of both the fetus and newborn is to deliver nutrients to metabolizing organs. It also has to return deoxygenated blood to the lungs to replenish the oxygen and eliminate the waste product CO_2. In the fetus, the organ responsible for gas exchange is the placenta, and its vascular connections are in a parallel arrangement with the other systemic organs, remote from the pulmonary circulation. In order to supply deoxygenated blood to the placenta and return oxygenated blood to the systemic organs, a series of extra cardiac shunts (ductus venosus, ductus arteriosus) and an intracardiac communication (foramen ovale) are necessary. Following birth, the function of gas exchange is transferred from the placenta to the lungs, and then from the systemic circulation to the pulmonary circulation. The venous and arterial circulations are separated, and not only are the fetal shunts unnecessary, but their persistence may lead to circulatory compromise (Moss & Adams, 1968; Godfrey & Baum, 1979; Larsen William, 2001).

b) **Circulatory Transition**

The transition from the fetal to the neonatal circulation includes the elimination of the placental circulation, lung expansion, and an increase in lung blood flow. In doing so, the entire cardiac output can be accommodated, and closure of the foramen ovale, ductus arteriosus, and ductus venosus can occur (Agata *et al*., 1991; Klabunde, 2005).

Hyaline Membrane Disease (HMD), hypoxemia and acidemia keep the pulmonary pressures high but slightly lower than the aortic pressure. The hypoxemia also keeps the ductus arteriosus patent. Closure is dependent on the rise in Partial Pressure Oxygen pressure (PaO_2). The muscle in the ductus wall constricts when PaO_2 rises. Prostaglandin E, low calcium (Ca), low glucose and high pulmonary artery pressure all tend to keep the ductus patent open, whereas adrenaline and noradrenalin constrict it (Godfrey & Baum, 1979; Chesler, 1986; Klabunde, 2005).

For most structural congenital heart diseases, the fetal shunt pathways allow redistribution of ventricular blood flow so that systemic blood flow is adequate and fetal growth and development is therefore normal. With severe left heart obstruction, the burden of systemic and pulmonary blood flow is transferred to the fetal right ventricle, with reversal of blood flow at the foramen ovale, and systemic blood flow almost entirely transmitted via the ductus arteriosus. This "ductal-dependent" systemic circulation is poorly tolerated in the newborn, because normal closure of the ductus arteriosus progressively decreases systemic blood flow and progresses to circulatory failure and shock. Severe right heart obstruction is well tolerated in the fetus, because the combined fetal cardiac output can be transferred to the aorta, with the ductus arteriosus supplying predominantly lung blood flow. After birth, such "ductal-dependent" pulmonary blood flow can lead to critically low levels of pulmonary blood flow and severe cyanosis following constriction of the ductus arteriosus (Moss & Adams 1968; Chesler 1986; Moore 2006).

c) **Changes in Pulmonary Pressures**

Changes at birth in the infant's vascular system are caused by the termination of placental blood flow and the onset of respiration. The ductus arteriosus closes by muscular contraction of its wall and the amount of blood flowing through the lung vessels increases rapidly. This in turn, raises the pressure in the left atrium. Simultaneously, pressure in the right atrium decreases as a result of interruption of placental blood flow. The septum primum is then pressed against the septum secundum and functionally the oval foramen closes. However, during the first days of life, especially in preterm infants, this closure is reversible. Since the newborn's lungs aren't fully developed, a series of pulmonary factors also influences the circulatory system (Godfrey & Baum, 1979; Agata *et al*., 1991; Moore, 2006).

The mean pulmonary artery pressure in the infant falls from fetal levels of 40–80 mmHg to values between 20-50 mmHg at 6-8h and to 20-35 mmHg at 36h after birth. The pressure usually reaches a level close to that of the adult within 2 weeks of birth but continues to fall slightly more until 6 weeks of age (Godfrey & Baum, 1979; Chesler, 1986).

Decreased alveolar ventilation results in ventilation: perfusion mismatch and pulmonary arteriolar vasoconstriction. Pulmonary vasoconstriction can lead to an increase in right heart volume and pressure, resulting in a shunting of blood back from the right atrium through the patent foramen ovale of the newborn, and directly into the left atrium. Likewise, high pulmonary vascular resistance can result in deoxygenated blood bypassing the lungs and being delivered directly to the systemic circulation, via the ductus arteriosus. Crying by the baby creates a shunt from right to left, which accounts for cyanotic episodes in the newborn (Chesler, 1986; Agata *et al*., 1991; Klabunde, 2005).

d) **Respiration**

When respiration begins at birth, most of the lung fluid is rapidly absorbed by the blood and lymph capillaries, and expelled via the trachea and bronchi during delivery. When the fluid is reabsorbed from the alveolar sac, surfactant remains deposited as a thin phospholipid coating on the alveolar membranes. With air entering alveoli during the first breath, the surfactant coating prevents development of an air-water interface with high surface tension. Surfactant is particularly important to the survival of the premature infant. When surfactant is insufficient the air water (blood) surface membrane tension becomes high, creating the risk that alveoli will collapse during expiration. As a result, respiratory distress syndrome (RDS) develops. The more premature the infant, the more likely RDS will develop due to HMD (Chesler, 1986; Moore, 2006).

RDS which is also known as HMD accounts for approximately 20% of deaths among newborns (Moss *et al*., 1968; Moore, 2006). Infants with RDS and ventilatory insufficiency have elevated levels of Partial Pressure Carbon dioxide ($PaCO_2$) and a low pH. The enzymatic pathways for lecithin synthesis are sensitive to cold, hypoxia and acidemia. Post natal exposure to temperatures less than 35˚C and a pH less than 7.25 causes a rapid fall in the amount of surfactant detectable in the pharyngeal aspirates, thus decreasing the rate of synthesis of surfactant in an *in vitro* lung system by 50% (Moss & Adams, 1968; Moore, 2006).

Importantly, type II alveolar cells that produce surfactant do not mature until between 28 and 32 weeks gestation. The total number of premature alveoli in the full term infant is only 8% of the full adult complement; therefore any infant born before surfactant is present in the alveoli encounters high alveolar surface tension with each breath. This elevated blood pressure in the pulmonary vascular systems may be due to serious respiratory or cardiovascular disease. Premature infants have weak immature chest muscles making it almost impossible for an infant without surfactant to successfully expand the alveoli (Godfrey & Baum, 1979; Chesler, 1986; Agata *et al*., 1991; Klabunde, 2005).

The pulmonary circulation is usually a low pressure, low resistance circulation (Agata *et al*., 1991; Larsen, 2001). Therefore, according to Chesler (1986) the main reasons why pulmonary hypertension occurs are:

(a) Prolonged increase in pulmonary blood flow PDA; left to right shunt.

(b) Increase in pulmonary resistance to flow.

(c) Vasoconstriction (narrowing of the blood vessels resulting from contraction of the muscular wall of the vessels, particularly the large arteries, small arterioles and veins).

When the heart is unable to meet the oxygen and nutrient demands of the body, heart failure can result from either diastolic or systolic dysfunction. When the right ventricle must pump continually against a very high afterload (increased resistance), vascular musculature cells hypertrophies and become stiff. Stiffness of the muscle cells causes a reduction in ventricular compliance, leading to a decrease in stroke volume. Right ventricular end diastolic relaxation and right ventricular end diastolic pressure are elevated and reflected back into the venous system. Because stroke volume and hence blood pressure fall, baro-receptor reflexes are activated (Godfrey & Baum, 1979; Klabunde, 2005; Moore, 2006).

Ultimately, longstanding pulmonary hypertension would cause the right ventricle to fail and long standing systemic hypertension would cause the left ventricle to fail (Godfrey & Baum, 1979; Chesler, 1986).

2.3.2.1 THE UPSTREAM EFFECTS OF RIGHT HEART FAILURE

- Decreased pulmonary flow
- Decreased blood oxygenation
- Fatigue
- Decreased systemic blood pressure due to decreased left heart filling (Moss & Adams, 1968; Klabunde, 2005).

2.3.2.2 THE DOWNSTREAM EFFECTS OF RIGHT HEART FAILURE

Echocardiography is useful in assessing the underlying cause and severity of pulmonary hypertension. The echocardiographic features of pulmonary hypertension (PHT) are seen on a 2-Dimensional Echocardiography and are listed below:

a) Dilated Pulmonary artery (normally the pulmonary artery diameter should not be greater than the aortic diameter).

b) Right ventricle dilatation and/or hypertrophy.

c) Right atrium dilatation.

d) Abnormal interventricular septum motion.

e) Measuring Pulmonary artery systolic pressure using tricuspid regurgitation velocity.

The normal newborn elektrocardiogram (ECG) would be interpreted as showing right ventricular hypertrophy, this effect is even more pronounced in premature infants, since the ECG reflects predominantly the weight of the cardiac chambers. Following birth, the relative weight of the right to the left ventricle falls to its adult value of 40% at around 9 months of age (Godfrey & Baum, 1979).

2.3.3 DIFFERENCES IN INFANT CIRCULATION: PRE TERM VERSUS FULL TERM

The cardiac muscle is immature at birth and heart rate is an important determinant of cardiac output (Godfrey & Baum, 1979). Cardiac output in neonates is high due to high sympathetic tone, especially around the times of birth, and this also explains the high resting heart rate of neonates. By comparing fetal with adult sheep moderator bands or papillary muscles, it has been demonstrated that fetal and neonatal myocardial strips have higher resting tension and lower developed active tension during isometric contraction. This is probably due to the lower proportion of sarcomeres, which is about half of that in the adult (Godfrey & Baum, 1979). Therefore heart rate is an important determinant of cardiac output, if the heart beats faster; there is less filling time, and thus less cardiac output.

Fetal sarcomeres are randomly arranged compared to the parallel arrangement in the adult. The reduction in fetal myocardial contractility is reflected in experiments. However, neonatal cardiac muscle is much less susceptible to anoxia than mature muscle. This probably reflects a greater ability to metabolize anaerobically. There are differences between fetal, neonatal, and adult ventricles. Distensibility though these differences may depend upon the definition of distensibility employed (Godfrey & Baum, 1979), but in general, the fetal heart is less compliant.

Afterload is also a major determinant of cardiac output. The neonatal heart is exquisitely sensitive to increases in systemic or pulmonary vascular resistance which will reduce the cardiac output. The myocardium is dependent on extracellular calcium for contraction and ionized hypocalcaemia is poorly tolerated. These effects are amplified in the heart of the premature infant (Godfrey & Baum, 1979).

Fetal haemoglobin is the main oxygen transport protein in the fetus during the last seven months of development in the uterus and in the newborn until roughly 6 months old. Functionally, fetal haemoglobin differs from adult haemoglobin in that it is able to bind oxygen with greater affinity than the adult form, giving the developing fetus better access to oxygen from the mother's bloodstream. Its oxygen dissociation curve is shifted to the left, meaning that it will take up oxygen at a lower concentration than adult haemoglobin will. This enables fetal haemoglobin to absorb oxygen from adult haemoglobin in the placenta, which has a lower oxygen pressure than the lungs (Chesler, 1986; Larsen, 2001).

2.3.4 INTRAUTERINE GROWTH RETARDATION (IUGR)

When fetal size is less than expected, the condition is known as intrauterine growth retardation (IUGR) also called fetal growth restriction (FGR). These babies are small for gestational age (Steer, 2005) and defined as babies whose birth weight lies below the 10th percentile for a specific gestational age (Goldenberg *et al*., 2008).

IUGR causes both perinatal and neonatal medical complications. Both epidemiological and experimental evidence suggest that IUGR contributes to a wide array of metabolic disorders and chronic diseases in adult life (Steer, 2005).

Low birth weight (LBW) is sometimes incorrectly used synonymously with SGA, defined as a fetus that weighs less than 1000g regardless of gestational age (Sadler, 2006).

CAUSATIVE FACTORS INCLUDE:

- Chromosomal abnormalities (10%).
- Teratogens.
- Congenital infections (rubella, cytomegalovirus, toxoplasmosis, and syphilis).
- Poor maternal health (hypertension and renal and cardiac disease).
- The mother's nutritional status and socioeconomic level.
- Maternal use of cigarettes, alcohol, and other drugs.
- Placental insufficiency and multiple births (e.g. twins, triplets) Sadler, 2006).

One third of babies born with a low birth weight are also small for gestational age. Whether the cardiac size of small for gestational age (SGA) fetuses is smaller or larger than appropriate for gestational age (AGA)

foetuses remains unanswered. Ultrasonic studies have reported that the cardiac dimensions for SGA foetuses can be smaller or greater than AGA infants but are not significantly different (Goldenberg *et al*., 2008).

Fetal growth restriction has the potential to be associated with both growth restriction and enlarged hearts. Two different pathways may account for cardiomegaly in SGA foetuses. Firstly, increased resistance in the systemic and placental circulation typical of fetal growth restriction may lead to an increase in afterload. This over time could result in compensatory myocardial hypertrophy. Ream and co-workers (2008) observed that the cardiomegaly associated with fetal growth restriction was due to hypertrophy of the myocardial free wall. Secondly, longstanding hypoxemia, possibly compounded by an increased oxygen demand of the hypertrophic fetal heart, may lead to cardiac dysfunction and cardiac failure, with a consequent increase of cardiac dimensions in relation to body weight. Hypoxia is frequently present in SGA foetuses and fetal growth restriction is considered one of the mechanisms by which the fetus adapts to hypoxia (Ream *et al*., 2008).

Infants with congenital heart disease are approximately twice as likely to be small for gestational age and this may affect clinical management decisions, therapeutic response and prognosis of these neonates (Ream *et al*., 2008).

2.3.5 FACTORS AFFECTING FETAL GROWTH

There are a number of factors that have an effect on fetal growth and some of these include:

2.3.5.1 MATERNAL FACTORS LEADING TO PLACENTAL INSUFFICIENCY

(a) Maternal weight

Maternal weight plays an important role since obesity increases the risk of medically – indicated preterm birth and very early spontaneous preterm birth. On the other hand being underweight also increases the risk of both preterm birth subtypes (Guayao, Fuller, Bazer, Timothy, Cudd, Cynthia, Menininge & Spencer, 2004).

(b) Maternal age

The mother's age seems to play an important role in optimal fetal growth. If the mother is under the age of 18 or older than 35 the risk of impaired fetal growth escalates *(*Krupa *et al*., 1994).

(c) Nutritional status

The nutritional status of the mother is important for fetal development and a diet low in saturated fat and cholesterol may help reduce the risk of a preterm delivery. Nutrition is the major intrauterine environmental factor that alters expression of the fetal genome and may have lifelong consequences. Alterations in fetal nutrition and endocrine status may result in developmental adaptations that permanently change the structure, physiology, and metabolism of the offspring, thereby predisposing individuals to metabolic, endocrine, and cardiovascular disease in adult life (Guayao *et al*., 2004).

Impaired placental synthesis of nitric oxide, a major vasodilator and angiogenesis factor and polyamines (key regulator of DNA and protein synthesis) may provide a unified explanation for intrauterine growth retardation in response to the two extremes of nutritional problems with the same pregnancy outcome. Maternal malnutrition during gestation reduces placental and fetal growth. Evidence suggests that fetal growth is most vulnerable to maternal dietary deficiencies peri-implantation, during the period of rapid placental development (Guayao *et al.,* 2004). However, maternal over nutrition can retard placental and fetal growth, and may result in fetal growth restriction and increased risk of neonatal mortality and morbidity.

(d) Substance abuse

Toxin exposure (tobacco, alcohol, heroin, and other drugs which can also harm the fetus in other ways) contributes significantly to low birth weight. Chronic increased resistance in the uterine, umbilical and fetal cerebral arteries are associated with mothers that smoke (Albuquergue, Smith, Johnson, Chao & Harding, 2004).

(e) Diabetes

Maternal diabetes (disturbances in carbohydrate metabolism during pregnancy) causes a high incidence of still births, neonatal deaths, abnormally large infants, and congenital malformations. The risk of congenital anomalies in children of diabetic mothers is 3-4 times that for the offspring of non-diabetic mothers (Krupa *et al*., 1994; Goldenberg *et al*., 2008).

(f) Anatomy of the Uterus

Abnormal uterine/cervix cavity for example a short cervix, or the stretching of the uterus or over distension of the uterus, has also been linked to preterm labor and birth. This can be caused by

fibroids, multiple pregnancies (twins, triplets, etc), or even having too much amniotic fluid (polyhydramnios). Woman who has tried to conceive for more than a year before getting pregnant is at a 40% higher risk for premature birth (Krupa *et al*., 1994).

2.3.5.2 FETAL AND PLACENTAL FACTORS

As the fetus increases in size, its nutritional demands increase, causing major changes in the placenta. Foremost is an increase in surface area between the maternal and fetal components to facilitate exchange. The disposition of fetal membranes is also altered as production of amniotic fluid increases.

As a result of the continuous growth of the fetus and expansion of the uterus, the placenta also enlarges. Its increase in surface area roughly parallels that of the expanding uterus, and throughout pregnancy it covers approximately 15% to 30% of the internal surface of the uterus (Sadler, 2006).

The exchange of metabolic and gaseous products between the maternal and fetal bloodstream, such as O_2, CO_2, and carbon monoxide is accomplished by simple diffusion. At term the fetus extracts 20-30ml of oxygen per minute from the maternal circulation, and even a short term interruption of the oxygen supply is fatal to the fetus. Placental blood flow is critical to oxygen supply, since the amount of oxygen reaching the fetus primarily depends on delivery, not diffusion (Sadler, 2006).

Exchange of nutrients and electrolytes, such as amino acids, free fatty acids, carbohydrates and vitamins, is rapid and increases as pregnancy advances. By the end of the forth month, the placenta produces progesterone in sufficient amounts to maintain pregnancy if the corpus luteum is removed or fails to function properly. In addition to progesterone, the placenta produces increasing amounts of estrogenic hormones predominantly estriol, until just before the end of pregnancy. These high levels of estrogens stimulate uterine growth and development of the mammary glands. Another hormone produced by the placenta is somatommamotropin. It is a growth hormone like substance that gives the fetus priority on maternal blood glucose and makes the mother somewhat diabetogenic and it also promotes breast development for milk production (Sadler, 2006).

2.3.5.2.1 Fetal factors

(a) Fetal hypoxia

Fetal hypoxia causes intrauterine growth restriction and low birth weight, and is associated with prematurity, infant mortality and elevated risk of adult cardiovascular disease. High altitude hypoxia

is thought to be responsible for the 100g decrease in birth weight associated with each 1,000 meter increase in elevation of maternal residence. Hypoxia severely compromises the cardiovascular system. Hypoxia induces ventricular dilation and myocardial hypoplasia, decreasing ventricular tissue by 50% (Ream *et al*., 2008).

(b) Drugs

The use of antenatal steroids has largely demonstrated its effectiveness in reducing the incidence of respiratory distress syndrome (RDS). Meta analysis of the clinical trials performed has confirmed its effectiveness when administered to the mother one week before delivery to reduce neonatal mortality, incidence and severity of bronchopulmonary dysplasie (BPD), intracranial haemorrhage (ICH), retinopathy of prematurity (ROP) and necrotizing enterocolitis (NEC)(Krupa *et al*., 1994).

Dexamethazone is often administered to preterm babies during the early neonatal period in order to prevent chronic lung disease and this is known to produce hypertrophy of the left ventricle (Moss & Adams, 1968; Silverman, 1993).

2.3.5.2.2 Placental factors

(a) Perinatal Asphyxia

Perinatal asphyxia, (a rare condition in premature infants) is a medical condition resulting from deprivation of oxygen (hypoxia) to an infant for a long enough period to cause apparent harm. It commonly results from a drop in maternal blood pressure or interference with blood flow to the infant's brain. This may occur due to inadequate circulation or perfusion, impaired respiratory effort, or inadequate ventilation. Perinatal asphyxia happens in 2 to 10 per 1000 newborns that are born at term (Krupa *et al.,* 2006). An infant suffering severe perinatal asphyxia usually has cyanosis, accompanied by poor perfusion, responsiveness, muscle tone, and respiratory effort, as reflected in a low 5 minute Apgar score. A bad degree of asphyxia can lead to cardiac arrest and ultimately death. Hypoxic damage can affect the infant's heart, but brain damage is of most concern for it is least likely to heal completely (Krupa *et al.,* 2006).

2.4 ECHOCARDIOGRAPHY

2.4.1 DEFINITION

Also known as a cardiac ultrasound, echocardiography uses standard ultrasound techniques to image two-dimensional slices of the heart, currently 3D real-time imaging is also available (Silverman, 1993; Otto, 2004; Feigenbaum, Armstrong & Ryan, 2005).

Evaluation of ventricular systolic function is the most important application of echocardiography, so that even when evaluation of systolic function is not the focus of the examination, it plays an essential role in every study (Otto, 2004).

In addition to creating two-dimensional pictures of the cardiovascular system, it can also produce accurate assessment of blood velocity and cardiac tissue at any arbitrary point using pulsed or continuous wave Doppler ultrasound (Silverman, 1993).

This allows for the assessment of cardiac valve areas and function, abnormal communications between the left and right side of the heart, leakage of blood through the valves, and the calculation of cardiac output and ejection fraction (Silverman 1993; Feigenbaum *et al*., 2005).

Echocardiography has been available for the evaluation of cardiac abnormality and function for over 20 years. In fact, it is the most widely used diagnostic test for heart disease and can provide a wealth of helpful information. By assessing the motion of the heart wall echocardiography can help detect the presence and assess the severity of cardiac disease (Silverman, 1993; Otto 2004; Feigenbaum *et al*., 2005).

2.4.2 APPLICATION OF ECHOCARDIOGRAPHY

During a routine echocardiography examination, a transducer (or probe) is placed on the chest wall (or thorax) of the subject, and images are taken through the chest wall. This is a non-invasive, highly accurate and quick assessment of the overall health of the heart. When properly applied, the diagnostic and prognostic utility of echocardiography, are unmatched. Images are displayed on a monitor, and recorded either by videotape or by digital techniques (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

2.4.3 ADVANTAGES OF ECHOCARDIOGRAPHY

Echocardiography has a major advantage when assessing fragile, unstable premature or low birth weight infants for it is a non-invasive, easy to use procedure with no known risks or side effects (Silverman, 1993; Feigenbaum *et al*., 2005). Linear measurements from M-Mode and 2D images have proven to be reproducible with low intra-observer and inter-observer variability (Lang, Bierig, Devereux, Flachskampf, Foster, Pellikka, Picard, Roman, Seward, Shanewise, Solomon, Spencer, Sutton & Stewart, 2005).

2.4.4 DISADVANTAGES OF ECHOCARDIOGRAPHY

Reference ranges for cardiac measurement are available for adults, children and term infants. However, these have not been updated in line with improvements in scanning or extended to include the large numbers of extremely small, premature infants surviving as a result of modern intensive care. Normal values of blood flow velocities for these infants are even less well studied (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

2.4.5 CALCULATIONS OBTAINED FROM ECHOCARDIOGRAPHY

2.4.5.1 M-MODE

2.4.5.1.1 Definition

M-mode is a two-dimensional motion mode echocardiographic view of the heart (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

2.4.5.1.2 Application of M-Mode

By definition, M-mode assessment provides information regarding the size and contractility of the heart along a single line (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

2.4.5.1.3 INFORMATION OBTAINED FROM M-MODE EXAMINATION

- Motion and time which is displayed on the horizontal axis.
- Distance and depth which is displayed on the vertical axis.

