REFERENCE INTERVALS FOR THE ECHOCARDIOGRAPHIC MEASUREMENTS OF THE RIGHT HEART IN AFRICAN SCHOOL CHILDREN AND ADOLESCENTS

by

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DECLARATION

I, Carolina Elisabet Lemmer, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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List of abbreviations

2D	Two-dimensional
Aa	Late diastolic peak myocardial velocity
ASE	American Society of Echocardiography
BMI	Body mass index
BSA	Body surface area
DTI	Doppler tissue imaging
Ea	Early diastolic peak myocardial velocity
EF	Ejection fraction
IVC	Inferior vena cava
LV	Left ventricle
MPI	Myocardial performance index
MV	Mitral valve
PA	Pulmonary artery
PV	Pulmonary valve
RA	Right atrium
RV	Right ventricle
Sa	Tissue Doppler-derived peak systolic annular velocity
SD	Standard deviation
TAPSE	Tricuspid annulus peak systolic excursion
TV	Tricuspid valve
Y	year(s)

Terms and definitions

Establishing (or determining) a reference interval – the process used in creating a reference interval *de novo*, encompassing all of the steps from selection of reference individuals, through exact details of the analytical methods, and concluding with data collection and analysis.[1]

International Federation of Clinical Chemistry definitions:

The following terms permit relatively unambiguous description and discussion of the subject of reference values. These definitions represent what is becoming accepted universal terminology.[1]

Reference distribution – the distribution assumed by the reference values; NOTE: Hypotheses regarding the distribution of the reference population may be tested using the reference distribution of the reference sample group and adequate statistical methods.[1]

Reference individual or participant – a person selected for testing on the basis of well-defined criteria. NOTE: It is usually important to define the person's state of health.[1]

Reference interval – the interval between, and including, two reference limits; NOTE: It is designated as the interval of values from the lower reference limit to the upper reference limit.[1]

Reference limit – a value derived from the reference distribution and used for descriptive purposes.[1]

Reference population – a group consisting of all the reference individuals.[1]

Reference sample group – an adequate number of persons selected to represent the reference population.[1]

Reference value – the value (test result) obtained by the observation or measurement of a particular type of quantity on a reference individual. NOTE: Reference values are obtained from a reference sample group.[1]

Right heart – All chambers, valves, and great vessels that form part of the anatomical right side of the heart, including the superior- and inferior- vena cava, the right atrium, the tricuspid valve, the right ventricle and the pulmonary artery.

List of figures and tables

Abstract

Background

Echocardiography is the primary imaging modality for the diagnosis and management of right ventricular (RV) failure.[2-5] Besides aiding in the diagnosis and management of conditions such as arrhythmogenic right ventricular cardiomyopathy, pulmonary embolism, and RV infarction, the echocardiographic evaluation of the right heart plays a critical role in the diagnosis and management of congenital heart diseases where the RV often serves as the main pumping chamber.[6-10]

The absence of reference intervals for cardiac structures in children continues to be an important problem.[7] Publications dedicated to the echocardiographic study of the right heart, the reference values of the structure and function of the right heart, and their clinical interpretation are rare.[11] Many of the previous studies had limited sample sizes, and were conducted predominantly in North American and European populations. Thus there is potential for interpretation errors when assessing African children, given that environmental, social, economic and racial factors may influence the anthropometric standards of a population.[12]

Objectives

1. To collate, from published studies, normative data for echocardiographic evaluation of the right heart in children, in order to identify gaps in knowledge in this field.
2. To establish reference intervals for the echocardiographic evaluation of the right heart in a random sample of South African school-going children and young adults.
3. To compare the measurements in the South African cohort with the recommended variables of the American Society of Echocardiography.
4. To design a tool for the calculation and reporting of echocardiographic right heart measurements in children.

Methods

A systematic literature search was performed to identify studies of reference intervals for right heart measurements as determined by transthoracic echocardiography in healthy children of school-going age. Articles were retrieved from Pubmed and ISI Web of Knowledge databases with a

combination of the following terms: ECHOCARDIOGRA, NORMAL VALUES, NORMAL RANGES, REFERENCE VALUES, REFERENCE RANGES, REFERENCE INTERVALS from the earliest date available until August 2010.

Secondly, a detailed echocardiographic assessment of the right-sided cardiac structures and their function were performed on 213 healthy volunteers between the ages of 5 and 21 years who were selected from the schools in the Vanguard Communities of Cape Town, South Africa. These participants were used to establish reference intervals for various echocardiographic measurements of the right heart.The newly established reference intervals then were compared with existing reference data.

Finally, using Microsoft Excel®, a right heart calculator and report generator was designed and programmed to reduce post-processing time as compared with the manual calculations and report compilation.

Results

Reference data were available for a broad range of variables. Fourty studies from 2207 publications were included. The sample sizes of the reference populations ranged from 13 to 2036 with ages ranging from birth to 23 years. Based on the guidelines from the American Society of Echocardiography[2, 8] and our finding from the systematic review, we identified areas lacking sufficient reference data.These include reference data for determining right atrial size, tricuspid valve area, RV dimensions and areas, the RV % fractional area change , RV ejection fraction using the area-length method, pulmonary artery pressure gradients, and the right-sided haemodynamics, including the inferior vena cava dimensions and collapsibility.

We established reference intervals for multiple parametes. RV dimensions,-areas and volumes demonstrated increases in parameters of cardiac growth with advancing age and body surface area (BSA). Measures of RV function showed little or no change with increasing age or BSA. Estimated systolic pulmonary artery pressure values increased with advancing age and BSA. The pulmonary artery end-diastolic velocity and pulmonary artery end-diastolic pressure values increased after age 10 and BSA category 3 (1.40-1.60 m^2), with no significant increase thereafter. A decrease in collapsibility of the inferior vena cava (IVC) at age 10 and BSA category 3 was observed, with no significant change thereafter.

Compared with available literature, the values obtained in this study are similar to those previously reported: right atrial width and RV length compared well with existing values ($p = 0.11$ and $p = 0.09$, respectively).[13], [14] However, in other instances, there were significant differences between our data and the values reported by other authors: Larger, were RV width and RV length[13] ($p < 0.001$) and RV outflow tractvalues[14, 15] ($p < 0.001$). RV width measurements were smaller[14] ($p < 0.001$) as were RV end-diastolic and end-systolic areas[14, 16] ($p < 0.001$). Furthermore, mean values for tricuspid annulus peak systolic excursion were lower[13, 17], while peak systolic Doppler tissue imaging velocities measured at the tricuspid annulus and myocardial performance index values were irresolute.

Our RV end-diastolic volumes were similar to, or lower than, the values presented, suggesting a much higher stroke volume (and RV ejection fraction) in our African population.[18] Similarly, our calculated RV ejection fraction were significantly higher ($p < 0.001$)[16],[14] The RV-to-right atrial peak velocities were higher when compared with values in the literature[19] ($p < 0.001$) as were our inferior vena cava values ($p < 0.001$). The percentage inferior vena cava collapse was significantly lower than previously presented ($p < 0.001$).[13]

The purpose-designed right heart calculator based on the Microsoft Excel® platform performed all calculations efficiently. Furthermore, the calculator places measured values into context of normal values, flagging outliers according to the patient's age and BSA.

Conclusions

There are insufficient reference data available for determining right heart size, function and haemodynamics in children and adolescents.This study establishes reference intervals derived from a large population of healthy school children in a methodical manner using accepted methods and employing modern echocardiographic equipment. In summary, RV dimensions and –volumes of African children are smaller, while RV outflow tract diameter is larger as compared with existing literature. Currently, no such work has been done in Africa using representative samples of African children free of cardiovascular disease. In addition, this is the first community-based study of its kind in the world.

Finally, this research informed the design of a useful algorithm forright heart computations. A useful adjunct to echocardiography, it reduces post-processing time involved in the right heart assessment and serves as a guide and example as to how the right heart measurements could be included in an echocardiographic report.

1 Introduction

The accurate measurement of cardiac structure and function is a crucial aspect of the evaluation and management of children with various types of congenital and acquired cardiac disease. Decisions on the type and timing of interventions to a large extent, often relyon the changes in these measurements with respect to what is considered to be the normal range.[20]

The assessment of the right heart has been neglected in the field of echocardiography for many years. Reasons for the neglect include the technical difficulty to image the right side of the heart by echocardiography, limitations in ultrasound technology and a widely-held belief that the right heart was clinically "less important".[6] However, there has been a recent resurgence of interest in the echocardiographic evaluation of the right side of the heart.[6, 7, 11]

A comprehensive evaluation of the RV can be a highly informative component of the overall cardiac examination. Besides aiding in the diagnosis and management of conditions such as arrhythmogenic right ventricular cardiomyopathy, pulmonary embolism, and RV infarction, the evaluation of the right heart plays a critical role in the diagnosis, management and treatment of many congenital heart diseases where the RV often serves as the main pumping chamber.[6]

The absence of a comprehensive set of reference intervals for cardiac structures in children continues to be a crucial problem.[7] Publications dedicated to the protocol of the echocardiographic study of the right heart, the reference values of the structure and function of the right heart, and their clinical interpretation are rare.[11] All published reference values of older indices (2-Dimensional & M-mode echocardiography) date back to the start of routine echocardiography (mid 1970s to 1980s). Published reference values of newer indices such as tissue myocardial velocity, strain and strain rate and the global myocardial performance index (MPI) are based on small and heterogeneous samples of healthy infants, children and young adults.[21] It is also important to emphasize that the choice of reference individuals, who may be free of detectable cardiovascular disease determined by echocardiography, may not represent the normal population.

To the best of our knowledge, no such study has been done in Africa using representative samples of African children who are free of cardiovascular

disease. Many of the existing studies, not only comprised cohorts of limited sample size, but were also conducted in predominantly North American and European populations. Thus,there is a potential for interpretation errors when assessing African children against these values, given that environmental, social, economic and racial factors can influence the anthropometric standards of a population.[12]

2 Literature review

2.1 Reference data: guidelines and terminology

When diagnostic classifications are being developed, reference intervals are used as yardsticks to discern specific disease from general disability or physiological variations. The best reference value for an individual is derived from his or her own prior data; however, because these are often not available, population-based reference values are widely used.[22]

Usually, reference intervals are established from a population of healthy, nonpregnant, nonobese individuals, who have neither ingested any drugs nor smoked prior to sample collection[22]; however, the concept of health oftendiffers between cultures and countries. The World Health Organization defines health as 'a state of complete physical, mental and social wellbeing and not merely absence of disease or infirmity, which is not always a realistic starting point.[23] Consequently, a more pragmatic approach in choosing a reference population may be needed with health being judged objectively as the absence of signs of disease specifically related to the measurement.[23]

Previously, reference intervals were usually named 'normal values' or 'normal ranges' without a clear definition of the term.[24] The use of the term 'normal' has, however, been discouraged, because it has different meanings. It may be subjective and ambiguous. Moreover, it implies that everything outside the reference range is 'abnormal'; however, due to the way the so-called normal range is calculated, this may not be true. For these reasons, the International Federation of Clinical Chemistry introduced the term 'reference values'. Usually these values are health-associated, but they can also reflect specific physiological conditions like pregnancy, or refer to specific population groups, such as professional athletes.[23] The International Federation of Clinical Chemistry expert panel published the first official document on the theory of reference values.[23] Through the 1980s, they continued developing and refining the theories on reference values and reference intervals and published a series of recommendations in a series of papers.[25] More than 20 years later, the International Federation of Clinical Chemistry recommendations have universally become the gold standard for establishing reference intervals for chemical and non-chemical parameters, as are relevant echocardiographic measurements of the heart.

These recommendations however, have not been widely adopted when establishing reference intervals for echocardiography in the younger population. Authors often fail to explore the fundamental reference value concepts. Studies are not population-based and questions often arise as to the health of the participants and the normality of the sample. The lack of detail about statistical methods often makes it impossible to assign scientific weight to the published result. Furthermore, categorization of the sample for age and/or body size differs markedly between studies, making it difficult to pool or compare data resulting in a less likelihood of data being applied in clinical practice.

2.2 The right heart: The role of echocardiography

Echocardiography is often the first test used in the evaluation of patients presenting with cardiovascular symptoms.[2] As a result, potentially life-altering decisions are constantly made on the basis of quantitative echocardiographic measurements.[3]

Echocardiographic quantification is crucial in the diagnosis and management of patients with acquired and congenital heart disease.[8] Assessment of RV volume and function is needed during the decision-making process and repair of pathologies such as tetralogy of Fallot, corrected transposition of the great arteries, and atrial switch procedures or for demonstration of volume load in cardiac defects with left-to-right shunting.[7] In the clinical management of patients with cardiopulmonary disorders and congenital heart disease, the evaluation of the global RV function is of major importance.[9] Certain conditions have the RV supporting the systemic circulations or it becomes the sole pumping chamber following surgical repair.[10]

Although echocardiographic criteria for the evaluation of the right heart are still being refined and their application requires familiarity with the echocardiographic variants of the right heart, in clinical practice, echocardiography is already the mainstay of evaluation of RV structure and function.[4]

Echocardiography is considered a cornerstone in the diagnosis and management of RV failure.[5] Moreover, it is a leading technology, is less costly, is non-invasive and offers the advantages of wide applicability and availability when compared with other imaging modalities.[4]

2.3 Principles and methods for adjusting measurements of cardiovascular structures for the effects of body size

The size of cardiovascular structures is influenced not only by haemodynamics of disease states and their treatments, but also by growth, age, genes, gender, race, body composition, basal metabolic rate, hematocrit, exercise, and altitude. Aside from abnormal haemodynamics, body size is the most powerful determinant of the size of cardiovascular structures: all cardiovascular structures increase in size relative to somatic growth, a phenomenon known as cardiovascular allometry.[8]

Expressing measurements relative to body size allows for a meaningful distinction between normal and abnormal values in children. It requires the collection of quantitative data from a normal paediatric population to function as the standard against which all measurements are compared.[8]

In normal children, BSA appears to be a more accurate parameter of somatic growth than height or weight alone. "Indexing" the size of structures relative to the BSA has become a common practice because of the linear relationship between cardiac output and BSA and the mostly linear relationship between cardiac output and the size of cardiovascular structures.[8]

Calculation of *z* scores has become a popular approach in paediatric cardiology to account for the effects of body size and age.[26] Z-scores serve to indicate the extent to which a calculated or measured value deviates from a mean value for that particular point for say, BSA. The use of *z* scores has the advantage of eliminatingany reliance on predetermined relationships between the size of a structure and BSA. However, the utility of published *z* score approaches has been limited by the fact that the studies do not always account for confounders such as gender and race and that the methods for performing measurements and calculating BSA are often inconsistent across the entire population being evaluated. Also, there can be no assumption that a constant variance exists across the range of body sizes within the paediatric population.[8] Calculation of *z* scores assumes a uniformity of measurement and biological variability.[27] It is for this reason that we chose to not use the *z* score in this study.

3 Reference values for echocardiographic measurement of the right heart in children: a systematic review

3.1 Introduction

Systematic reviews provide rigorous, objective evidence to assess the literature relating to a particular topic. This rigour is gained through the use of a pre-specified protocol incorporating an extensive literature search using a variety of database search engines. A purpose-designed form is used to capture extracted data described in pre-determined objectives. The use of explicit, systematic methods in reviews limits bias (systematic errors) and reduces chance of effects, thus providing more reliable results upon which to draw conclusions and make decisions. Systematic reviews are generally regarded as being superior to traditional non-systematic reviews.[28]

An extensive systematic literature search was performed to identify all studies reporting reference intervals for right heart measurements as determined by transthoracic echocardiography in healthy school children. Search results encompassed studies reporting reference values or reports ofright heart size and function in patients with specific disease states versus normal healthy controls. In the latter, only the control group was used in the determination of reference values. For each study, the measureable parameters presented were extracted, ensuring that the technique used to obtain the measurement was comparable with available literature.

We present the latest summary of published data of the right heart echocardiographic reference values in children. We believe that this information will assist clinicians in diagnosis of structural and functional cardiac conditions. For more background on reference intervals and the role of echocardiography in the evaluation of the right heart, we refer the reader to section 2 of this thesis (*Literature review*, Chapter 2).

3.2 Aim

The aim of this systematic review was to collate, from published studies, normative data for echocardiographic evaluation of the right heart in children, in order to identify gaps in knowledge in this field.

3.3 Criteria for considering studies for this review

3.3.1 Types of studies

This review considered all publications reporting reference values for the right heart in healthy children determined by echocardiographic evaluation.

3.3.2 Types of reference individuals

Participants included school children with no history or echocardiographic evidence of heart disease. No exclusion was set on sample sizes of the studies.

3.3.3 Inclusion and exclusion criteria

Inclusion criteria:

- Age range from 5 to 21 years.
- Documentation of age and/or an indicator body size for every reference individual. Indicators of body size included height and/or weight and/or body mass index (BMI) and/or BSA.
- Presentation of results as one reference value and/or -interval for the whole sample or, in relation to age and/or body size.
- Availability of English version of paper in the case of foreign-language articles.

Exclusion criteria:

- Preterm infants.
- Deceased participants (autopsy studies).
- Children with known cardiovascular disease.
- Measurements taken at high altitude ≥2400 metres above sea level).
- Age groups including adults (without subgroups for participants younger than 22 years).
- Presentation of reference values that had already been included in a previously published article.

3.4 Search strategy and selection of studies

Figure 1 details the process by which articles were selected for inclusion.

The scope of search aimed to include all published work dating back to the start of routine echocardiography. We searched the Pubmed and ISI Web of Knowledge databases with a combination of the following search terms: ECHOCARDIOGRA* [Title/Abstract] AND ("NORMAL VALUES"[Title/Abstract]) OR ("NORMAL RANGES"[Title/Abstract]) OR ("REFERENCE VALUES"[Title/Abstract]) OR ("REFERENCE RANGES"[Title/Abstract]) OR ("REFERENCE INTERVALS"[Title/Abstract]) from the earliest date available until August 2010. This process was complemented by reviewing citations, searching with Google Scholar, expert referrals, hand-searching and scanning reference lists of articles. Additional articles were included as they became available.

We combined the outputs from the databases *Pubmed* and *ISI Web of Knowledge* using a Referencing program, Endnote®. After duplicate entries were removed, titles of citations were screened for possible inclusion. The abstracts of potentially relevant studies were reviewed, after which the fulltext articles were examined for possible inclusion. We attempted to find an English copy of the fulltext article for all of the selected abstracts. Articles were graded as eligible, potentially eligible, or not eligible based on the inclusion and exclusion criteria.

3.5 Data extraction and analysis

Data on the year of study, participants' characteristics including age range, number, sex and race, study setting, sample selection, measurements and methods of measurements were extracted onto the pre-specified data extraction form. For each age-group, the sample size with reported summary statistics (i.e., mean, median, centiles, standard deviation, confidence intervals, or standard error) for measurements were also documented.

In 2010, the American Society of Echocardiography published recommendations for performing echocardiography examination in the paediatric population.[8] The recommendations emphasized 24 key measurements of the right heart and documented strengths and weaknesses of each. For each quantification method, the availability of little or no normal paediatric data was identified as a weakness, while the availability of normal paediatric data was recognized as a strength. Included studies were evaluated against these 24 criteria.

3.6 Data management and quality control

The systematic review was conducted along the methods of the Cochrane Collaboration.[29]

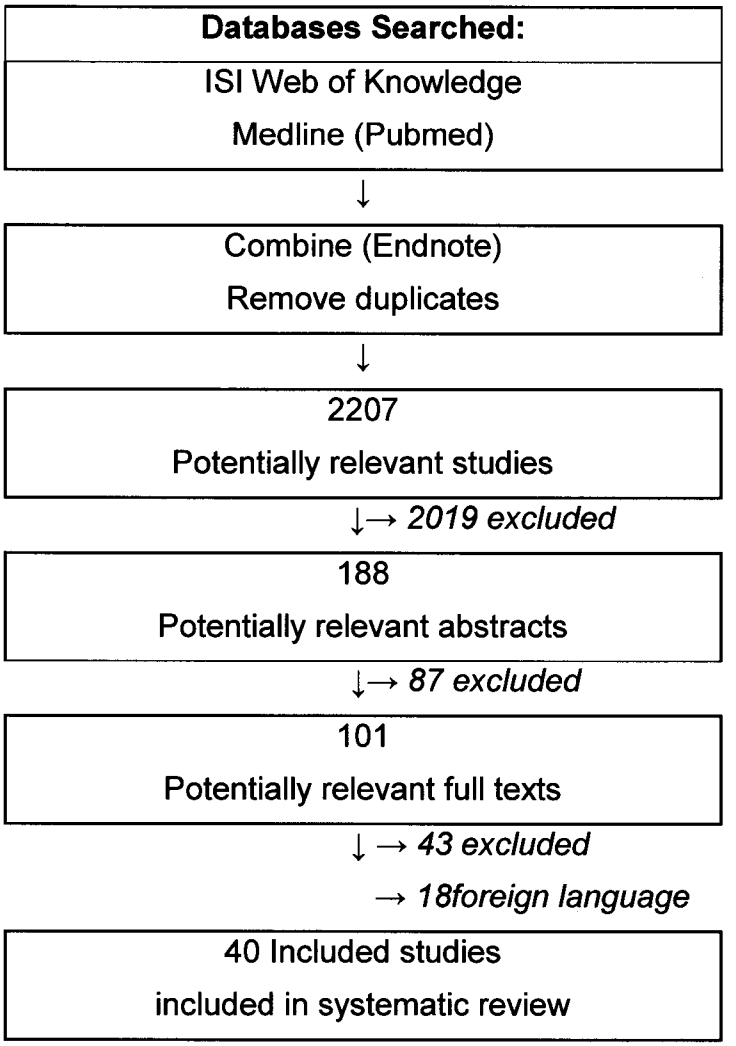
In an attempt to minimise publication bias, we included all available published reference values of echocardiographic evaluation of the right heart in children and young adults.

3.7 Results

I identified 40 studies for inclusion in this study from the 2207 publications retrieved from the databases. Two thousand and nineteen articles were excluded on the basis of title alone, while a further 87 abstracts and 43 articles failed to meet the inclusion criteria. Eighteen of the 19 foreign language articles were excluded because no English translation was available; on inspection, none of these were affiliated to an African institution. We were able to include data from the remaining foreign language article as the sub-headings of the tables containing reference data, were English.