2.4.5.1.4 Advantages of M-Mode

The advantage of M-mode echocardiography is the simplicity of measurement. Its high frame rates guarantee superior time resolution. The dimensions of the cardiac chambers, walls and valve leaflets can be easily traced, providing a rapid, accurate and repeatable method for assessing and measuring any changes that occur with growth and development (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

Particularly in the paediatric population where segmental wall motion abnormalities are rare, M-mode values are a good estimate of Left Ventricle performance (Table 2.2; Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

There are also numerous measurements and calculations that can provide indirect evidence of hemodynamic severity of cardiac lesions, and M-mode echocardiography is also able to identify the secondary consequences of the primary hemodynamic pathology (Table 2.1; Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

TABLE 2.1 M-MODE ECHOCARDIOGRAPHIC MEASUREMENTS (adapted from Feigenbaum *et al*., 2005; Otto, 2004; Silverman, 1993)

Cardiac chamber dimensions	➢ Aorta and left atrium ➢ Left ventricle ➢ Right ventricle
Left ventricular systolic function	➢ Fractional shortening ➢ Ejection fraction ➢ Stroke volume and cardiac output ➢ Systolic time intervals of the aortic valve ➢ Mitral E point septal separation
Left ventricle mass	➢ American Society of Echocardiography (ASE) method
Hemodynamic abnormalities pulmonary hypertension	➢ Absent or diminished pulmonary A wave ➢ Mid systolic closure or notching of the pulmonary valve ➢ Alterations in right ventricle systolic time intervals ➢ D-shaped left ventricle
Increased right atrial pressure	➢ Dilated Inferior Vena Cava with lack of collapse ➢ Bowing of interatrial septum toward the left atrium
Increased left atrial pressure	➢ Bowing of interatrial septum towards the right atrium

2.4.5.1.5 Disadvantages of M-Mode

As mentioned before, M-mode assessment provides information regarding the heart's size and contractility along a single line (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).
This may either underestimate the severity of dysfunction if only a normal region is interrogated or can overestimate an abnormality if the M-Mode beam transits exclusively through the wall motion abnormality. Thus, although conceptually simple, M-mode derived linear measurements have the disadvantage of only determining ventricular function along a single interrogation line. In presence of normal geometry and symmetric function, linear measurements provide an adequate assessment of ventricular function. However, they are limited, in acquired heart disease, in which there may be substantial regional variation in function, and are subjected to error with respect to determining true minor–axis dimensions. Two–dimensional imaging allows correction for off-axis heterogeneity of function (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

Available results from other studies on intra-observer and inter-observer variations of echocardiographic measurements are limited. Previous studies on inter-observer variation of echocardiographic measurements have shown different results. Most studies varies within the limits of 10% (Shifan, Ayres, Harris, Bricker & Labarthe, 1999; Sahn, DeMaria, Kisslo & Weyman, 1987).

TABLE 2.2 CARDIAC STRUCTURES AND DETECTABLE ABNORMALITIES (adapted from Feigenbaum *et al*., 2005; Otto, 2004; Silverman, 1993)

CARDIAC STRUCTURE	DETECTABLE ABNORMALITIES
Aortic Root	➢ Dilatation ➢ Dissection flaps ➢ Ascending aorta aneurysms ➢ Sinus of Valsalva aneurysm ➢ Supravalvular stenosis
Aortic valve	➢ Reduced leaflet excursion: valvular stenosis or reduced cardiac output ➢ Calcification ➢ Prolapse ➢ Vegetations ➢ Bicuspid valve

	➢ Systolic doming ➢ Premature aortic valve closure
Left atrium	➢ Dilatation ➢ Thrombus ➢ Myxomas ➢ Cor triatriatum ➢
Mitral valve and supporting structures	➢ Reduced mobility, valvular stenosis or reduced cardiac output ➢ Valvular or annulus calcification ➢ Prolapse ➢ Ruptured chordae ➢ Failure of leaflet coaptation ➢ Vegetations ➢ Diastolic mitral valve flutter ➢ Systolic anterior motion of the mitral leaflet
Left ventricular outflow tract	➢ Outflow obstruction, muscular or membranous or due to systolic anterior motion of the anterior mitral leaflet
Aorta-septal and Mitral- Aortic Continuity	➢ Discontinuity as seen in certain congenital heart lesions
Interventricular septum	➢ Increased thickness or hypertrophy ➢ Thinning associated with myocardial infarction ➢ Reduced systolic thickening ➢ Hypokinesia or akinesia associated with ischemic heart disease ➢ Abnormal motion due to ischemia or infarction. Left bundle branch block, pacemaker rhythm, post open heart surgery, volume or pressure overload right ventricle
Inferolateral wall	➢ Increased thickness or hypertrophy ➢ Thinning: associated with myocardial infarction ➢ Aneurysm or pseudo aneurysm ➢ Reduced systolic thickening ➢ Hypokinesia or akinesia: associated with ischemic heart disease
Left ventricle cavity	➢ Dilatation ➢ Systolic dysfunction

	➢ Thrombus ➢ Intracavity masses or tumors
Right ventricle cavity	➢ Dilatation ➢ Impaired systolic function ➢ Increased right ventricular thickness
Coronary sinus	➢ Dilatation: most commonly associated with a persistent left superior vena cava
Descending aorta	➢ Dilatation ➢ Aortic dissection flaps ➢ Differentiation between pleural and pericardial effusions
Right atrium	➢ Dilatation ➢ Intracardiac masses/tumours
Tricuspid valve	➢ Reduced mobility: valvular stenosis or reduced cardiac output ➢ Systolic doming ➢ Prolapse ➢ Ruptured chordae ➢ Vegetations
Right ventricle outflow tract	➢ Dilatation ➢ Infundibular narrowing ➢ Increased free wall thickness
Pulmonary valve	➢ Stenosis ➢ Prolapse ➢ Vegetations ➢ Dysplasia
Pulmonary artery	➢ Dilatation ➢ Supra valvular stenosis ➢ Branch of peripheral pulmonary artery narrowing or stenosis

2.4.5.2 LEFT VENTRICULAR FUNCTION (LVF)

Left Ventricular systolic function is a major prognostic factor in cardiac disease and has important implications for treatment. Left Ventricular systolic function can be assessed by M- mode, 2-D and Doppler techniques (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

2.4.5.2.1 Left Ventricle Wall Dimensions

This measurement determines the thickness of the left ventricle of the heart. It can be used as the global index of systolic function and one of the most commonly used markers of systolic function (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

2.4.5.2.2 Systolic Function

Left Ventricle internal dimension measurements in end-systole (LVESD) and end-diastole (LVEDD) are measured at the level of the mitral valve leaflet tips in the parasternal long axis view. LVEDD is at the end of diastole, and LVESD is at the end of systole. The LVEDD and LVESD measurements can be used to calculate LV fractional shortening, LV ejection fraction and LV volume, which give some indication of LV systolic function (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

The ejection fraction (EF) is the percentage change in left ventricle volume between systole and diastole:

$$EF= (LVEDD)^3 – (LVESD)^3/ (LVEDD)^3 \text{ X } 100\%$$

Normal range of EF is 50-58% (Silverman, 1993).

2.4.5.2.3 Shortening fraction (SF)

Shortening fraction (SF) is commonly used and is the percentage of change in LV internal dimensions (not volumes) between systole and diastole:

$$SF = LVEDD\text{-}LVESD/LVEDD \text{ X } 100\%$$

The shortening fraction is a slightly different way of measuring left ventricular performance. Instead of measuring and rationing blood volumes, the shortening fraction measures and ratios the change in the diameter of the left ventricle between the contracted and relaxed states (Silverman 1993).

The normal range is 0.18-0.42%, or 18-42%, above 30% is considered normal, with 26-30% representing a mild decrease in function (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

2.4.5.2.3.1 Advantage of Shortening Fraction (SF) in Premature Infants

The shortening fraction is most often used to determine left ventricular function. Since it is relatively independent of changes in heart rate as seen with age, or loading conditions of the heart, it is thus independent of pre-load/afterload (Silverman, 1993; Otto, 2004; Feigenbaum *et al*., 2005).

2.4.6 CALCULATIONS OBTAINED FROM DOPPLER ECHOCARDIOGRAPHY

MYOCARDIAL PERFORMANCE INDEX (MPI)

2.4.6.1.1 Definition

Myocardial performance index (MPI) is a non-invasive, quantitative, Doppler-based measurement of global cardiac function, which integrates systolic and diastolic function (Tei, Ling, Hodge, Bailey, Oh, Rodeheffer, Tajik & Seward, 1995).

MPI is a ratio derived from the sum of isovolumic contraction time and isovolumic relaxation time divided by left ventricle ejection time. The normal value for this parameter is 0.39 ± 0.05 (Tei *et al.,* 1995).

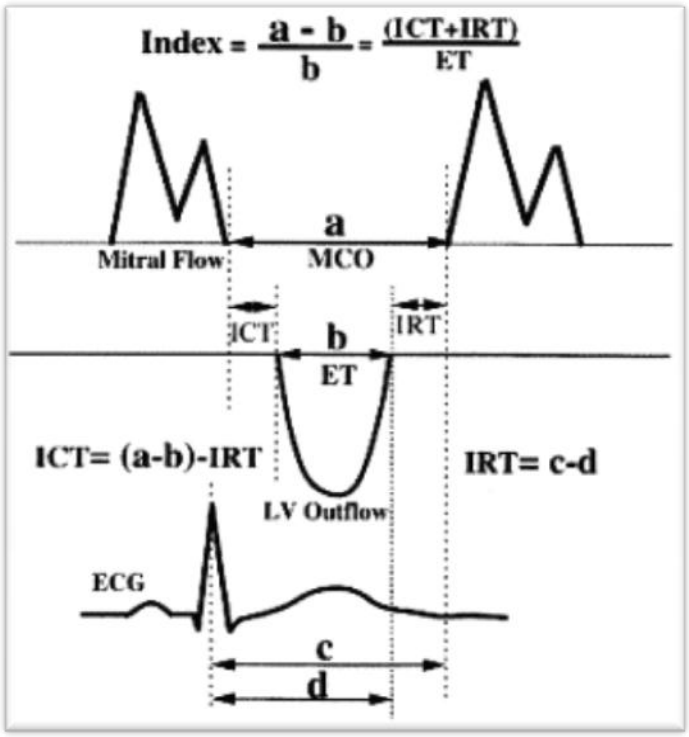


Figure 2.1 Method used to calculate MPI (adapted from Tei *et al*., 1995).

2.4.6.1.2 Application and Importance of MPI

The method used for calculating left ventricular index of myocardial performance, defined as (a-b)/b, where a, is the interval between cessation and onset of mitral inflow, and b is ejection time (ET) of LV outflow. Isovolumic relaxation time (IRT) is measured by subtracting interval c between R wave and onset of mitral flow. Isovolmetric contraction time (ICT) is obtained by subtracting IRT from (a-b) (Figure 2.1; Tei *et al*., 1995).

Patients with congestive heart failure, and signs and symptoms of heart failure have been associated with isolated diastolic dysfunction (Tei *et al*., 1995) the prevalence and annual mortality differ from those with other forms of heart failure. Published criteria for diastolic heart failure includes the presence of signs or symptoms of heart failure, evidence of abnormal relaxation or filling, and an ejection fraction of at least 45%. However a single measurement of an ejection fraction ≥45% seems inappropriate to exclude the presence of mild or moderate impairment of systolic function (Tei *et al*., 1995).

The myocardial performance index has been used as a combined systolic-diastolic index and is prognostic for patients with dilated cardiomyopathy (Harada, Tamura, Toyono & Yasuoka, 2002).

2.4.6.1.3 Advantages of the MPI

MPI index is easy to perform, reproducible, and independent of heart rate and blood pressure, and is relatively independent of age. In adults, the MPI correlates well with invasive measurements of left ventricular systolic and diastolic function (Tei *et al*., 1995). It is also a sensitive indicator of generalized cardiac dysfunction in patients with mild to moderate congestive heart failure. MPI is particularly useful in congenital heart disease, where the anatomy is not suitable for conventional methods to assess ventricular function (Eto, Ishii, Tei, Tsutsumi, Akagi & Kato, 1999).

2.4.6.1.4 Disadvantages of MPI

Systematic evaluation of this index in the normal and abnormal left ventricle has not been performed in experimental preparations. This is specifically important with regard to the influence of heart rate, preload and afterload alterations. Research has been limited to assessing the effect of resting heart rate or arterial pressure on index of myocardial performance in groups with normal and abnormal function (Tei *et al*., 1995; Bruch, Schemermund, Marin, Bartel, Schaar & Erbel, 2000).

Normal values for the MPI index have been determined for adults and are in the process of being developed for children. A need to determine normal values for premature neonates thus unmistakably exists.

2.5 PUBLISHED ECHOCARDIOGRAPHIC REFERENCE VALUES

Nearly all published normal reference ranges, are either data from the start of routine echocardiography in the USA (mid 1970 to mid 1980) or consists of small and heterogeneous samples (Skelton *et al*., 1998). The largest paediatric cohort consisted of 205 healthy children. The wide range of change during the normal development of the cardiac structure requires a large study group for accurate data on normal values (Skelton *et al*., 1998). In the last 15-20 years there have been dramatic improvements in echocardiography. It is now possible to obtain direct digital measurements and can be extended to include large numbers of extremely small, premature infants.

There was considerable variation in the values for the reference limits reported by various studies (Roge *et al*., 1978; Walther *et al*., 1986; Skelton *et al*., 1998). A few studies had small sample sizes, although, the majority had modest though not ideal sample sizes (120 to 200 participants). Only 3 studies were based on large sample sizes (Roge *et al*., 1978; Walther *et al*., 1986; Skelton *et al*., 1998). Besides the variation in sample sizes, differences in selection criteria and measurement techniques (2-D vs. M-mode) may have

contributed to the variability of reference limits. The contribution of differences in statistical analyses to this heterogeneity in reference values was difficult to ascertain. Generally, the descriptions of the statistical methods (parametric vs. nonparametric methods and the transformation of data) used for developing the reference limits in the studies were brief, and descriptions of the handling of outliers and the distribution of the data (caucasian vs. non-caucasian) were frequently lacking (Roge *et al*., 1978).

2.5.1 PARTITIONING

When developing cut-off points that separate "pathology" from "healthy", echocardiographers one must consider which covariates is appropriate to refer to, because echocardiographic dimensions vary according to characteristics such as sex, age, and gender (Roge *et al*., 1978; Walther *et al*., 1986).

2.5.2 AGE

In the field of echocardiography, it is necessary to account for the impact of age in the paediatric age groups, given the continuing postnatal growth (Roge *et al*., 1978; Skelton *et al*., 1998).

2.5.3 INDEXATION/ADJUSTMENT

Because cardiac dimensions vary with body size, it would seem reasonable to interpret echocardiographic measurements in the context of the body size of an individual. Adjusting or indexing by body surface area ("traditional" method) has been criticized because it "forgives" obesity-related variations in echocardiographic dimensions and has theoretic and mathematic limitations. Height indexation (height raised to an appropriate power) has been used by some investigators because of several advantages. Height is easy to measure, is a "non-derived" variable, and is not subject to change during illness (Roge *et al*., 1978; Skelton *et al*., 1998).

2.5.4 DEVIATION FROM REFERENCE VALUES

Cardiologists frequently use the terms "mild," "moderate," and "severe" to describe the degree of abnormality of cardiac structures. Such a description of echocardiographic observations in relation to their deviation from reference limits enables the clinician to interpret the degree of abnormality. With the emphasis on primary care and the explosion of imaging modalities, non-specialist physicians and allied health care professionals

are increasingly required to order and interpret the resultant echocardiographic reports. Because it is virtually impossible for a non-specialist to keep track of various reference limits, such interpretative reporting of echocardiographic measurements is useful for the treating clinician. It has been suggested that values exceeding reference limits be divided empirically into categories based on the number of standard deviations above the reference limits. Another classification scheme categorizes echocardiographic measurements exceeding reference limits (formulated from a healthy reference sample) on the basis of percentile values (i.e., 95th, 98th, and 99th percentiles) derived in a larger community-based sample, which included people with prevalent disease. The validation of these approaches merits further exploration.
Skelton and co-workers (1998) conducted a study consisting of 79 infants of less than 34 weeks gestation. Echocardiography was done on days 0,7 and 28 after birth to produce a set of reference ranges. Cardiac dimensions correlated well with gestation and birth weight. However, they found a close correlation between both gestation and birth weight for all physical measurements.

Walther and colleagues (1986) investigated normative data on intracardiac dimensions and systolic time intervals in very low birth weight infants. M-mode echocardiograms were collected from 210 healthy preterm and term neonates with birth weights between 780 and 5,350g and gestational ages ranging from 26 to 43 weeks. Fifty-nine neonates were less than 24h, 62 were between 25-48h, and 89 were between 48-144h of age. Diastolic and systolic left ventricular dimensions increased gradually with advancing birth weight (r = +0.84 and 0.78). Left atrial and aortic root dimensions tended to show a parabolic relationship with birth weight, increments were reduced at higher birth weights (r = +0.92 and 0.85). The shortening fraction of the left ventricle (mean +/- SD 33.8 +/- 4.9%) and the left atrial/aortic ratio (1.16 +/- 0.10) were constant throughout all weight subgroups. Pre-ejection periods and ejection times of both ventricles were reduced in preterm infants due to their higher heart rates, but left and right ventricular PEP/ET ratios in preterm and term infants were comparable. Septal thickness in diastole and in systole tended to increase slowly with advancing birth weight, but correlation coefficients were low (Walther *et al*., 1986).

2.6 THE RELEVANCE OF THE STUDY

THE IMPORTANCE OF NORMAL REFERENCE VALUES

- Echocardiography is a leading technology for evaluating cardiovascular structure and function in children. As a result life-altering decisions are constantly made on the basis of quantitive echocardiographic measurements.

IT IS A USEFUL AND EFFECTIVE TOOL IN CHILDREN FOR:

- Assessing the effects of medical therapy on the severity of valvular regurgitation and on ventricular compensation and function when it might change medical management.
- Assessing patients with known cardiac defects to determine the timing of medical or surgical therapy.
- Assessing suspected cardiomyopathy, heart failure, and changes in clinical status or to guide medical therapy.
- Screening patients for genetically transmitted cardiovascular disease, such as cardiomyopathy, Marfan syndrome, or Ehlers-Danlos syndrome.
- Conducting baseline evaluation and re-evaluation of patients receiving cardio toxic chemotherapy to determine the advisability of additional or increased dosages.
- Monitoring patients with suspected or documented Kawasaki disease, myopericarditis, human immunodeficiency virus (HIV), rheumatic fever, neuromuscular disorder with known myocardial involvement, post cardiac or cardiopulmonary transplant, thrombus or cardiac growth, pulmonary hypertension, re-evaluation after surgery or initiation of oral or parenteral vasodilator therapy for pulmonary hypertension, re-evaluating withdrawal of extracorporeal cardiopulmonary support therefore the reliability and validity of these measurements are of great importance(Cheitlin, Armstrong, Aurigemma, Beller, Bierman, Davis, Douglas, Faxon, Gillam, Kimball, Kussmaul, Pearlman, Philbrick, Rakowskie, Thys, Antman, Smith, Alpert, Gregoratus, Anderson, Hiratsuka, Hunt, Fuster, Jacobs, Gibbons & Russell 2003; Cheitlin, Alpert, Armstrong, Beller, Bierman, Davidson, Davis, Douglas & Gilliam, 1997).

CHAPTER 3

METHODOLOGY

3.1 AIM

To establish reference echocardiographic values for preterm infants of Central South Africa and compare them with international standards.

3.1.1 OBJECTIVES

- to conduct a prospective cross sectional study.
- with at least 50 children in each weight subgroup (0>0.999g; 1000 g-1499g; 1500 g-2500g).
- perform size and functional (Doppler Left and Right ventricle) measurements.
- identify correlations for gestational age and weight & BSA.
- compare findings to international standards

SUB-OBJECTIVES

- effect of Small for Gestational age (SGA) versus Average for Gestational age (AGA) on cardiac dimensions.
- effect of growth on cardiac dimensions.

3.2 STUDY LOCATION

The study was a multicentre trial involving Universitas Academic, Rosepark and Medi-Clinic Hospitals, situated in Bloemfontein, the capital city of the Free State province, South Africa. All infants born in these hospitals during the study period were echocardiographically screened to see whether they met the inclusion criteria for the study.

3.3 STUDY POPULATION

There was endeavored to include a minimum of 50 preterm/low birth weight infants in each weight subgroup. The weight subgroups were divided into three groups namely, Group 1 (infants weighing less than 1000g), Group 2 (infants between 1000-1500g) and Group 3 (infants between 1500-2500g).

3.3.1 IN- AND EXCLUSION CRITERIA

INCLUSION CRITERIA

- Gestational period ≤ 37 weeks.
- Birth weight less than 2500g.
- Absence of congenital heart defects excluding:
  Asymptomatic Patent Ductus Arteriosus (PDA) and Patent Foramen Ovale (PFO).
- Informed consent obtained from parents/guardian.
- Age 1 – 28 days.

EXCLUSION CRITERIA

- Congenital heart defects (excluding hemodynamically insignificant PDA, PFO).
  Definition of hemodynamic significant PDA (exclusion criteria):
  * murmur > gr2/6 on auscultation
  * clinical symptoms and signs of significant shunt (including cardiac failure)
  * any PDA that requires cardiac medication
  * LA: AO ratio of more than 1,4:1
- Birth asphyxia.
- Infants with HIV or suspected HIV or clinical criteria of HIV infection.
- Clinical heart failure.
- Cardiac involvement in infectious, neuromuscular or metabolic disorders.
- Dysrrhythmias.
- Chronic obstructive airways disease including BPD.
- Cardio active drugs causing hypertrophy (insulin, inotropes).
- Clinical, radiological, ECG or echocardiographic evidence of cardiac disease.
- Babies of mothers with diabetes (gestational and non-gestational).
- Babies receiving Dexamethazone for chronic lung disease.
- Major chromosomal abnormalities (e.g. trisomy 21).

3.3.2 SUBJECT IDENTIFICATION

Patient confidentiality was maintained throughout the study. All information (data) was considered confidential and no patient names were used to identify the patient but rather the hospital number. The study was conducted according to the rules and regulations from the Ethics Committee of the University of the Free State (UFS).

3.4 STUDY DESIGN

The study design was a prospective, cross sectional study.

3.5 RESEARCH TEAM

INVESTIGATOR

Salomi Jacobs- registered degree Master Technologiae Clinical Technology (M.Tech).

PROJECT LEADER/S

Prof SC Brown (M. Med. FCPaed DCH).

Dr L Botes (D.Tech Molecular Biology).

COLLABORATORS

Dr DG Buys (MBChB.M.Med), Miss. R Engelbrecht (B.Tech Clinical Technology).

3.6 STUDY LAYOUT

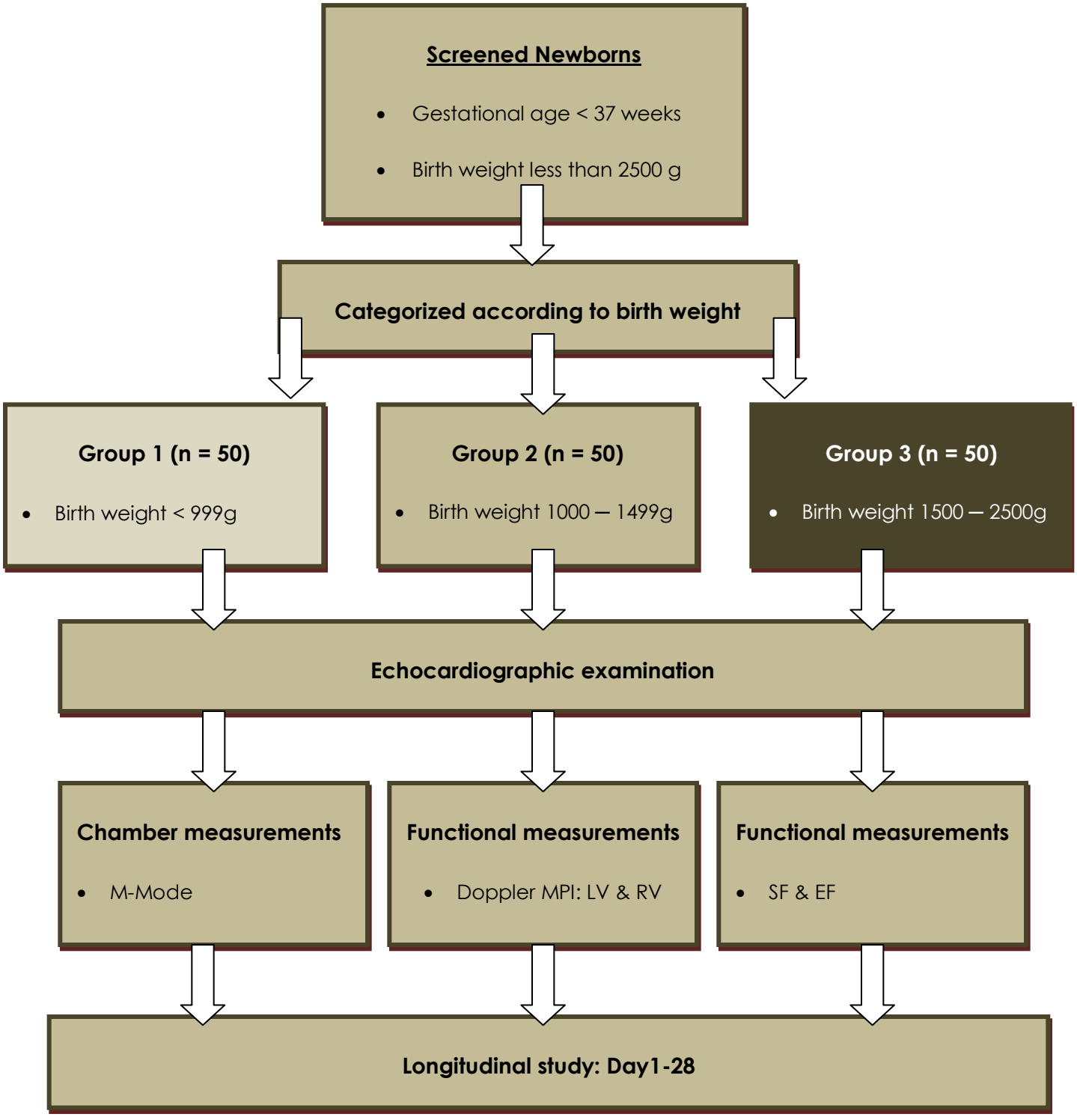


Figure 3.1 Study Layout

The infants born in the mentioned hospitals during the study period were echocardiographically screened. Newborns who met the inclusion criteria (<37 weeks gestational age and birth weight less than 2500g) were included in the study group. These newborns were divided in 3 weight group categories according to birth weight. The research team aimed for each group to consist of at least 50 infants. An echocardiogram was performed on each participant and included specific chamber measurements and functional measurements. In addition, longitudinal chamber measurements were repeated in a number of infants (n-15) between days' 1-28 post birth to gain insight in the change and growth (refer to ***Sub-objective***).

3.7 SPECIAL INVESTIGATIONS

3.7.1 GESTATIONAL AGE

Gestational age was obtained from the clinical records as recorded by the Neonatologist in charge of each patient, using the Ballard score (Ballard *et al.,* 1991; Appendix E).

3.7.2 DEMOGRAPHIC DATA

The following demographic data was recorded from patient files, by the person performing the echocardiogram:

- Date of birth
- Weight (kg)
- Length (cm)

Admission diagnosis

- Administered drugs
- Sex (M/F)
- Gestational age (days)

3.7.3 ECHOCARDIOGRAPHIC EXAMINATION

The echocardiograms were performed in the respective Neonatal Care Units of the three hospitals, where they were placed under a warmer or in an Isolette incubator with controlled temperature where careful observation and care were given. The participants were not sedated when the echocardiogram was performed. Strict measurements to maintain sterility were adhered to.

A Philips Envisor (model: MCMD02AA Type: M2540-66500; Universitas and Rosepark hospitals) and Toshiba (serial no: SSA 350A, using 7.5MgHz probe from Toshiba Medical systems, Crawley, UK) (Medi Clinic) echocardiography system was used and all images were digitally captured using the Philips Excelera software package. Scanning was done using 5 – 7.5 MHz transducers (S8 or S12). An echocardiogram is non-invasive and not harmful or painful to the infants in any way.

Measurements were performed according to the guidelines set by the American Society of Echocardiography (ASE)(Sahn *et al.,* 1978). All M-mode values were recorded and an average for 3 sequential beats was calculated. In order to control inter-observer variability, a Pediatric Cardiologist randomly selected patients and re-measured them to confirm accuracy and repeatability.

All M-mode and 2D measurements were repeated 3 times and the MPI index, 5 times, during the same echocardiographic examination and the results averaged.

Factors related to the clinical interpretation of the echocardiogram, i.e. the selection of the structure interfaces, and the specific criteria for echocardiography measurements, were addressed by standardized criteria and examination practices beforehand. This assured consistency and quality as far as possible.

REPRODUCIBILITY

Intra-observer variability of the M-mode and MPI-index measurements were addressed by randomly selecting 15 cases that were analyzed by observers as well as by one independent observer. The measurements were performed on digital recordings; each was blinded to the results obtained by the others. Variability was calculated as the mean percentage error, derived as the difference between the four sets of measurements, divided by the mean of the observations.

- SHORTENING FRACTION (SF %)
- EJECTION FRACTION (EF %)
- LEFT VENTRICLE END DIASTOLIC MEASUREMENT (LVEDD) IN MM
- LEFT VENTRICLE END SYSTOLIC MEASUREMENT (LVESD) IN MM
- POSTERIOR WALL THICKNESS IN DIASTOLE (PW) IN MM
- INTERVENTRICULAR SEPTUM THICKNESS IN DIASTOLE (IVS) IN MM
- LEFT ATRIAL MEASUREMENT 2D AND 4 CHAMBER (LA2D & LA) IN MM
- AORTIC ROOT MEASUREMENT (AOR) IN MM
- AORTIC CUSP SEPARATION (ACS) IN MM
- MUSCLE PERFORMANCE INDEX (MPI)-INDEX (LEFT AND RIGHT VENTRICLE)
- MITRAL AND TRICUSPID VALVE ORIFICES IN MM.

3.7.3.1 CARDIAC M-MODE AND 2D MEASUREMENTS

A diagram indicating the methods for measuring M-Mode are displayed in Appendix D. M-mode measurements were done on the parasternal long-axis view. The left ventricle internal dimension in systole and diastole (LVESD & LVEDD) was measured from the trailing edge of the left side of the septum to the leading edge of the posterior endocardium. Posterior left ventricular wall thickness (PW) represents the distance between the leading edge of the posterior left ventricular endocardium and the leading edge of the epicardium. Interventricular septal wall thickness (IVS) was the distance between the leading edge of the left septal echo and the trailing edge of the right septal echo. PW and IVS measurements are recorded in diastole, (IVSd and PWd). Left atrial (LA) dimension represented the distance between the trailing edge of the posterior aortic wall echo and the leading edge of the posterior left atrial wall echo at the level of the aortic valve at end-systole. Left atrial 2–dimensional (LA 2D) dimension represented the area from inner edge to inner edge on a diagonal and on a longitudinal view .

Aortic root (AoR) dimension is the distance between the leading edge of the anterior aortic wall and the leading edge of the posterior aortic wall immediately pre-systolic.

Tricuspid valve orifice and mitral valve orifice was measured from hingepoints to hingepoints, at the point where valves were most opened during diastole.

Aortic cusp separation (ACS) represents the distance between the trailing edge of the anterior aortic valve leaflet and the leading edge of the posterior aortic valve leaflet in early systole.

According to the recommendations of the American Society of Echocardiography (ASE) end-diastole should be measured at the beginning of the QRS-complex. However, in children this may lead to errors and measuring at the largest and smallest ventricular dimension may be more appropriate than measuring at specific times on the electrocardiogram. Measuring from leading edge to leading edge of the M-mode trace was the preferred technique. Measurements for premature infants was done as recommended by Silverman and co-workers (1993) and accepted by ASE (Sahn *et al.,* 1978; Appendix D).

3.7.3.2 CALCULATING MUSCLE PERFORMANCE INDEX (MPI)

The MPI was calculated by measurements done in the supine position in the apical 4 chambers and apical long axis views. An average of 5 consecutive cycles was used. A pulsed-wave Doppler sample volume (set at 2mm width) was taken at certain specific points on a four-chamber view. The first sample was taken at the left ventricle outflow tract right below the aortic valve cusps. Another sample volume was taken at the tips of the mitral valve leaflets in diastole. The size of the Doppler sample volume was set between 2-4mm with a 400Hz wall-filter setting. Care was taken to align the transducer beam as close as possible to the Doppler beam at $\leq$ 20 degrees in the selected planes. No angle correction of the Doppler beam was allowed. The sample volumes represented isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT) and ejection time (ET).

LEFT HEART MPI

- The MPI formula is **(a-b)/b**; **a** being ICT + IRT + ET and **b** equaling ET (Tei *et al*., 1995).
- **a** was measured from the end of one mitral valve inflow profile to the beginning of the following mitral valve inflow pattern.
- **b** was the measured length of the aortic valve outflow profile.
- Mitral valve (MiV) flow: trailing edge – leading edge for measurement.
- Aortic valve (AoV) flow: outer – inner edge (Tei *et al*., 1995).

- The MPI formula is **(a-b)/b**; **a** being ICT + IRT + ET and **b** equaling ET (Tei *et al*., 1995).
- **a** was measured from the end of one tricuspid valve inflow profile to the beginning of the following tricuspid valve inflow pattern.
- **b** was the measured length of the pulmonary valve outflow profile.
- Tricuspid Valve (TV) flow: trailing edge – leading edge for measurement.
- Pulmonary Valve (PuV) flow: outer – inner edge (Tei *et al*., 1995).

3.8 STATISTICAL ANALYSIS

All the statistical analyses were performed by the department of biostatistics, University of the Free State. The values for all measured dimensions were expressed as a function of body surface area (BSA) and weight. Raw data was captured on Excell spreadsheets. Normal ranges were calculated using means plus/minus 2 standard deviations or 2.5 and 97.5 percentiles depending on the distribution of the data, for different categories of underweight babies. Comparisons with the literature were carried out using 95% confidence intervals or P-values depending on the data available. Analysis was done using Statistical Analysis Software (SAS).

3.9 ETHICAL ASPECTS AND GOOD CLINICAL PRACTICE

3.9.1 ETHICAL CLEARANCE

Permission was obtained from the Ethical Committee of the Free State (ETOVS 166/05; Appendix C) and permission to use clinical records from the Chief Executive Officer of the respective hospitals (Appendix B). Fully informed, written consent were obtained from the parent/ legal guardian of each participating infant (Appendix A). Each parent or legal guardian received an information leaflet to explain the study in lay terms (Appendix A).

3.9.2 SAFETY VARIABLES

3.9.2.1 PROJECT SAFETY

The investigations were painless, non-invasive and completely safe. Any abnormality detected was reported to the treating physician with recommendation for referral to a Cardiologist.

3.9.2.2 PREMATURE DISCONTINUATION OF THE STUDY

The study would have been discontinued prematurely if the researcher or any of the study leaders felt that a patient's confidentiality might have been breached or if any unethical procedures may have occurred.

3.9.2.3 GOOD CLINICAL PRACTICE (GCP) / QUALITY ASSURANCE

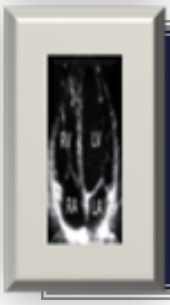
All clinical work conducted under this dissertation was subjected to the South African Good Clinical Practice guidelines (The Principles of ICH GCP, 2004).

3.9.2.4 FINANCIAL IMPLICATIONS TO THE PATIENT

There were no financial implications to the families of any of the participants in the study.

3.9.2.5 WITHDRAWAL CRITERIA

Participation was completely voluntarily. Patients had the right to withdraw from the study at any time, irrespective the reason(s), without detriment to their medical care then or in the future. The elimination of a patient from this study did not involve any penalty.



CHAPTER 4

RESULTS

4.1 BACKGROUND

All data were captured electronically on a Microsoft Excel spreadsheet. Statistical analysis was carried out by a bio-statistician using Statistical Analysis Software (SAS) Version 9.1.3. Descriptive statistics including frequencies and percentages were calculated for categorical data. Means and standard deviations or medians and percentiles were calculated for numerical data. Analytical statistics was used to compare intra- and inter-observer variation. Original data is presented in tabular format followed by modified tables for clinical use. All p-values <0.05 were classified as being statistically significant. All data will be presented in the order of raw data, then data for clinical use followed by regression analysis figures.

4.2 STUDY POPULATION

4.2.1 DEMOGRAPHIC DATA

During a 12 month (1st May 2009 - 30 May 2010) study period two hundred and ninety (n = 290) infants met the inclusion criteria and participated in the research study for low birth weight infants. The study was conducted in 3 hospitals in Central South Africa namely Universitas Academic hospital, Life- Healthcare Rose Park hospital and Medi- clinic hospital in Bloemfontein. The racial distribution consisted of the following: 15/290 (5.1%) Caucasian and the rest, non-Caucasian (94.8%).

The gender distribution was almost equal for male and female with a slight female preponderance. There were 135 (46%) male and 155 (53%) female infants that participated in the study (Figure 4.1). The gestational age ranged between 26-38 weeks, with a median of 31 weeks.

Eleven infants (3.8%) who were exposed to HIV during pregnancy were included in the study because they did not meet any of the clinical exclusion criteria. The age at which the infants received the echocardiogram ranged between one and 24 days, with a median of 4 days-excluding the longitudinal study where infants received an echocardiogram on day 1-7 after birth, at day 14 and at 28 days after birth.

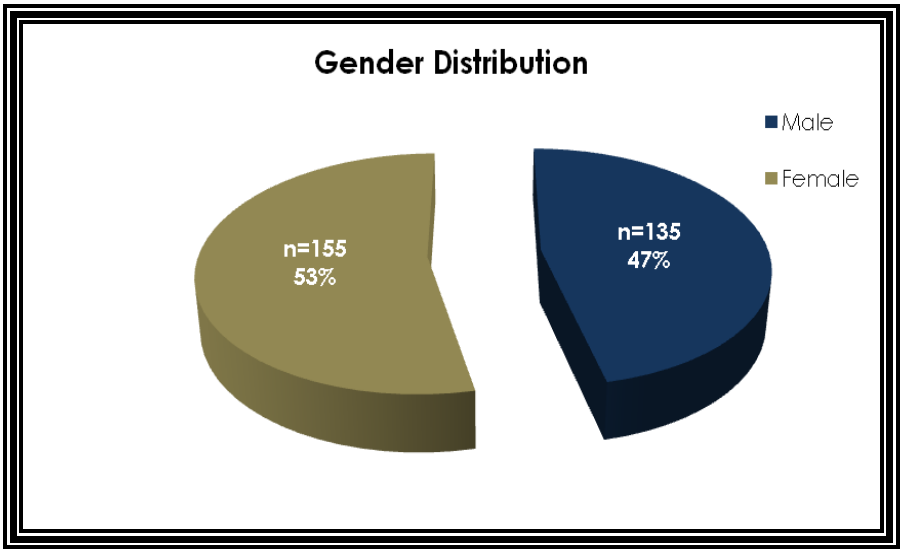


Figure 4.1 Gender Distribution

4.2.2 ANTHROPOMETRIC MEASUREMENTS

Body surface area (BSA) ranged between a minimum of 0.076 m^2 and a maximum of 0.184 m^2, with a median of 0.121 m^2. The body weight (BW) ranged between a minimum of 0.69 kg and a maximum of 2.5 kg, with a median of 1.36 kg for the entire study population (n=290)(Table 4.1).

TABLE 4.1 ANTHROPOMETRIC DATA (n=290)

Variable	Minimum	Maximum	Median
Weight	0.69 kg	2.5 kg	1.36 kg
Length	28 cm	51 cm	38 cm
BSA	0.076 m^2	0.184 m^2	0.121 m^2
Age at time of investigation	1 day	24 days	4 days

[kg = kilogram; cm = centimetre; m^2 = meters squared; BSA = Body Surface Area; Age = days after birth)

4.3 DATA PER WEIGHT CATEGORY

Infants were classified into 3 groups according to their weight (Figure 4.2); Group 1 (<0.999g), Group 2 (1000-1499g), and Group 3 (1500- 2500g). The majority of the infants fell in Group 2 (n=135; 45%) and the minority in Group 1(n=44; 15%).

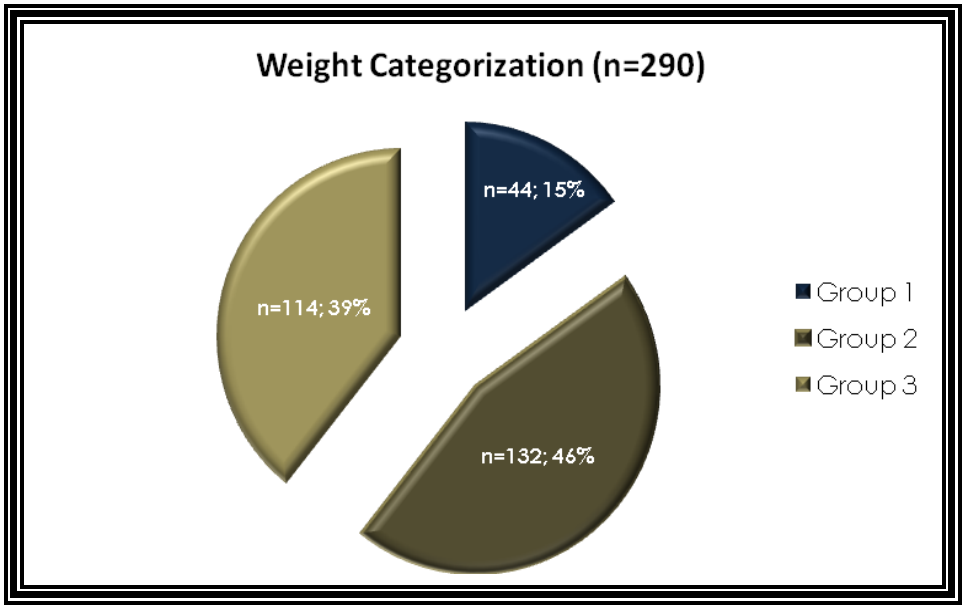


Figure 4.2 Weight Categorization

(Group 1 = <0.999g; Group 2 = 1000-1499g; Group 3 = 1500-2500g)

4.3.1 DEMOGRAPHIC DATA

For the entire study population and for all the weight categories the gender was almost equal with a very slight female preponderance. The gender distribution percentages were as follow: Group 1 (43% male & 56% female) Group 2 (46% male & 54% female) Group 3 (48% male & 52% female).

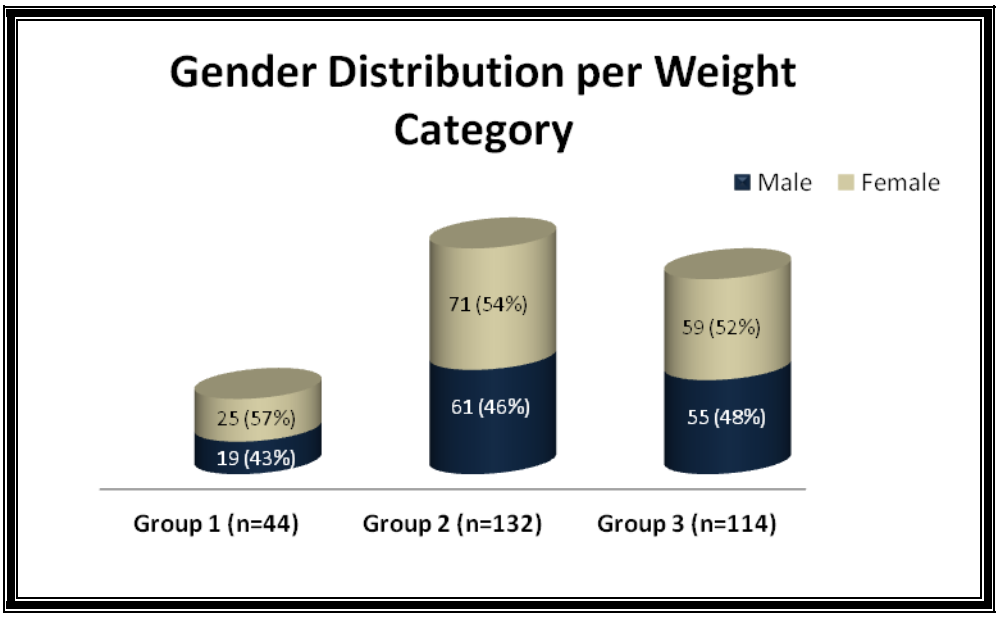


Figure 4.3 Gender distributions per Category

(Group 1 = <0.999g; Group 2 = 1000-1499g; Group 3 = 1500- 2500g)

4.3.2 ANTHROPOMETRIC MEASUREMENTS PER WEIGHT CATEGORY

The BSA increased with an increase in weight for all three the groups. The median BSA for the 3 groups was; Group 1 (0.09 m^2), Group 2 (0.11 m^2) and Group 3 (0.14 m^2) respectively (Table 4.2).

TABLE 4.2 ANTHROPOMETRIC DATA PER WEIGHT CATEGORY

VARIABLE		GROUP 1	GROUP 2	GROUP 3
Weight	*minimum*	0.69 kg	1.01 kg	1.54 kg
	maximum	1.00 kg	1.50 kg	2.50 kg
	median	0.91 kg	1.25 kg	1.93 kg
Length	*minimum*	29 cm	28 cm	30 cm
	maximum	39 cm	45 cm	51 cm
	median	34 cm	37 cm	42 cm
BSA	*minimum*	0.076 m^2	0.096 m^2	0.123 m^2
	maximum	0.103 m^2	0.129 m^2	0.184 m^2
	median	0.094 m^2	0.113 m^2	0.149 m^2

(Group 1 = <0.999g; Group 2 = 1000-1499g; Group 3 = 1500- 2500g; kg = kilogram; cm = centimetre; m^2 = meters squared; BSA = Body Surface Area)

4.3.3 WEIGHT VS. BODY SURFACE AREA (BSA)

The weight correlated well with BSA and a strong correlation was observed between the BSA and weight in these infants (r= 0.98; Figure 4.4).