Figure 1 depicts the study selection process.

Figure 1: Flowchart of systematic search



3.7.1 Description of studies

The majority of included studies were done in clinical settings (e.g., hospitals, clinics, or medical centres), and research laboratories. Some studies did not specify the setting. Fifteen of the included 40 studies were published before the year 2000, while 25 were published during or after 2000. The oldest publication dates back to 1977.[30] Seventeen studies were from reference populations in North or South America, 13 from European countries, 8 from Asia, 1 from the Middle East and 1 from Australia.

The sample size of the reference populations ranged from 13 [31] to 2036 [32]. The ages of the reference populations ranged from 5 to 21 years.

In 19 studies, the reference population consisted of individuals that were referred for echocardiography to exclude cardiac disease, while in 10, the reference population comprised volunteers. There were 2 studies sampling reference participants from wards, 1 study sampled participants from a database and 1 study reported reference values of a normal control group. Thirteen studies were unclear as to the method of sample selection. None of the included studies had a population-based design.

Table 1 summarizes the sample characteristics of all 40 included studies. *Table 2* summarizes the measurements recorded in each of the 40 included studies.

Table 1. Sample characteristics of included studies.

No	Author	Year	Sampling method	Sample size	Age-range	Age-categories	Sample size per age-category
1	Ayabakan	2003	REF	72	03 days - 16 y	<02 y	18
			V			02 - 07 y	18
			O			07 - 11 y	18
						> 11 y	18
2	Boettler	2005	U	129	01 day - 16.9 y	1	129
3	Bonatto	2006	REF	595	01 mnth - 144 mnths	*(Data presented acc to BSA)*	
4	Cui	2008	REF	593	01 day - 18 y	1	593
5	Daubeney	1999	REF	125	01 mnth - 207 mnths	*(Regression equations and Nomograms)*	
			U				
6	Eidem	1998	V	152	03 y - 18 y	1	152
7	Eidem	2004	REF	325	01 day - 18 y	<01 y	63
						01 - 05 y	68
						06 - 09 y	55
						10 - 13 y	58
						14 - 18 y	81
8	Frommelt	2002	REF	141	03 days - 18 y	<12 mnths	27
						>12 mnths	114
9	Goebel	2006	V	45	05 y – 23 y	1	45
10	Gutgesell	1991	U	70	01 day – 18 y	*(Data presented acc to BSA)*	
11	Hanseus	1988	U	120	03 days – 15.5 y	*(Regression equations and Nomograms)*	
12	Harada	2000	REF	48	07 days - 18 y	1	48
13	Ichida	1987	O	173	0 days – 15 y	< 12 hrs	10
			V			12 - 24 hrs	10
						03 – 06 days	15
						01 – 04 weeks	8
						01 – 03 mnths	21
						03 – 06 mnths	17
						06 – 12 mnths	12
14	Innelli	2009	REF	40	10 y - 19 y	1	40
			V				
15	Ishii	2000	REF	150	30 days - 18 y	1	150
16	Jin	1997	REF	108	07 days - 17 y	0 - 1 y	12
						01 - 04 y	24
						04 - 08 y	29
						08 - 12 y	23
						>12 y	20
17	Kampmann	2000	REF	2036	01 day - 18 y	*(Data presented acc to BSA / weight)*	
			V				
18	Kapusta	2000	V	160	04 y - 17.9 y	1	160
19	King	1985	REF	103	01 day – 15 y	*(Data presented acc to BSA)*	
20	Koestenberger	2009	REF	640	01 day - 18 y	0 – 30 days	41
						01 – 03 mnths	45
						04 – 06 mnths	20
						07 – 12 mnths	22
						01 y	25
						02 y	39
						03 y	27
						04 y	47

Table 2. Variables of included studies.

			Sample		
	Author	**Year**	**size**	**Age-range**	**Echocardiography measurement**
1	Ayabakan	2003	72	03 days - 16 y	SVC: A_praf
					VTI: A_praf
					SVC: S
					VTI: S
					SVC: D
					VTI: D
					A_praf-R
					R-D
					D-A_praf
2	Boettler	2005	129	01 day - 16.9 y	RVAd
					RVAs
					S duration
					E duration
					A duration
					Ss
					Se
					Sa
					SRs
					SRe
					SRa
					RVEF
3	Bonatto	2006	595	01 mnth - 144 mnths	RVID (RV mid)
					RVOT
4	Cui	2008	593	01 day - 18 y	RV MPI
					RV IVCT
					RV IVRT
					St
					Dt
					St/Dt ratio
					PV EP
5	Daubeney	1999	125	01 mnth - 207 mnths	PV ann
					PAd
					"RV inflow" (RVILd)
					TVann
					RVAd
					RV outflow length
6	Eidem	1998	152	03 y - 18 y	RV MPI
					IVCT
					IVRT
					RV PEP
					RV EP
					RV PEP / ET
7	Eidem	2004	325	01 day - 18 y	RV MPI
					Sa RV free wall
					Ea RV free wall
					Aa RV free wal
					E/Ea
					TV E velocity
					TV A velocity
					E:A ratio
					IVCT
					IVRT

8	Frommelt	2002	141	03 days - 18 y	Sa RV free wall
					Ea RV free wall
					Aa RV free wal
					Ea/Aa
					Ac
					DT
					IVCT prior to Sa
					IVRT prior to Ea
9	Goebel	2006	45	05 y – 23 y	Sa RV free wall
					Ea RV free wall
					Aa RV free wal
					SRs
					SRe
					SRa
					% Strain
					Tissue displacement
10	Gutgesell	1991	70	01 day – 18 y	RVOT
					RVOT velocity
					PA vel
					PVA
11	Hanseus	1988	120	03 days – 15.5 y	RVOT
					PAd (valvular level)
					RVID (RV base)
					RVILd
					RVAd
					Raw
					Ral
					RAAd
					MV-TV distance
12	Harada	2000	48	07 days - 18 y	Sa RV free wall
					Ea RV free wall
					Aa RV free wal
					Ea/Aa
13	Ichida	1987	173	Birth – 15 y	PAd (valvular level)
14	Jin	1997	108	07 days - 17 y	RV EDV
					RV ESV
					RV MV
					MVI (ratio: MV to EDV)
					RV SV
					RV EF
15	Innelli	2009	40	10 y - 19 y	RVID (RV base)
					RVID (RV mid)
					RVILd
					Raw
					RV TAPSE
					PV EP
					Sa RV free wall
					Ea RV free wall
					Aa RV free wal
					E'/A'
					E/E'
					TV E velocity
					TV A velocity
					E:A
					RVOT velocity
					PV PEP
					IVCID

					IVC % collapse
16	Ishii	2000	150	30 days - 18 y	RV MPI
					E:A
					PV EP
					IVCT + IVRT
					TR
17	Kampmann	2000	2036	01 day - 18 y	RVID (RV mid)
					Pad
					RVAWd
18	Kapusta	2000	160	04 y - 17.9 y	PV vel
					RVAWd
					RVAWs
					TV E velocity
					TV A velocity
					E:A
					Sa RV free wall
					Ea RV free wall
					Aa RV free wal
					Ea/Aa
					Ea/Sa ratio
19	King	1985	103	01 day – 15 y	TV ann
20	Koestenberger	2009	640	01 day - 18 y	RV TAPSE
21	Lange	1983	185	Birth - 15 y	RVID (RV mid)
22	Lester	1987	202	25 days - 23 y	RVID (RV mid)
					RVAWd
23	Matsui	2007	22	01.6 - 10.8 y	Strain: RV inflow, -outflow and pulm annulus
				Table: 01.7 - 11 y	Time-to-peak strain: RV inflow, -outflow and pulm annulus
					PV ann
24	McQuillan	2001	856	< 20 y	RV-RA gradient
					PASP
25	Moiduddin	2010	13	5.7 y ± 1.8 y	RV %FAC
					RV MPI
					Strain: RV free wall
					Tissue Displacement: RV free wall
					Strain Rate: RV free wall
					Time to peak strain (RV dyssynchrony)
26	Mori	2004	396	Birth - 19 y	Sa RV free wall
					Ea RV free wall
					Aa RV free wal
					Aa/Ea
					TV E velocity
					TV A velocity
					A:E
					E/Ea
27	Norgard	1992	15	06 y - 16 y	RVID (RV mid)
					RVID (RV mid)
					RVOT
					RVID (RV mid)
					RVILd
					RVAd
					RVAs
					RV EDV
					RV ESV
					RV SV
					RV EF
28	Pettersen	2008	782	01 day - 18 y	RVID (RV mid)

					PV ann
					Pad
					TVann
29	Rafeiyian	2005	100	1 mnth - 15 y	Sa RV free wall
					Ea RV free wall
					Aa RV free wal
					Ea/Aa
					IVRT
					IVCT
					DT (deceleration time)
30	Roberson	2007	634	01 day - 18 y	Sa RV free wall
					Ea RV free wall
					Aa RV free wal
31	Roberson	2007	308	01 day - 18 y	IVRT + IVCT
					ET
					IVRT + IVCT + ET
					RV MPI
32	Sarnari	2009	179	0.02 mnths - 19 y	RV systolic duration
					RV diastolic duration
					S/D Ratio (Systolic-to-diastolic ratio)
33	Suleymanoglu	2007	213	15 days - 15 y	RV EDV
					RV ESV
34	Singh	1994	78	02 mnths - 50 y	RVOT
					RVOT vti *(one group)*
					TV vti *(one group)*
					TV area
35	Vignola	1977	17	03 y - 17 y	RVID (RV mid)
36	Weidemann	2002	33	04 - 16 y	Ss RV free wall
					Se RV free wall
					Sa RV free wall
					SRs RV free wall
					SRe RV free wall
					SRa RV free wall
					Ss RV inferior wall
					Se RV inferior wall
					Sa RV inferior wall
					SRs RV inferior wall
					SRe RV inferior wall
					SRa RV inferior wall
37	Wessel	1985	30	*Age-range unclear*	RV geometry
38	Yusuoka	1999	99	07 days - 22 y	Ea RV free wall
			30(TDI)		Aa RV free wal
					Ea:Aa
					TV E velocity
					TV A velocity
					E:A
39	Zhendong	1998	88	03 y - 12 y	TV E velocity
					TV A velocity
					E:A
					APE
					DPE
					FVI: E area
					FVI: A area
					Total area: (E and A)
					TDFT
					TAPE

					TDPE
40	Zilberman	2005	748	Birth - 18 y	PV ann
					TV ann

SVC, Superior Vena Cava; A_praf, peak reverse atrial flow;VTI, velocity time integral; S, peak systolic flow; D, peak diastolic flow;R, R-wave on ECG;ECG, Electrocardiography; RVAd, right Ventricular Area in diastole; RVAs, right Ventricular Area in systole; S duration, duration of the tissue velocity peak systolic wave; E duration, duration of the tissue velocity early diastolic E wave; A duration, duration of the tissue velocity late diastolic A wave; Ss, peak systolic strain; Se, early diastolic strain; Sa, late diastolic strain; SRs, peak systolic strain rate; SRe, early diastolic strain rate; SRa, late diastolic strain rate; RVEF, right ventricle ejection fraction; RVID, right ventricle internal diameter; RVOT, right ventricle outflow tract; RV EDV, right ventricle end-diastolic volume; RV ESV, right ventricle end-systolic volume; RV SV, right ventricle stroke volume; RV EF, right ventricle ejection fraction; RV, right ventricle; MPI, myocardial performance index; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; St, systolic time; Dt, diastolic time; PV, pulmonary valve; EP, ejection period; ann, annulus; PAd, pulmonary artery diameter; RVILd, right ventricle internal length in diastole; TVann, tricuspid valve annulus; PEP, pre-ejection period; ET, ejection time; Sa, tissue velocity peak systolic velocity; Ea, tissue velocity early diastolic wave; Aa, tissue velocity late diastolic wave; TV, tricuspid valve; E, early diastolic; A, late diastolic; Ac, systolic annular acceleration;DT, early diastolic annular deceleration time; PA, pulmonary artery; Vel, velocity; PVA, pulmonary valve area; RAw, right atrium width; RAl, right atrium length; RAAd, right atrium area in diastole; MV, mitral valve; TV, tricuspid valve; MV, muscle volume; MVI, muscle volume index; EDV, End-diastolic volume;TAPSE, tricuspid annulus peak systolic excursion; E', tissue Doppler early diastolic myocardial velocity; A' tissue Doppler late diastolic myocardial velocity; E, early diastolic wave; A, late diastolic wave; IVCID, inferior vena cava internal diameter; IVC, inferior vena cava; TR, tricuspid regurgitation; RVAWd, right ventricle anterior wall in diastole; RVAWs, right ventricle anterior wall in systole; vti, velocity time integral; RA, right atrium; PASP, pulmonary artery systolic pressure; E, early diastolic velocity; EDV, end-diastolic volume; ESV, end-systolic volume;APE, acceleration time to peak E velocity; DPE, deceleration time from peak E velocity; FVI, flow velocity integrals; TDFT, total diastolic filling time; TAPE, time of acceleration to peak E velocity; TDPE, time of deceleration from peak E velocity.

There were insufficient published data for the following measurements: right atrial size (width, length and area) for children younger than 10 yrs, tricuspid valve area, right ventricular dimensions (base, mid and length) and areas (diastolic and systolic), the right ventricular fractional area change and the RV-to-right atrialpeak pressure gradient. There were no published reference data for the right ventricular mid-cavity dimensions presented as a sub-group for children younger than 10 years; pulmonary artery peak pressure gradient for children older than 12 years; inferior vena cava diameter and percentage collapse for children younger than 10 years. None of the studies estimated pulmonary artery systolic pressure using an estimate of right atrial pressure that was based on the dimension and percentage collapse of the inferior vena cava. Lastly, there were no published data for right ventricular volumes and ejection fraction using the area-length method.

3.7.2 Categorized summary of publications

The right heart examination should include a measure of right atrial (RA) size and right ventricular (RV) size, RV systolic function and pulmonary artery (PA) pressure.[2] Our findings are presented in Table 3 (measurements ofright heart**size/volume**), Table 4 (measurements of RV **morphology/structure**), Table 5 (measurementss of RV- and valve **function**),and Table 6 (measurements of right heart **haemodynamics**).

Table 3. Measurements of right heart size/volume.

	Variable	View	Method	Boettler 2005	Bonatto 2006	Daubeney 1999	Hanseus 1988	Innelli 2009	Jin 1997	Kampmann 2000	Lange 1983	Lester 1987	Norgard 1992	Suleymanoglu 2007	Vignola 1977	Wessel 1985
RV Diameters and Area																
Mid RV	RVID (mid RV)	PLAX	M-mode		x					x	x	x	x			
	RVID (mid RV)	Unspecified	M-mode												x	
	RVID (mid RV)	PLAX	2D										x			
	RVID (mid RV)	A4C	2D					x					x			
RV Base	RVID (RV base)	A4C	2D				x	x								
	RVID (RV base)	S4C	2D				x									
RV Length	RVIL	A4C	2D			x	x	x					x			
	RVIL	S4C	2D				x									
RV Area	RVAd	A4C	2D Trace	x		x	x						x			
	RVAs	A4C	2D Trace	x									x			
	RVA	S4C	2D Trace				x									
Right Ventricle Volume																
	RV EDV	A4C	Simpson's single-plane										x			
	RV EDV	A4C	Simpson's single-plane(30 discs)						x							
	RV EDV	SCC	Simpson's single-plane											x		
	MV	A4C	Simpson's rule						x							
	MVI		ratio: MV to volume						x							
	RV geometry		Algorithm of sphere volumes													x

RV, right ventricle; RVID, right ventricle internal dimension; PLAX, parasternal long-axis; A4C, apical four-chamber; 2D, two-dimensional; S4C, subcostal four-chamber; RVIL, right ventricle internal length; RVAd, right ventricle area in diastole; RVAs, right ventricle area in systole; RVA, right ventricle area; EDV, end-diastolic volume; MV, muscle volume; MVI, muscle volume index.

Table 3 continued. Measurements of right heart size/volume.

	Variable	View	Method	Bonatto 2006	Daubeney 1999	Gutgesell 1991	Hanseus 1988	Innelli 2009	Norgard 1992	Pettersen 2008	Singh 1993
RV Outflow Tract											
	RVOT(supraAo)	PSAX	2D				x		x		x
	RVOT(supraAo)	PSAX	M-mode	x						x	
	RVOT	PLAX / SX	2D			x					
	RVOL	SP	2D		x						
Right Atrium											
Width	Raw	A4C	2D				x	x			
	Raw	S4C	2D				x				
Length	Ral	A4C	2D				x				
	Ral	S4C	2D				x				
Area	RAA	A4C	2D Trace				x				
	RAA	S4C	2D Trace				x				

RVOT, right ventricle outflow tract; supraAo, supra aortic; PSAX, parasternal short-axis; 2D, two-dimensional; PLAX, parasternal long-axis; SX, short-axis; RVOL, right ventricle outflow length; SP, subcostal parasagittal; RAw, right atrium width; A4C, apical four-chamber; S4C, subcostal four-chamber; RAl, right atrium length; RAA, right atrium area.

Table 3 continued. Measurements of right heart size/volume.

	Variable	View	Method	Daubeney 1999	Gutgesell 1991	Hanseus 1988	Ichida 1987	Kampmann 2000	King 1985	Matsui 2007	Pettersen 2008	Singh 1993	Zilberman 2005
Area	TVA											x	
Annulus	TVann	A4C	2D	x					x		x		x
	MV-TV distance	A4C / S4C	2D			x							
Area	PVA				x								
Annulus	PVann	PLAX	2D				x				x		
	PVann	PSAX	2D	x		x	x			x			x
	PAd	PSAX	2D	x							x		
	PAd	Unspecified	M-mode					x					

TVA, tricuspid valve area; TVann, tricuspid valve annulus;A4C, apical four-chamber; 2D, two-dimensional;S4C, subcostal four-chamber;MV, mitral valve; TV, tricuspid valve; PVA, pulmonary valve area; PVann, pulmonary valve annulus; PLAX, parasternal long-axis; PSAX, parasternal short-axis; PAd, pulmonary artery diameter; SVC, superior vena cava; max, maximum; min, minimum; ave, average.

Table 4. Measurements of right heart morphology.

Variable		View	Method	Hanseus 1988	Kampmann 2000	Kapusta 2000	Lester 1987	Wessel 1985
Right Ventricle Anterior Wall								
	RVAWd	PLAX	M-mode		x	x	x	
	RVAWs	PLAX	M-mode			x		
MV-TV distance		A4C / S4C	2D	x				
RV geometry			Algorithm of sphere volumes					x

RVAWd, right ventricle anterior wall in diastole; PLAX, parasternal long-axis; RVAWs, right ventricle anterior wall in systole; MV, mitral valve; TV, tricuspid valve; A4C, apical four-chamber; S4C, subcostal four-chamber; 2D, two-dimensional; RV, right ventricle.

Table 5. Measurements of right heart chamber and valve function.

	Variable	View	Method	Boettler 2005	Clark 2001	Jin 1997	Moiduddin 2010	Norgard 1992	Suleymanoglu 2007
	RV EDV		Ellipsoid		x				
	RV ESV		Ellipsoid		x				
	RV EDV	A4C	Simpson's single-plane (30 discs)			x			
	RV ESV	A4C	Simpson's single-plane (30 discs)			x			
	RV EDV	A4C	Simpson's single-plane					x	
	RV ESV	A4C	Simpson's single-plane					x	
	RV EDV	SCP	Simpson's single-plane						x
	RV ESV	SCP	Simpson's single-plane						x
	RV SV		Ellipsoid		x				
	RV SV		Simpson's single plane (30 discs)			x			
	RV SV		Simpson's single-plane					x	
	%FAC						x		
	EF		Ellipsoid		x				
	EF	A4C	Simpson's single-plane (30 discs)			x			
	EF	A4C	Simpson's single-plane	x				x	
	RV Output		Ellipsoid		x				

RV, right ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; A4C, apical four-chamber; SCP, subcostal coronal plane; SV, stroke volume;. FAC, fractional area change; EF, ejection fraction.

Table 5 continued. Measurements of right heart chamber and valve function.

	Variable	View	Method	Cui 2007	Eidem 1998	Eidem 2004	Frommelt 2001	Innelli 2009	Ishii 2000	Kapusta 2000	Koestenberger 2009	Moiduddin 2010	Mori 2004	Roberson 2007	Singh 1993	Yasuoka 1999	Zhendong 1998
	TAPSE							x			x						
	Ac						x										
	DT						x										
	RV MPI		Pulsed Doppler		x	x			x					x			
	RV MPI		Tissue Doppler	x								x		x			
	E velocity					x		x		x			x			x	x
	A velocity					x		x		x			x			x	x
	E:A ratio					x		x	x	x						x	x
	A:E ratio												x				
	VTI														x		
	FVI: E		E area PWD													x	
	FVI: A		A area PWD													x	
	Inflow Area		Total area: (E and A) PWD													x	
	TR		N / % of total sample						x								
	E/Ea					x		x					x				

TAPSE, tricuspid annular plane systolic excursion; Ac, systolic annular acceleration; DT, deceleration time; RV, right ventricle;MPI, myocardial performance index; E, early diastole; A, late diastole; VTI, velocity time integral; FVI, flow velocity integral; PWD, pulsed wave Doppler; TR, tricuspid regurgitation; N, sample size; Ea, tissue Doppler early diastolic myocardial velocity.

Table 5 continued. Measurements of right heart chamber and valve function.

	Variable	View	Method	Ayabakan 2003	Innelli 2009	Kapusta 2000	Singh 1993	Zhendong 1998
	RVO velocity	PLAX/SX						x
	RVO velocity	PSAX			x			
	VTI		Lower left parasternal				x	
	Peak velocity					x		
	Peak velocity							x
	A			x				
	A VTI			x				
	S			x				
	S VTI			x				
	D			x				
	D VTI			x				
	A-R		R (R-wave on ECG)	x				
	R-D		R (R wave on ECG)	x				
	D-A		Diastolic Time interval	x				

RVO, right ventricle outflow; PLAX, parasternal long-axis; SX, short-axis; PSAX, parasternal short-axis;VTI, velocity time integral; SVC, superior vena cava; SC, subcostal; A, peak reverse atrial flow; S, peak systolic flow; D, peak diastolic flow; R, R-wave on ECG; ECG, electrocardiography.