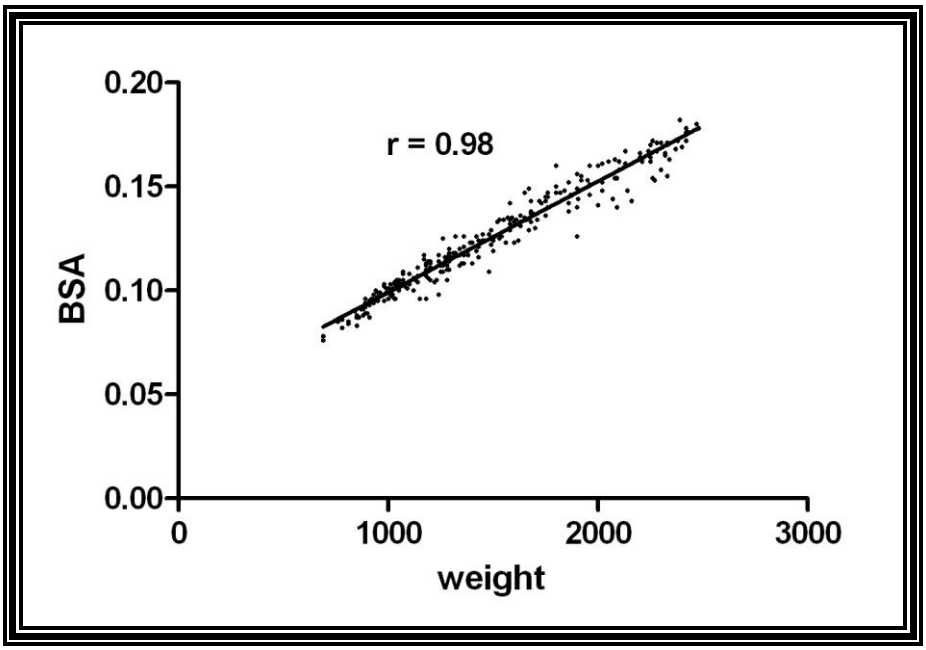


Fig. 4.4 Weight vs. Body Surface Area (BSA)

(BSA = Body Surface Area; Weight = weight in grams)

4.3.4 SMALL FOR GESTATIONAL AGE (SGA) VERSUS AVERAGE FOR GESTATIONAL AGE (AGA) FOR GROUPS 1-3

- Small for gestational age (SGA): "defined as babies whose birth weight lies below the 10th percentile for a specific gestational age, they may be full term or preterm infants"
- Average for gestational age (AGA): "defined as babies whose birth weight is within the normal percentiles for a specific gestational age, they may be full term or preterm infants"

SGA infants made up 29.7% (n= 87) of the entire study population. The number of SGA versus AGA infants for each group:

- Group 1: SGA (n = 18); AGA infants (n = 26)
- Group 2: SGA (n = 36); AGA infants (n = 96)
- Group 3: SGA (n = 33); AGA infants (n = 81)

The majority of SGA's were in Group 1 (41%) and the majority of AGA infants (73%) were in Group 2 (Figure 5.5).

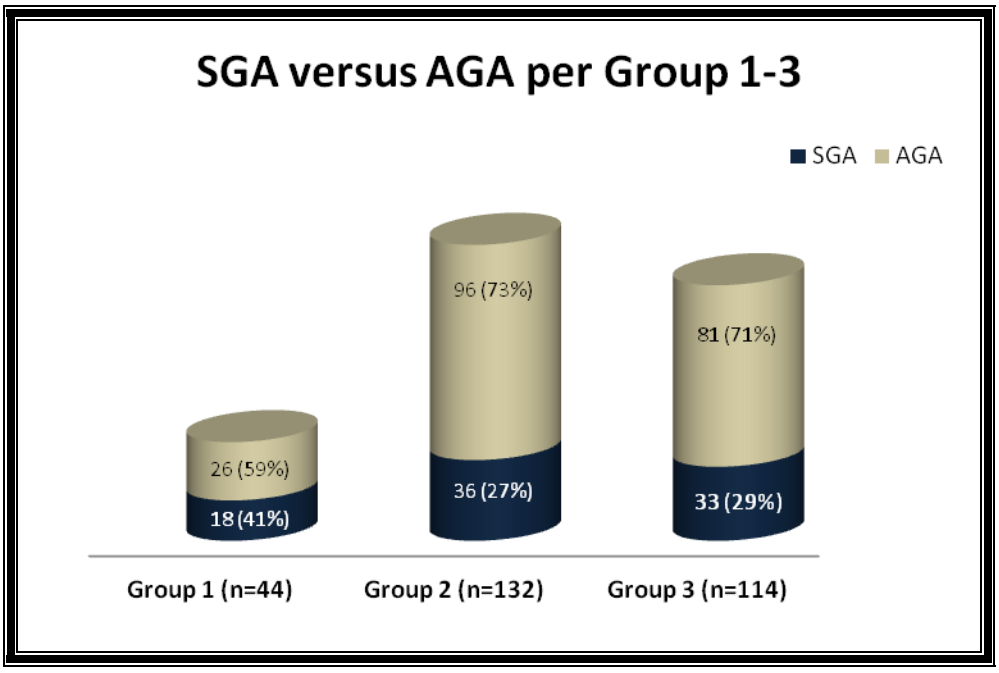


Figure 4.5 SGA versus AGA infants per Group 1-3

(Group 1 = <0.999g; Group 2 = 1000-1499g; Group 3 = 1500-2500g)

4.4. ECHOCARDIOGRAPHIC MEASUREMENTS

M-mode, 2D and functional measurements were analyzed for differences in appropriate for gestational age versus small for gestational age. There were no statistical differences between the two groups for any of the cardiac dimensions ($p<0.05$).

Comparisons between male and female for all weight groups were performed and no statistical differences were observed when the two gender groups were compared ($p<0.05$) for M-mode, 2D and functional measurements.

4.4.1. M-MODE MEASUREMENTS (GROUP 1-3)

Most cardiac dimensions measured larger on average in the heavier weight categories than in the smaller weight categories (Figure 4.3-4.5). The left ventricular diastolic and systolic, interventricular septum, posterior wall, aortic and left atrium dimensions showed a proportionate increase in diameter with an increase in body weight (Figure 4.6).

The M-mode examination consisted of left ventricle, left atrium and aortic root and cusp measurements. The M-mode left ventricle values per group are given in mm, with upper limits (z+2) and lower limits (z-2; Table 4.3-4.5). This is followed by the M-mode left ventricle values for SGA infants versus AGA infants (Table 4.6-4.8).

TABLE 4.3 M-MODE GROUP 1 (WEIGHT CATEGORY <0.999g)

Variable	Mean (n=44)	Std dev (n=44)	z-2	z+2
LVEDD	12.03	2.38	7.36	16.71
LVESD	7.86	1.51	4.39	10.84
PWd	3.18	0.60	2.00	4.36
IVSd	3.34	6.17	2.13	4.55
LA	8.76	2.00	4.88	12.68
AoR	6.85	1.20	4.49	9.21
ACS	4.05	0.78	2.50	5.50

(LVEDD = left ventricle end-diastolic diameter; LVESD = left ventricle end-systolic diameter; PW = posterior wall; IVS = interventricular septum; LA = left atrium; AoR = aortic root; ACS = aortic cusps separation; STD dev = standard deviation)

TABLE 4.4 M-MODE GROUP 2 (WEIGHT CATEGORY 1000-1499g)

Variable	Mean (n = 132)	Std dev (n = 132)	z-2	Z+2
LVEDD	12.45	1.87	8.77	16.13
LVESD	8.13	1.50	5.19	11.07
PWd	3.26	0.59	2.10	4.42
IVSd	3.33	0.61	2.05	4.61
LA	8.95	1.45	6.09	11.81
AoR	7.22	1.31	4.6	9.79
ACS	4.70	0.95	2.83	6.57

(LVEDD = left ventricle end-diastolic diameter; LVESD = left ventricle end-systolic diameter; PW = posterior wall; IVS = interventricular septum; LA = left atrium; AoR = aortic root; ACS = aortic cusps separation; STD dev = standard deviation)

TABLE 4.5 M-MODE GROUP 3 (WEIGHT CATEGORY 1500-2500g)

Variable	Mean (n = 114)	Std dev (n = 114)	z-2	z+2
LVEDD	14.24	2.13	10.06	18.43
LVESD	9.30	1.65	6.05	12.56
PWd	3.58	0.72	2.15	5.00
IVSd	3.77	0.69	2.42	5.13
LA	10.85	2.10	6.72	14.99
AoR	8.26	1.40	5.51	11.02
ACS	5.43	1.33	2.81	8.04

(LVEDD = left ventricle end-diastolic diameter; LVESD = left ventricle end-systolic diameter; PW = posterior wall; IVS = interventricular septum; LA = left atrium; AoR = aortic root; ACS = aortic cusps separation; STD dev = standard deviation)

TABLE 4.6 M-MODE AGA VS SGA GROUP 1 (WEIGHT CATEGORY <0.999g)

Variable	Mean(AGA) (n=26)	Std dev(AGA)	Mean(SGA) (n=18)	Std dev(SGA)
LVEDD	11.98	0.24	12.01	0.24
LVESD	8.01	0.17	7.66	0.13
PWd	3.26	0.07	3.07	0.03
IVSd	3.28	0.06	3.42	0.06
LA	8.84	0.21	8.64	0.19
AoR	6.83	0.13	6.89	0.11
ACS	4.16	0.09	3.88	0.05

(LVEDD = left ventricle end-diastolic diameter; LVESD = left ventricle end-systolic diameter; PW = posterior wall; IVS = interventricular septum; LA = left atrium; AoR = aortic root; ACS = aortic cusps separation; STD dev = standard deviation; AGA= Average for Gestational Age; SGA= Small for Gestational Age)

TABLE 4.7 M-MODE AGA VS SGA GROUP 2 (WEIGHT CATEGORY 1000-1499g)

Variable	Mean(AGA) (n=96)	Std dev(AGA)	Mean(SGA) (n=36)	Std dev(SGA)
LVEDD	12.61	0.19	12.03	0.19
LVESD	8.22	0.14	7.89	0.17
PWd	3.29	0.06	3.15	0.06
IVSd	3.39	0.07	3.17	0.05
LA	9.02	0.15	8.75	0.15
AoR	7.18	0.14	7.30	0.01
ACS	4.75	0.10	4.57	0.08

(LVEDD = left ventricle end-diastolic diameter; LVESD = left ventricle end-systolic diameter; PW = posterior wall; IVS = interventricular septum; LA = left atrium; AoR = aortic root; ACS = aortic cusps separation; STD dev = standard deviation; AGA= Average for Gestational Age; SGA= Small for Gestational Age)

TABLE 4.8 M-MODE AGA VS SGA GROUP 3 (WEIGHT CATEGORY 1500-2500g)

Variable	Mean(AGA) (n=81)	Std dev(AGA)	Mean(SGA) (n=33)	Std dev (SGA)
LVEDD	14.38	0.22	13.92	0.19
LVESD	9.37	0.18	9.13	0.13
PWd	3.58	0.08	3.55	0.06
IVSd	3.75	0.07	3.82	0.06
LA	10.85	0.20	10.86	0.24
AoR	8.23	0.13	8.35	0.16
ACS	5.42	0.13	5.43	0.15

(LVEDD = left ventricle end-diastolic diameter; LVESD = left ventricle end-systolic diameter; PW = posterior wall; IVS = interventricular septum; LA = left atrium; AoR = aortic root; ACS = aortic cusps separation; STD dev = standard deviation; AGA= Average for Gestational Age; SGA= Small for Gestational Age)

The measurements for clinical use are displayed in Table 4.9 and all the measurements are in mm. A z score of -3 is included in frequently used measurements as a quick reference to determine hypoplasia (Table 4.9).

TABLE 4.9 M-MODE LEFT VENTRICLE INTERNAL DIMENSIONS FOR CLINICAL USE

Variable	Mean & Z Score	GROUP 1 Weight Category <0.999g	GROUP 2 Weight Category 1000-1499g	GROUP 3 Weight Category 1500-2500g
LVEDD	**Mean**	**12**	**12.5**	**14.2**
(mm)	z+2	16.7	16.1	18.4
	z-2	7.4	8.8	10.1
	z-3	4.9	6.8	7.9
LVESD	**Mean**	**7.9**	**8.1**	**9.3**
(mm)	z+2	10.8	11.1	12.6

	z-2	4.4	5.2	6.l
	z-3	3.3	3.6	4.3
PWd	**Mean**	**3.2**	**3.3**	**3.6**
mm	z+2	4.4	4.4	5
	z-2	2	2.1	2.2
	z-3	1.4	1.5	1.40
IVSd	**Mean**	**3.3**	**3.3**	**3.8**
mm	z+2	4.6	4.6	5.1
	z-2	2.1	2	2.4
	z-3	1.5	1.4	1.7
LA	**Mean**	**8.8**	**8.9**	**10.9**
Mm	z+2	12.7	11.8	15
	z-2	4.9	6.1	6.7
	z-3	2.8	4.6	4.5
AoR	**Mean**	**6.9**	**7.2**	**8.3**
Mm	z+2	9.2	9.8	11
	z-2	4.5	4.6	5.5
	z-3	3.2	3.3	4.0
ACS	**Mean**	**4**	**4.7**	**5.4**
Mm	z+2	5.5	6.6	8
	z-2	2.5	2.8	2.8
	z-3	1.7	1.8	1.4

(LVEDD = left ventricle end-diastolic diameter; LVESD = left ventricle end-systolic diameter; PW = posterior wall; IVS = interventricular septum; LA = left atrium; AoR = aortic root; ACS = aortic cusps separation)

Regression analysis showed a positive correlation between LVEDD and body weight for the group as a whole (r= 0.49, p <0. 05).

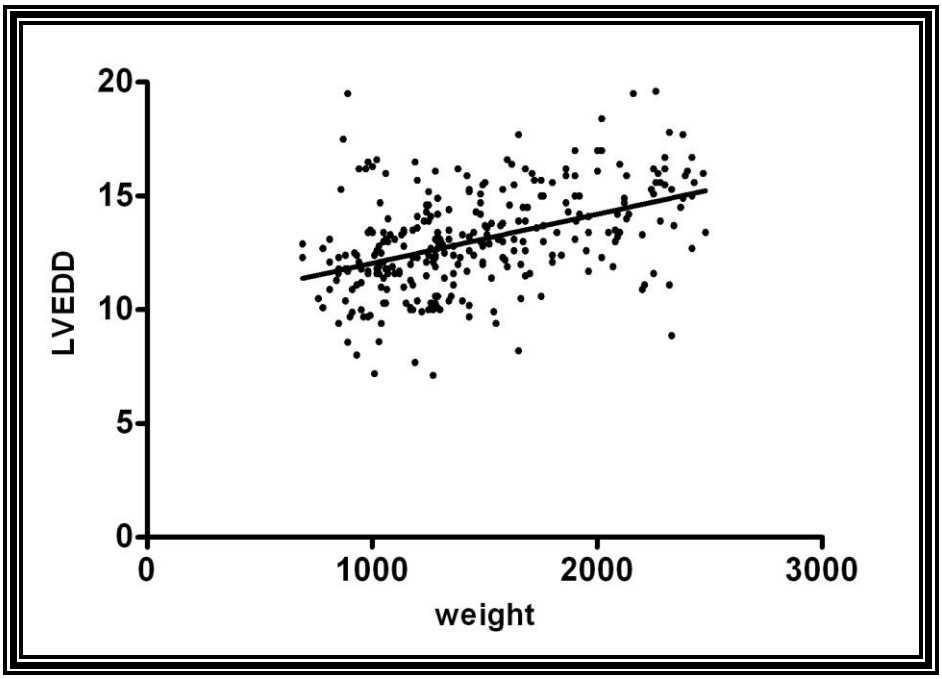


Figure 4.6 Linear regression analyses for LVEDD measurements.

(LVEDD = left ventricle end-diastolic diameter (mm) and weight (grams)

4.4.2 TWO DIMENSIONAL ECHOCARDIOGRAPHIC MEASUREMENTS: MITRAL AND TRICUSPID VALVE

The mitral and tricuspid annular diameter increased as weight increased in the three groups (Table 4.10-4.12 & Figure 4.7). Interestingly, tricuspid valve dimensions mirrored mitral valve diameters. There was a correlation between these two dimensions (r = 0.69 and p<0.05; Figure 4.8). the LA 2d measurements was not reported, we excluded these measuements due to the high variance and subjectivity of the measurements.

TABLE 4.10 MITRAL & TRICUSPID ANNULUS GROUP 1 (WEIGHT CATEGORY<0.999g)

Variable	Mean (n=44)	Std dev (n=44)	z-2	z+2
MV annulus	5.92	0.86	4.24	7.60
TV annulus	6.06	0.89	4.31	7.81

(MV = mitral valve; TV = tricuspid valve; STD dev = standard deviation)

TABLE 4.11 MITRAL & TRICUSPID ANNULUS GROUP 2 (WEIGHT CATEGORY 1000-1499g)

Variable	Mean (n=132)	Std dev (n=132)	z-2	z+2
MV annulus	6.40	0.96	4.53	8.28
TV annulus	6.50	1.00	4.54	8.47

(MV = mitral valve; TV = tricuspid valve; STD dev = standard deviation)

TABLE 4.12 MITRAL & TRICUSPID ANNULUS GROUP 3 (WEIGHT CATEGORY 1500-2500g)

Variable	Mean (n=144)	Std dev (n=144)	z-2	z+2
MV annulus	7.26	1.21	4.89	9.63
TV annulus	7.50	1.31	4.93	10.08

(MV = mitral valve; TV = tricuspid valve; STD dev = standard deviation)

The differences between the SGA and AGA infants for all weight categories are displayed in Table 4.13-4.15.

TABLE 4.13 MITRAL & TRICUSPID ANNULUS AGA VS SGA GROUP 1 (WEIGHT CATEGORY<0.999g)

Variable	Mean(AGA) (n=26)	Std dev(AGA)	Mean(SGA) (n=18)	Std dev(SGA)
MV annulus	5.84	0.98	6.04	0.65
TV annulus	6.05	0.99	6.08	0.76

(MV = mitral valve; TV = tricuspid valve; STD dev = standard deviation: AGA= Average for Gestational Age; SGA= Small for Gestational Age)

TABLE 4.14 MITRAL & TRICUSPID AGA VS SGA ANNULUS GROUP 2 (WEIGHT CATEGORY 1000-1499g)

Variable	Mean(AGA) (n=96)	Std dev(AGA)	Mean(SGA) (n=36)	Std dev(SGA)
MV annulus	6.48	0.95	6.20	0.96
TV annulus	6.63	1.02	6.16	0.87

(MV = mitral valve; TV = tricuspid valve; STD dev = standard deviation: AGA= Average for Gestational Age; SGA= Small for Gestational Age)

TABLE 4.15 MITRAL & TRICUSPID ANNULUS AGA VS SGA GROUP 3 (WEIGHT CATEGORY 1500-2500g)

Variable	Mean(AGA) (n=81)	Std dev(AGA)	Mean(SGA) (n=33)	Std dev(SGA)
MV annulus	7.26	1.30	7.25	0.96
TV annulus	7.51	1.37	7.47	1.18

(MV = mitral valve; TV = tricuspid valve; STD dev = standard deviation: AGA= Average for Gestational Age; SGA= Small for Gestational Age)

The measurements for clinical use for group 1-3 are measured in mm (Table 4.16).