Table 5 continued. Measurements of right heart chamber and valve function.

	Variable	View	Method	Boettler 2005	Cui 2007	Eidem 2004	Frommelt 2001	Goebel 2006	Harada 2000	Innelli 2009	Kapusta 2000	Mori 2004	Rafeiyian 2008	Roberson 2007	Yasuoka 1999
Pulsed TDI tracing:															
	Sa	A4C	TV annulus			x	x	x	x	x	x	x	x	x	
	Ea	A4C	TV annulus			x	x	x	x	x	x	x	x	x	x
	Aa	A4C	TV annulus			x	x	x	x	x	x	x	x	x	x
	Ea:Aa	A4C	TV annulus				x		x	x	x		x		x
	Aa:Ea	A4C	TV annulus									x			
	Sa	PLAX	RV anterior wall								x				
	Ea	PLAX	RV anterior wall								x				
	Aa	PLAX	RV anterior wall								x				
	Ea:Aa	PLAX	RV anterior wall								x				
	Ea:Sa	PLAX	RV anterior wall								x				
	Sa	PLAX	RV anterior wall								x				
	Ea	PLAX	RV anterior wall								x				
	Aa	PLAX	RV anterior wall								x				
	Ea:Aa	PLAX	RV anterior wall								x				
	Ea:Sa	PLAX	RV anterior wall								x				
	St			x	x									x	
	Dt				x										
	St/Dt				x										

TDI, tissue Doppler imaging;Sa, tissue Doppler peak systolic myocardial velocity; A4C, apical four-chamber; TV, tricuspid valve; Ea, tissue Doppler early diastolic myocardial velocity; Aa, tissue Doppler late diastolic myocardial velocity; PLAX, parasternal long-axis; RV, right ventricle; St, systolic time; Dt, diastolic time.

Table 5 continued. Measurements of right heart chamber and valve function.

	Variable	View	Method	Boettler 2005	Goebel 2006	Matsui 2007	Moiduddin 2010	Weidemann 2002
	Ss	A4C	RV free wall 3 segments	x			x	x
	Se	A4C	RV free wall 3 segments	x			x	x
	Sa	A4C	RV free wall 3 segments	x			x	x
	RV inflow	SC RAO				x		
	RV outflow	SC RAO				x		
	Pulm Ann	SC RAO				x		
	Ss	A2C	RV inferior wall 3 segments					x
	Se	A2C	RV inferior wall 3 segments					x
	Sa	A2C	RV inferior wall 3 segments					x
	Se duration			x				
	Sa duration			x				
	RV inflow	SC RAO				x		
	RV outflow	SC RAO				x		
	Pulm Ann	SC RAO				x		
	SRs	A4C	RV free wall 3 segments	x	x		x	x
	SRe	A4C	RV free wall 3 segments	x	x		x	x
	SRa	A4C	RV free wall 3 segments	x	x		x	x
	SRs	A2C	RV inferior wall 3 segments					x
	SRe	A2C	RV inferior wall 3 segments					x
	SRa	A2C	RV inferior wall 3 segments					x

Ss, tissue Doppler peak systolic strain; A4C, apical four-chamber;
RV, right ventricle; Se, tissue Doppler early diastolic strain;
Sa, tissue Doppler late diastolic strain; SC, subcostal;
RAO, right anterior oblique; Pulm, pulmonary; Ann, annulus;
A2C, apical two-chamber; SRs, tissue Doppler peak systolic strain rate;
SRe, tissue Doppler early diastolic strain;
SRa, tissue Doppler late diastolic strain rate.

Table 5 continued. Measurements of right heart chamber and valve function.

Variable	View	Method	Cui 2007	Eidem 1998	Eidem 2004	Frommelt 2001	Goebel 2006	Innelli 2009	Ishii 2000	Matsui 2007	Moiduddin 2010	Rafeiyian 2008	Roberson 2007	Sarnari 2009
Time to peak strain 3 seg RV free wall A4C											x			
%Strain							x							
Tissue displacement							x				x			
Time intervals Pulsed / Continuous Wave Doppler														
RV IVCT				x										
RV IVCT + IVRT		calculation							x		x		x	
RV SD		RV systolic duration (S)												x
RV DD		RV diastolic duration (D)												x
SD/DD		ratio												x
Time intervals Tissue Doppler TV Annulus														
RV IVCT			x			x		x		x		x		
RV IVCT		ECG and Sa			x		x							
RV IVRT			x	x	x	x	x	x		x		x		
RV IVCT + IVRT											x		x	
IVRT + IVCT + ET		a component									x		x	
DT										x		x		

RV, right ventricle; A4C, apical four-chamber; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; SD, systolic duration; DD, diastolic duration; ECG, electrocardiography; ET, ejection time; DT, deceleration time.

Table 6. Haemodynamic measurements of the right heart.

Variable		View	Method	Cui 2007	Daubeney 1999	Eidem 1998	Eidem 2004	Innelli 2009	Ishii 2000	Kampmann 2000	McQuillan 2001	Mori 2004	Pettersen 2008	Roberson 2007
Time Intervals														
	PV EP		CW / PW Doppler trace			x		x	x					x
	PV PEP		CW / PW Doppler trace			x								
	RV PEP / ET		CW / PW Doppler trace			x								
	PV EP		TDI trace	x										
Pulmonary Artery Diameter														
	PAd	PSAX			x								x	
	PAd		Unspecified							x				
Right Atrial Pressures														
	E/Ea						x	x				x		
RV Systolic Pressures														
	RV-RA gradient										x			
Pulmonary Arterial Systolic Pressures (PASP)														
	PASP		RAP assumed 10 mmHg								x			
Inferior Vena Cava														
	IVC % collapse							x						
	IVC diameter							x						

PV, pulmonary valve; EP, ejection period; CW, continuous wave; PW, pulsed wave; PEP, pre-ejection period; RV, right ventricle; TDI, tissue Doppler imaging; PAd, pulmonary artery diameter; PSAX, parasternal short-axis; E, early diastolic velocity; Ea, tissue Doppler early diastolic myocardial velocity; TR, tricuspid regurgitation; vel, velocity; RA, right atrium; PASP, pulmonary artery systolic pressure; RAP, right atrium pressure; IVC, inferior vena cava.

The studies that were excluded are summarized in Table 7.

Table 7. Excluded studies.

	Author	Year	Reason
1	Aessopos	2000	One age-category (ages: 14-55 y), including participants aged >21y.
2	Alam	1999	Sample contains participants aged >21y.
3	Arce	2002	Sample contains participants aged >21y.
4	Bussadori	2009	No right heart parameters
5	Carlhall	2004	Sample contains participants aged >21y.
6	Clark	2002	Participants aged <5y.
7	Conca	2009	Sample contains participants aged >21y; Measured parameters do not include that of the right heart.
8	Daimon	2008	Sample contains participants aged >21y.
9	Dalen	2010	Sample contains participants aged >21y.
10	Davidson	1990	RV Volume calculated but not presented as reference values, only correlation with CXR presented.
11	Dib	1997	Sample contains participants aged >21y.
12	Duzenli	2009	Sample contains participants aged >21y; Measured parameters do not include that of the right heart.
13	Emilsson	2004	Sample contains participants aged >21y.
14	Emilsson	2005	Sample contains participants aged >21y.
15	Friedman	1985	One age-category (ages: 19-43 y), including participants aged >21 y.
16	Galderisi	2002	Study objectives did not include obtaining and presenting of new reference data.
17	Gondi	2007	Study objectives did not include obtaining and presenting of new reference data.
18	Gopal	2006	Sample contains participants aged >21y.
19	Gournay	1998	Reference values on a great artery (LPA), not connected directly to the right heart.
20	Hanseus	1994	Measured parameters do not include that of the right heart.
21	Hirsimaki	1988	Measured parameters do not include that of the right heart.
22	Huicho	2005	Reference data on a sample of children living at high altitude.
23	Ilercil	2001	Sample contains participants aged >21y; Measured parameters do not include that of the right heart.
24	Kjaergaard	2006	In vivo study on a sample that contains participants aged >21y.
25	Klein	1999	Sample contains participants aged >21y.
26	Kluckow	2000	Participants aged <5y.
27	Knutsen	1989	Sample contains participants aged >21y.
28	Kovalova	2005	Sample contains participants aged >21y.
29	Kukulski	2000	Sample contains participants aged >21y.
30	Latson	1981	No reference data presented.
31	Lee	2009	Participants aged <5y.
32	Lindqvist	2009	Sample contains participants aged >21y.
33	Lindqvist	2009	Sample contains participants aged >21y.
34	Malakan	2004	Participants aged <5y.
35	Mikkola	2007	Study objectives did not include obtaining and presenting of new reference data.
36	Morner	2008	Sample of interest was a control group, but it contained participants aged >21y.
37	O'Learly	1998	Measured parameters do not include that of the right heart.
38	Overbeek	2006	Measured parameters do not include that of the right heart.
39	Oyer	2003	Participants were not alive when the data was obtained.

40	Pena	2009	Participants aged <5y.
41	Poutanen	2003	Measured parameters do not include that of the right heart.
42	Pye	1991	Sample contains participants aged >21y.
43	Raczek	2010	Measured parameters do not include that of the right heart.
44	Rein	2003	Sample contains participants aged >21y.
45	Schvartzman	2000	Sample contains participants aged >21y.
46	Snider	1984	Reference values on a great artery (RPA), not connected directly to the right heart.
47	Steed	1998	Sample contains foetuses.
48	Stevenson	1995	Study objectives did not include obtaining and presenting of new reference data.
49	Tamborini	2009	Sample contains participants aged >21y.
50	Tugertimur	2000	Measured parameters do not include that of the right heart.
51	Uiterwaal	1989	Sample contains participants aged >21y.
52	Van de Veire	2006	Sample contains participants aged >21y.
53	Van Oort	1988	Sample contains participants aged >21y.
54	Vasan	2000	Measured parameters do not include that of the right heart.
55	Vitarelli	1996	Sample contains participants aged >21y.
56	Yoerger	2005	Sample of interest was a control group, but it contained participants aged >21y.
57	Zhang	2006	Sample contains participants aged >21y.
58	Zoghbi	1990	Sample contains participants aged >21y.

y, years; CXR, chest x-ray; LPA, left pulmonary artery; RPA, right pulmonary artery.

Most articles were excluded due to the inclusion of adult or infant participants. Furthermore, some did not present a new set of reference data for echocardiographic evaluation of the right heart. In one of the publications the reference population comprised deceased participants. There was also a publication on a study containing a sample of unborn foetuses.

The evaluation of the included studies against the 2010 American Society of Echocardiography (ASE) recommendations of 24 key measurements for performing a right heart echocardiography examination in a paediatric population are presented in *Table 8.* No study documented reference intervals on all 24 criteria.

Table 8. American Society of Echocardiography recommended measurements.

	Year of Publication	RAw *	RAl *	RAA *	TV ann	TV area	RV base A4C #	RV mid A4C #	RV length A4C #	RVAd #	RVAs #	RVOT	PVd	PAd	TAPSE	RV %FAC #	S'	E'	A'	IVRT	IVA	RVOT PPG	PA PPG	TR vel	IVC d #
Boettler	2005									x	x														
Bonatto	2006											x													
Cui	2008																			x					
Daubeney	1999				x				x	x			x	x											
Eidem	1998																			x					
Eidem	2004																x	x	x	x					
Frommelt	2002																x	x	x	x					
Goebel	2006																x	x	x	x					
Gutgessell	1991											x													
Hanseus	1988	x	x	x			x		x	x		x	x												
Harada	2000																x	x	x						
Ichida	1987												x												
Innelli	2009	x					X	x	x						x		x	x	x	x		x			x
Kampmann	2000													x											
Kapusta	2000																x	x	x						
King	1985				x																				
Koestenberger	2009														x										
Matsui	2007												X							x					
McQuillan	2001																							x	
Moiduddin	2010															x									
Mori	2004																x	x	x						
Norgard	1992							x	x	x	x	x													
Pettersen	2008				x							x	x	x											
Rafeiyian	2005																x	x	x	x					
Roberson	2007																x	x	x						
Singh	1994					x						x													
Yasuoka	1999																	x	x						
Zhendong	1998																					x	x		
Zilberman	2005				x								x												

RAw, right atrium width; RAl, right atrium length; RAA, right atrium area; TV, tricuspid valve; ann, annulus; RV, right ventricle; A4C, apical four-chamber; RVAd, right ventricle area in diastole; RVAs, right ventricle area in systole; RVOT, right ventricle outflow tract; PV d, pulmonary valve diameter; TAPSE, tricuspid annular plane systolic excursion; FAC, fractional area change; S', tissue Doppler peak systolic myocardial velocity; E', tissue Doppler early diastolic myocardial velocity;A', tissue Doppler late diastolic myocardial velocity; IVRT, isovolumic relaxation time; IVA, isovolumic acceleration; PPG, peak pressure gradient; PA, pulmonary artery; TR, tricuspid regurgitation; vel, velocity; IVC d, inferior vena cava diameter.

** Little pediatric data according to the publication by the ASE.*[8]

 # No pediatric data according to the publication by the ASE.[8]

3.8 Discussion

This systematic review presents the most complete review of existing data on right heart reference intervals in children and young adults. Nine studies from an earlier review[27] is included in this review. [12, 15, 20, 32-37]

Based on the guidelines from the American Society of Echocardiography[2, 8], and the systematic review of the literature, we report on the availability of reference data in children and young adults, highlighting areas lacking sufficient data with respect to measurements of the right atrium, the tricuspid valve, right ventricular size and function, the pulmonary valve, the pulmonary artery, and right heart haemodynamics.

The right atrium

We identifiedonly one publication presenting reference data for right atrial (RA) size for children younger than 10 years of age. In 1988, Hanseus *et al.* published a set of reference values on the RA on a sample of 120 healthy infants and children, aged 3 days to 15.5 years. His RA measurements included the width, length and area for the RA. He presented the data for the entire sample according to BSA using regression equations and nomograms.[35]

Innelli *et al.* published a set of reference values for RA width on a sub-group of 40 healthy children and adolescents, aged 10-19 years. In this recent publication (2009), reference values for the entire sub-group, aged 10-19 years were presented as one value.[13]

Tricuspid valve area

Sufficient data exist on the diameter of the tricuspid valve (TV) annulus, but we discovered only one publication presenting reference data on the TV area. Singh *et al.* published reference values on the TV area based on a reference population aged 2 months to 50 years. The data for participants less than 16 years were presented in 3 different age-categories.[15]

Right ventricular size and/or volume

We identified one publication presenting reference data for RV basal diameter for children younger than 10 years of age. This two decades old study obtained a reference population of 120 healthy infants and children, aged 3 days to 15.5 years. The data were adjusted for BSA, using regression equations and nomograms.[35] Innelli *et al.* recently published reference values on a sub-group of 40 healthy children and adolescents, aged 10-19 years as one value.[13]

Two publications exist on reference values of the RV mid diameter measured in the apical four-chamberview. Norgard *et al.* presented reference values for RV mid diameter on only 15 individuals, aged 6-16 years as one value for the entire sample.[14]More recently, Innelli*et al.* published reference values of a sub-group of 40 healthy children and adolescents, aged 10-19 years as one value.[13] We found no publications presenting reference values for RV mid diameter measured in the apical four-chamber view for children younger than 10 years.

Two publications were found on reference values of the RV end-systolic area measured in the apical four-chamber view[14, 16]. The usefulness of both of these publications however, is limited as they both present the data for the entire sample spanning more than 10 years as one value. This study by Norgard *et al.* had only 15 individuals, aged 6-16 years.[14] Boettler *et al.* published reference values of a larger series containing 129 reference individuals, aged 1 day to 16.9 years.[16]

Right ventricular function

Only one publication was identifiedon RV % fractional area change in a sample of healthy children. The sample of healthy children was a control-group consisting of 13 healthy individuals. One of the objectives of the study was to compare quantitative measurements of the RVin single RV's to normal RV's. The % fractional area change of the control-group consisting of 13 healthy individuals was presented. The mean age of the healthy control-group was 5.7±1.8y.[31] A study aiming to generate reference values for RV fractional area change, containing a larger sample with greater age-span and categorization may be more useful in clinical practice.

We did not find any existing reference data on isovolumic acceleration.

Pulmonary artery peak pressure gradient

Zhendong *et al.* published reference values of the pulmonary artery(PA) peak pressure gradient in 1998 in a reference population consisting of 88 healthy individuals, aged 3-12 years. The sample was divided into two age-categories.[38] No publications were found containing data for children older than 12 years.

Right-sided haemodynamics

According to our results, the publication by McQuillan *et al.* was the only study publishing reference data on right-sided haemodynamics for children and adolescents. In 2001, McQuillan published reference data for the TV RV-RA gradient in a reference population consisting of 856 participants younger than 20 years. Mcquillan *et al.* presented estimatedpulmonary artery systolic pressure values assuming that the RA pressure for all reference individuals is 10 mmHg. The reference data were presented graphically, according to BSA.[19] Pena *et al.* recently published reference data for the tricuspid regurgitation (TR) peak velocity on 55 newborn infants. The authors also presented estimated PA systolic pressure values assuming that the RA pressure for all reference individuals was 5 mmHg.[39]

No reference values for the diameter and percentage collapse of the inferior vena cava (IVC) for children younger than 10 years were found. Innelli *et al.* published reference values for the IVC diameter and percent IVC collapse in a sub-group consisting of 40 healthy children and adolescents but presented the data for the entire sample, aged 10-19 years as one value.[13]

Accordingly, we could not find any publication presenting reference values for estimated PA systolic pressure with an estimate of RA pressure on the basis of IVC size and collapse.

There is sufficient reference data for the following variables:

Tricuspid valve annulus

Four authors have published reference data on the annulus of the tricuspid valve (TV)based on reference populations ranging from infants to young adults, according to BSA. The oldest publication was by King *et al.* in 1985.

The most recent publication was by Pettersen *et al.* in 2008. The sample sizes ranged from the smallest by King (N=103) to the largest by Pettersen (N=782).[20, 33, 36, 37]

Right ventricular length

Four existing publications presented reference values for the RV length, measured in the apical four-chamber view. Hanseus *et al.* (N=120) and Daubeney *et al.* (N=125) presented data for the entire sample (birth to adolescent age), according to BSA whereas Inneli *et al.* (N=40, 10-19years) and Norgard *et al.* (N=15, 6-16years) presented data for the entire sample, as one value.[14, 35, 36, 40]

Right ventricular end-diastolic area

Four authors have published reference values for the RV end-diastolic area, measured in the apical four-chamber view. Authors Hanseus *et al.* (1988, N=120) and Daubeney *et al.* (1999, N=125) presented data for the entire sample (birth to adolescent age), according to BSA. Boettler *et al.* (2005, N=120, 0-17years) and Norgard *et al.* (1992, N=15, 6-16years) presented data for the entire sample, as one value.[14, 16, 35, 36]

Right ventricular outflow tractdimension

There are six existing publications reporting the dimension of the RV outflow tract, measured anterior to the aortic valve in the parasternal short-axis view. The oldest publication dates back to 1988[35] and the most recent publication was published in 2008 by Pettersen*et al.*[20] The sample sizes range from 15[14] to 782[20]. The ages of the samples range from birth to adolescent ages. Four authors presented data according to BSA [12, 20, 35, 41]. Singh *et al.* divided the sample into 3 age-categories for children younger than 16 years. Norgard and Vik-Mo published reference data for the entire sample (aged 6-16years) as one value.[12, 14, 15, 20, 35, 42]

Pulmonary valve diameter

Six publications reported reference values for the pulmonary valve (PV) diameter in children and adolescents. Hanseus *et al.*, Daubeney *et al.*, Pettersen *et al.* and Zilberman *et al.* reported reference values for PV diameter in samples of healthy children ranging from birth to adolescent age

and presented the data according to BSA. Ichida *et al.* presented a set of reference intervals for children aged from birth to 15 years stratified by different age-categories. Matsui *et al.* presented the measured PV diameter in a sample of 22 healthy children, aged 0-11 years as one reference interval. The oldest study by Ichida *et al.* date back to 1987. The most recent publication was by Pettersen *et al.* in 2008. The sample sizes for these publications range from the smallest 22 to 782 (Pettersen).[20, 34-37, 43]

Pulmonary artery diameter

Daubeney *et al.*, Pettersen *et al.* and Kampmann *et al.* published reference data on the diameter of the PA in children ranging from infancy to adolescent age. The sample sizes were 125, 782 and 2036 respectively. All three authors presented the results according to BSA.[20, 36, 44]

Tricuspid annulus peak systolic excursion

Two recent (2009) publications detailed reference values for tricuspid annulus peak systolic excursion (TAPSE) in children. The first publication by Innelli *et al.* presented the TAPSE values for a sub-group of 40 children and adolescents, aged 10-19 years. The second publication by Koestenberger *et al.* presented the TAPSE values in a large sample (N=640) of infants, children and adolescents. The data were presented according to BSA and age-categories.[40, 45]

Tissue myocardial velocities at the lateral tricuspid annulus

There are nine publications containing reference values for tissue myocardial velocity of the lateral tricuspid annulus in the apical four-chamber view. These publications were published between 2000 and 2009. Eidem *et al.*, Frommelt *et al.*, Harada *et al.*, Mori *et al.*, Rafeiyian *et al.* and Roberson *et al.* published reference values in samples ranging from infancy to adolescent age. Four authors (Eidem *et al.*, Harada *et al.*, Mori *et al.* and Rafeiyian *et al.*) presented the reference values stratified by age. Frommelt *et al.* presented the data for the sub-group aged 1-18 years as one value. Roberson *et al.* presented reference data according to BSA. Innelli*et al.*, Goebel *et al.* and Kapusta *et al.* presented their data as a single value for the entire sample. The sample size for these publications ranged from 40 (Innelli *et al.*) to 634 (Robersone*t al.*).[40, 46-53]

4 The establishment of reference intervals for the right heart in African school-going children

4.1 Objectives:

1. To establish reference intervals for the echocardiographic evaluation of the right heart in a random sample of South African school-going children.
2. To compare the measurements in the South African cohort with the recommended variables of the American Society of Echocardiography.
3. To design a tool for the calculation and reporting of echocardiographic right heart measurements in children.

4.2 Introduction to the study design

Reference intervals forechocardiographic measurements of the right heart were established in a sample of South African school children and adolescents. Reference individuals were selected from the school-going population within the Vanguard Communities of Cape Town, South Africa. To the best of our knowledge, this is the first set of reference intervals for echocardiographic measurements of the right heartin children and adolescents established using a community-based design and the first in African children.

Section 2 of this thesis (*Literature review*) contains a comprehensive background on reference intervals and the role of echocardiography in the evaluation of the right heart.

4.3 Reference population

This research forms part of a larger population-based surveillance study investigating the prevalence of rheumatic heart disease within the Vanguard Communities of Cape Town. We selected two periods in 2008 and 2009 during which more than 200 school children between the ages of 5 and 21 years participated in the surveillance study. These participants were without any known cardiac abnormalities or acquired disease.

The Vanguard Communities comprise people living in the black African township of Langa and people of mixed ancestry who live in Bonteheuwel. The population estimates were around 49 664 (Langa) and 50 676 (Bonteheuwel) respectively in 2001 (Total 100 340). Approximately 50% of this population are under the age of 20 years.[54]

To characterize age-related changes more appropriately, the study population was divided into 3 sub-groups for age: group 1, 5-9 years; group 2, 10-14 years; and group 3, 15 years and older. In order to characterize changes related to body surface area (BSA), we divided the study population into 4 quartiles for BSA.

4.4 Inclusion / Exclusion criteria

Reference individuals had to have no history or echocardiographic evidence of heart disease, including cardiac masses, valvular dysfunction, congenital defects, pericardial or muscle heart disease at the time of the echocardiogram.

Only participants who gave informed consent to perform an echocardiogram were included.

Participants with a history of infectious, neuromuscular, or metabolic disorders were excluded. Any arrhythmias on surface electrocardiogram were also an exclusion criterion.

4.5 Echocardiographic evaluation of the right heart: methods, technique and variables

This section describes the ultrasound techniques that were used in the evaluation of right heart structure, function, and haemodynamics. These recommendations are reviewed in more detail in the American Society of Echocardiography Guidelines published in 2010.[2] Other leading Echocardiography Associations, such as the European Association of Echocardiography and British Society of Echocardiography have also included the measurement of right ventricle (RV) dimensions, -function and haemodynamics as part of their recommendations.

All echocardiographic studies were performed in the left lateral supine position using a Vivid *i* machine (GE Ultrasound, South Africa), equipped with a 5.0 MHz phased-array transducer and tissue Doppler technology. Simultaneous electrocardiography was used to correlate timing of electrical events with mechanical events. No sedation was used.

The author performed all the measurements for every reference individual.

4.5.1 Baseline data

For each reference individual, the height and weight, as well as the following demographic data were recorded: date of birth, age, sex, race and heart rate. Body mass index (BMI) and BSA were calculated, the latter using the Mosteller formula.[55]

4.5.2 Echocardiographic modalities

Complete two-dimensional (2D), M-mode, pulsed-wave Doppler, continuous-wave Doppler, and colour flow Doppler echocardiographic examinations were performed and recorded on all reference individuals. Colour-coded tissue velocity cineloops of at least three cardiac cycles was acquired from the apical four-chamber view.

4.5.3 Size, volume and morphology

Right atrium

The recommended methods to assess right atrium (RA) size include the measurement of major and minor axis lengths and planimetered area in the apical four-chamber view.[8]

The RA size was measured in an apical four-chamber view at end-systole just before the tricuspid valve (TV) opens. The major(length) and minor(width) axis (in cm) and planimetered the RA area (cm^2) were measured. The tricuspid contour was defined as the semi-automatically drawn linear connection between the end points of the outline. Atrial length

was measured from the tricuspid contour (mid-annular point) to the posterior wall of the atrium. The width was measured as the maximal distance between the mid point of the atrial septa and RA lateral wall, perpendicular to the length. Planimetry of the atrial area was done by tracing the endocardial outline and drawing a straight line through the atrioventricular orifice.

Tricuspid valve

The recommended method to assess TV annular size which includes measurement of lateral diameter in apical four-chamberview was used. The largest TV diameter during peak filling in early diastole was measured using an apical four-chamber view, at the frame after maximum excursion of the leaflets from inner edge to inner edge at the hinge points of the leaflet attachments.[8]

The mitral valve (MV) annular diameter was also measured using the same technique and the TV:MV ratio was calculated.

Right ventricle

The simplest and most routinely used method for assessing RV volume includes linear dimensions and areas obtained from single tomographic echocardiographic planes.[4]

We imaged the RV using an apical four-chamber view with the septum as vertical as possible, the TV as horizontal as possible, and the apex in view.[56]

The recommended measurements to determine RV size include the measurement of end-diastolic diameters at the basal and midcavity levels, end-diastolic length, and end-diastolic and end-systolic planimetered areas in the apical four-chamber view. [8] The RV basal and midcavity minor-axis (width) diameters and RV major-axis length were measured at end-diastole (defined as the frame at which the TV closes and the RV is at its largest), taking care not to foreshorten the RV. The basal border was defined as the line connecting the RV lateral and septal basal segments, about 1 cm below the hinge points of the TV annulus. The RV length was measured from the semi-automatically drawn tricuspid contour (mid-annular point) to the apex. The RV long-axis area was measured by planimetry.

Similarly, the left ventricular (LV) area was measured using the same technique and the RV:LV ratio was calculated.

M-mode echocardiography has contributed in a major way to our ability to non-invasively assess and quantitate certain aspects of cardiac anatomy and function, and remains widely used, despite the technologic advances in two-dimensional (2D) echocardiography and Doppler ultrasound, which offer many advantages.[57] The two available age-categorized reference intervals on the size of the RV using M-mode echocardiography are based on small samples and date back to the early 1990s and 1970s. Therefore, this modality and measurement were included in our protocol.

In the parasternal long-axis view, we positioned an M-mode beam through 2D echocardiographic monitoring. The M-mode cursor was placed at the tips of the MV leaflets. The maximal dimension of the RV in end-diastole where the RV was at its largest was measured. The RV internal dimension was taken as the vertical distance between the endocardial echo of the anterior wall of the RV and the echo from the right side of the interventricular septum.[30]

Right ventricular volumes

Multiple formulae have been proposed to estimate RV volume by 2D echocardiography. However, the best method for routine 2D measurement of RV volume however still remain controversial.[8]

Using the apical four-chamber view, the RV area and length in diastole and systole were measured. End-diastole was defined as the frame where the ventricles were at their largest. End-systole was defined as the frame where the ventricles were at their smallest. The RV cavity was outlined using the trackball in end-diastole and end-systole. The endocardium was traced at the cavity black-grey interface. The tricuspid contour was defined as the semi-automatically drawn linear connection between the end points of the outline. Papillary muscles and smaller trabeculations were not taken into consideration. RV end-diastolic and end-systolic volumeswere calculated using the area-length method. The area-length method is useful when only one apical view of the RV is recorded, as with the standard echocardiogram.

Volume is calculated by an equation [$0.85\ (A^2/L)$], using the area (A) and long-axis length (L) of the RV.[2]

Right ventricular outflow tract and pulmonary artery

We measured the diameters of the RV outflow tract in parasternal long-axis and parsternal short-axis views during mid-systole, using the largest diameters for documentation.[8] In the short-axis view, the RV outflow tract linear dimension was be measured from the anterior aortic wall to the RV free wall above the aortic valve (supra-aortic) and just proximal to the pulmonary valve (PV) (sub-pulmonic).[2] The measurements were obtained perpendicular to the long axis of the outflow tracts and parallel to the plane of the annulus at the time of maximum diameter in early systole. Measurements were made from the continuous inner margins of the outflow tract.[15]

The pulmonary annular diameter was measured in the parasternal short-axis view, from the inner edge to the inner edge at the hinge points of the leaflet attachments, at the frame of maximum excursion of the leaflets.

The pulmonary artery (PA) diameter was measured in the parasternal short-axis view, halfway between the PV and the bifurcation to the left and right PA, inner edge to inner edge, at the moment of maximum expansion.[8]

Septal motion

It is known that volume overload will induce an increase in RV end-diastolic pressure at or above the level of the LVend-diastolic pressure, provoking a flattening and subsequent bulging of the interventricular septum towards the LV when RV volume overload is longstanding.[5] We evaluated and categorized the septal motion as normal, paradoxical, flattening in diastole, or other.

Right ventricular morphology

The RV free wall thickness is difficult to quantify, though it can be measured in subxiphoid long-axis or parasternal views.[8] The RV free wall thickness was measured in end-diastole (mm)in the parasternal long-axis view using M-mode. Care was taken to avoid regions with significantly coarse trabeculations.

In the apical four-chamber view, the distance between septal insertion of the MV and TV was measured.

4.5.4 Chamber and valve function

RV systolic function has been evaluated using several parameters, namely RV myocardial performance index (MPI), TAPSE, 2D RV fractional area change, 2D RV EF, three-dimensional RV EF, tissue Doppler-derived Sa, longitudinal strain and strain rate. Among these, more studies have demonstrated the clinical utility and value of TAPSE, RV MPI, 2D RV fractional area change, and the Sameasured at the tricuspid annulus. [2] RV systolic function should include at least one of the following: TAPSE, RV % fractional area change and Sa, with or without RV MPI.[2]

TheRVwas imaged in an apical four-chamber view with the septum as vertical as possible, the TV as horizontal as possible, and the apex in view.[56]

We measured TAPSE by 2D-guided M-mode with the cursor placed at the free wall through the lateral tricuspid annulus.[8] Maximal TAPSE was determined by the total excursion of the tricuspid annulus from the lowest point of descent during systole to its highest position after atrial descent.

The **MPI or Tei index** is defined as the sum of *isovolumetric contraction time*and *isovolumetric relaxation time*divided by *ejection time*.[9] For the RV, the sum of the isovolumic times is calculated by subtracting *ejection time*from the *TV closing time (a-b)*. *TV closing time* can be measured as the time-period between the cessation of the TV A wave to the next TV E wave or, the duration of tricuspid regurgitation. *Ejection time(b)* is measured from the start to the end of PVoutflow, using pulsed-wave or continuous-wave Doppler.[2]

RV *ejection time*was measured using the continuous-wave Doppler trace of the PV outflow. *TV closing time* was taken as the time-period between the cessation of the TV A wave to the next TV E wave. We calculated the RV MPI by subtracting the *ejection time(b)* from the *TV closing time (a)* and dividing it by the *ejection time[(a-b)/b*].

2D Right ventricular percent fractional area change

The RV areas was obtained by tracing the RV endocardium both in systole and diastole. Care was taken to exclude trabeculations. RV % fractional area changewas calculated using the formula: [RV end-diastolic area – RV end-systolic area) / RV end-diastolic area X 100].[2]

Volumetric right ventricular ejection fraction (area-length method)

The RV end-diastolic and end-systolic volumeswere calculated using the area-length method.(*See section 4.5.3Right ventricular volumes)*.[2] We calculated the volumetric RV ejection fraction (EF) using the formula: [*RV end-diastolic volume – RV end-systolic volume) / RV end-diastolic volume X 100*].[2, 6]

The **right ventricular peak systolic annular velocity**

Doppler Tissue Imaging (DTI)was performed using low gain and low filter settings to exclude high-frequency signals. A sample volume gate length of 2 to 3 mm was used. Adjustments were made on a case-by-case basis to optimize DTI waveforms to define clear borders and minimize background noise. An apical 4-chamber window was used. The pulsed Doppler sample volume was placed in the tricuspid annulus of the RV free wall.[2] Care was taken to aim the ultrasound beam along the RV free wall to minimize the angle of incidence between the beam and the longitudinal direction of wall motion. Sa was measured during periods of stable heart rate and stable DTI waveforms.

RV diastolic function

Assessment of RV diastolic function were carried out by pulsed Doppler of the tricuspid inflow, tissue Doppler of the lateral tricuspid annulus, pulsed Doppler of the hepatic vein, and measurements of inferior vena cava (IVC) size and collapsibility. The most validated and recommended parameters include the E/A ratio, deceleration time, the E/Ea ratio, and RA size. It is recommended that at least one of the above quantitative measures be incorporated, especially when RV dysfunction is suspected and/or when the clinical indication for the study relates to condition that may affect the right ventricle.[2]

Pulsed Doppler of the RV inflow in the apical four-chamber view was performed The sample volume was placed at the tip of the tricuspid valve leaflets. The tricuspid peak early inflow (E wave), deceleration time, peak atrial inflow (A wave), and calculated the TV E/A ratio was measured.

DTI was performed. The sample volume was placed in the lateral tricuspid annulus in the apical four-chamber view. The DTI waveforms were optimized (*see section 4.5.4, The* right ventricular peak systolic annular velocity).[2] The peak early diastolic annular velocity (Ea) and late diastolic annular velocity (Aa) during periods of stable heart rate and stable DTI waveforms were measured.

Combining pulsed-wave Doppler and DTI techniques, the E/Ea ratio predicts elevated filling pressures. The E/Ea ratio was calculated by dividing transtricuspid peak E velocity by the peak early diastolic velocity myocardial velocity measured at the TV lateral annulus(Ea).[13]

The effect of respiration on the early diastolic phase.

The effect of respiration on the early phase of the RV diastolic filling was investigated as it is known that abnormal variation of the early diastolic phase ("E" wave) could indicate abnormal cardiac haemodynamic states such cardiac tamponade or pericardial constriction. In a series of 6-10 recorded cycles, the maximum and minimum E velocity was measured. The percentage variation between the minimum and maximum measured values was calculated.

Tricuspid valve

Increased peak velocities and elevated pressure gradients across the TV may suggest valve stenosis. Therefore, pulsed Doppler of the RV inflow was performed in the apical four-chamber view. The sample volume was placed at the tip of the TV leaflets. The TV inflow peak velocity was measured and the TV inflow pattern traced to obtain the TV mean pressure gradient.

The tricuspid regurgitation was graded as none, mild, moderate, or severe by assessment of the colour-flow jet in relation to the RA in multiple orthogonal views.

Pulmonary valve

Doppler interrogation of the main pulmonary artery is best performed in the parasternal short-axis view or modified apical views with anterior angulation.[8] The peak velocity and peak pressure gradient across the pulmonary valve was measured in the parasternal short-axis view by positioning a continuous-wave Doppler signal across the PV. Using colour Doppler to guide the positioning of the continuous-wave signal, the continuous-wave signal was positioned to be in the direction of flow across the PV.

4.5.5 Right heart haemodynamics

Right atrial pressure and the inferior vena cava

The IVC size and inspiratory collapsibility (change in diameter) was measured from the subcostal view just before the widening of the vessel, approximately 1-2 cm before the entrance to the RA.[8] For simplicity and uniformity of reporting, specific values of RA pressurewas used in the determination of systolic PA pressure.[2] We used an IVC collapsibility index (*Appendix B*).[58]

The calculated RV E/Ea (*See section 4.5.4, RV diastolic function*) was also recorded as an index of RA pressure.[13]

Right ventricular and pulmonary artery pressures

PA systolic pressure is equivalent to RV systolic pressurein the absence of obstruction to flow between the RV and PA. The best validated Doppler technique for evaluation of the estimation of PA systolic pressure is the sum of the RV systolic pressure and the estimated RA pressure. The tricuspid regurgitation systolic pressure is calculated by applying the modified Bernoulli equation to the measured peak tricuspid regurgitation velocity.[59]

The tricuspid regurgitation jet was detected using continuous wave Doppler and the peak tricuspid regurgitation velocity (v) was measured to determine the RV systolic pressure using the simplified Bernoulli equation.[19] The RV systolic pressure was estimatedby applying the modified Bernouilli equation ($4v^2$), where v is the peak velocity of the TV regurgitant jet (measured in

metres per second), to the detected peak tricuspid regurgitation velocity.[5] The estimated RA pressure (see *Appendix A*)[58]was added to the estimated RV systolic pressure to calculate an estimated systolic PA pressure.

In patients with PA hypertension or heart failure, an estimate of PA end-diastolic pressurefrom either the mean gradient of the tricuspid regurgitation jet or from the pulmonary regurgitantjet should be reported. PAend-diastolic pressure can be estimated from the velocity of end-diastolic pulmonary regurgitation jet using the modified Bernoulli equation: [PA end-diastolic pressure = 4 x (end-diastolic pulmonary regurgitation velocity)^2 + RA pressure].[2]

PAend-diastolic pressurewas estimated by applying the modified Bernouilli equation ($4v^2$) to the detected pulmonary regurgitation end-diastolic velocity. The estimated RA pressure (see *Appendix A*)[58] was added to generate the estimated pulmonary artery end-diastolic pressure.[5]

4.6 Data analysis and statistical considerations

A sensitivity-analysis was performed to determine the effect of off-axis images and poor image quality on the mean values of the parameters in order to determine if studies with images that are off-axis and/or of poor resolution should be excluded from analysis.

Body surface area categories

The reference population was divided into quartiles per BSA. This assumed that there was a linear correlation between age and BSA. Recommended statistical methods were employed for the different age-categories.[23]The mean ± 2standard deviation (SD) for all the variables and BSA-categories were calculated. Stata 11 was used to generate Z-score graphs for right heart variables of size and relative to body surface area.

Detecting outliers

Outliers for each age-category were detected via the D/R ratio, where D is the absolute value of the difference between the outlier and the next or preceding value and the R represents the entire range of the observations (maximum – minimum), outlier included. According to the Clinical and

Laboratory Standards Institute, a value is considered to be an outlier ifthe calculated D/R ratio is greater than one-third.[23]

Histograms and transformation of data

After removing all outliers, a histogram was generated for every variable by age-category. For all variables deemed to have a Gaussian distribution on visual inspection, the reference intervals were calculated as the mean ± 2SD. These values were entered into thereference value table.

Data were transformed (log_{10} or square root) for each of the variables that did not have a Gaussian distribution by age category. A histogram of the transformed data-setwas generated to confirm the presence of a Gaussian distribution, and the mean ± 2SD for the transformed data-sets were calculated. The mean ± 2SD values were back-transformed and enteredinto the reference value tables.

Bootstrapping

For a few variables, a Gaussian distribution could not be achieved in all the age-categories, even if the data weretransformed. The recommended "bootstrapping"-method was followed to statistically generate a larger data-set. For these variables, the median, 2.5thpercentile and the 97.5thpercentile valueswere calculated. These values were considered as the reference interval and were enteredinto the reference value tables.

Statistical significance

Using the *Open Epi* epidemiologic calculator, we performed a *t test* to compare newly established reference values with the mean values of existing published reference data, according to age. A *p value* ≤ 0.05 was considered statistically significant.

4.7 Data management and quality control

All cineloops and images were stored digitally and later analyzed by one machine (Vivid i, GE, South Africa) and one investigator (C.L.).

Data were captured on paper Case Report Forms. Case Report Forms were stored in a secure location.

Numeric data were imported into a custom-made Microsoft Access database.

4.8 Intraobserver variability

Echocardiographic measurements were repeated by the author in 13 participants to assess reproducibility and intraobserver variability. Comparisons among data were performed with Student's t test, $p < 0.05$, with 95% limits of agreement. None of the repeated measurements on of the subset of 21 variables showed a significant difference between the two measurements.

4.9 Ethical aspects

This sub-study complies with all institutional guidelines related to patient confidentiality and research ethics including institutional review board approval. It falls within the approved protocol 028 / 2006 as reviewed by the University of Cape Town Ethics Committee on 13 January 2006.

Parents/caregivers were asked to provide informed consent for permission to have a participant's codified echocardiogram performed. Consent was provided by signing a consent form. Assent to participate was sought in individuals 8 years and older. Adolescents who were 18 years and older were entitled to provide their own informed consent.

Only participants for whom informed consent for permission to have a participant's codified echocardiogram performed was given, were included.

4.10 Results

The reference population consisted of 213 reference participants with normal cardiac structure and function. Their ages ranged from 5-21 years. Their body weight ranged from 14.97 to 93.74 kg and their body surface area from 0.47 to 2.02 m^2.

To characterize changes in reference data with age, the reference population was divided into three subgroups of 5-6 yearly intervals. Thirty two of the reference individuals were 5 to 9 years of age (*age-category 1*), 104 participants were 10 to 14 years of age (*age-category 2*), and 77 participants were 15 years and above (*age-category 3*).

The demographic data in *Table 10* are presented according to the age-categories.

Table 9. Demographic data according to age-categories.

Variables		AGE category 1	AGE category 2	AGE category 3
		5-9 y	10-14 y	15-21 y
Height (m)	Mean	1.18	1.48	1.61
	- 2SD	0.95	1.30	1.45
	+ 2SD	1.42	1.67	1.77
Weight (kg)	Mean	25.09	41.92	62.92
	- 2SD	3.14	19.05	36.61
	+ 2SD	47.05	64.79	89.23
BMI(kg/m^2)	Mean	17.34	18.89	24.34
	- 2SD	9.62	10.75	13.74
	+ 2SD	25.07	27.03	34.94
BSA(m^2)	Mean	0.90	1.30	1.67
	- 2SD	0.47	0.91	1.31
	+ 2SD	1.33	1.70	2.02
Heart rate (bpm)	Mean	90.34	78.97	74.08
	- 2SD	64.74	56.74	53.58
	+ 2SD	115.95	101.20	94.57

cm, centimetres; SD, standard deviatio;. m, metres;kg, kilograms; BMI, body mass index; BSA, body surface area; bpm, beats per minute.

As expected, our results revealed an increase in BSA and a decrease in heart rate with increasing age.

We divided the reference population into 4 quartiles by BSA. There was a linear correlation between age and BSA ($r = 0.83$, $P < 0.001$).

The demographic data in *Table11*are presented according to the four different BSA-categories.

Table 10. Demographic data according to body surface area categories.

Variables		BSA category 1	BSA category 2	BSA category 3	BSA category 4
		<1.15 m^2	1.15-1.39 m^2	1.40-1.60 m^2	1.61m^2 +
Age	Mean	8.29	11.67	14.60	16.79
	- 2SD	2.59	8.58	9.23	11.98
	+ 2SD	14.00	14.77	19.97	21.60
Height (m)	Mean	1.25	1.48	1.56	1.62
	- 2SD	0.99	1.36	1.41	1.47
	+ 2SD	1.50	1.60	1.71	1.78
Weight (kg)	Mean	25.35	38.53	52.18	69.87
	- 2SD	14.97	30.99	42.80	45.99
	+ 2SD	35.74	46.07	61.55	93.74
BMI(kg/m^2)	Mean	16.21	17.67	21.45	26.73
	- 2SD	12.61	13.27	15.13	15.83
	+ 2SD	19.80	22.06	27.79	36.64
Heart rate (bpm)	Mean	86.46	78.00	76.51	75.17
	- 2SD	58.37	59.18	54.24	52.41
	+ 2SD	114.55	96.82	98.78	97.93

m, metres;kg, kilograms;SD, standard deviation; BMI, body mass index; bpm, beats per minute.