TABLE 4.16 MITRAL AND TRICUSPID VALVE ANNULAR DIAMETERS FOR CLINICAL USE

Variable	Mean & Z score	GROUP 1 Weight Category <0.999g	GROUP 2 Weight Category 1000-1499g	GROUP 3 Weight Category 1500-2500g
MV annulus	**Mean**	**5.9**	**6.4**	**7.3**
	z+2	7.6	8.3	9.7
	z-2	4.2	4.5	4.9
	z-3	3.3	3.5	3.6
TV annulus	**Mean**	**6.1**	**6.5**	**7.5**
	z+2	7.8	8.5	10.1
	z-2	4.3	4.5	4.9
	z-3	3.4	3.5	3.5

(MV = mitral valve; TV = tricuspid valve; STD dev = standard deviation)

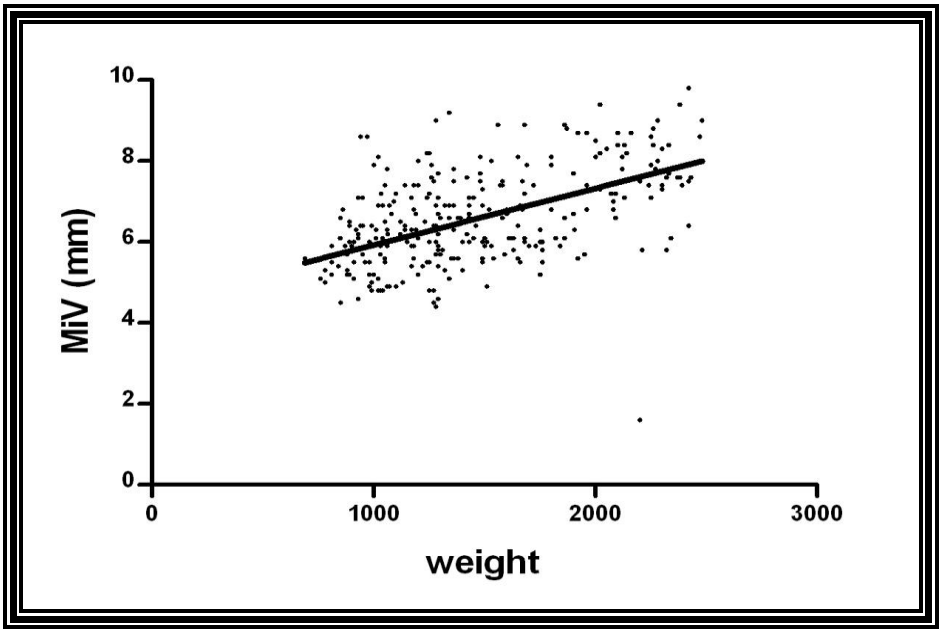


Figure 4.7 Linear regression analysis for all mitral valve annulus measurements (n=290)

(MiV = Mitral valve orifice in (mm) and weight (grams)

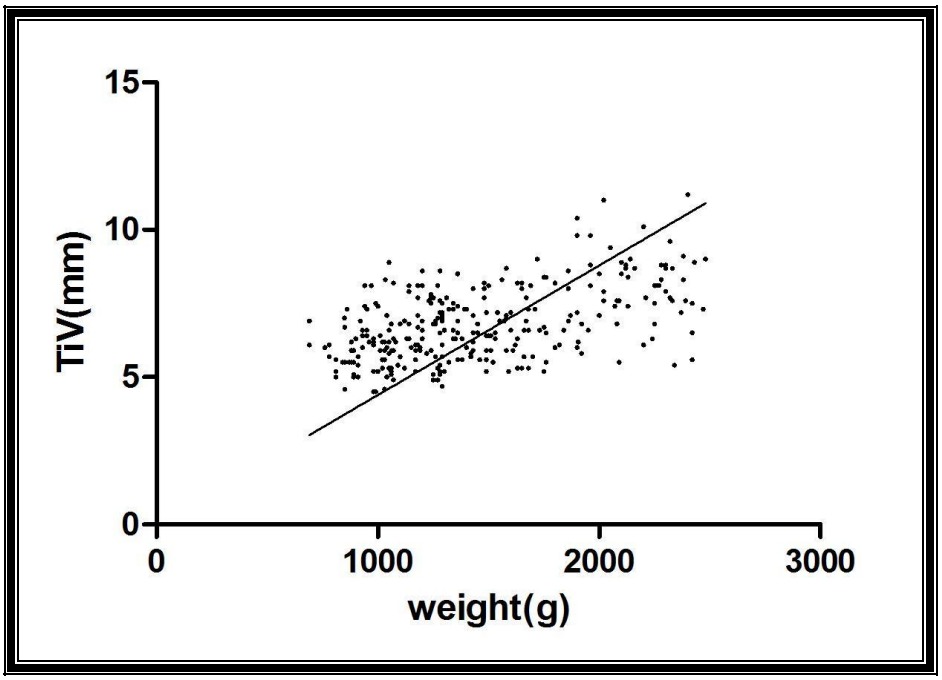


Figure 4.8 Linear regression analysis for all tricuspid valve annulus measurements (n=290)

(TiV = Tricuspid valve orifice in (mm) and weight (grams)

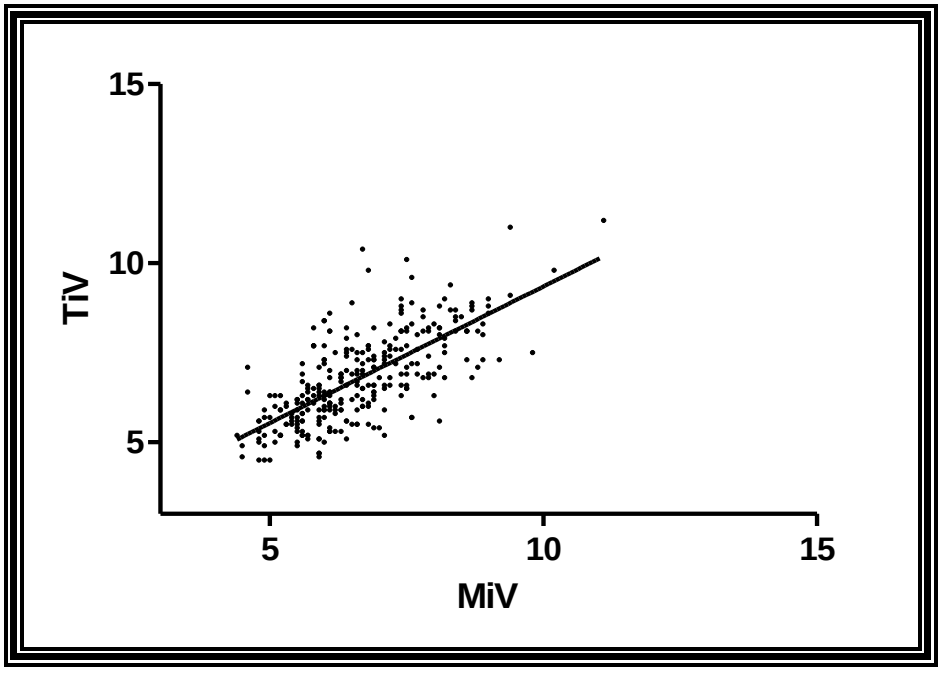


Figure 4.9 Linear regression analysis between the Mitral valve annulus and Tricuspid valve annulus (n=290).

(TiV = Tricuspid valve orifice in (mm); MiV = Mitral valve orifice in (mm))

4.4.3 FUNCTIONAL ASSESSMENT

Functional measurements included systolic assessment via the shortening and ejection fraction derived from M-mode measurements as well as global systolic and diastolic derived functional assessments using Doppler for the calculation of the myocardial performance index (MPI) for the RV and LV.

4.4.3.1 M-MODE FUNCTIONAL ANALYSIS

The ejection fraction and shortening fraction remained constant over all the weight categories with a mean shortening fraction of 34% and mean ejection fraction of 67%. There was no correlation between SF and weight (Figure 4.10). The SF remained constant although there was an increase in the weight of the infants (r = 0.02).

The Doppler MPI for the left ventricle was 0.22 and for the right 0.29 (Table 4.30) and also remained more or less unchanged for all weight categories. There was a positive correlation between the left ventricular Doppler MPI and the SF (Fig.4.14) and EF (r = 0.68).

The data for the shortening fraction and ejection fraction per weight category are displayed in Table 4.17-4.19.

TABLE 4.17 SHORTENING & EJECTION FRACTION GROUP 1 (WEIGHT CATEGORY<0.999g)

Variable	Mean (n = 44)	Std dev (n = 44)	z-2	z+2
SF%	34.8	5.8	23.4	46.3
EF%	68.4	7.7	53.3	83.5

(SF = shortening fraction; EF = ejection fraction; STD dev = standard deviation)

TABLE 4.18 SHORTENING & EJECTION FRACTION GROUP 2 (WEIGHT CATEGORY 1000-1499g)

Variable	Mean (n = 132)	Std dev (n = 132)	z-2	z+2
SF%	34.5	6.3	22.1	46.9
EF%	67.6	8.5	50.9	84.3

(SF = shortening fraction; EF = ejection fraction; STD dev = standard deviation)

TABLE 4.19 SHORTENING & EJECTION FRACTION GROUP 3 (WEIGHT CATEGORY 1500-2500g)

Variable	Mean (n = 114)	Std dev (n = 114)	z-2	z+2
SF%	34.5	6.0	22.8	46.3
EF%	66.8	8.1	51.1	83.0

(SF = shortening fraction; EF = ejection fraction; STD dev = standard deviation)

The differences for shortening fraction and ejection fraction between SGA and AGA infants for all weight categories are displayed in Table 4.20-4.22.

TABLE 4.20 SHORTENING & EJECTION FRACTION AGA VS SGA GROUP 1 (WEIGHT CATEGORY<0.999g)

Variable	Mean(AGA) (n=26)	Std dev(AGA)	Mean(SGA) (n=18)	Std dev(SGA)
SF %	34.5	5.3	35.3	6.7
EF %	68.0	7.2	69.0	8.6

(SF = shortening fraction; EF = ejection fraction; STD dev = standard deviation: AGA= Average for Gestational Age; SGA= Small for Gestational Age)

TABLE 4.21 SHORTENING & EJECTION FRACTION AGA VS SGA GROUP 2 (WEIGHT CATEGORY 1000-1499g)

Variable	Mean(AGA) (n=96)	Std dev(AGA)	Mean(SGA) (n=36)	Std dev(SGA)
SF %	34.7	6.3	34.1	6.6
EF %	67.7	8.4	67.4	9.0

(SF = shortening fraction; EF = ejection fraction; STD dev = standard deviation: AGA= Average for Gestational Age; SGA= Small for Gestational Age)

TABLE 4.22 SHORTENING & EJECTION FRACTION AGA VS SGA GROUP 3 (WEIGHT CATEGORY 1500-2500g)

Variable	Mean(AGA) (n=81)	Std dev(AGA)	Mean(SGA) (n=330	Std dev(SGA)
SF %	34.7	6.2	34.2	5.5
EF %	67.1	8.4	66.7	7.5

(SF = shortening fraction; EF = ejection fraction; STD dev = standard deviation: AGA= Average for Gestational Age; SGA= Small for Gestational Age)

TABLE 4.23 SHORTENING & EJECTION FRACTION FOR CLINICAL USE

Variable	Mean & Z score	GROUP 1 Weight Category <0.999g	GROUP 2 Weight Category 1000-1499g	GROUP 3 Weight Category 1500-2500g
SF %	***Mean***	**35**	**35**	**35**
	z+2	46	47	46
	z-2	23	22	23
EF %	***Mean***	**68**	**68**	**67**
	z+2	84	84	83
	z-2	53	50	51

(SF = shortening fraction; EF = ejection fraction)

Shortening fractions for the group (n=290) remained constant (Figure 4.10) including for the SGA and AGA infants. Due to the fact that ejection fraction is not commonly applied in children; a regression analysis was not done for EF.

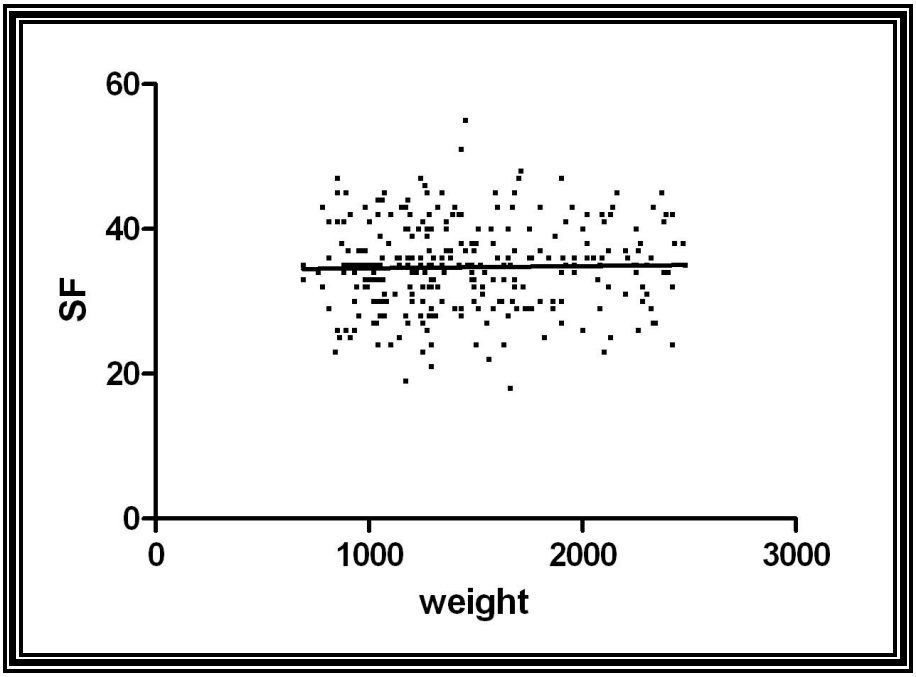


Figure 4.10 Linear regression analysis for all SF % measurements (n=290; weight (g))

4.4.3.2 DOPPLER MPI

Doppler echocardiography was used to determine left and right ventricle MPI (Table 4.24-4.26). Overall, MPI remained similar for the whole study population (n=290). The left and right ventricle MPI was calculated for the SGA versus the AGA infants (Table 4.24-4.26) followed by a table for clinical use per weight category (Table 4.30). No correlation was observed between weight and LV MPI values for preterm/low birth weight infants ($r = 0.02$, $p = 0.69$; Figure 4.10). A similar finding was demonstrated for RV MPI values (Figure 4.11). Although there was a tendency for the RV MPI to be lower as weight increased, no correlation was present ($r = 0.02$, $p = 0.68$).

TABLE 4.24 MPI LEFT AND RIGHT VENTRICLE GROUP 1 (WEIGHT CATEGORY<0.999g)

Variable	Mean (n=44)	Std dev (n=44)	z-2	z+2
MPI LV	0.31	0.12	0.07	0.55
MPI RV	0.23	0.18	0.13	0.59

(MPI= Myocardial performance index; RV = right ventricle, LV = left ventricle; STD dev = standard deviation)

TABLE 4.25 MPI LEFT AND RIGHT VENTRICLE GROUP 2 (WEIGHT CATEGORY 1000-1499g)

Variable	Mean (n=132)	Std dev (n=132)	z-2	z+2
MPI LV	0.29	0.15	0.00	0.59
MPI RV	0.22	0.15	0.08	0.52

(MPI= Myocardial performance index; RV = right ventricle, LV = left ventricle: STD dev = standard deviation)

TABLE 4.26 MPI LEFT AND RIGHT VENTRICLE GROUP 3 (WEIGHT CATEGORY 1500-2500g)

Variable	Mean (n=114)	Std dev (n=114)	z-2	z+2
MPI LV	0.29	0.15	0.00	0.59
MPI RV	0.23	0.13	0.03	0.48

(MPI= Myocardial performance index; RV = right ventricle, LV = left ventricle: STD dev = standard deviation)

TABLE 4.27 MPI LEFT AND RIGHT VENTRICLE AGA VS SGA GROUP 1 (WEIGHT CATEGORY<0.999g)

Variable	Mean(AGA) (n=26)	Std dev(AGA)	Mean(SGA) (n=18)	Std dev(SGA)
MPI LV	0.32	0.10	0.29	0.15
MPI RV	0.23	0.17	0.23	0.20

(MPI= Myocardial performance index; RV = right ventricle, LV = left ventricle: STD dev = standard deviation: AGA= Average for Gestational Age; SGA= Small for Gestational Age)

TABLE 4.28 MPI LEFT AND RIGHT VENTRICLE AGA VS SGA GROUP 2 (WEIGHT CATEGORY 1000-1499g)

Variable	Mean(AGA) (n=96)	Std dev(AGA)	Mean(SGA) (n=36)	Std dev(SGA)
MPI LV	0.27	0.13	0.26	0.17
MPI RV	0.22	0.16	0.22	0.12

(MPI= Myocardial performance index; RV = right ventricle, LV = left ventricle; STD dev = standard deviation: AGA= Average for Gestational Age; SGA= Small for Gestational Age)

TABLE 4.29 MPI LEFT AND RIGHT VENTRICLE AGA VS SGA GROUP 3(WEIGHT CATEGORY 1500-2500g)

Variable	Mean(AGA) (n=81)	Std dev(AGA)	Mean(SGA) (n=33)	Std dev(SGA)
MPI LV	0.32	0.16	0.24	0.12
MPI RV	0.24	0.12	0.20	0.16

(MPI= Myocardial performance index; RV = right ventricle, LV = left ventricle: STD dev = standard deviation: AGA= Average for Gestational Age; SGA= Small for Gestational Age)

TABLE 4.30 MPI LEFT AND RIGHT VENTRICLE FOR CLINICAL USE

Variable	Mean & Z score	GROUP 1 Weight Category <0.999g	GROUP 2 Weight Category 1000-1499g	GROUP 3 Weight Category 1500-2500g
MPI LV	**Mean**	**0.31**	**0.29**	**0.29**
	Z+2	0.60	0.60	0.60
	Z-2	0.06	0.001	0.001
MPI RV	**Mean**	**0.23**	**0.22**	**0.23**
	Z+2	0.60	0.50	0.50
	Z-2	0.10	0.08	0.03

(MPI= Myocardial performance index; RV = right ventricle, LV= left ventricle)

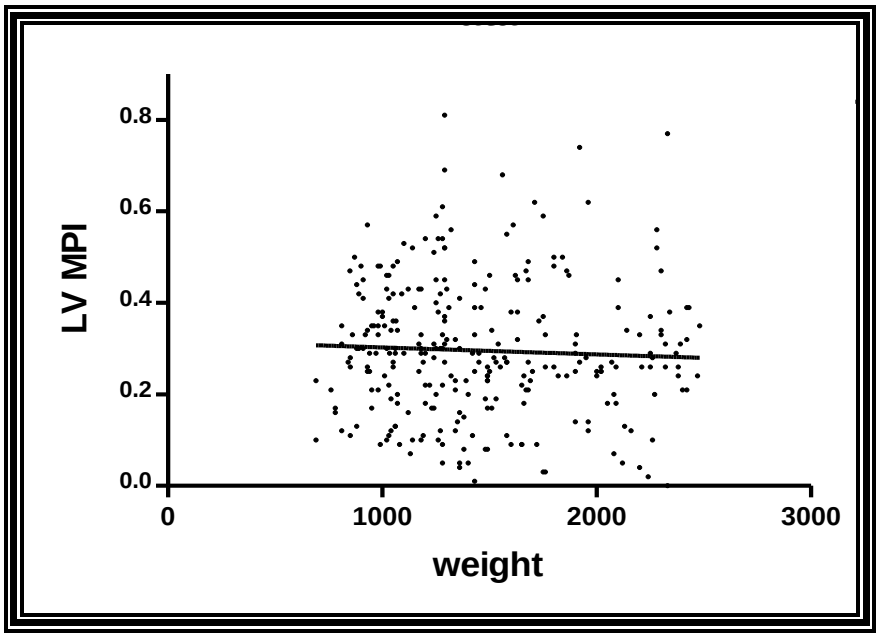


Figure 4.11 Linear regression analysis for Left ventricle MPI index values versus weight (n=290).

(MPI= Myocardial performance index, LV = left ventricle; weight in grams).

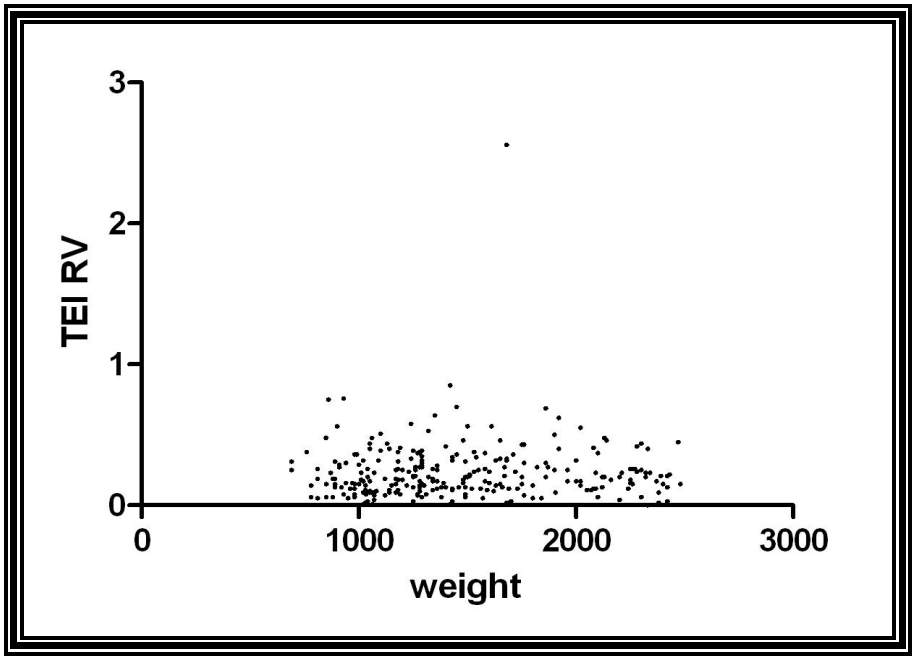


Figure 4.12 Linear regression analysis for Right ventricle MPI index values versus weight (n=290).

(MPI= myocardial performance index; RV = right ventricle: weight in grams)

Weight had little to no effect on the MPI for the 3 groups (Figure 4.11 and 4.12). The mean LV MPI was 0.30 (Group 1: 0.31; Group 2: 0.29; Group 3: 0.29) and the mean for the RV MPI was 0.23 (Group 1: 0.23; Group 2: 0.22; Group 3: 0.23). Left ventricle and right ventricle MPI values were compared and regression analysis showed that there was some correlation of these measurements (r = 0.63; Figure 4.13). There was no correlation (Figure 4. 14) between the MPI of the LV and the SF (r=0.24).

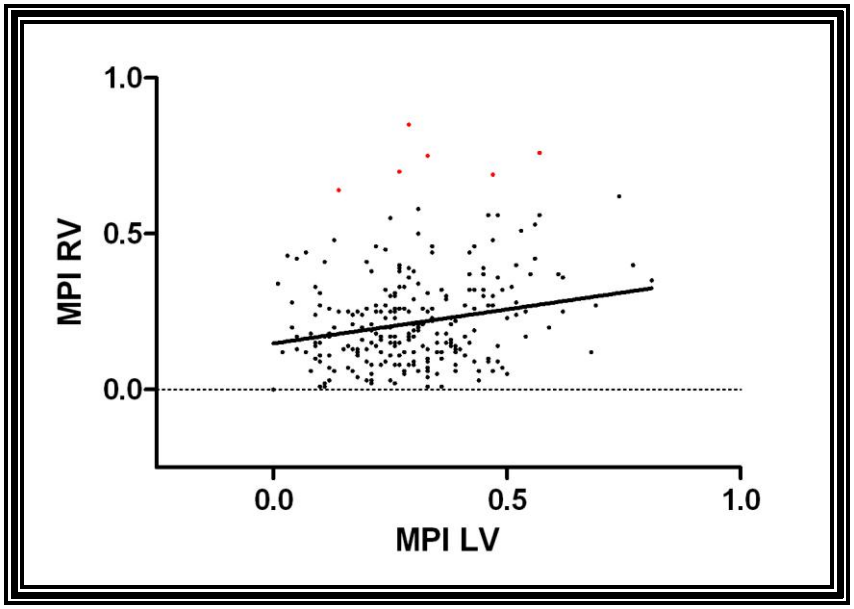


Figure 4.13 MPI: Left ventricle versus right ventricle (n=290).

(MPI = Myocardial performance index; RV = right ventricle, LV = left ventricle)

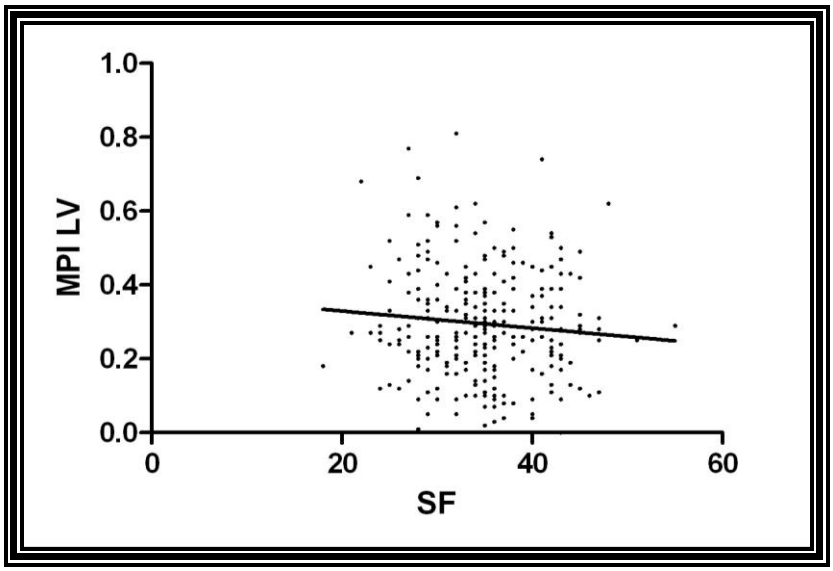


Figure 4.14 Left ventricle MPI versus SF (n=290).