As expected, participants with a higher BMI had significantly poorer image quality.

We observed a significant difference in image quality, namely right heart resolution and endocardial definition (apical view) between children of different sex (p=0.002; and p=0.005 respectively). Boys had better image resolution and endocardial definition than girls (good resolution: males 81.7%; females 58.0%; good endocardial definition: males 79.3%; females 58.0%.).

Excluding values of studies that containedoff-axis images or that were of poor resolution did not cause a significant change in the mean values and reference intervals.

There was a significant difference in the visualization of the RV trabeculations between children of different sex (p=0.005). The RV trabeculations were reported to be visible but not excessive in 89.0% of the males. In the other 11%, the trabeculations could not be visualized. In females, the trabeculations were visible in 73.0%. Visualization of the other

27% was not possible. This finding can be attributed to the better image quality in males, causing the trabecular pattern to be more visible.

The right heart examination should include a measure of RA size and RV size, RV systolic function and PA pressure.[2] We presented our reference intervals for every measured parameter as the mean value ± 2 SDs or, themedian value with the central 95% values for each age- and BSA-category. Tables were constructed as follows:

Table 11. Meausrements of right heart **size/volume** according to age-categories (*a*) and BSA-categories (*b*).

*Table 12.*Meausrements of RV **morphology/structure** according to age-categories (*a*) and BSA-categories (*b*).

*Table 13.*Meausrements of RV- and valve **function** according to age-categories (*a*) and BSA-categories (*b*).

*Table 14.*Meausrements of right heart **haemodynamics** according to age-categories (*a*) and BSA-categories (*b*).

Figures 2, 3, 4, 5, 6, 7, 8 presents results of the relationship between measured right heart parameters of size relative to body surface area.

Table 11 a. Mean ± 2SDs of measurements of right heart size / volume, according to age.

Variable		AGE category 1	AGE category 2	AGE category 3
		5-9 y	10-14 y	*5-21 y
RV end-diastolic dimension (PLAX) M-mode (cm)	Mean	* 1.55	* 1.70	1.95
	- 2SD	* 0.90	* 1.10	1.38
	+ 2SD	* 2.00	* 2.30	2.69
RV ouflow tract dimension (PSAX) (supra AO) (cm)	Mean	2.19	2.44	2.74
	- 2SD	1.74	1.73	1.89
	+ 2SD	2.82	3.15	3.59
RV outflow tract max dimension (PSAX) (sub PA) (cm)	Mean	1.66	1.81	2.02
	- 2SD	1.32	1.23	1.34
	+ 2SD	2.09	2.40	2.70
PV annulus (PSAX) (cm)	Mean	1.48	1.60	1.79
	- 2SD	0.99	1.11	1.21
	+ 2SD	1.97	2.10	2.36
PA diameter (PSAX) (cm)	Mean	1.55	1.84	1.91
	- 2SD	0.90	* 30	* 21
	+ 2SD	2.21	2.38	2.60
RV end-diastolic dimension (A4C) (RV base) (cm)	Mean	2.74	2.95	3.24
	- 2SD	2.13	2.25	2.51
	+ 2SD	3.23	3.65	4.17
RV end-diastolic dimension (A4C) (RV mid) (cm)	Mean	1.94	2.43	2.51
	- 2SD	1.14	1.82	1.34
	+ 2SD	2.75	3.13	3.29
RV end-diastolic length (A4C) (cm)	Mean	5.15	6.03	6.61
	- 2SD	4.41	4.90	5.50
	+ 2SD	5.95	7.41	7.94
RV end-diastolic Area (A4C) (cm)	Mean	10.15	13.55	15.81
	- 2SD	7.35	8.54	9.61
	+ 2SD	12.34	18.56	22.00
RV:LV ratio	Mean	0.54	0.54	0.53
	- 2SD	0.38	0.38	0.38
	+ 2SD	0.70	0.70	0.68
RV end-diastolic volume (mL)	Mean	17.24	25.20	30.90
	- 2SD	5.08	13.03	16.22
	+ 2SD	29.39	41.36	58.88
TV annulus (cm)	Mean	1.74	2.04	2.29
	- 2SD	1.23	1.38	1.74
	+ 2SD	2.51	2.71	3.02
TV:MV ratio	Mean	0.85	* 0.86	0.87
	- 2SD	0.62	* 0.64	0.66
	+ 2SD	1.15	* 1.08	1.08
RA minor axis (width) (cm)	Mean	* 2.90	3.24	3.53
	2SD	* 2.40	2.47	2.68

	+ 2SD	* 3.30	4.01	4.49
RA major axis (length) (cm)	Mean	3.20	3.72	4.19
	- 2SD	2.52	2.82	3.32
	+ 2SD	3.88	4.62	5.06
RA end-diastolic Area (cm^2)	Mean	7.80	13.01	14.83
	- 2SD	5.37	10.03	11.32
	+ 2SD	11.35	16.38	18.81

RV, right ventricle; PLAX, parasternal long-axis view; cm, centimetres; SD, standard deviation; PSAX, parasternal short-axis view; AO, aortic;max, maximum; PA, pulmonary artery; PV, pulmonary valve; A4C, apical four-chamber view; LV, left ventricle; mL, millilitres, TV, tricuspid valve; MV, mitral valve, RA, right atrium.

**Median values with central 95% values.*

As expected and reported by others[7, 34] RV dimensions, -areas and -volumes demonstrated increases in parameters of cardiac growth with advancing age and BSA.

The mean ratio of the right- to the left-sided structures did not differ significantly with advancing age or BSA. The TV:MV ratios for the three age groups were 0.85, 0.86 and 0.87 respectively. The RV:LV ratios for the three age groups were 0.54, 0.54, and 0.53.

Table 11 b. Mean ± 2SDs of measurements of right heart size / volume, according to BSA.

Variable		BSA category 1	BSA category 2	BSA category 3	BSA category 4
		<1.15 m^2	1.15-1.39 m^2	1.40-1.60 m^2	1.61 m^2 +
RV end-diastolic dimension (PLAX) M-mode (cm)	Mean	1.55	1.67	1.80	2.02
	- 2SD	0.91	0.98	1.13	1.39
	+ 2SD	2.20	2.36	2.47	2.64
RV end-systolic dimension (PLAX) M-mode (cm)	Mean	1.18	1.32	1.38	1.59
	- 2SD	0.63	0.69	0.81	1.09
	+ 2SD	1.74	1.95	1.95	2.09
RV end-diastolic dimension (PLAX) 2D (cm)	Mean	1.75	1.91	2.04	2.23
	- 2SD	1.24	1.33	1.42	1.67
	+ 2SD	2.26	2.50	2.66	2.79
RV end-systolic dimension (PLAX) 2D (cm)	Mean	1.17	1.37	1.41	1.53
	- 2SD	0.61	0.84	0.85	0.91
	+ 2SD	1.73	1.90	1.98	2.15
RV inflow tract max dimension (PLAX inflow) (cm)	Mean	3.17	3.33	3.97	4.28
	- 2SD	2.27	2.91	2.41	2.70
	+ 2SD	4.08	3.74	5.54	5.86

RV inflow tract min dimension (PLAX inflow) (cm)	Mean	2.03	1.98	2.46	2.90
	- 2SD	0.91	1.29	0.98	1.30
	+ 2SD	3.15	2.66	3.94	4.51
RV outflow tract max (PSAX) (supra AO) (cm)	Mean	2.25	2.41	2.58	2.83
	- 2SD	1.69	1.68	1.78	2.08
	+ 2SD	2.81	3.14	3.38	3.58
RV outflow tract min (PSAX) (supra AO) (cm)	Mean	1.17	1.28	1.40	1.47
	- 2SD	0.51	0.58	0.69	0.65
	+ 2SD	1.82	1.98	2.12	2.29
RV outflow tract max (PSAX) (sub PA) (cm)	Mean	1.64	1.75	1.92	2.12
	- 2SD	1.18	1.30	1.34	1.42
	+ 2SD	2.10	2.20	2.51	2.83
RV outflow tract min (PSAX) (sub PA) (cm)	Mean	1.03	1.15	1.10	1.22
	- 2SD	0.55	0.75	0.54	0.58
	+ 2SD	1.51	1.55	1.67	1.86
PV annulus (PSAX) (cm)	Mean	1.47	1.60	1.65	1.89
	- 2SD	1.06	1.13	1.08	1.41
	+ 2SD	1.87	2.06	2.22	2.37
PA diameter (PSAX) (cm)	Mean	1.58	1.85	1.85	1.99
	- 2SD	1.06	1.31	1.35	1.23
	+ 2SD	2.10	2.38	2.35	2.75
RV end-diastolic dimension (A4C) (RV base) (cm)	Mean	2.69	2.94	3.11	3.37
	- 2SD	2.11	2.28	2.29	2.64
	+ 2SD	3.28	3.59	3.93	4.09
RV end-systolic dimension (A4C) (RV base) (cm)	Mean	1.80	2.00	2.09	2.27
	- 2SD	1.24	1.33	1.28	1.42
	+ 2SD	2.36	2.66	2.90	3.12
RV end-diastolic dimension (A4C) (RV mid) (cm)	Mean	2.04	2.49	2.43	2.58
	- 2SD	1.37	1.77	1.71	1.62
	+ 2SD	2.77	3.21	3.15	3.54
RV end-systolic dimension (A4C) (RV mid) (cm)	Mean	1.11	1.42	1.35	1.53
	- 2SD	0.51	0.78	0.67	0.87
	+ 2SD	1.72	2.06	2.03	2.19
RV end-diastolic length (A4C) (cm)	Mean	5.34	6.07	6.38	6.83
	- 2SD	4.39	5.01	5.23	5.48
	+ 2SD	6.28	7.14	7.53	8.18
RV end-systolic length (A4C) (cm)	Mean	3.71	4.33	4.58	4.96
	- 2SD	2.73	3.33	3.39	3.78
	+ 2SD	4.68	5.33	5.77	6.13
TV annulus (cm)	Mean	1.79	2.01	2.14	2.42
	- 2SD	1.25	1.35	1.53	1.86
	+ 2SD	2.32	2.67	2.76	2.98

TV:MV ratio	Mean	0.85	0.86	0.85	0.89
	- 2SD	0.63	0.65	0.61	0.65
	+ 2SD	1.07	1.07	1.09	1.13
RV end-diastolic area (A4C) (cm^2)	Mean	10.58	13.31	14.58	16.98
	- 2SD	7.12	9.58	9.71	10.92
	+ 2SD	14.04	17.05	19.45	23.03
RV:LV ratio	Mean	0.54	0.54	0.54	0.54
	- 2SD	0.37	0.40	0.39	0.37
	+ 2SD	0.71	0.68	0.68	0.71
RV end-diastolic volume (mL)	Mean	17.98	25.07	28.66	36.67
	- 2SD	8.04	13.55	12.95	15.69
	+ 2SD	27.91	36.59	44.37	57.64
RA minor axis (width) (cm)	Mean	2.96	3.25	3.31	3.66
	- 2SD	2.32	2.56	2.51	2.72
	+ 2SD	3.60	3.94	4.11	4.60
RA major axis (length) (cm)	Mean	3.26	3.67	3.91	4.36
	- 2SD	2.57	2.96	3.10	3.56
	+ 2SD	3.95	4.37	4.72	5.17
RA end-diastolic area (cm^2)	Mean	8.58	10.07	11.04	13.49
	- 2SD	2.60	6.91	6.94	8.04
	+ 2SD	14.55	13.23	15.14	18.94

BSA, body surface area;RV, right ventricle; PLAX, parasternal long-axis view; cm, centimetres; SD, standard deviation; 2D, two-dimensional;PSAX, parasternal short-axis view; AO, aortic; PA, pulmonary artery; A4C, apical four-chamber view;PV, pulmonary valve; TV, tricuspid valve; MV, mitral valve; LV, left ventricle; mL, millilitres; RA, right atrium.

Figure 2: Z-score graph displaying the measures pulmonary artery diameter (PAd) as a linear function of body surface area (BSA). The solid line on the plot indicates the mean value. The shaded area indicate limits of agreement (95 % confidence interval).

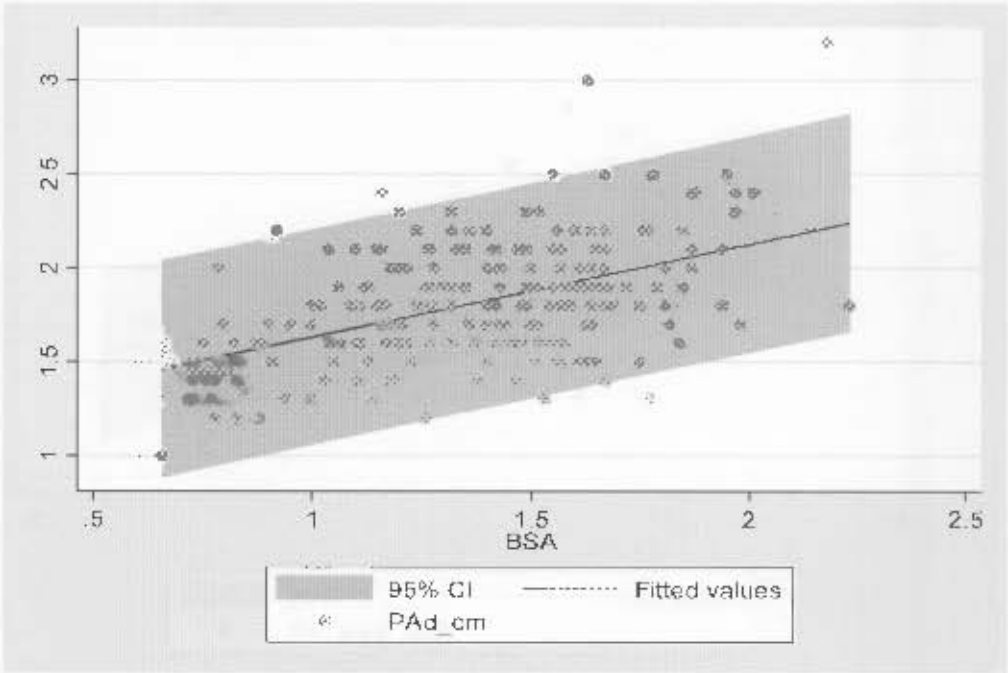


Figure 3: Z-score graph displaying the measures right ventricular outflow tract (supra aortic) diameter (RVOT supraAo) as a linear function of body surface area (BSA). The solid line on the plot indicates the mean value. The shaded area indicate limits of agreement (95 % confidence interval).

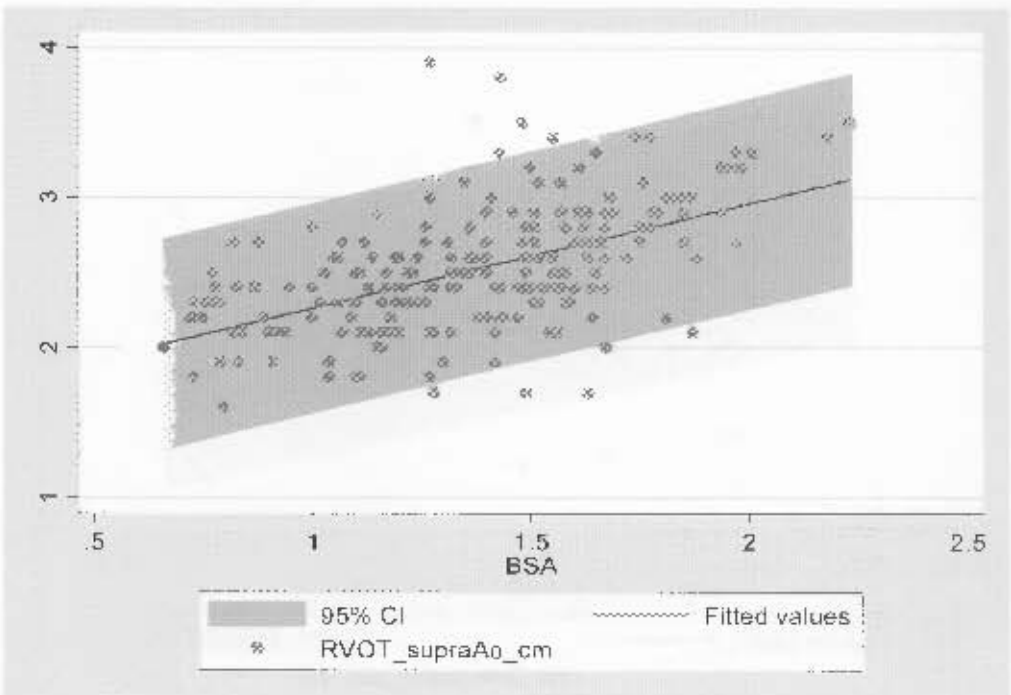


Figure 4: Z-score graph displaying the measures right atrial area (RA area) as a linear function of body surface area (BSA). The solid line on the plot indicates the mean value The shaded area indicate limits of agreement (95 % confidence interval).

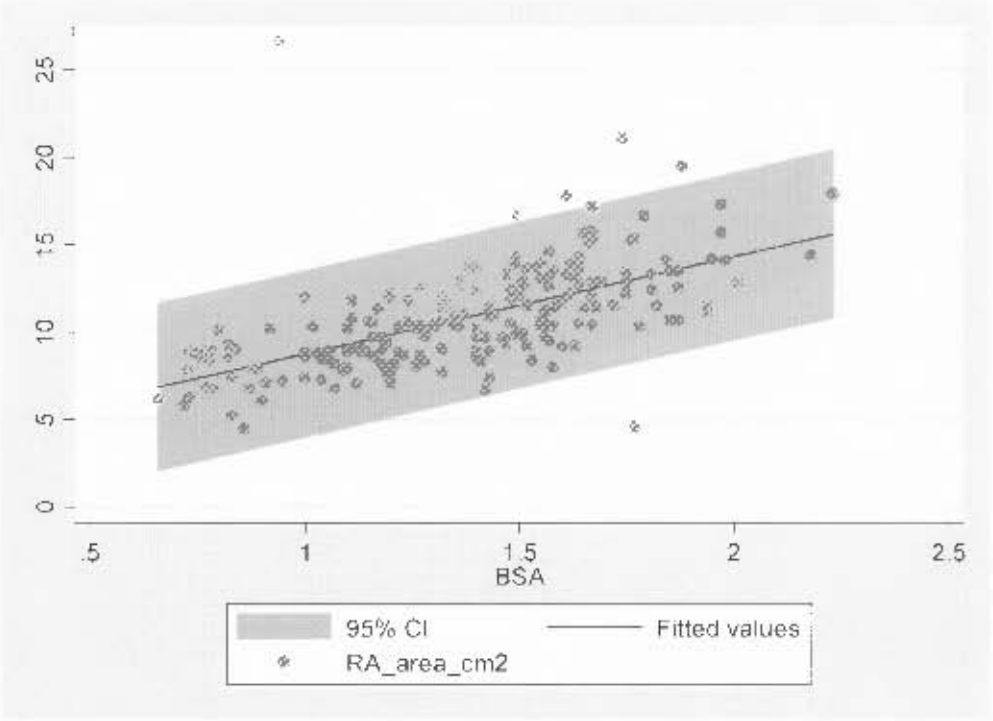


Figure 5 Z-score graph displaying the measures the right ventricular mid-cavity diameter (RV mid diam) measured in the apical four chamber view (A4C) as a linear function of body surface area (BSA). The solid line on the plot indicates the mean value. The shaded area indicate limits of agreement (95 % confidence interval).

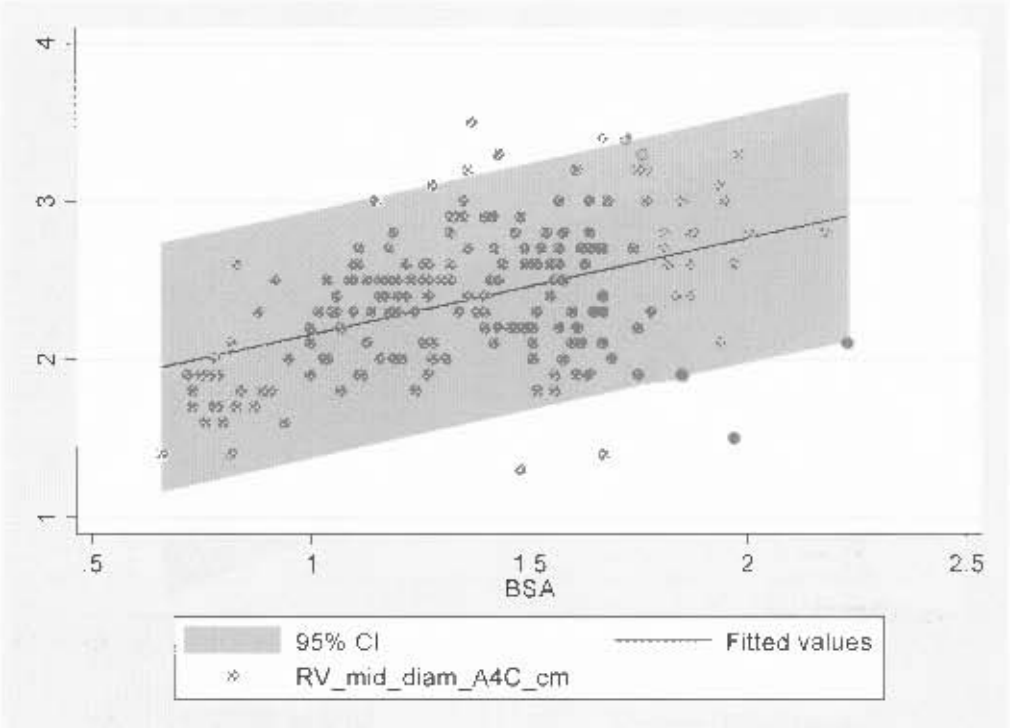


Figure 6. Z-score graph displaying the measures the right ventricular length (length) as a linear function of body surface area (BSA). The solid line on the plot indicates the mean value. The shaded area indicate limits of agreement (95 % confidence interval).

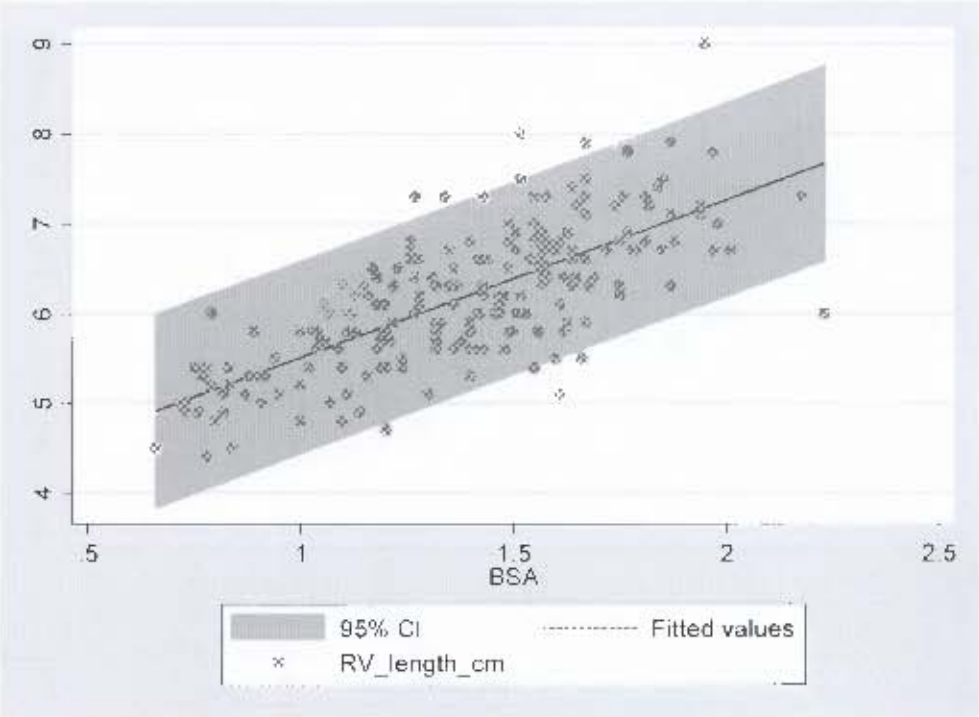


Figure 7: Z-score graph displaying the measures the right ventricular end-diastolic area (RV end diastolic area) as a linear function of body surface area (BSA). The solid line on the plot indicates the mean value. The shaded area indicate limits of agreement (95 % confidence interval).

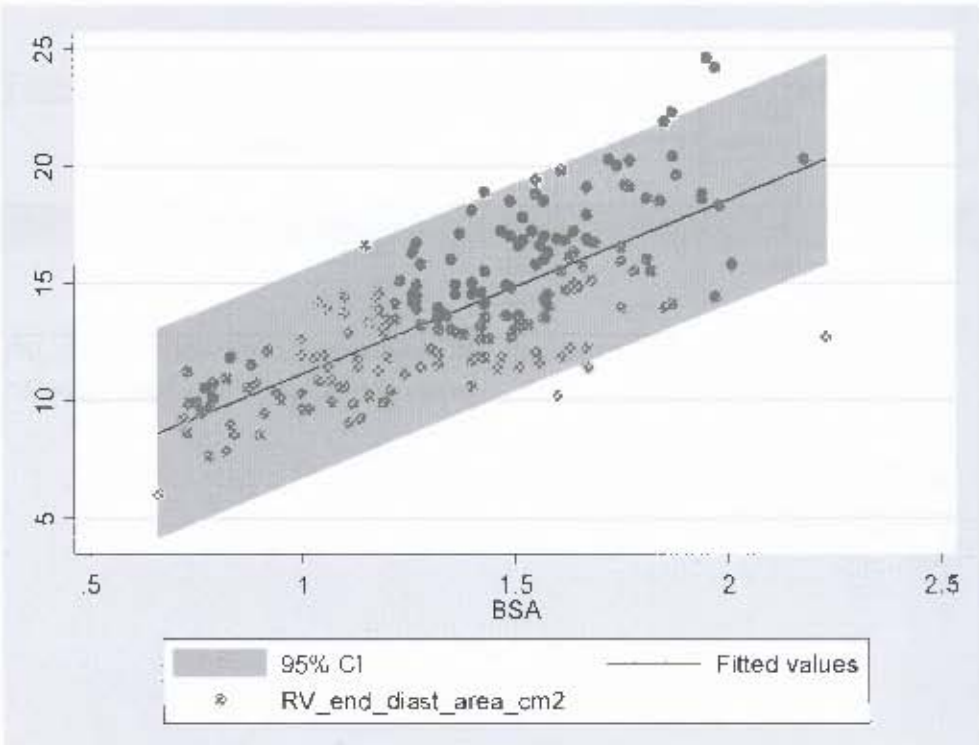


Figure 8: Z-score graph displaying the measures inferior vena cava diameter (IVC) as a linear function of body surface area (BSA). The solid line on the plot indicates the mean value. The shaded area indicate limits of agreement (95 % confidence interval).

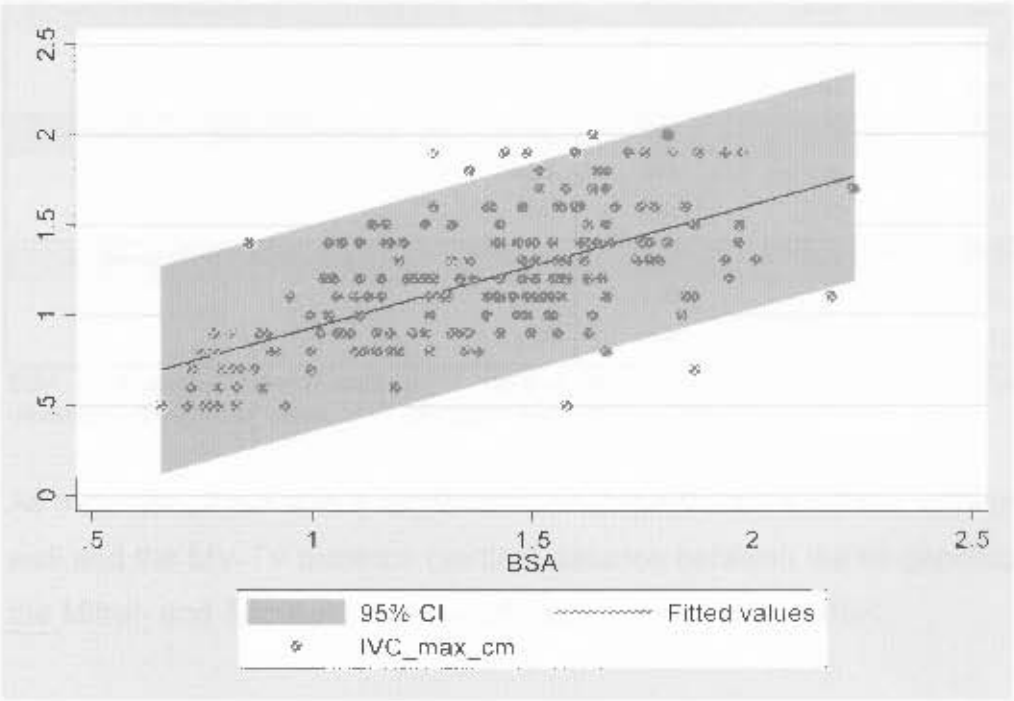


Table 12 a. Mean ± 2SDs of measurements of right heart morphology, according to age.

Variable		AGE category 1	AGE category 2	AGE category 3
		5-9 y	10-14 y	15-21 y
RV anterior wall thickness in diastole (cm)	**Mean**	*** 0.30**	**0.30**	**0.34**
	- 2SD	* 0.20	0.20	0.19
	+ 2SD	* 0.40	0.47	0.53

RV, right ventricle; cm, centimetres. SD, standard deviation.

** Median values with central 95% values.*

Table 12 b. Mean ± 2SDs of measurements of right heart morphology, according to BSA.

Variable		BSA category 1	BSA category 2	BSA category 3	BSA category 4
		<1.15 m^2	1.15-1.39 m^2	1.40-1.60 m^2	1.61m^2 +
RV anterior wall thickness in diastole (cm)	Mean	0.26	0.31	0.33	0.36
	- 2SD	0.14	0.18	0.18	0.17
	+ 2SD	0.38	0.44	0.47	0.54
RV anterior wall thickness in systole (cm)	Mean	0.68	0.76	0.83	0.85
	- 2SD	0.42	0.39	0.41	0.45
	+ 2SD	0.94	1.12	1.24	1.24
Valves MV-TV distance(mm)	Mean	6.94	7.43	8.00	8.66
	- 2SD	3.40	4.12	4.38	3.75
	+ 2SD	10.47	10.75	11.62	13.57

BSA, body surface area;m, metres;RV, right ventricle; cm, centimetres; SD, standard deviation; MV, mitral valve, TV, tricuspid valve; mm, millimetres.

As expected, there was a slight increase in the thickness of the anterior RV wall and the MV-TV distance (vertical distance between the hingepoints of the Mitral- and Tricuspid valves) with advancing age and BSA.

Table 13 a. Mean ± 2SDs of measurements ofright heart chamber and valve function, according to age.

Variable		AGE category 1	AGE category 2	AGE category 3
		5-9 y	10-14 y	15-21 y
RV end-diastolic area (A4C) (cm^2)	Mean	10.15	13.55	15.81
	- 2SD	7.35	8.54	9.61
	+ 2SD	12.34	18.56	22.00
RV end-systolic area (A4C) (cm^2)	Mean	3.89	6.01	6.54
	- 2SD	2.63	2.88	2.62
	+ 2SD	5.89	9.14	10.46
RV % Fractional Area Change (%)	Mean	* 61.00	56.29	57.54
	- 2SD	* 47.00	34.25	43.65
	+ 2SD	* 70.00	77.87	77.62
RV EF (Area-Length method) (%)	Mean	* 75.00	* 75.00	75.66
	- 2SD	* 61.00	* 50.00	56.82
	+ 2SD	* 87.00	* 88.00	90.66
RV TAPSE (mm)	Mean	18.35	18.49	20.72
	- 2SD	12.44	12.89	14.45
	+ 2SD	22.78	25.10	26.99
RV MPI (Pulsed Doppler method)	Mean	0.13	0.20	0.16
	- 2SD	0.00	0.00	0.00
	+ 2SD	0.66	0.52	0.49

TV annulus Sa (m/s)	Mean	0.15	0.16	0.16
	- 2SD	0.11	0.13	0.11
	+ 2SD	0.19	0.19	0.21
TV annulus Ea (m/s)	Mean	0.21	0.21	0.20
	- 2SD	0.13	0.15	0.12
	+ 2SD	0.28	0.27	0.27
TV annulus Aa (m/s)	Mean	0.09	* 0.07	0.12
	- 2SD	0.01	* 0.05	0.00
	+ 2SD	0.17	* 0.10	0.36
Ea/Aa	Mean	2.61	2.86	1.90
	- 2SD	0.53	0.44	0.77
	+ 2SD	4.68	5.28	3.53
TV E:A	Mean	1.70	1.98	1.86
	- 2SD	1.10	0.77	1.10
	+ 2SD	3.16	3.19	3.09
TV Mean Pressure Gradient (mmHg)	Mean	0.69	1.06	0.55
	- 2SD	0.32	0.41	0.20
	+ 2SD	1.48	1.99	1.06
TV Deceleration Time (msec)	Mean	157.05	188.82	198.81
	- 2SD	80.45	89.02	66.45
	+ 2SD	236.22	288.63	331.16
E/Ea	Mean	3.47	* 3.33	3.47
	- 2SD	2.29	* 2.45	2.19
	+ 2SD	5.37	* 4.37	5.50
PV Peak velocity (m/s)	Mean	1.23	0.96	1.14
	- 2SD	0.88	0.66	0.75
	+ 2SD	1.58	1.27	1.52
PV Peak Pressure Gradient (mmHg)	Mean	6.03	3.80	5.01
	- 2SD	3.06	* 66	2.57
	+ 2SD	9.97	6.86	10.00

RVA, right ventricle; A4C, apical four-chamber view; cm, centimetres; SD, standard deviation; EF, ejection fraction; TAPSE, tricuspid annular plane systolic excursion, mm, millimetres; MPI, myocardial performance index; TV, tricuspid valve; ann, annulus; Sa, tricuspid annular peak systolic tissue myocardial velocity, m/s, metres per second; Ea, tricuspid annular early diastolic tissue myocardial velocity; Aa, tricuspid annular late diastolic tissue myocardial velocity;msec, milliseconds; E, right ventricular inflow early diastolic velocity.

** Median values with central 95% values.*

Table 13 b. Mean ± 2SDs of measurements of right heart chamber and valve function, according to BSA.

Variable		BSA category 1	BSA category 2	BSA category 3	BSA category 4
		<1.15 m^2	1.15-1.39 m^2	1.40-1.60 m^2	1.61m^2 +
RV end-diastolic area (A4C) (cm^2)	**Mean**	**10.58**	**13.31**	**14.58**	**16.98**
	- 2SD	7.12	9.58	9.71	10.92
	+ 2SD	14.04	17.05	19.45	23.03
RV end-systolic area (A4C) (cm^2)	**Mean**	**4.35**	**5.79**	**6.23**	**7.30**
	- 2SD	2.20	2.70	2.84	3.91
	+ 2SD	6.50	8.88	9.61	10.69
RV % Fractional Area Change (%)	**Mean**	**59.00**	**56.48**	**57.58**	**56.67**
	- 2SD	43.37	36.34	39.05	41.18
	+ 2SD	74.63	76.61	76.11	72.15
RV end-diastolic volume (mL)	**Mean**	**17.98**	**25.07**	**28.66**	**36.67**
	- 2SD	8.04	13.55	12.95	15.69
	+ 2SD	27.91	36.59	44.37	57.64
RV end-systolic volume (mL)	**Mean**	**4.46**	**6.83**	**7.48**	**9.45**
	- 2SD	1.01	0.50	0.63	2.23
	+ 2SD	7.91	13.15	14.32	16.67
RV EF (Area-Length method) (%)	**Mean**	**75.39**	**72.59**	**74.30**	**73.33**
	- 2SD	60.21	50.08	55.09	57.56
	+ 2SD	90.57	95.09	93.51	89.11
RV TAPSE (mm)	**Mean**	**17.90**	**18.89**	**19.44**	**20.88**
	- 2SD	12.59	12.48	13.88	14.01
	+ 2SD	23.21	25.30	25.00	27.76
Sa TV annulus (m/s)	**Mean**	**0.15**	**0.16**	**0.15**	**0.16**
	- 2SD	0.12	0.13	0.10	0.11
	+ 2SD	0.19	0.18	0.20	0.22
Ea TV annulus (m/s)	**Mean**	**0.21**	**0.21**	**0.19**	**0.20**
	- 2SD	0.14	0.18	0.13	0.13
	+ 2SD	0.29	0.25	0.26	0.28
Aa TV annulus (m/s)	**Mean**	**0.09**	**0.08**	**0.11**	**0.13**
	- 2SD	0.01	0.05	0.03	-0.18
	+ 2SD	0.16	0.10	0.19	0.44
Ea/Aa	**Mean**	**2.74**	**2.74**	**2.12**	**1.96**
	- 2SD	0.46	1.02	0.00	0.63
	+ 2SD	5.02	4.45	4.26	3.28
E/Ea	**Mean**	**3.50**	**3.68**	**3.74**	**3.52**
	- 2SD	1.65	2.76	2.08	1.68
	+ 2SD	5.34	4.60	5.40	5.37
RV MPI (Pulsed Doppler method)	**Mean**	**0.14**	**0.21**	**0.14**	**0.20**
	- 2SD	0.00	0.00	0.00	0.00
	+ 2SD	0.62	0.61	0.38	0.55
TV E velocity (max)	**Mean**	**0.77**	**0.98**	**0.77**	**0.68**

	- 2SD	0 42	0.58	0 41	0.41
	+ 2SD	1.13	1.38	1.12	0.94
TV A velocity (m/s)	**Mean**	**0.46**	**0.51**	**0.42**	**0.37**
	- 2SD	0 16	0.29	0 17	0.14
	+ 2SD	0 76	0.74	0.67	0.60
TV E:A	**Mean**	**1.80**	**1.99**	**1.90**	**1.94**
	- 2SD	0.58	0.78	0.90	0.82
	+ 2SD	3 02	3.19	2 89	3.06
TV Mean Pressure Gradient (mmHg)	**Mean**	**0.77**	**1.14**	**0.75**	**0.57**
	- 2SD	0 16	0.43	0 13	-0 06
	+ 2SD	1 38	1.85	1 37	1 19
TV Deceleration Time (msec)	**Mean**	**164.72**	**187.31**	**198.14**	**195.65**
	- 2SD	50.75	72.43	73.71	67.55
	+ 2SD	278.70	302.19	323 17	323.75
% Variation TV E velocity (%)	**Mean**	**23.72**	**19.58**	**23.12**	**23.08**
	- 2SD	3.41	1.46	6.23	5.23
	+ 2SD	44 03	37 70	40 01	40.93
TR Area (cm^2)	**Mean**	**0.90**	**1.34**	**1.31**	**1.21**
	- 2SD	0 00	0.22	0.00	0.00
	+ 2SD	1 89	2.47	2.94	2.16
PV Peak velocity (m/s)	**Mean**	**1.12**	**0.97**	**1.01**	**1.18**
	- 2SD	0.70	0.64	0.63	0.85
	+ 2SD	1 55	1.29	1 39	1.51
PV Peak Pressure Gradient (mmHg)	**Mean**	**5.30**	**3.95**	**4.24**	**5.75**
	- 2SD	1 35	1 16	0.49	2.38
	+ 2SD	9 24	6 75	7 99	9.12

BSA, body surface area;RV, right ventricle; A4C, apical four-chamber view; cm, centimetres; SD, standard deviation; mL, millilitres; EF, ejection fraction; TAPSE, tricuspid annular plane systolic excursion;mm, millimetres; Sa, tricuspid annular peak systolic tissue myocardial velocity; TV, tricuspid valve; m/s, metres per second; Ea, tricuspid annular early diastolic tissue myocardial velocity; Aa, tricuspid annular late diastolic tissue myocardial velocity; E, right ventricular inflow early diastolic velocity; MPI, myocardial performance index;max, maximum; A, right ventricular late diastolic velocity; PV, pulmonary valve; msec, milliseconds; TR, tricuspid regurgitation.

We found a significant difference in the RV filling period ($p<0.001$) and the RV MPI ($p<0.001$) upon respiration.

Table 14 a. Mean ± 2SDs of measurements of right heart haemodynamics, according to age.

Variable		AGE category 1	AGE category 2	AGE category 3
		5 9 y	10 14 y	15 2' y
PA diameter (PSAX) (cm)	Mean	1.55	1.84	1.91
	- 2SD	0 90	1.30	1 2'
	+ 2SD	2 21	2 38	2 60
E/Ea	Mean	3.47	* 3.33	3.47
	- 2SD	2.29	* 2.45	2.19
	+ 2SD	5.37	* 4.37	5.50
TR maximum velocity (m/s)	Mean	* 2.20	1.94	2.19
	- 2SD	* 1.88	1.40	1.47
	+ 2SD	* 2.52	2.48	2.73
PR end-diastolic velocity (m/s)	Mean	0.96	1.04	1.06
	- 2SD	0.55	0 68	0 61
	+ 2SD	1.24	1 40	1 51
TR Peak Pressure Gradient (mmHg)	Mean	* 19.30	15.37	19.26
	- 2SD	* 8 80	7 07	8 64
	+ 2SD	* 25 40	23 65	29 87
PR end-diastolic Pressure Gradient (mmHg)	Mean	3.68	*4.46	* 4.43
	- 2SD	1.22	*1.39	* 1.14
	+ 2SD	6.14	*7.52	* 7.72
PA Systolic Pressure (mmHg)	Mean	24.39	25.99	30.06
	- 2SD	14.12	11 74	7.90
	+ 2SD	31.47	40.24	41.77
PA end-diastolic Pressure (mmHg)	Mean	9.38	13.90	13.30
	- 2SD	2.89	7.30	7.50
	+ 2SD	19.62	26.50	22.80
IVC dimension (max) (cm)	Mean	* 0.70	1.14	1.42
	- 2SD	* 0.50	0.59	0.90
	+ 2SD	* 0.90	1.70	2.07
IVC % collapse (%)	Mean	68.68	50.85	51.62
	2SD	15.74	17.02	18.95
	+ 2SD	95.85	84.67	84.29

PA, pulmonary artery; PSAX, parasternal short-axis view; cm, centimetres. SD, standard deviation; E, right ventricular inflow early diastolic velocity; Ea, tricuspid annulus early diastolic myocardial velocity; TR, tricuspid regurgitation; m/s, metres per second; PR, ulmonary regurgitation; PA SP, pulmonary artery systolic pressure;IVC, inferior vena cava; max, maximum.

** Median values with central 95% values.*

Table 14 b. Mean ± 2SDs of measurements of right heart haemodynamics, according to BSA.