(MPI: Muscle performance index; LV = left ventricle, SF = Shortening fraction)

4.5 CARDIAC FINDINGS

Clinically insignificant cardiac abnormalities were present in a large number of infants (Figure 4.15). The most common findings consisted of PDA's (n=104; 36%) or PFO's (n=96; 33%). A total of 200 (69%) had both a PDA and PFO and the remainder of the infants (31%) had no cardiac lesions. PDA's were present in 26/44, 48/132 and 30/114 in groups I, II and III, respectively. Using the Fisher's exact test, no difference were present in the prevalence of small PDA's in SGA vs. AGA infants (p = 0.69).

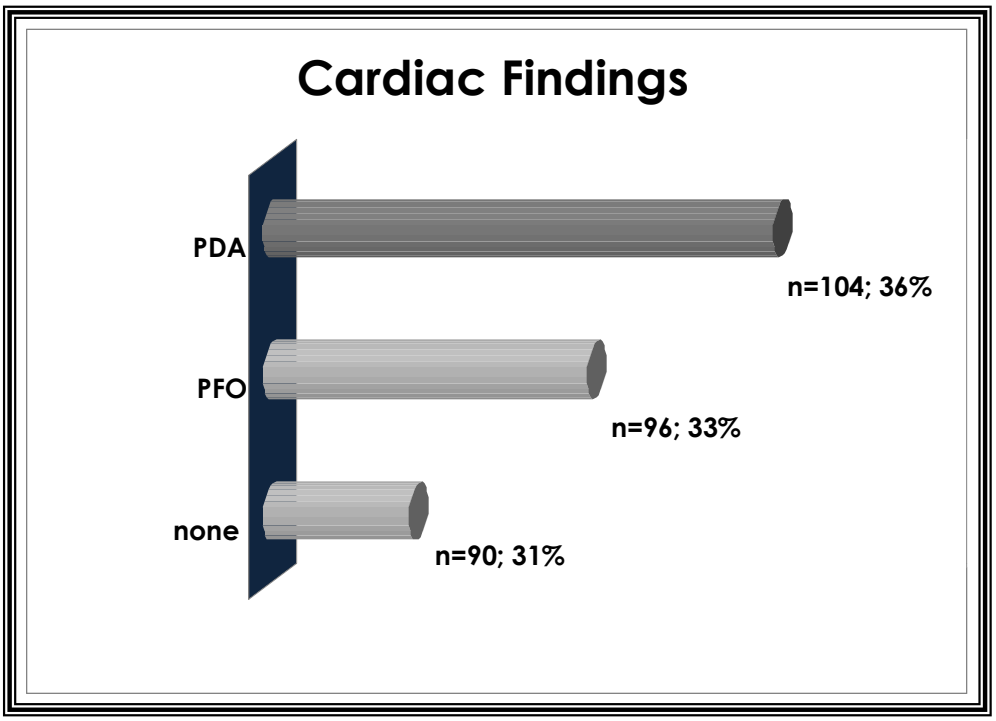


Figure 4.15 Cardiac findings

(PDA = Patent ductus arteriosus ; PFO = Patent foramen ovale)

4.6 LONGITUDINAL STUDY

A longitudinal study was performed as a sub-objective. Fifteen preterm infants were investigated at different time intervals: 2-3 days after birth, 14 days and 28 days. All 14 cardiac dimensions (M-mode, 2-D and functional) measurements were calculated and manually plotted against the normative ranges as obtained from the study. Cardiac dimensions increased parallel to weight gain for all the infants. Results showed that all the measurements from these 3 periods were within the upper and lower limits produced by the study for

all three weight groups (Fig.4.17-4.20). Plotted values are according to weight measured on the day of the cardiac echo and comp aired to the normative range of infants of comparable weight.

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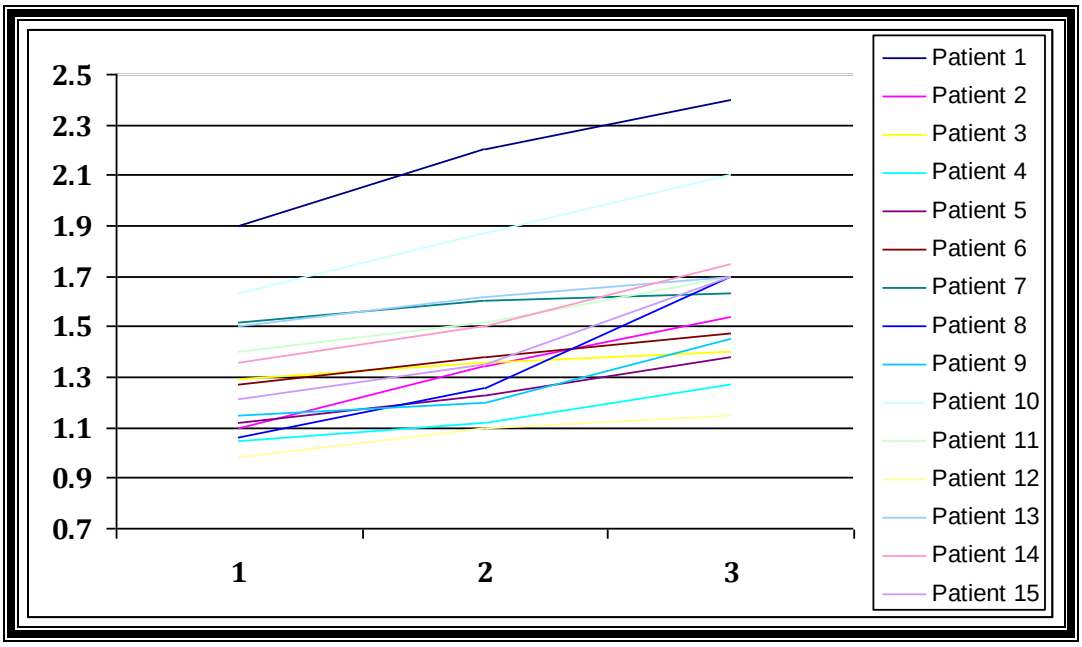


Figure 4.16 Weight gain 1-28 days

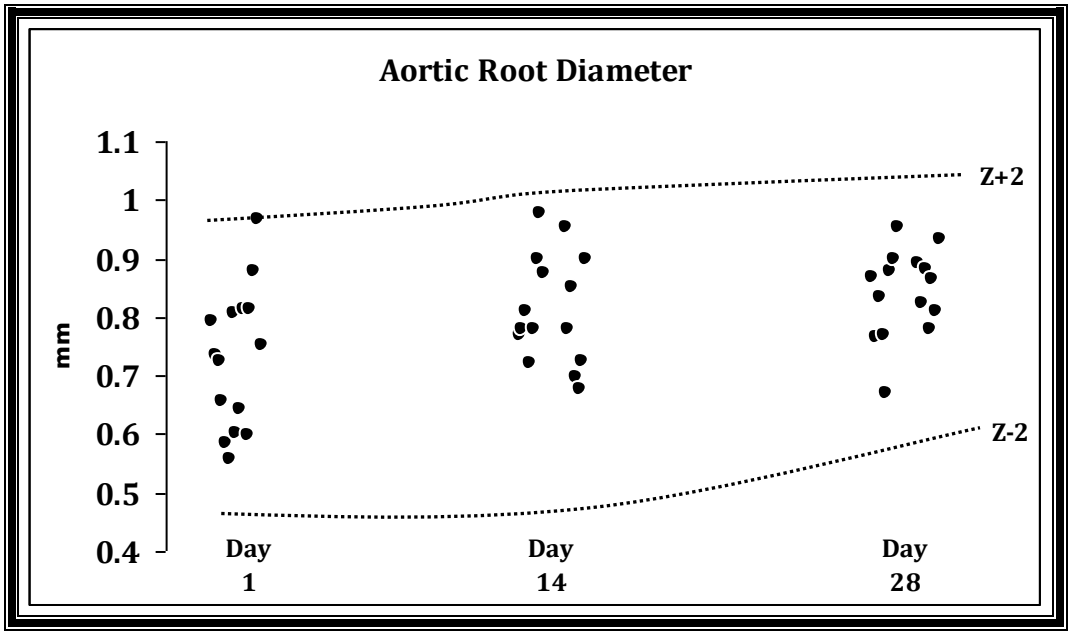


Figure 4.17 Aortic root diameter 1-28 days

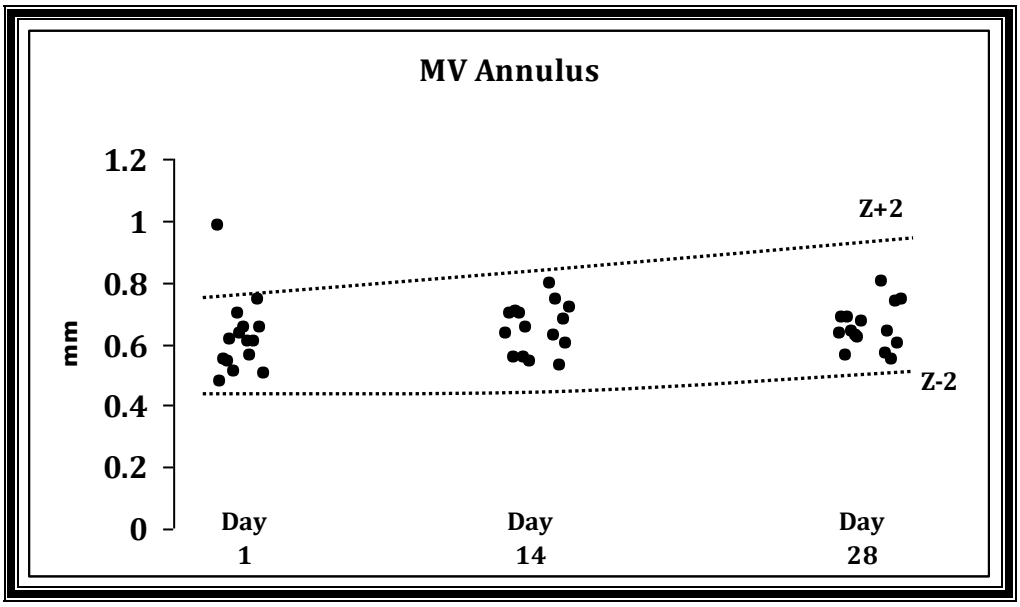


Figure 4.18 Mitral valve annulus 1-28 days

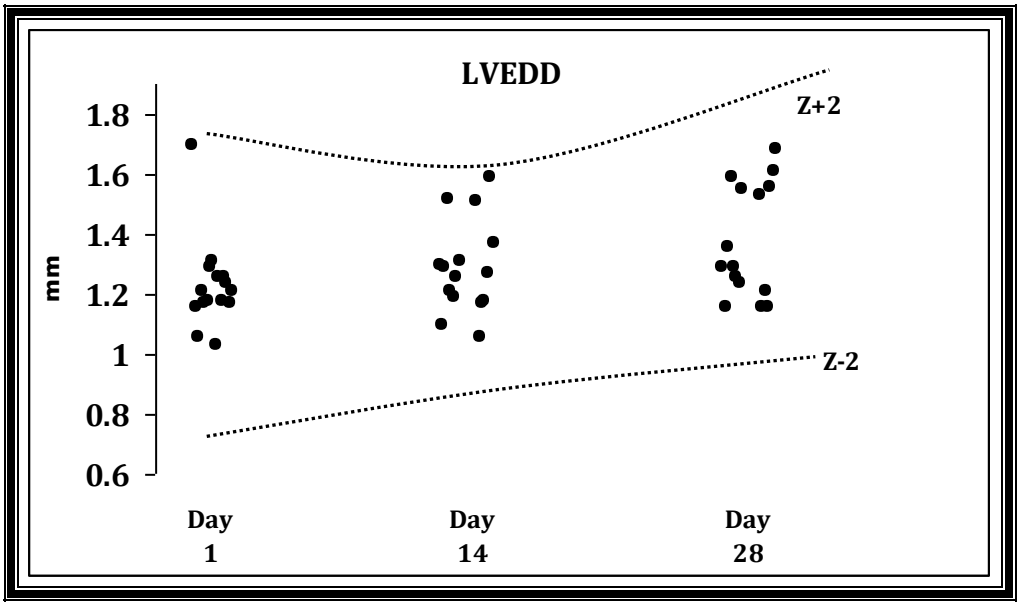


Figure 4.19 Left ventricle end- diastolic diameter 1-28 days

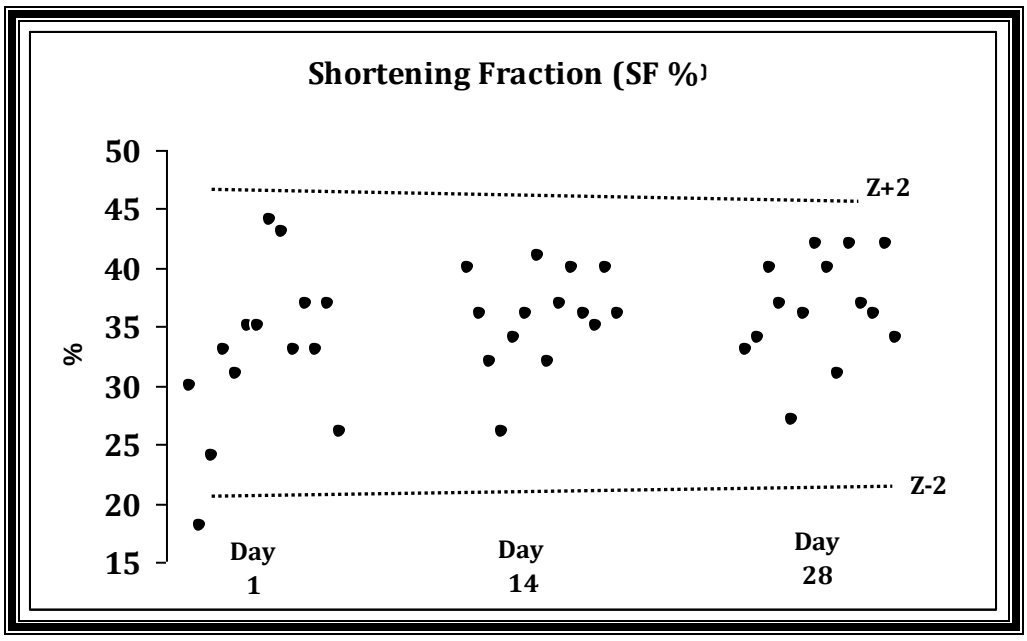


Figure 4.20 Shortening fractions 1-28 days

4.7 INTER-OBSERVER ERROR

Before the study commenced, all echocardiographers attended a training session specifically aimed at measuring all dimensions according to the standardized ASE recommendations (Sahn *et al.*, 1978). Immediately after this training, 10 infants' cardiac dimensions were measured and one set of inter-observer data was produced. Retraining was given after two weeks and a second set of data (n = 15) was generated. Inter-observer error was calculated for all 3 Echocardiographers who participated in the study and calculated by the Bland and Altman method for the variability between scans.

Table 4.31 depicts the differences in measurements between the first set of inter-observer analysis versus the second set. There were no statistically important differences between the observers ($p < 0.05$).

TABLE 4.31 INTER-OBSERVER DIFFERENCES

Variable	Mean difference 1st set (n=10)	Mean difference 2nd set (n=15)	p-value for the 2nd set
SF%	7.0	6.2	0.20
LVEDD (mm)	1.7	0.6	0.98
PW (mm)	1.1	0.4	0.99
IVS (mm)	0.8	0.1	0.11
LA (mm)	1.1	0.1	0.28
AOR (mm)	1.6	0.7	0.69
ACS (mm)	2.5	0.2	0.72
LV MPI	0.22	0.25	0.36
RV MPI	0.31	0.23	0.29

(SF = shortening fraction; LVEDD = left ventricle end -diastolic diameter; PW = posterior wall; IVS = inter ventricular septum; LA = left atrium; AOR = aortic root; ACS = aortic cusps separation; LVMPI-= left ventricular myocardial performance index; RVMPI = right ventricular myocardial performance index)

The LVEDD initially had an interobserver difference of 1.7 mm during the first measurements, but this improved after retraining by decreasing to only 0.6 mm. Similar observations were obtained for IVS (0.8 mm for the first set and 0.1 mm for the second). The PW's first inter-observer value was 1.1 mm and for the second set 0.4 mm.

None of the differences observed during the second set of measurements were statistically significant (p= <0.05). The PW (1st-1.1, 2nd-0.4) and the IVS (1st-0.8, 2nd-0.1) showed the largest variations, but were not statistically significant.

4.8 LOCAL VS. INTERNATIONAL VALUES

The findings of this study were compared to International values. Mean, sample size and standard deviations were compared and statistically analyzed. The majority of measurements were within the ranges of the international values for preterm and low birth weight infants. Interestingly, when compared with Skelton *et*

al., (1998), significant differences were observed for diameters of the IVSd, PWd and LA across all weight groups with as well as the aortic root measurement in Group 1, were all of these measurements, measured larger than the international values (Table 4.32).

TABLE 4.32 LOCAL VS. INTERNATIONAL VALUES A

Variable	GROUP 1 Weight Category <0.999g			GROUP 2 Weight Category 1000-1499g			GROUP 3 Weight Category 1500-2500g		
	Study data (n=290)	(Skelton *et al.*, 1998)	p value	Study data (n=290)	(Skelton *et al.*, 1998)	p value	Study data (n=290)	(Skelton *et al.*, 1998)	p value
LVEDD	12.03	11.40	0.8770	12.45	12.30	0.9900	14.24	15.10	0.8300
LVESD	7.86	7.80	0.8840	8.13	8.50	0.3970	9.30	11.50	0.5910
PWd	3.18	2.60	0.0001	3.26	2.70	0.0001	3.58	2.70	0.0001
IVSd	3.34	2.70	0.0001	3.33	2.80	0.0001	3.77	3.40	0.0100
LA	8.76	7.90	0.0150	8.95	7.80	0.0180	10.85	9.50	0.0240
AoR	6.85	6.50	0.0350	7.22	7.20	0.7800	8.26	8.40	0.2770

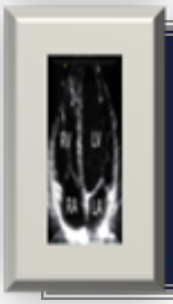
(LVEDD= left ventricle end-diastolic diameter; LVESD= left ventricle end-systolic diameter; PW= posterior wall; IVS= interventricular septum; LA= left atrium; AoR= aortic root)

When compared with, Walther *et al.,* (1986) significant differences were observed for diameters of the LA, AO, IVSd, PWd and SF in weight groups 1 and 2 weight groups, and measured larger than the international values (Table 4. 33).

TABLE 4.33 LOCAL VS. INTERNATIONAL VALUES B

Variable	GROUP 1 Weight Category 750-1249g			GROUP 2 Weight Category 1250-1749g			GROUP 3 Weight Category 1750-2249g		
	Study data (n=290)	(Walther *et al.*, 1986)	p value	Study data (n=290)	(Walther *et al.*, 1986)	p value	Study data (n=290)	(Walther *et al.*, 1986)	p value
LVEDD	12.1	12.6	0.2	12.9	13.3	0.17	14.5	15.2	0.08
SD	2.1	1.5		1.9	1.2		2.1	1.5	
LVESD	7.9	8.5	0.58	8.5	9.1	0.15	9.4	9.8	0.28
SD	1.4	1.2		1.6	1.0		1.7	1.5	
SF%	34.5	33	<0.007	34.7	31	<0.001	35	36	1.2
SD	5.9	0.5		6.5	0.4		5.5	0.6	
IVSd	3.3	2.3	<0.001	3.4	2.6	<0.001	3.8	2.8	0.03
SD	0.6	1		0.7	0.8		0.7	0.8	
LA	8.7	7.2	<0.001	9.7	8.5	<0.001	11.0	9.6	0.43
SD	1.6	0.7		1.8	1		2.3	0.8	
AoR	6.8	6.3	<0.005	7.8	7.3	<0.002	8.2	8.4	0.31
SD	1.2	0.6		1.2	0.6		1.5	0.5	
PWd	3.3	2.1	<0.001	3.3	2.5	<0.001	3.6	2.6	<0.001
SD	0.7	0.6		0.6	0.7		0.8	0.6	

(LVEDD= left ventricle end-diastolic diameter; SD = Standard deviation; LVESD= left ventricle end-systolic diameter; SF% = shortening fraction; IVS= interventricular septum; LA= left atrium; AoR= aortic root)



CHAPTER 5

DISCUSSION

Detailed measurements of cardiac structures remain a clinically important aspect to guarantee modern and scientific management of children with various types of congenital or acquired cardiac disease. Decisions regarding the type and timing of interventions, initiation and tailoring of pharmacological management often rely to a large extent on cardiac chamber measurements. For this reason the cardiac structures develop and grow with the child throughout childhood and interpretation of these measurements must take into account a patient's body size or weight.

Despite the importance of these measurements in practice, a comprehensive set of normative data in premature and low birth weight infants, derived from a large cohort of patients, are generally lacking. Some paediatric centres have developed their own reference normative data to use in their echocardiographic reporting and as a part of their clinical decision making.

The use of echocardiography has also been expanded to include re-evaluation after surgery or initiation of oral or parenteral vasodilator therapy for pulmonary hypertension as well as re-evaluating withdrawal of extracorporeal cardiopulmonary support. It is also important in infants with respiratory distress where changes in the right and left heart dimensions occur. Therefore the reliability and validity of these measurements are of great importance.

Standardization of chamber measurements has been a problem since the early development of echocardiography. Dramatic changes in echocardiographic methods and techniques during the past ten years has improved imaging and strengthened its position as a dominant diagnostic instrument in cardiology in general (Lang *et al*., 2005). The preceding 15-20 years have introduced important developments in echocardiographic techniques, technology and resolution so that it is now possible to obtain more clearly identified M-mode waves and measurements.

This study represents the first reported data for a sub-Saharan third world population. It establishes a comprehensive set of normative data. The study population included all the different race groups and especially a significant number of non-Caucasian patients who made up more than 90% of the sample. It should be emphasized that the data of this sample reflects the Free State and Northern Cape population, but

the author speculates that this data may be applicable to South Africa as a whole. This study included two hundred and ninety preterm and low-birth weight infants (n = 290). Compared to previous international studies, this study is one of the largest and most recent.

5.1 STUDY POPULATION

Low birth weight is an increasing problem in both developed and developing countries. According to United Nations International Children's Emergency fund (UNICEF), 22% of all low-birth weight infants born in developing countries are born in Africa. They state that the number of low- birth weight infants is more than double the number born in developed regions (UNICEF 2009:Online). Locally, low birth weight in South Africa is reported at a level of 14.6% for the private sector and this percentage increases to as much as 25% affecting dominantly the lower income groups of the public sector (Statistics South Africa 2011: Online).

Although normative data is reported in the literature, a number of important differences should be noted. The majority of work has been performed in first world populations and this is one of the few studies representing third world populations. It is particularly noteworthy that this represents the only study in Sub Saharan Africa. A sub-objective was to determine whether differences in cardiac size are present in small for gestational age infants since little could be found in existing literature and as a result infants were also classified according to gestational age. The overwhelming majority of work in reported literature had been performed in term new-borns and only a limited number of studies were performed on exclusively premature infants or low-birth weight infants. Skelton and co-workers (1998) conducted a study consisting of 79 infants of less than 34 weeks gestation. Echocardiography was performed on days 0, 7 and 28 after birth to produce a set of reference ranges. Cardiac dimensions correlated well with gestational age and birth weight. There was a significant increase in measurements over time as these infants gained weight.