Variable		BSA category 1 <1.15 m^2	BSA category 2 1.15-1.39 m^2	BSA category 3 1.40-1.60 m^2	BSA category 4 1.61m^2 +
PA diameter (PSAX) (cm)	Mean	1.58	1.85	1.84	2.00
	- 2SD	1.06	1.31	1.32	1.25
	+ 2SD	2.10	2.38	2.35	2.75
PV Ejection Period (msec)	Mean	292.78	312.83	306.47	302.43
	- 2SD	247.16	263.36	268.44	251.79
	+ 2SD	338.41	362.32	344.51	353.07
PV Pre-Ejection Period (msec)	Mean	45.33	47.89	51.14	51.49
	- 2SD	20.19	24.63	26.74	28.27
	+ 2SD	70.47	71.14	75.54	74.71
PA Acceleration Time (msec)	Mean	106.36	121.49	121.95	118.35
	- 2SD	69.68	85.23	89.14	78.85
	+ 2SD	143.04	157.75	154.76	157.86
TR maximum velocity (m/s)	Mean	2.06	2.00	2.11	2.18
	- 2SD	1.53	1.44	1.49	1.52
	+ 2SD	2.60	2.55	2.73	2.84
PR end-diastolic velocity (m/s)	Mean	0.98	0.98	1.10	1.05
	- 2SD	0.65	0.63	0.65	0.65
	+ 2SD	1.30	1.33	1.54	1.45
E/Ea	Mean	3.50	3.68	3.74	3.52
	- 2SD	1.65	2.76	2.08	1.68
	+ 2SD	5.34	4.60	5.40	5.37
TR Peak Pressure Gradient (mmHg)	Mean	17.28	16.25	17.46	19.41
	- 2SD	8.49	7.34	7.58	8.14
	+ 2SD	26.06	25.17	27.34	30.68
PR end-diastolic Pressure Gradient (mmHg)	Mean	3.92	3.99	4.68	4.58
	- 2SD	1.47	1.21	1.39	1.13
	+ 2SD	6.37	6.76	7.98	8.03
PA Systolic Pressure (mmHg)	Mean	24.28	27.65	28.29	28.49
	2SD	12.54	12.52	14.57	12.67
	+ 2SD	36.03	42.77	42.01	44.32
PA end-diastolic Pressure (mmHg)	Mean	10.89	14.20	15.82	13.47
	- 2SD	1.71	2.86	4.52	4.03
	+ 2SD	20.07	25.53	27.12	22.90
IVC dimension (max) (cm)	Mean	0.87	1.12	1.27	1.45
	- 2SD	0.32	0.53	0.69	0.83
	+ 2SD	1.42	1.71	1.86	2.07
IVC % collapse (%)	Mean	62.49	49.41	51.28	53.19
	- 2SD	28.65	15.08	12.87	25.37
	+ 2SD	96.33	83.75	89.69	81.02

BSA, body surface area; PA, pulmonary artery; PSAX, parasternal short-axis view; cm, centimetres; SD, standard deviation; PV, pulmonary valve; msec, milliseconds; TR, tricuspid regurgitation; m/s, metres per second; PR, pulmonary regurgitation;E, right ventricular inflow early diastolic velocity; Ea, tricuspid annulus early diastolic myocardial velocity; IVC, inferior vena cava; max, maximum.

Tricuspid regurgitation was either absent or mild in 94% of the reference participants. Of these, triscuspid regurgitation was absent in 12 participants.

Pulmonary regurgitation was detected in 96% of all participants.

The E/Ea index of RA pressureand the tricuspid regurgitation peak velocity did not change significantly with increasing age and BSA.

Estimated PA systolic pressure values increased with advancing age and BSA.

The values of pulmonary regurgitation end-diastolic velocity and pulmonary regurgitationend-diastolic increased after age 10 and BSA category 3, with no significant increase thereafter. A decrease in IVC collapsibility at age 10 and BSA category 3 was observed, with no significant change thereafter.

Table 15. American Society of Echocardiography-recommended measurements in this study compared with others, according to age-categories.

	Variable	Age category	Previous Study		Lemmer 2011	BSA or BMI difference (p-value)	mean difference (95% CI)	p-value
			Author, Year	Mean value (SD)	Mean value (SD)			
Size and volume	RV Area (d)	6 - 16 y	Norgard, 1992	16.1 (1.5) cm2	13.59 (2.73) cm2	p = 0.89	2.51 (1.59 to 3.44)	p < 0.001
	RV Area (s)	6 - 16 y	Norgard, 1992	9.7 (0.8) cm2	5.95 (1.64) cm2	p = 0.89	3.73 (3.24 to 4.26)	p < 0.001
	RV Length	10 - 19 y	Innelli, 2009	3.8 (0.8) cm	6.33 (0.69) cm	P = 0.39	- 2.53 (- 2.78 to -2.29)	p < 0.001
		6 - 16 y	Norgard, 1992	6.4 (0.8) cm	6.07 (0.69) cm	p = 0.89	0.33 (-0.05 to 0.71)	p = 0.09
	RV width (mid)	10 - 19 y	Innelli, 2009	1.5 (0.3) cm	2.46 (0.39) cm	P = 0.39	- 0.86 (-1.0 to -0.73)	p < 0.001
		6 - 16 y	Norgard, 1992	2.9 (0.5) cm	2.39 (0.38) cm	p = 0.89	0.51 (0.30 to 0.72)	p < 0.001
	RA width	10 - 19 y	Innelli, 2009	3.2 (0.6) cm	3.36 (0.45) cm	P = 0.39	-0.16 (-0.36 to 0.04)	p = 0.11
	RV outflow tract	6 - 16 y	Norgard, 1992	2.1 (0.3) cm	2.48 (0.38) cm	p = 0.89	-0.38 (-0.58 to -0.18)	p < 0.001
		6 - 10 y	Singh, 1994	1.54 (0.15) cm	2.33 (0.34) cm	p < 0.001	-0.79 (-0.94 to -0.65)	p < 0.001
		11 - 15 y	Singh, 1994	1.67 (0.15) cm	2.49 (0.37) cm	p = 0.003	-0.82 (-0.97 to -0.67)	p < 0.001
		>/= 16 y	Singh, 1994	1.95 (0.24) cm	2.73 (0.44) cm	p = 0.28	-0.78 (-0.91 to -0.65)	p < 0.001
Function	TAPSE	10 - 19 y	Innelli, 2009	2.3 (0.4)	2.53 (3.29)	p = 0.39	3.87 (2.69 to 5.05)	p < 0.001
	Sa	5 - 23 y	Goebel, 2006	83 (19) mm/s	0.16 (0.02) cm/s		0.67 (0.61 to 0.73)	p < 0.001
		6 - 9 y	Eidem, 2004	13.4 (2.0) cm/s	0.15 (0.02) cm/s		- 0.02 (-0.03 to -0.01)	p = 0.001
		10 - 13 y	Eidem, 2004	13.9 (2.4) cm/s	0.16 (0.01) cm/s		-0.02 (-0.03 to -0.01)	p < 0.001
		14 - 18 y	Eidem, 2004	14.2 (2.3) cm/s	0.16 (0.03) cm/s		-0.02 (-0.03 to -0.01)	p < 0.001
		10 - 19 y	Innelli, 2009	14.8 (2.1) cm/s	0.16 (0.03) cm/s	p = 0.39	-0.01 (-0.02 to -0.001)	p = 0.03
HD	IVC	**10 - 19 y**	**Innelli, 2009**	**1.0 (0.2) cm**	**1.28 (0.32) cm**	**p = 0.39**	**-0.28 (-0.36 to -0.20)**	**p < 0.001**
	TR velocity	<20 y	McQuillan, 2001	17.2 (4.6) cm/s	2.08 (0.31) m/s		-0.36 (-0.57 to -0.15)	p < 0.001

CI, confidence interval; BSA, body suface area; BMI, body mass index; RV, right ventricle; d, diastolic; y, years; s, systolic; mid, mid-ventricular; RA, right atrium; TAPSE, tricuspid annulus peak systolic excursion; Sa, Tissue Doppler-derived peak systolic annular velocity; TR, tricuspid regurgitation; HD, haemodynamics; IVC inferior vena cava.

Compared with available literature, the values obtained in this study are similar to those previously presented: RA width and RV length compared well with existing values ($p = 0.11$ and $p = 0.09$, respectively). [13, 14]

There were significant differences between our data and the values reported by other authors: significantly larger were RV width and RV length ($p < 0.001$) [13] and RV outflow tract values($p < 0.001$)[14, 15]. In one study, RV width measurements,RV end-diastolic and end-systolic areas were smaller($p < 0.001$)[14, 16]. Furthermore, mean values for tricuspid annulus peak systolic excursion were lower[13, 17], while peak systolic Doppler tissue imaging velocities measured at the tricuspid annulus and myocardial performance index values were irresolute.

Due to differing methods, it was not possible to compare RV volumes and RV ejection fraction. The RV-to-right atrial peak velocities were higher when compared with values in the literature[19] ($p < 0.001$) as were the inferior vena cava values ($p < 0.001$). The percentage inferior vena cava collapse was significantly lower than previously presented ($p < 0.001$).[13]

4.11 Tools aiding right heart examination

The echocardiographic examination of the right heart is known to be technically difficult.[6] Publications dedicated to the protocol of the echocardiographic study of the right heart, reference intervals of its structure and function, and their clinical interpretation are rare.

In addition, echocardiographers are also challenged by the lack of detailed illustration of the method used in the echocardiographic measurements; the complex and time-consuming calculations involved in the evaluation of right heart function; and the knowledge of the correct interpretation of measurements.

We have developed Microsoft Excel®-based tools to aid in making the findings of this work easy to use in clinical practice. The heart calculator and report generator was designed and programmed to reduce post-processing time as compared with the manual calculations and report compilation.

4.11.1 Right heart calculator

The purpose-designed right heart calculator performed all calculations efficiently. Itallows a user to enter all measured parameters in an input-column. Immediately after all the required input-values are entered, the calculator performs all the calculations, according to the relevantprogrammed formulas and displays the answers in an output column.

Figure 9. Snapshot of the right heart calculator.

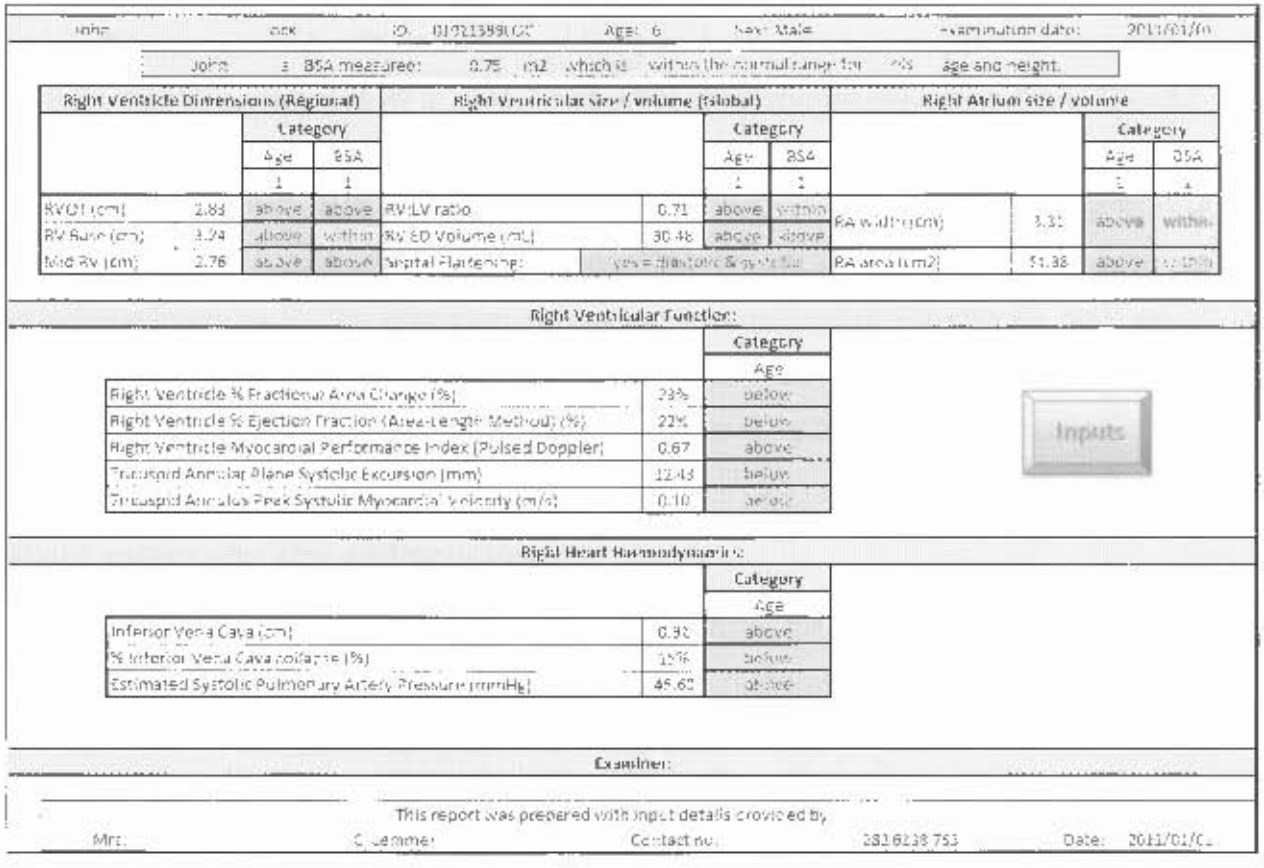
Input		Result	
Height(cm)	100	1.00	Height(m)
Weight(kg)	20	0.75	BSA
RVAd	14.62	30.5	RVED volume
RVLd	5.96		
LVAd	20.59	0.71	RVEDV
RVAs	11.2	23%	RV%FAC
RVLs	4.5	23.7	RVES volume
		23%	RV % FAC
		22%	RVFA LIEF
PWD: End A to start E	499.33	0.67	RVTX (PWD)
PV Ejection period	299		
RVOD(max)	0.91	15%	RVC degree of
RVOD(min)	0.77	20	Estimated RAP
TR Vmax	2.53	45.6	Estimated SPAP

4.11.2 Right heart report

The electronic right heart report allows a user to enter all measured parameters in an input-sheet. Immediately after the required input-values are entered, the right heart calculator performs all the calculations, according to the correctly programmed formulas. All the measured parameters (inputs) and calculated outputs are displayed in an output-sheet. The calculator places measured values into the context of reference values, flagging outliers according to the patient's age and BSA.

In this era of structured reporting, the right heart report is a tool, guide and example of how the right heart measurements could be included in an echocardiographic report.

Figure 10. Snapshot of the right heart report.



The electronic version of the right heart calculator and report is available on a disc as an attachent to this document.

4.12 Discussion

This study attempts to address many of the limitations involved in the echocardiographic evaluation of the right heart by establishing reference intervalsusing community-based sampling of healthy children. The focus was to develop reference intervals for African children and compare our findings with the available reference data.

4.12.1 Significant contributions to available data

The right atrium

According to the results of the systematic review, there previously existed only one publication presenting reference data of RA size for children younger than 10 years of age. In 1988, Hanseus *et al.* published a set of reference values on the RAbased on a sample of 120 healthy infants and children, aged 3 days to 15.5 years, which included the width, length and area for the RA for the entire sample according to BSA using regression equations and nomograms.[35] This study is the second to present reference intervals for the echocardiographic measurement of RA size for children younger than 10 years and, the first set of reference intervals for echocardiographic measurement of the RA size that is presented according to age-categories in children younger than 10 years.

Right ventricular size and/or volume

This study is the second to present reference intervals for the echocardiographic measurement of the RV basal diameter (apical four-chamber view) for children younger than 10 years and, the first set of reference intervals for echocardiographic measurement of the RV basal diameter (apical four-chamber view) that is presented according to age-categories in children younger than 10 years. The first study was by Hanseus *et al.* in 1988 which presented the data for the entire sample according to BSA using regression equations and nomograms.[35] Innelli *et al.* recently reported reference values of a sub-group of 40 healthy children and adolescents, aged 10-19 years, but the reference values for the entire sub-group, aged 10-19 years were presented as one summary value.[13]

Our set of reference intervals for the RV mid-cavity diameter (apical four-chamber view) contributes significantly to the currently insufficient available data. The previous two existing publications containing reference intervals for the RV mid-cavity diameter (apical four-chamber view) consisted of small samples, and the reference values for the entire sample were presented as one value. Norgard and Vik-Mo had a reference population of 15 individuals, aged 6-16 years and the data were presented as one value for the entire sample.[14] The second more recent publication by Innelli *et al.*contained reference values of a sub-group of 40 healthy children and adolescents, aged 10-19 years. In this publication, the reference values for the entire sub-group, aged 10-19 years were presented as one value.[13] Ourstudy contains the first set of reference intervals for RV mid-cavity diameter, measured in the apical four-chamber view, that is presented as a sub-group for children younger than 10 years.

Right ventricular length

There were four existing publications presenting reference values for the RV length, measured in the apical four-chamber view. Our data did however contribute significantly as authors Hanseus *et al.* (1988, N=120) and Daubeney *et al.* (1999, N=125) presented data for the entire set (birth to adolescent age), according to BSA only, whereas Inneli *et al.* and Norgard and Vik-Mo (1992, N=15, 6-16years) presented data for the entire sample, as one summary value.[14, 35, 36, 40] This study present RV length reference values for the different age groups and BSA categories.

Right ventricular areas

To the best of our knowledge, this is the first age-categorized presentation of reference intervals for the echocardiographically measured RV end-diastolic and end-systolic area in children.

Four authors have published reference values for the RV end-diastolic area, measured in the apical four-chamber view. For the RV end-diastolic area, Hanseus *et al.* and Daubeney *et al.* presented data for the entire sample (birth to adolescent age), according to BSA. Boettler *et al.* and Norgard and Vik-Mo presented data for the entire sample, as one summary value.[14, 16, 35, 36]

There are two publications of reference values for RV end-systolic area, measured in the apical four-chamber view. The usefulness of both of these publications however

is limited as they both present the data for the entire sample, spanning more than 10 years, as one summary value. Norgard and Vik-Mo published reference values for RV end-systolic area of a reference population with only 15 individuals, aged 6-16 years[14] while Boettler *et al.* published reference values for RV end-systolic area in a sample of 129 reference individuals, aged 1 day to 16.9 years.[16]

Right ventricular function

Only one previous publication exists on RV % fractional area change in a sample of healthy children. The sample of healthy children was a control-group consisting of 13 healthy individuals. One of the objectives of the study was to compare quantitative measurements of the RV in single RVs with normal RVs. The RV % fractional area change of the control-group of 13 healthy individuals was presented. The mean age of the healthy control-group was 5.7±1.8years.[31] With a much larger sample size and a greater age-span, our study contributes significantly as the first study with the objective to generate reference values for the echocardiographically determined RV fractional area change in children.

We also report the first set of reference intervals for echocardiographically determined RV EF, using the area-length method.

Pulmonary artery peak pressure gradient

Zhendong *et al.* published reference intervals of the PA peak pressure gradient in 1998. The reference population consisted of 88 healthy individuals, aged 3-12 years. Zhendong *et al.* divided the sample into two age-categories.[38] According to our systematic review, we present the first set of reference intervals for the echocardiographically determined PA peak pressure gradient for children older than 12 years.

Right-sided haemodynamics

Our study is the first age-categorized presentation of reference intervals for echocardiographically estimated right-sided haemodynamics in children. We also present the first set of echocardiographically estimated PA pressures that is calculated by adding an estimated RA pressure, estimated using the IVC collapsibility index, to the RV-RA gradient.

McQuillan *et al.* were the only study to publish reference data on right-sided haemodynamics for children and adolescents. They reported estimate PA systolic pressure values assuming that the RA pressure for all reference individuals was 10

mmHg. McQuillan *et al.* presented the reference data graphically, according to BSA.[19] Pena *et al.* recently (2009) published reference data for the tricuspid regurgitation peak velocity in 55 newborn infants. Pena *et al.* also presented estimated the PA systolic pressure assuming that the RA pressure for all reference individuals is 5 mmHg.[39]

To the best of our knowledge, our study is the first to provide insight into the collapsibility of the IVC and its changes with increasing age in children younger than 10 years.

4.12.2 Comparisons with existing data

Right heart size

RV end-diastolic diameter has been identified as a predictor of survival in patients with chronic pulmonary disease and the dimension of the RV outflow tract is used in particular in the evaluation for arrhythmogenic right ventricular cardiomyopathy.[2]

The values obtained in this study are comparable withthose previously presented: RA width compared well with the values presented by Innelli *et al.*[13](p = 0.11) RV lengthwassimilar to data reported by Norgard and Vik-Mo[14] (0 = 0.09).

There were differences between our data and the data reported by previous authors as follows:

(1) RV width and length (measured in an apical four-chamber view) were larger than the values published Innelli *et al.*[13] ($p < 0.001$); (2) RV outflow tractvalues were significantly larger when compared with published studies by Singh *et al.* and Norgard and Vik-mo.[12, 14, 15] ($p < 0.001$); The weight and BSA of our reference population were also higher than those of Singh *et al.* However, the BSA values of our sample were similar to those of Norgard and the BMI values similar to those of Innelli. (3) TheRV width, RV end-diastolic and RV end-systolic areaswere smaller in comparison to the values reported by Norgard and Vik-Mo[14, 16] ($p < 0.001$).

It was difficult to compare our RV volumes with those of Jin et al. because the method used (Simpson's single-plane) was different to our method (area-length). However, it was intersting to note that the RV end-diastolic volumes of this study were either similar to or lower than the values of Jin *et al.* and the RV end-systolic

volumes of this studywere significantly lower than the values presented by Jin *et al.*[18]

Tricuspid valve

Measurement of TV size helps characterize valvar pathology and diagnose ventricular hypoplasia.

King *et al.*[33] reported data on the tricuspid valve annular diameter in normal children. They presented a mean ratio of the MV to TV of 1.02 with a SD of 0.1.[33] We calculated the mean ratio of the TV to MV. The mean values for the TV to MV ratio for our three age-categories respectively were 0.85, 0.87 and 0.86 (range 0.60 – 1.11). The average TVdiameter of our reference population was smaller in relation to the MV when compared with the results presented by King *et al.*

Pulmonary valve and pulmlonary artery diameters

Assessment of pulmonary artery size is important in children with various forms of congenital heart disease. When pulmonary arterial flow is diminished (as in tetralogy of Fallot), the branch pulmonary arteries are typically small. In contrast, isolated PV stenosis, tetralogy of Fallot with dysplastic PV, Marfan syndrome, and pulmonary hypertension are all associated with PA dilation.[8] We observed a steady increase in the pulmonary trunk size that was related to BSA, similar to the results of Ichida *et al.*[34]

Valve function

We detected less-than-moderate tricuspid regurgitation in 94% of the reference participants. This result is difficult to compare with other studies as the sensitivity for the detecting of trivial tricuspid regurgitation is different between studies due to difference in the quality and resolution of different machines. Pulmonary regurgitation was detected in 96% of the reference participants.