Sollinger *et al*., (1973) published a series of measurements which included preterm infants, all over 2750g in birth weight. Lange *et al.,* (1983) reported a series of 91 premature infants, 49 of whom were less than 2500g in weight. Both studies included infants up to three weeks of age. Walther *et al.,* (1986) also produced new reference ranges for the left heart and interventricular septum. Between them they examined over 300 babies, but only between one and two thirds were preterm, and again very few were of low birth weight. In these studies- values were given in terms of birth weight but not gestation. However, this research project included 290 preterm and low-birth weight infants, with a gestational age ranging from 26-40 weeks- with a median of 31 weeks. Of particular note, a large sample (n=44) of extremely low birth weight infants was included in the final cohort of patients whereas Skelton *et al*., (1998) only had 8 infants between 500-1000g.

Walther and colleagues (1986) investigated normative data on intracardiac dimensions and systolic time intervals in very low birth weight infants. M-mode echocardiograms were collected from 210 healthy preterm and term neonates with birth weights between 780 and 5,350g and gestational ages ranging from 26 to 43 weeks.

5.2 CARDIAC DIMENSIONS AND GENERAL CONCEPTS

Overall, results of this study show that cardiac dimensions increased with an increase in body size/mass. LV dimensions, volumes, and wall thicknesses are echocardiographic measurements widely used in clinical practice and research. LV size and performance are still frequently visually estimated. However, qualitative assessment of LV size and function may have inter-observer variability and is a function of interpreter skill. Therefore, it should regularly be compared with quantitative measurements. Strict quality control for the proposed reference measurements was applied in this study. The American Society of Echocardiography has previously published standardized quantitative guidelines for chamber and vessel quantification during performance of a paediatric echocardiogram (Sahn *et al*., 1978). Because the sizes of cardiovascular structures increase with somatic growth, paediatric quantification requires the adjustment of measurements for the effects of body size in order to determine when a measurement is outside the normal range. A universal paediatric normative database of measurements from a normal population encompassing the full range of body sizes encountered in paediatrics would provide clinicians and researchers with a powerful tool to distinguish normal from abnormal values and too aid in the management of children with heart disease.

It is important to highlight the fact that in this study all M-mode dimensions were calculated according to the American Society of Echocardiography's (ASE) standards. Reported literature rarely states whether accepted, standardized criteria were used during conducting of studies. Few other studies used standardized published criteria (Kampman *et al.,* 2000 and Guzeltas *et al.,* 2011) but their studies were carried out in term infants. This emphasizes the lack of standardized, repeatable measurements. Moreover, the majority of previously published work is all over ten years old and most did not specify that they used the ASE method or did not make use of this standardised method of measuring. Rapid technological advances have been seen over the past decade; it is important to realize that equipment has shown marked refinement since the early 80's. All these factors combined gave rise to a considerable improvement in the quality of scanning. It is thus logical to reason that modern echocardiography equipment will thus enable more refined and accurate measurements, especially of tiny morphological structures in a small hyper mobile heart.

Cardiac dimensions have been expressed as a percentage of the mean normal value, but this does not take into account normal variation. Another commonly used method for expressing normal values is the use of percentile charts. Although these are useful for determining whether a given value lies within the population, values that lie above or below the uppermost or lowermost percentile lines, respectively, cannot be

quantified. This limitation is overcome by the use of *z*-scores (i.e. the number of standard deviations a measurement departs from the normal mean). The use of *z*-scores enables a more precise assessment of cardiac measurements, which is particularly important in conditions associated with very small chamber dimensions (e.g. hypoplastic left heart syndrome, pulmonary atresia) or very large measurements (e.g. wall thickness in hypertrophic cardiomyopathy). In this study, upper and lower limits were established for all variables (z-2 and z+2). A separate table for easy clinical reference with upper and lower limits were thus developed. We expect to use this in neonatal units as a quick reference guide. A cut-off value of z-3 was included for rapid determination of hypoplastic left hearts as the ultimate cut-off point for any intervention in clinical practice.

5.2.1 TWO- DIMENSIONAL MEASUREMENTS

To our knowledge there are no other studies available for mitral and tricuspid valve annular measurements in premature and low birth weight infants. This parameter is especially important in congenital heart lesions where cardiac structures are underdeveloped affecting especially the left heart such as hypoplastic left heart, congenital mitral stenosis as well as for the right heart with lesions such as pulmonary atresia, tricuspid atresia and tricuspid stenosis. Quick reference values including values for z+3 and z-3 were also developed in the study for these in order to be used for selection for palliative or reparative surgery when dealing with these very small infants.

5.2.2 FUNCTIONAL MEASUREMENTS

As expected standard M-mode functional measurements (SF, EF) remained constant for all weight groups. The shortening fraction is most often used to determine left ventricular function, especially in newborns. Since it is relatively independent of changes in heart rate- (therefore ideal in newborns which usually have very high heart rates), or loading conditions of the heart, it is independent of preload/afterload.

The Myocardial Performance Index (MPI) has the advantage that it is simple, non-invasive, easy to estimate and is reproducible. The index combines systolic and diastolic function and can thus be viewed to represent global heart function. It is a combination of systolic and diastolic time intervals based on ejection time, relaxation period and contractility. It has been shown to be reliable and reproducible and in clinical practice it could be viewed as a rough indication of global cardiac function, comparable to erythrocyte sedimentation rate for infection. However, as a measurement, it is independent of ventricular geometry, heart rate, atrioventricular valve regurgitation, afterload and preload conditions. Limitations of the MPI include the fact that measurements are obtained during two different cardiac cycles. One should not overlook the fact that a

pseudo normalization phenomenon occurs when the shortening of the IVRT due to both systolic and diastolic dysfunction lowers the MPI index under certain conditions, resulting in less accurate estimation of cardiac function. Therefore, in this study, five cardiac cycles were measured and averaged to compensate for external influences.

In this study the MPI index values for the right ventricles were overall 0.23 and for the left ventricle 0.30. The right ventricle was slightly lower than the left ventricle indicating a more forceful right ventricular function. One can anticipate this since the right ventricle is more dominant during fetal life. The fact that the results show that the two MPI values correlate well indicates that the left ventricle and right ventricle developed in parallel postnatally.

5.3 COMPARISONS

5.3.1. GENDER

The results of this study showed that gender did not have any effect on cardiac dimensions or function. In contrast to our findings gender differences have been reported in some studies (Kampman *et al*., 2000). However the population consisted mostly of older children – a finding most likely linked to the hormonal influences during puberty (Kampman *et al*., 2000). But for these young low birth weight infants in the Free State and Northern Cape, gender has no influence on cardiac dimensions. Our findings are in agreement with similar results of Kampman *et al*., (2000) who conducted a study on 2036 children in an age group ranging from one day to 18 years of age and Guzeltas et *al.,* (2011) in a study consisting of 250 newborn infants, weighing between 2000-4500g, who also found no significant differences between the genders. A limited number of previous studies have shown that measurements were either not or only minimally influenced by sex differences in these small infants and that hormonal influences only start playing a role during puberty (Henry, Ware, Gardi, Hepner, McKay & Weiner, 1974).

5.3.2. SGA, AGA, WEIGHT AND BSA

A particularly noteworthy and clinically significant finding is that weight and body surface area (BSA) are closely related and can be used interchangeably. As a matter of fact, there was an excellent correlation

(r=0.98) between BSA and birth weight for all measurements. Roge *et al.,* (1978) also tested these correlations and found that in fact, each of the variables (height, weight, BSA, and cube root of weight) were so strongly correlated with one another (r>0.90) that regression using any one of the four as independent variables were equivalent for all practical purposes. This finding has a number of important clinical applications. Weight is much quicker and easier to perform on a standardized scale opposed to body surface which is a calculated value consisting of weight and length. Weight is also more likely to be accurate and can be performed by anybody after minimal training on a digital scale. In units of the Free State and Northern Cape weight is a standard measurement available in all documents related to newborns and thus freely available to any physician doing cardiac interrogation.

Limited data exist comparing cardiac dimensions between AGA and SGA infants. The good correlation between weight and BSA was also present when the two groups were compared and also an important finding to take note of. Cardiac dimension and function of SGA and AGA infants were separately analysed but statistical analysis demonstrated that no significant differences in cardiac dimensions of functional measurements existed for comparable weight and BSA.

This is interesting, since we expected AGA to be slightly larger than those of SGA infants whose measurements we speculated could be influenced by the long periods of intrauterine growth retardation. SGA infants are usually taller and thinner and it could be speculated that their cardiac development may thus also differ. However, the results show that there were no differences in cardiac contractility or in the size of cardiac dimensions. This is supported by the fact that the study groups' cardiac measurements remained the same whether it was compared or plotted against BSA or weight. As a result, the investigator thus opted to plot the values against weight due to the fact that weight has less probability of mathematical error if used rather than BSA and is also much easier and less time consuming to determine. To conclude, there is no significant difference between BSA and weight in all low-birth weight preterm infants and this can also be extended to SGA infants. It is therefore not necessary to develop separate tables for cardiac dimensions for SGA infants. This is supported by international studies that have reported that the cardiac dimensions for SGA fetuses can be smaller or greater than AGA infants but are not significantly different (Goldenberg *et al*., 2008).

Henry *et al*., (1974) found that M-mode echocardiographic measurements in infants and children up to early adulthood followed a linear regression either directly related to the body surface area or its square root. Also, Epstein, Goldenberg, Allen, Konecke & Wood (1975) referenced their data solely to BSA. They found that, in small children and infants, BSA correlated poorly as a result of wide variations in height. Henry and co-workers *(*1974) pointed out the importance of considering age as well as BSA or weight in normal predicting equations. Thus there was not complete agreement on the best reference point for reporting normal data. Therefore, after the analysis of this data, only one set of reference values was developed to make it clinically useful and applicable for general use as a quick reference guide.

A study conducted by Leipala, Boldt, Turpeinen, Vuolteenaho and Fellman (2009) found that fetal growth restriction is associated with alterations in early hemodynamic adaptation in low birth weight infants. Increased ventricular output and cardiac hypertrophy occur in fetal animals in chronic anaemia and hypoxia. The septal and left ventricular hypertrophy observed in the infants could be explained by increased left ventricular work load *in utero* resulting from the shift in the left to right output ratio (Leipala *et al.,* 2009). The authors speculated that another possible explanation for an increase in left ventricular afterload is impaired systemic vascular resistance. Low birth weight has been reported to be linked with decreased endothelium –dependant vascular dilatation later in life (Leipala *et al.,* 2009). Cardiac hypertrophy observed in the infants is in accordance with previously reported hypertrophy of both ventricles in growth – retarded foetuses. The most probable mechanism of this hypertrophy is prolonged exposure to an increase in myocardial workload (Leipala *et al.,* 2009). In this study however, no differences could be found between SGA and AGA infants to validate these findings.

In summary, the data provided evidence for the importance of weight and BSA as predictors of cardiac size and function in all types of low birth weight infants and are applicable to small and normal for gestational age infants. Due to the strong correlation between weight and BSA we preferred body weight to standardize the M-mode echocardiographic measurements in our population. In newborns, because of the small body surface area, body weight was preferred for accuracy of measurements. This is further supported by the work of Guzeltas *et al.,* (2011) which also revealed a good correlation with body weight. When body weight increased, the measured values also increased in parallel. The measured values were not influenced by gender. Functional parameters did not change with body weight and gender.

5.3.3 LONGITUDINAL STUDY

The infants in the longitudinal study showed, as expected, an increase in body mass and surface area over the 28 day period. Parallel increases in cardiac dimensions were seen over time as the infants developed and gained small amounts of weight. All the cardiac dimensions and functional indices however, when plotted against body weight of the main group, remained within the upper and lower limits found in the study. No obvious changes were observed in ejection fraction, shortening fraction or MPI index. Similar findings have been well documented in term and older infants. The data obtained from the longitudinal arm of this study thus illustrates that our reference ranges can be applied to all LBW infants with gestational ages ranging from 1-28 days.

The longitudinal study is particularly noteworthy. Some infants were re-measured at different ages up to 28 days. In these, body weight at the time of echocardiographic analysis was performed and the cardiac

dimensions compared to infants in the same weight group (as determined by the study) as the infant at the time of measurement. All these measurements from 0 – 28 days were within the normal ranges for weight as determined by the study. Cardiac dimensions increased parallel to increase in body weight. This has important clinical implications: it would seem to indicate that the reference ranges can be used for low birth weight infants from 0 -28 days. This is supported by a number of other studies. Skelton *et al*., (1998) found a close correlation of gestational age and birthweight and concluded that either can be used for reference ranges. Zecca, Romagnoli, Vento, De Carolis, De Rosa and Tortorolo (2001) longitudinal study did not find the same correlation with gestational age, but demonstrated that dimensions increase parallel to increase in body weight. This was also shown by Walther *et al.,* (1986). Results of the longitudinal study showed that increase in body weight is closely correlated with an increase in cardiac diameter and that as an infant ages and gains weight, cardiac dimensions increase in parallel. We therefore conclude that, based on the fact that all measurements between 1 - 28 days were within z -2 and +2 when analysed for weight at the time of measurement, the reference ranges as determined for weight can be used for all low birthweight infants between 1 - 28 days of age and that body weight, rather than gestational age is an important determinant of cardiac dimensions.

5.3.4 LOCAL VERSUS INTERNATIONAL VALUES

The sample size of this study is larger than other studies performed on low birth weight and premature infants. The study included 290 infants and also included functional assessment of the LV and the RV together with M-mode measurements. Skelton *et al*., (1998) only included 79 infants but had the largest sample for preterm infants and it is the most recent reference values for cardiac dimensions. Walther and colleagues (1986) investigated normative data on intracardiac dimensions and systolic time intervals in very low birth weight infants. M-mode echocardiograms were collected from 210 healthy preterm and term neonates with birth weights between 780 and 5,350g and gestational ages ranging from 26 to 43 weeks.

The investigator intended to compare our local values with the “golden standard” as proposed by Roge, Silverman, and Hart & Ray, 1978. However, this study only consisted of 93 patients, infants and children up to 18 years of age. The exact numbers of premature infants were not stated by the authors. On closer inspection of the original study, it became clear that the dimensions for BSA were extrapolated where data was not available. The nomograms for cardiac dimensions according to BSA are also difficult to read for patients with low/small body surface areas. The data was compiled in 1978 and we thus resorted to more recent and comparable work.

When compared with Skelton *et al*., (1998) and Walther *et al.,* (1986) the investigated overall values were very similar although minor but statistically significant differences existed.

When compared with Skelton *et al*., (1998) significant differences were found in the measurements for the PWd, IVSd and LA, with our measurements measuring statistically larger. Possible explanations for these findings include the fact that the IVS and PW are very small muscular structures and with the improvement in scanning equipment and transducers to measure these fine structures, outlines become more clearly visible and thus more accurate measurements can be obtained. Alternatively, it could be due to the fact that this sample size is much larger than Skelton *et al*., (1998) and the study has more accurate measurements due to the larger sample size.

When compared with Walther *et al.,* (1986) significant differences were also observed for the diameters of the LA, AO, IVSd, PWd and SF across weight groups. Note should be taken that our weight categories were different to that of Walther *et al.,* (1986) but we reanalysed and re-arranged our data into similar weight categories to ensure comparable data. It may be that the weight categories may have had an effect on the dimensions, although it is highly unlikely, since similar significant differences were observed when compared to the Skelton *et al*., (1998) data as mentioned. The fact that similar differences were observed between this comparison as well as those of Skelton *et al*., (1998) highlights the fact that regional differences may exist.

Additional explanations for these variations could be explained on the basis of ethnical and racial differences. One could speculate that this difference could thus be a racial or regional difference and that the average African infants' septum and posterior wall might be thicker than the average European infant's. Alternatively, the inclusion of SGA infants may have had some influence on the results, but PWd and IVSd were compared for AGA and SGA infants and no significant difference in thicknesses were observed. We did not record IVSs and PWs, which should become even denser in systole, and this may be a focus for future studies. The presence of "physiological" hypertrophy is important for neonatologists to take note of since certain drugs (e.g. steroids) may induce hypertrophy and if international ranges are used, infants may incorrectly be considered to have secondary cardiac effects of these drugs.

This highlights why it is so important to develop normative values for specific populations. The majority of African infants are more likely to battle with high blood pressure and left ventricle hypertrophy in their adulthood and this inclination towards left ventricular hypertrophy may even start in infanthood. Cardiac dimensions of preterm babies differ from those seen in older children and adolescents and it is important to know these for a given population in order to accurately evaluate measurements in sick children.

The left atrial diameters also measured larger than Skelton *et al*., (1998) and Walther *et al.,* (1986) averages for all weight groups. It is difficult to explain but, from a physiological perspective, one can speculate that it

might be due to the fact that the posterior wall and interventricular septum is thicker, and thus maybe less complaint in diastole. This can lead to a more dilated LA in order to handle retrograde pressure.

Another important factor regarding LA size is that it is used to determine the size and effect of the PDA on the left heart and all left to right shunt abnormalities like a ventricle septal defect (VSD). The LA is an important indicator of how well the pulmonary system and systemic system is functioning. The aortic root: LA ratio gives an indication regarding the size of the PDA. It should be noted that we included infants with small PDA's (haemodynamically significant PDA's were excluded – Chapter 3: Methodology (Section: 3.3.1 In and Exclusion Criteria, pg 33) and another explanation may therefore be the presence of ductuses in a third of the study population which may give rise to the slightly larger LA sizes. However, in the Skelton *et al*., (1998) study only "congenital heart lesions other than PDA" were excluded, which would indicate that even large PDA's may have been included. In the Walther *et al.,* (1986) study the only reference to exclusion criteria were "clinical or radiological evidence of cardiovascular abnormalities" and they only looked for PDA when LA/Ao ratio were > 1.25 while in the Silverman (1993) studies, PDA's were not even mentioned. We therefore included these silent PDA's since it represents a true reflection of "normal" and theoretically should yield real life clinically relevant reference values.

This result would thus seem to indicate that the LA may be naturally larger in African infants and this ratio needs to be adapted before the size of the PDA or any other congenital abnormality affecting the left heart and its effects can be evaluated in our population. In this study - the LA /aortic root ratio was calculated and the results were as follow: Group 1(1.27:1), Group 2(1.23:1) and Group 3(1.31:1), compared to Walther and colleagues (1986) with a ration of (1.16 +/- 0.10). The fact that minor PDA's were included support the conclusion that a LA/Ao root ratio of ≤ 1.3 is unlikely to be of any haemodynamic significance in our population.

Regarding MPI index values, in a study by Eidem, O'Leary, Tei, and Seward (2000) they found the RV MPI in 152 normal children (ages 3-18 years) to be 0.32 ± 0.03 this is slightly higher than our mean for LV MPI: 0.30 (Group 1: 0.31; Group 2: 0.29; Group 3: 0.29) and RV MPI 0.23 (Group 1: 0.23; Group 2: 0.22; Group 3: 0.23). In another study by Tsutsumi, Masahiro, Eto, Hota, and Kato (2002), the MPI index was prospectively and longitudinally determined in 50 normal foetuses. The MPI index of the left ventricle decreased linearly with advancing gestational age during 18-33 weeks and decreased more rapidly with increasing gestational age after 34 weeks (LV MPI- 0.43 +_0.03). The index of the right ventricle decreased slightly and linearly with advancing gestational age during 18-41 weeks (0.49+_ 0.05). In neonates, the MPI index of the left and right ventricle increased immediately and transitorily after birth and decreased and stabilized after 24 hours of life. Considering most of the infants in our study was seen 72-96h after birth- our values correlate well with theirs given for that time frame (LV MPI- 0.38, RV MPI- 0.28).

5.3.5 INTER-OBSERVER VARIABILITY

Only a few studies have taken inter-observer variability into account when producing normative values. Before the study commenced all echocardiographers were trained to measure all dimensions according to the standardized ASE methods (Sahn *et al*., 1978). After this training, 15 infants' cardiac dimensions were measured and one set of inter-observer data was produced, evaluated and differences inspected. Inaccuracies in measurements were addressed and a second set of data after re-training was produced. The second set showed little to no differences between the observers. The study then proceeded. Therefore, the data collected during the whole study period was accurate and reproducible because a systematic method was followed. This ensured qualitative control and reliability of all measurements.

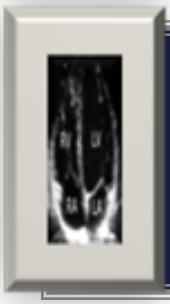
Results from other studies looking at intra-observer and inter-observer variations of echocardiographic measurements are limited, especially in children. Previous studies on inter-observer variation of echocardiographic measurements have shown different results. Most studies varied within the limits of 10% which is generally considered clinically insignificant (Shifan, Ayres, Harris, Bricker & Labarthe, 1999; Sahn, DeMaria, Kisslo, and Weyman, 1987). In this study the interobserver variations also fell bellow the limits of 10% which is found to be non significant in the clinical measurements.

5.4 STUDY LIMITATIONS

Although thorough scientific rules and methods were employed in the execution of this study it is important to take note of the limitations that might affect the results of this study. The infants in this study were not randomly selected since the study wanted to look at the profile of infants who had no cardiac abnormalities and who met the inclusion criteria. Although the study aimed to include a minimum of 50 infants in a weight group- only 44 very low – birth weight infants were included in group 1: (<0.999g). However, this is still the largest amount of these small infants of this weight group in an echocardiographic study. Cross sectional studies are relatively quick and easy to perform but do not permit distinction between cause and effect. Another limitation is the fact that the study did not record IVS and PW in both systole and in diastole, the study only measured in diastole. We also did not analyse the IVS/LVPW ratio in the groups to determine the presence of asymmetrical hypertrophy for the reason that the aim was to yield a set of normal reference ranges. It would have been helpful to record blood pressures in our study population to compare with international data, but this was primarily an echocardiographic analysis.

The study had more than 2 investigators which could have influenced the quality of the measurements but this was compensated for by evaluating interobserver variation which showed no statistically important

differences. Further studies need to be carried out to explore possible causes for difference in sizes of cardiac walls in systole especially in very low birth weight infants.



CHAPTER 6

CONCLUSION & RECOMMENDATIONS

The strength of this study lies in the fact that it is a first for Africa. Although the sample consisted of mostly children of the Free State and Northern Cape, the study reflects our population as a whole.
It is also one of the largest and most recent series on low-birth weight and preterm infants worldwide.

It is the first study that provides normative data for cardiac measurements of low birth weight infants for South Africa. The study data is accurate and reproducible, interobserver analysis was performed and monitored to improve the accuracy of the measurements. The study assessed normative cardiac measurements divided in M-mode, 2-D and functional measurement for premature infants in 3 weight groups.

The study developed normative ranges for cardiac measurements for the Free State and for use in South Africa. The study values differ slightly from the international values.

Weight correlated well with BSA and the data suggest that weight can be used to develop tables for clinical use. Cardiac chambers increased with BSA and weight and functional measurements stayed the same throughout the weight groups. Gender and race played no role in any functional measurements or with the cardiac sizes.

There were also no differences between Average for gestational age (AGA) and Small for gestational age (SGA) infants in this study group- therefore indicating the development of only one set of reference range values for both SGA and AGA infants.

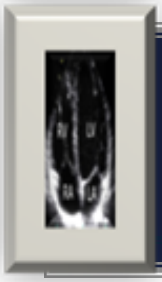
The longitudinal study also confirmed that the values are applicable to all low birth weight infants up to 28 days of age.

The average South African infant's cardiac chambers differ in some from international values. The IVS and PW measured thicker and the LA larger. This could be due to numerous factors that should be investigated further. It also support the fact that population specific reference values should be developed and used. Systolic and global functions were remarkably similar and constant throughout weight categories.

In conclusion- the study emphasised the profound effect of growth and weight gain on the cardiac structure and the importance of measuring these structures according to a standardized specified protocol (ASE). Normative values are a useful and effective tool in children for assessing the effects of medical therapy on the severity of valvular regurgitation and on ventricular compensation and function when it might change medical management. Also in assessing patients with known cardiac defects to determine the timing of medical or surgical therapy and assessing suspected cardiomyopathy, heart failure, and changes in clinical status or to guide medical therapy. It is also important in the screening patients for genetically transmitted cardiovascular disease, such as cardiomyopathy, Marfan syndrome, or Ehlers-Danlos syndrome and for conducting baseline evaluation and re-evaluation of patients receiving cardio toxic chemotherapy to determine the advisability of additional or increased dosages.

RECOMMENDATION

Future aims should focus on constructing studies to monitor possible causes for the increase in IVS, LA, and PW sizes. Further studies could also be aimed at the follow up of these infants to see whether with aging- the septum and posterior walls increase or decrease in size or normalizes.



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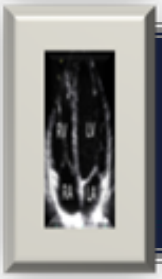


APPENDICES

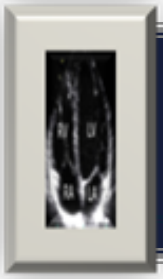
Appendix A: Information and consent documents (AFR/ENG/Sesotho)

Appendix B: Correspondence-Universitas, Rosepark, Medi-clinic

Appendix C: Ethical clearance

Appendix D: Location of M-Mode measurements

Appendix E: Ballard scoring method



APPENDIX A

TOESTEMMING TOT DEELNAME IN NAVORSING

STUDIE: VERWYSINGS VAN HARTSONAR WAARDES VIR PREMATURE EN PASGEBORE BABAS VIR DIE VRYSTAAT EN NOORD KAAP

Studie Dokter Naam: Prof. SC Brown, Dr DG Buys, S.Jacobs

U is ingelig oor die studie deur:

Hiermee word u gevra om deel te neem aan 'n navorsings studie.Let daarop dat as u hierdie vorm voltooi, u vrywilllig instem om deel te neem aan die navorsings projek. U sal anoniem bly en u data sal as konfidensieel behandel word ten alle tye.U mag u kind onttrek van hierdie studie op enige oomblik gedurende die voltooiing van die vorm/ prosedure.

Die doel van hierdie studie is om inligting te versamel so dat pasiënte soos u kind en ander in die toekoms meer akkurate, vinnige, en effektiewe gesondheidsorg en behandeling kan ontvang. Dit sal ook die mediese wetenskap bevoordeel en nuwe inligting verskaf aan gesondheidspersoneel.

Let daarop dat geen vergoeding vir u deelname beskikbaar/betrokke is nie.U mag Prof S.C Brown/S.Jacobs skakel indien u enige navraag het in verband met die studie.

U mag die Etiek kommitee skakel by die Fakulteit van Gesondheidswetenskappe OFS, by (051) 4052812 indien u enige navraag het.
U deelname aan die navorsing is vrywillig en u sal nie gepenaliseer word of verlies lei indien u deelname weier nie.

Daar is geen risiko verbonde aan Eggokardiografie nie en dit is suiwer diagnosties van aard.

Let wel: Hierdie is nie 'n volledige hartsonar nie,indien enige abnormaliteite gevind word,sal dit aan 'n Kardioloog gerapporteer word,wat dan verdere ondersoek sal instel.

U herken hiermee dat die bogenoemde inligting verbaal aan u oorgedra is. Ek verstaan my betrokkenheid in hierdie studie en neem vrywillig deel.

HANDTEKENING VAN OUER/VOOG: _____

INFORMASIE DOKUMENT

Studie titel**:**
Verwysings van hartsonar waardes vir premature en pasgebore babas vir die Vrystaat en Noord Kaap

Dankie vir u deelname aan hierdie vrywillige studie.

Voorwoord:

Ons, die Department van Pediatriese Kardiologie is tans besig met navorsing om normale waardes van eggokardiografie te bepaal op kinders in die Vrystaat en Noord-Kaap provinsie.

Uitnodiging om deel te neem: Ons vra u toestemming om u kind in die studie in te sluit.

Wat is in die studie ingesluit – Die studie bestaan uit 'n roetine hart sonar wat gedoen sal word deur 'n gekwallifiseerde eggokardiograaf ten minste een keer gedurende die studie periode. Die toets prosedure neem ongeveer 10 minute en is nie pynlik nie. Die hart sonar sal by u kind se saal gedoen word. Ons beoog om sowat 500 kinders in die studie te gebruik en ons sal u ondersteuning waardeur.

Risiko's om deel te neem aan die studie: Die mediese wetenskap is tans nie bewus van enige risiko's wat met roetine eggokardiografie gepaard gaan nie.

Voordele om deel te wees van hierdie studie: U kind se hart se grootte en funksies sal geevalueer word en afmetings sal geneem word,enige abnormaliteite sal ook gerapporteer word aan 'n Kardioloog

Deelname is vrywillig, en om te weier om aan die studie deel te neem, sal geen nadeel aan die pasiënt wees nie. Die pasiënt mag ten enige tyd onttrek vanaf die studie sonder om enige voordele te verloor.

Konfidensialiteit: Moeite sal gedoen word om alle informasie persoonlik en vertroulik te hou. Absolute konfidensialiteit kan egter nie gewaarborg word nie. Die Etiese kommitee mag deel van die studie gebruik vir mediese navorsing.

Kontak besonderhede van navorsers :

Mej. S.Jacobs, Dr. DG Buys Departement Pediatriese Kardiologie; tel: 051 405 3302

Prof S C Brown, Departement van Pediatriese Kardiologie; tel: 051 405 3241

U mag ook die Etiese kommitee skakel by die Fakulteit van Gesondheidswetenskappe by (051) 4052812, indien u enige navrae het in verband met die navorsingsprojek.

INFORMATION DOCUMENT

Study title: **Reference Echocardiographic measurements for premature and newborn infants of the Free State & Northern Cape**

Introduction:

We, the department of Paediatric Cardiology are doing research on the size and function of the heart chambers in all newborn infants. Research is just the process to learn the answer to a question. In this study we want to learn what the normal size of cardiac chambers are for children in central South Africa.

Invitation to participate: We are asking for your permission to include your child in this research study.

What is involved in the study: the study consists of routine heart sonar being done by qualified echocardiographers at least once during the period of the trial. An examination lasts about 10 minutes and is not painful. This will be done on your baby in his/her bed and the infant will not have to be moved anywhere. We intend to study at least 500 infants in this study and shall appreciate your support to help our children.

Risks: Science is currently not aware of any risks involved in routine echocardiography. This is also not painful and presents no discomfort for the children.

Benefits of being in the study:

Firstly you will assist us to determine normal values for children of central South Africa and help us to treat them better in future; secondly, if any abnormality is detected, your treating physician will immediately be notified and he will be able to arrange correct management.

Participation is voluntary, and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

There are no costs involved for you or your child.

Confidentiality: Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Ethics Committee for Medical Research and the Medicines Control Council *(where appropriate).*

If results are published, this may lead to individual/cohort identification.

Contact details of researcher(s) – for further information/reporting of study-related adverse events.

Prof S C Brown, Department of Pediatric Cardiology; tel: 051 405 3241

You may also contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4052812 if you have questions about your rights as a research subjec

CONSENT TO PARTICIPATE IN RESEARCH

You have been asked to participate in a research study.

You have been informed about the study by …….. .

You may contact department Paediatric Cardiology at 051 405 3241 any time if you have questions about the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4052812 if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate you will be given a participant information sheet, which is a written summary of the research.

The research study, including the above information has been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate.

_____

Signature of Participant Date

_____

Signature of Witness Date

Appendices

TUMELLO HO NKA KAROLO DIPALOPALONG

THUTO: HO LEKALEKANYA DIPALO TSE TLWAELEHILENG TSA SONAR/ECHO BANENG BA HLAHILENG PELE HO NAKO.

O kopilwe ho nka karolo thutong ya dipalopalo.

O tsebisitswe ka thuto ena ke …… .

Tseba hore ha ho na hlapiso ya chelete e tla bang teng.

O ka letsetsa Prof SC Brown ho 405 3241 nakonngwe le nngwe, ha o naledipotso mabapi le patlisiso ena, kapa ha patlisiso ena e o thefula.

O ka letsetsa mongodi wa Komiti ya Ethics (molao o laolang) ya lefapha la saense ya tsa bophelo ya Yunivesithi ya Foreisetata mohaleng ona 051-405 2812, ha o na le dipotso ka ditokelo tsa hao ha o nka karolo dipalopalong.

Ha o dumela ho nka karolo, o tla fiwa setshoano (copy) sa tokomane ena, le pampiri e ngotsweng e hlalosa tsohle ka monka karolo, e hlalosang ka bokhutshwane ka patlisiso.

Thuto ya patlisiso, le hlaloso e ka hodimo, ke e hlaloseditswe.

Ke ya dumela honka karolo thutong ena, ho bolela hore ke dumela ntle le qhobello ho nka karolo.

_____

Tekeno ya monka karolo Letsatsi

_____

Tekeno ya Paki Letsatsi

(Ha ho hlokahala)

Appendices

TOKOMANE YA HLALOSO

Sehloho sa thuto: Ho lekalekanya dipalo tse tlwaelehileng tsa M-mode le Doppler echo (sonar) baneng ba hlahileng pele ho nako.

Re lebohela ho nka karolo ha hao thutong ena e sa qhobellweng.

Tsebiso: Rona, lefapha la Pediatric Cardiology, re etsa patlisiso ya boholo bo tlwaelehileng ba dipelo baneng ba hlahileng pele ho nako Profinsing ya Foreistata. Patlisiso ka tsela ya ho fumana karabo potsong. Thuto ena, re batla ho tseba boholo bo tlwaelehileng ba dipelo le hore di sebetsa jwang baneng ba mona ha rona, hobane ha jwale re sebetsa ho ya ka ditekanyo tsa bana ba mafatshe a mang, tse nako nngwe di sa lekalekaneng. Le ha ese patlisisiso e tlwaelehileng baneng ba hlahileng pele ho nako, diteko tse ngata di etswa tsatsi le letsatsi baneng ba hlahileng pele ho nako, tse kenyeletsang dipatlisiso tseo re ikemiseditseng ho di etsa.

Taletso ho nka kanolo: Re kopa tumello ya hao to Kenya ngwana wa hao patlisisong ena.

Ho kenyeletswang thutong ena: Thuto e kenyeletsa sonar e tlwaelehileng, e etswa ke motho ya phethilengdithuto tsa sonar, bonyane hangwe nakong ya patlisiso ena. Teko e nka metsotso e ka bang 10, ha e bohloko. E etswa ngwana wa hao a robetse betheng ya hae, ebile ha ho moo a tlwa iswa teng. Re ikemiseditse ho sheba bana ba ka ba 50 ho qaleng ha thuto ena. Re tla thabelo tshehetso ya hao ho thusa bana ba rona.

Bothata ba ho kena thutong ena: Saense ha ena bopaki ba bothata bo ka bakwang ke sonar e tlwaelehileng.

Molemo wa ho kena thutong ena: Pelo ya ngwana wa hao e tla shejwa hore ha ena phoso, ka jwalo e tla thusa nakong e tlang ha mohlomong ho ka ba le ngwana ya nang le pelo e tshwanang le ya hae, ho e lekalekanya le yone.

Ho nka karolo ha ho qhobellwe: E bile ha o hana ho nka karolo ha o na ho ahlolwa, kapa wa tingwa menyetla e mohlomong e o tshwanetseng; monka karolo a ka tlohela nako nngwe le nngwe ntle le ho lahlehelwa ke menyetla e mo tshwanetseng.

Sephiri: Ho tla etswa matsapa hore boitsibitso ba hao ebe sephiri. Sephiri se felletseng ha se na ho hlapanyetswa. Boitsibiso ha hao boka nna ba ntshiwa ha bo batlwa ke molao.

Mekgatlo e ka kopisang/shebisisa kapa ho kopisa patlisiso ena ho sheba hore e entswe ka makgethe e kenyeletsa dikopano tse kang komiti ya Ethics ya dipatlisiso tsa Bongaka.

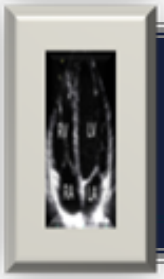
Ha diphetho di phahlalatswa, ho ka hlaha boitsibiso ba batho/bana ba itseng.

Ho iteyanya le ya etsang dipatlisiso –

Prof S C Brown, Dr.DG Buys, Miss S Jacobs

Lefapha Pediatric Cardiology; Mohala: 051 405 3241

O ka iteyanya le mongodi wa Komiti ya Ethics ya lefapha la Saense ya tsa bophelo, Yunivesithi ya Foreistata nomoro yamohala: 051 405 2812 ha o na le dipotso ka ditokelo tsa hao jwalo ka monka karolo dipatlisisong.



APPENDIX B

Correspondence

Date: Tuesday, 10 March 2009

Dr N v Zyl

CEO: Universitas Academic Hospital

Bloemfontein 9300

Dear Dr van Zyl

RE: *Reference Echocardiographic measurements for premature and newborn infants of the Free State & Northern Cape*

I would like to apply for approval of the above project (ETOVS:) and provide the following details for your perusal:

1) I am the chief researcher for this project.
2) This is a study to evaluate normal echocardiographic chamber size in healthy premature infants
3) The study will take place within the domain of paediatrics
4) This is an echocardiographic study, non painful and with no effect on patient
5) Duration : roughly 4-6months
6) The results will be published and presented.
7) There is no additional cost to either the patient or the hospital.
8) I include a protocol for your perusal.

Regards

PROF SC BROWN

HEAD: PAEDIATRIC CARDIOLOGY

Date: Tuesday, 10 March 2009

Mr L Bekker

CEO: Mediclinic Hospital

Bloemfontein 9300

Dear Mr Bekker

RE: *Reference Echocardiographic measurements for premature and newborn infants of the Free State & Northern Cape*

I would like to apply for approval of the above project (ETOVS:) and provide the following details for your perusal:

9) I am the chief researcher for this project.
10) This is a study to evaluate normal echocardiographic chamber size in healthy premature infants
11) The study will take place within the domain of paediatrics
12) This is an echocardiographic study, non painful and with no effect on patient
13) Duration : roughly 4-6months
14) The results will be published and presented.
15) There is no additional cost to either the patient or the hospital.
16) I include a protocol for your perusal.

Regards

PROF SC BROWN

HEAD: PAEDIATRIC CARDIOLOGY

Date: Tuesday, 10 March 2009

Mr C Buhrmann

CEO: Rosepark Hospital

Bloemfontein 9300

Dear Mr Buhrmann

RE: *Reference Echocardiographic measurements for premature and newborn infants of the Free State & Northern Cape*

I would like to apply for approval of the above project (ETOVS:) and provide the following details for your perusal:

17) I am the chief researcher for this project.
18) This is a study to evaluate normal echocardiographic chamber size in healthy premature infants
19) The study will take place within the domain of paediatrics
20) This is an echocardiographic study, non painful and with no effect on patient
21) Duration : roughly 4-6months
22) The results will be published and presented.
23) There is no additional cost to either the patient or the hospital.
24) I include a protocol for your perusal.

Regards

PROF SC BROWN

HEAD: PAEDIATRIC CARDIOLOGY

APPENDIX C

UNIVERSITEIT VAN DIE VRYSTAAT
UNIVERSITY OF THE FREE STATE
YUNIVESITHI YA FREISTATA

Direkteur: Fakulteitsadministrasie / Director: Faculty Administration
Fakulteit Gesondheidswetenskappe / Faculty of Health Sciences
Research Division
Internal Post Box G40
☎(051) 4052812
Fax nr (051) 4444359

E-mail address: StraussHS.md@ufs.ac.za

Ms H Strauss

2010-05-20

MS S JACOBS
DEPT PAEDIATRICS AND CHILD HEALTH
(CARDIOLOGY)
FACULTY OF HEALTH SCIENCES
UFS

REC Reference number: REC-230408-011

Dear Ms Jacobs

ETOVS NR 166/05A
PROF SC BROWN **DEPT OF PAEDIATRICS AND CHILD HEALTH**
PROJECT TITLE: DETERMINATION OF M-MODE AND DOPPLER ECHOCARDIOGRAPHIC INDICES IN SOUTH AFRICAN PREMATURE INFANTS: AN INITIAL EVALUATION.

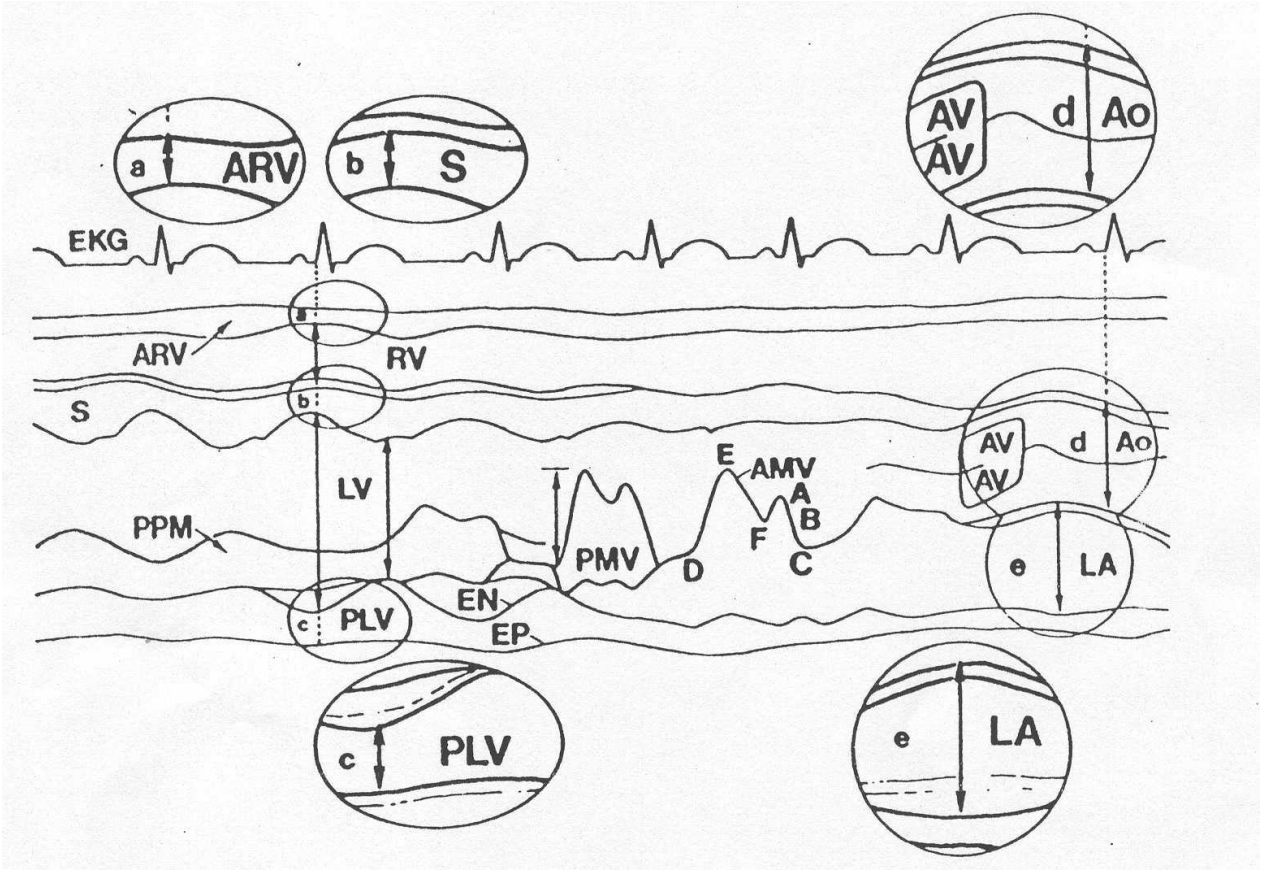
- You are hereby informed that The Ethics Committee approved the following at the meeting held on18 May 2010:
  - ***CV of M.Tech CUT student, Ms S Jacobs who will be involved in the sub-study Etovs nr 166/05C with project title: "Reference Echocardiographic measurements of premature and low-birth weight infants"***
- Committee guidance documents: Declaration of Helsinki, ICH, GCP and MRC Guidelines on Bio Medical Research. Clinical Trial Guidelines 2000 Department of Health RSA; Ethics in Health Research: Principles Structure and Processes Department of Health RSA 2004; Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Second Edition (2006); the Constitution of the Ethics Committee of the Faculty of Health Sciences and the Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines.
- Any amendment, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.
- The Committee must be informed of any serious adverse event and/or termination of the study.
- A progress report should be submitted within one year of approval of long-term studies and a final report at completion of both short term and long term studies.
- Kindly refer to the ETOVS reference number in correspondence to the Ethics Committee secretariat.

.....
CHAIR: ETHICS COMMITTEE
Cc Prof SC Brown, Dept of Paediatrics and Child Health, Faculty of Health Sciences, UFS

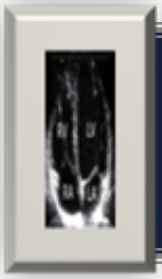
339, Bloemfontein 9300,RSA ☎ (051) 405 2812 StraussHS.md@ufs.ac.za
Republiek van Suid-Afrika / Republic of South Africa

APPENDIX D

LOCATION OF MEASUREMENTS



Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantification in M-Mode echocardiography : results of a survey of echocardiography measurements. *Circulation* 1978; 6; 1-72-1081



APPENDIX E

Ballard Scoring Method

ASSESSING GESTATIONAL AGE BY SIMPLE INSPECTION.

There are a number of easily observable clinical signs that can help you decide whether an infant is term or preterm:

TERM PRETERM

Sucks well.

Yes No

Flexes arms and legs.

Yes No

Veins seen under skin.

No Yes

Nipple clearly seen.

Yes No

Palpable breast bud.

Yes No

Descended testes.

Yes No

Covered labia minora.

Yes No

SCORING GESTATIONAL AGE.

The Ballard scoring method

The accuracy of the method depends on the experience of the examiner. With practice and careful attention to detail, the infant's true gestational age can be estimated with an accuracy of about 2 weeks. If the scored age is within 2 weeks of the gestational age suggested by the mother's dates, then accept her dates as correct. However, if the scored age is more than 2 weeks higher or lower than the mother's dates, then her dates are probably incorrect and the scored age should be used. The scored gestational age can also be used to decide whether the gestational age, determined by obstetric assessment, is correct or not.