RV function

Our measures of RV function, namely RV fractional area change, RV area-length EF, the RV MPI and tissue Doppler velocities showed little or no change with increasing

age and BSA. We analysed the following additional measures of RV systolic function:

Tricuspid annulus peak systolic excursion

Tricuspid annulus peak systolic excursion (TAPSE) is an easily obtainable measure of RV longitudinal function.[2] Recent publications have shown that TAPSE measurement is more reproducible than other echocardiographic indices of RV function.[45] Heart rate has been shown not to have an influence on the longitudinal motion of the atrioventricular annuli in children. Therefore, its usefulness can be extended to the paediatric age group.[17]

As expected and reported by previous authors[17], we found that TAPSE values increased with age and BSA. However, our mean values for the different age- and BSA-categories were lower compared with the results presented by others ($p < 0.05$).[13, 17]

Although it measures longitudinal function, TAPSE has shown good correlation with echocardiographic techniques estimating RV global systolic function such as 2D RV fractional area change and 2D RV EF.[2] It still remains unclear how well TAPSE will perform as in index of RV function in children with heart disease. It has been reported that in patients with pulmonary hypertension, there may be changes in the atrioventricular annuli in the paediatric age group; specifcally, in patients with primary pulmonary hypertension, the percentage displacement and ascent velocities were blunted[17] possibly limiting the usefulness of TAPSE in patients with abnormal right-sided haemodynamics.

Myocardial performance index

The MPI or Tei index, is a global estimate of both systolic and diastolic function of the RV.[2] This index has been reported to be simple, reproducible, and independent of heart rate, blood pressure, degree of TR, and severity of pulmonary hypertension.[9] The MPI has been shown to correlate well with other quantifiable, noninvasive, and invasive measures of ventricular function.[60] Recently, this MPI was reported to correlate well with the severity of congestive heart failure and clinical outcome in adult patients

with pulmonary hypertension. Because this index is essentially a time ratio, it is therefore independent of geometry and may be particularly useful in the assessment of the global RV function in children with complex RV shape.[9]

The measure remains accurate within a broad range of heart rates, though the components should be measured with a constant R-R interval to minimize error. Although the MPI was initially thought to be relatively independent of preload, this has been questioned in more recent studies. In addition, the MPI has been demonstrated to be unreliable when RA pressure is elevated.[2]

The right-sided MPI can be obtained by two methods: the pulsed Doppler method and the tissue Doppler method.[2] Measurement of the MPI via the Doppler Tissue Imaging (DTI) method provides a measurement of the MPI at one site of the ventricle only. Hence, this measurement may not reflect overall ventricular function.[61] Reference intervals for the RV MPI obtained from these two approaches (DTI and pulsed wave Doppler), however, can be significantly different, and appropriate reference values should be used.[8]

Roberson *et al.*[62] performed a study on the MPI in children, exploring the effect of method, age, BSA and heart rate on the RV MPI. Overall, our mean MPI values (using pulsed-wave Doppler) were higher than theirs, using the same method ($p < 0.001$). However, they did note that multiple echocardiographic systems were used and that inter-machine variability studies were not performed. They concluded that the DTI method has certain disadvantages over the pulsed-wave Doppler method The limited availability of DTI in Africa may also limit the use of this method. They also reported a small but significant effect of the method by which the RV MPI is measured, emphasizing the need to create a set of reference intervals for each method separately. They also report that age, heart rate and BSA affect the MPI. They reported the RV MPI to increase by increasing BSA and age.[62]

Although not the main objective of the study, Eidem *et al.*[46] presented the RV MPI for the different age-categories of their sample of healthy people. They reported that the RV MPI did not change significantly with advancing age. Similarly, we also found no correlation between the RV MPI and age. However, compared with our results, the RV MPI presented in the study by Eidem *et al.* were significantly lowerthan our findings ($p < 0.001$).[46]

Ishii*et al.*[63] reported on the MPI in a sample of healthy children aged 30 days to 18 years. Ishii *et al.* concluded that the MPI was not affected by age in healthy children. It was difficult to compare our results with their data as the sample characteristics were different between the two studies in terms of the age-range.[63]

We did not investigate the correlation of heart rate and the RV MPI. Ishii *et al.*[63] reported a correlation of heart rate and ejection time and the sum of *isovolumic contraction time* and *isovolumic relaxation time*. They also reported that the MPI was independent of heart rate.[63] Eidem*et al.*[60] recognized the impact of heart rate variability on the MPI. This could potentially limit the use of this parameter in patients with arrhythmias.

It is known that respiration markedly influences the RV time indices, thus influencing the result of the MPI.[38] To our knowledge, our study is the first to investigate the impact of respiratory variation inTV inflow on the RV MPI. We found a significant difference in the RV filling period (inspiration vs expiration meansof 351 msvs 309 msrespecitvely, $p<0.001$). For RV MPI, the values were 0.17 vs 0.03 respectively ($p<0.001$). Our results indicate that the influence of respiration on RV filling time was significant and may be another limitation of the RVMPI.

Right ventricular ejection fraction

It was difficult to compare our result with those of Jin*et al.*[18] as the method used (Simpson's single-plane) was different to our method (area-length). However, it was interesting to note that our RV end-diastolic volumes were either similar to or lower than the values presented by Jin *et al.* and, our RV end-systolic volumes were significantly less, suggesting a much higher stroke volume (and RV EF) in African children.[18]

Norgard and Vik-Mo[14] reported RV volumes using the Simpson's single plane method. It was difficult to compare our result with that of Norgard and Vik-Mo as our method used to calculate the estimated RV volumes (area-length method) was different. Norgard and Vik-Mo also had a very small sample size (N=15) across a wide age-range (6-16years). Though difficult to compare,our calculated RV EF was significantly higher ($p < 0.001$) when compared to the values presented by Norgard and Vik-Mo. In fact, the lower

limit of our reference interval was similar to the average EF reported by Norgard and Vik-Mo.[14]

Boettler *et al.*[16] reported RV EF estimated using RV end-diastolic and end-systolic volumes determined using Simpson's single-plane method. It was difficult to compare our result with those of Boettler as our method used to calculate the estimated RV volumes (area-length) was different.Similar to our finding when comparing our reported EF to that of Norgard and Vikmo and Jin *et al.*, our reported EF was significantly higher (mean 74.6%) compared to the EF reported by Boettler *et al.*(55.7% ± 11.0%) ($p < 0.001$).[14]

Doppler tissue imaging velocities

Our data overcomes many of the limitations of prior studies of smaller sample size. Our DTI velocities at the tricuspid annulus were higher than the values presented by Harada *et al.*[49] However, these values were difficult to compare as Harada presented the data of the reference population as a summary value for a single group, aged 7 days to 18 y. In contrast to our findings, Harada *et al.* also reported a correlation of DTI velocities with advancing age.[49]

Our DTI velocities at the tricuspid annulus were also higher than the values reported by Frommelt*et al.*[47] Frommelt presented the data of a reference population as a single group, aged >12mo, which included younger participants, than in our sample. The reference interval (min and max values) of our early peak diastolic velocitycompared well.[47]

Our results were different to the DTI velocities reported by Roberson*et al.*[53] Our lower limits were significantly higher and our reference interval (range) smaller. We suspect that the interstudy differences could have been as a result of the difference in the age-distribution of the two reference populations. More than 40% of Roberson's reference population were less than 1 year and included preterm infants. As mentioned by authors Roberson and Eidem *et al.*, there are major changes in DTI parameters in the first year of life. There have also been various studies indicating that there is a strong positive correlation of Tissue Doppler velocities and age.[46, 53]

We compared our result to that of Kapusta *et al.*[50] and found the upper limits of our TDI velocities were higher. Similar to Kapusta *et al.*, we did not find any of the assessed myocardial velocities nor the calculated Ea/Aa ratio to have a practically relevant correlation with age, BSA or heart rate. This is at odds with what have been reported by Roberson *et al.*[53] who reported a strong positive correlation between DTI parameters and age, BSA and heart rate. We agree with Kapusta et al.[50], suggesting that DTI parameters could provide additional information about the regional function of the healthy myocardium.

Eidem *et al.*[46] investigated tissue Doppler velocities of the basal cardiac segments (lateral mitral annulus, interventricular septum, and lateral tricuspid annulus) and reported that with advancing age, a significant increase in systolic and early diastolic myocardial velocities were demonstrated in these segments, especially in the age-category less than 1 year.[46] Overall, our DTI velocities at the tricuspid annulus were higher than the values presented by them.[46] Eidem *et al.*[46] reported a decrease in E/Ea ratio with advancing age, but also commented that this change was primarily the result of an increase in the myocardial Ea with advancing age, which was different to what we discovered.[46]

We compared our DTI velocities with those of Rafeiyian*et al.*[64] as two of our age-categories were very similar in age-range. Our lateral tricuspid Sa and Ea velocities were higher, whilstour mean late diastolic myocardial velocity (Aa) values were lower. As a result, our Ea:Aa ratio were also significantly higher to the Ea:Aa ratio presented by Rafeiyian.[64] Our lateral tricuspid Sa DTI velocities at the lateral tricuspid annulus were higher than the values presented by Innelli*et al*[13] ($p = 0.03$).

Conflicting data exist regarding the impact of age on various DTI velocities in pediatric patients. Previous published studies in children disagree on the affect of age on DTI velocities. Swaminathan *et al.*[65] reported a lack of linear correlation of age with the majority of DTI velocities in healthy children aged 1 to 18 years. Kapusta *et al.*[50] reported similar findings in a group of healthy children aged 4 to 18 years. In contrast, there have also been studies indicating that there is a strong positive correlation of DTI velocities and age.[46, 53]

Diastolic function

Pulsed-wave Doppler tricuspid flow velocity helps evaluate the RV filling and, indirectly, RV diastolic function.[6] Although RV diastolic profiles have not been well correlated with chamber compliance or ventricular pressures, an increased E/A ratio and short deceleration time suggest restrictive pathology.[4] We compared our results of the diastolic pattern of both Pulsed Doppler and DTI velocities with those in published studies.

The reference data in the publication by Kapusta *et al.*[50] were presented as median values (5^{th}- 95^{th} percentiles). Our result was presented as mean values ± 2SDs. Even so, the values presented by Kapusta *et al.* were very similar to those that we have established.

We found no correlation between the transtricuspid E or E/A ratio and age in contrast to what was reported by Yasuoka *et al.*[66], who reported that tricuspid peak E and E/A ratio was mainly affected by age. Our DTI velocities (Ea, Aa and Ea/Aa) were higher and did not show a significant correlation with age.[66]

We investigated the influence of respiration on RV filling patterns. We discovered that peak E velocity were lower at end-expiration than during inspiration, similar to what was reported by Zhendong *et al.*[38]. They reported the peak E velocities of end-inspiration to be on average 10.7% higher than those of end-expiration. We found that on average, our peak E velocity was 22.85% higher on end-inspiration than on end-expiration (range: 4.06 – 41.65%). Further, our results concur with Zhendong *et al.* that peak E velocity is independent of age.

Haemodynamics

The E/Ea ratio of the RV is a well established indicator of invasive RA pressure in adults. In adults, the age-dependent increase of RA pressure can be attributed to the RV overload developing with advancing age.[13] Eidem *et al.*[46] reported a decrease in E/Ea ratio with advancing age, but also commented that this change was primarily the result of an increase in the myocardial Ea with advancing age, which was different to what we discovered.[46] We have found that there was no significant difference in the ratio of TVpulsed-wave Doppler E velocity to the lateral tricuspid Ea with advancing age. The difference in the E/Ea ratio in our study cannot be explained by respiratory variations, given that we used the maximum E velocity (end inspiration) for the calucation of the ratio in each instance. We attribute this

difference in Eidem's study to the fact that the Ea increased with increasing age amongst their participants.Of interest, it has been previous Inoted that data are conflicting as regards the impact of age on various DTI velocities in paediatric participants. Innelli *et al.* found an age-dependent increase of the RV E/Ea ratio in a sample of healthy adults. They also noted that other echocardiographic indexes of RA pressure (RA minor axis diameter / width, IVC diameter, and IVC collapsibility index) change significantly with aging.[13] We compared our results to that of Innelli[13]. According to our results, the E/Ea index of RA pressure remained constant with advancing age and BSA. We noted that some of our results conflicted with published work: our E/Ea ratio were lower; our IVC diameter values were significantly higher (p , 0.001) and our mean values of IVC collapsibility were lower when compared to that of Innelli*et al.* ($p < 0.001$).[13] We acknowledge that a limitation in comparing these IVC values could be lack of sufficient reported detail in studies as regards the participants' position (left lateral decubitus versus supine positions) when examined.

Tricuspid regurgitation was detected in 94% of our reference participants. Pena*et al.*[67] reported the presence of tricuspid regurgitation in 40% of the neonates that they assessed. This result was difficult to compare between studies as the sensitivity for the detecting of trivial tricuspid regurgitation is different between studies due to difference in machine quality. The increased sensitivity for the detection of tricuspid regurgitation and the recording of systolic PA pressure is acknowledged and can be attributed to the dramatic improvements in echocardiographic instrumentation and recording techniques in the last 15-20 years.[19]

According to the results of our systematic review, the only available normative data on the tricuspid regurgitation peak velocity were obtained on a sample of healthy neonates. Pena *et al.* reported on the presence of tricuspid regurgitation as well as the mean systolic PA pressure, calculated using the simplified Bernoulli equation, assuming the RA pressureto be 5 mmHg. Our study was the first to document the tricuspid regurgitation velocity in children and adolescents. We could not compare our results of our study with those of Pena et al.[67] as the children in our sample were older. According to our results, the tricuspid regurgitation peak velocity remained constant with advancing age and BSA. The systolic PA pressure however, increased with advancing age and BSA. As the IVC diameter and collapse was used to estimate RA pressure, the age-dependent increasing PA systolic pressure values

could be as a result of the increase in IVC diameter and decrease in IVC collapse with advancing age and BSA.

Our RV-to-RA peak pressure gradient values were higher to the values reported by McQuillan *et al.*[19] ($p < 0.001$). We could not compare our estimated systolic PA pressure values they calculated the systolic PA pressure assuming that the RA pressure was 10mmHg, whereas we calculated the systolic PA pressure by adding the estimated RA pressure(using the IVC collapsibility index) to the RV-to-RA peak pressure gradient.

We observed an increase in the pulmonary regurgitation end-diastolic velocity (and the PA end-diastolic pressure) after age 10 and BSA category 3, remaining constant thereafter. This could be related to the decrease in IVC collapsibility after age 10 and BSA category 3 as the IVC diameter and collapsibility was used to estimate RA pressure. We observed a decrease in IVC collapsibility at age 10 and BSA category 3 in our reference population.

5 Conclusions

5.1 Systematic review

We conclude that reference data are still lacking for important recommended quantitative measurements.

There were insufficient published data of the following variables: right atrial size (width, length and area) for children younger than 10 yrs, tricuspid valve area, right ventricular dimensions (base, mid and length) and areas (diastolic and systolic), the right ventricular fractional area change and the RV-to-RA peak pressure gradient. There were no published reference data for the right ventricular mid-cavity dimensions presented as a sub-group for children younger than 10 years. There were no published data for right ventricular volumes and ejection fraction using the area-length method. There were no published reference intervals for the pulmonary artery peak pressure gradient for children older than 12 years. There were no published reference intervals for the inferior vena cava diameter and percentage collapse for children younger than 10 years. None of the studies estimated systolic pulmonary artery pressure using an estimate of right atrial pressure that was based on the dimension and percentage collapse of the inferior vena cava.

We recommend a global standard for generating reference data for echocardiographic measurements set by the International Federation of Clinical Chemistry.

5.2 Reference intervals

This study establishes reference intervals derived from a large population of healthy children and adolescents in a careful and methodical manner using accepted means of establishing reference intervals and employing modern echocardiographic equipment.

This study represents an evolution in our attempts to develop an accurate and readily utilizable set ofreference values for echocardiography in the young. It is the first study presenting normative data for echocardiographic evaluation of the right heart in African children. It is also the first set of reference intervals for echocardiographic evaluation of the right heart in children and adolescents established using a community-based setting.

According to our observation and our systematic review, our study contributed significantly in establishing and improving reference intervals for RA size, RV dimensions and -areas, the RV % fractional area change, RV volumes and EF using the area-length method, PA pressure gradients and, the right-sided haemodynamics, including the IVC dimensions and -collapsibility.

RV dimensions and –volumes of African children are smaller, while RV outflow tract diameter is larger when compared with existing literature. RV function is more dynamic in African children and indicators of right heart haemodynamics reveal higher values.

A combination of indices and measurement of different dimensions might provide the best assessment, as they each have different specificities and sensitivities for identifying right heart pathology and -dysfunction. Proper evaluation of the right heart requires quantitative assessment as well as a detailed morphological study, perhaps deviating from the more traditional standardized methods of measurement.

Finally, this research informed the design of a useful algorithm for right heart computations. A useful adjunct to echocardiography, it reduces post-processing time involved in the right heart assessment and serves as a guide and example as to how the right heart measurements could be included in an echocardiographic report.

It is our hope that these reference intervals and tools will aid in reliably guiding surveillance and the detecting and treating cardiovascular diseases, not only in Africa, but also in the rest of the world.

6 Limitations

We do acknowledge the possible effect of heart rate (anxiety or excitement) and respiration on some of our parameters, which we did not investigate.

Previous authors have reported differences between races, with larger cardiac dimensions for black individuals.[12] The issue of ethnicity is however becoming indistinct as our multicultural societies have populations of mixed race with disease prevalence that do not necessarily reflect the original endogenous pattern.[68]

Conflicting data still exist on the influence of gender on the values of cardiac dimensions. We did not investigate the influence of gender on the values of cardiac dimensions.

In our study, the normative data obtained by the present study are restricted to a certain age range, namely 5 – 21years, who represent the school going population in the Vanguard Communities of Cape Town. Similar data should still be derived from a younger paediatric age group.

This work does not explore the relative value of each measurement as it pertains to prognosis and outcome and therefore does not represent a list of measurements which should be performed on the basis of prognostic importance. Patient-level data were not available to divide the abnormal categories into mild, moderate, and severe degrees of abnormality.

Measurements obtained by three-dimensional echocardiography and myocardial deformation analysis were not addressed in this study. Although 3-D RV EF seems to be more reliable with fewer reproducibility errors, there are currently insufficient data demonstrating its clinical value at present. [2] However, these two techniques are currently undergoing extensive evaluation and will likely play an important role in clinical practice.

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19. McQuillan, B.M., et al., *Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects.* Circulation, 2001. **104**(23): p. 2797-2802.
20. Pettersen, M.D., et al., *Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: An echocardiographic study.* Journal of the American Society of Echocardiography, 2008. **21**(8): p. 922-934.
21. Schvartzman, P.R., et al., *Normal values of echocardiographic measurements. A population-based study.* Arq Bras Cardiol, 2000. **75**(2): p. 107-14.
22. Kouri, T.K., V. Virtanen, A. Uusipaikka, E. Rajamaki, A. Finneman, H. Juva, K. Koivula, T. Nanto, V., *Reference Intervals Developed from Data for Hospitalized Patients: Computerized Method Based on Combination of Laboratory and Diagnostic Data.* CLIN. CHEM, 1994. **40**(12): p. 2209-2215.
23. Ceriotti, F.H., R. Panteghini, M., *Reference intervals: the way forward.* Annals of Clinical Biochemistry., 2009. **46**: p. 8-17.
24. Carapetis, J.R., M. McDonald, and N.J. Wilson, *Acute rheumatic fever.* Lancet, 2005. **366**(9480): p. 155-68.
25. Petersen, H. *The Latest on Reference Values and Reference Intervals.* [cited 2010 December 03, 2010]; Available from: http:www.westgard.com/the-latest-on-reference-values-and-reference-intervals.htm.
26. Weiss, R.a.o., *Obesity and the Metabolic Syndrome in Children and Adolescents.* N. Engl J Med, 2004. **350**: p. 2362-2374.
27. Awori, M.N.F., K. Gentles, T.L., *Optimal Normative Pediatric Cardiac Structure Dimensions for Clinical Use.* World Journal for Pediatric and Congenital Heart Surgery, 2011. **2**: p. 85.
28. Cook, D.J.S., D.L. Spitzer, W.O., *Methodologic guideline for Systematic Reviews of randomized control trials in health care from the Potsdam Consultation on meta-analysis.* Journal of Clinical Epedemiology, 1995. **48**(1): p. 167-171.
29. *Higgins, J.P.T. and Green, S. (editors) Cochrane Handbook for Systematic Reviews of Interventions 4.2.5.* 2005 May 2005; Available from: www.cochrane-handbook.org.
30. Vignola, P.A.B., A. Kaplan, A.D. Walker, H.J. Chiotellis, P.N. Myers, G.S., *Interobserver variability in echocardiography.* Journal of Clinical Ultrasound, 1977. **5**(4): p. 238-242.
31. Moiduddin, N., et al., *Two-Dimensional Speckle Strain and Dyssynchrony in Single Right Ventricles Versus Normal Right Ventricles.* Journal of the American Society of Echocardiography. **23**(6): p. 673-679.
32. Kampmann, C., et al., *Normal values of M mode echocardiographic measurements of more than 2000 healthy infants and children in central Europe.* Heart, 2000. **83**(6): p. 667-72.
33. King, D.H., et al., *Mitral and tricuspid valve anular diameter in normal children determined by two-dimensional echocardiography.* Am J Cardiol, 1985. **55**(6): p. 787-9.
34. Ichida, F., et al., *Cross sectional echocardiographic assessment of great artery diameters in infants and children.* Br Heart J, 1987. **58**(6): p. 627-34.
35. Hanseus, K., G. Bjorkhem, and N.R. Lundstrom, *Dimensions of cardiac chambers and great vessels by cross-sectional echocardiography in infants and children.* Pediatr Cardiol, 1988. **9**(1): p. 7-15.
36. Daubeney, P.E.F., et al., *Relationship of the dimension of cardiac structures to body size: an echocardiographic study in normal infants and children.* Cardiology in the Young, 1999. **9**(4): p. 402-410.
37. Zilberman, M.V., P.R. Khoury, and R.T. Kimball, *Two-dimensional echocardiographic valve measurements in healthy children: Gender-specific differences.* Pediatric Cardiology, 2005. **26**(4): p. 356-360.
38. Zhendong, Y., *Effects of Age and Respiration on Right Ventricular Diastolic Filling Patterns in Normal Children.* Pediatr Cardiol, 1998. **19**: p. 218-220.
39. Pena, J.L.B., et al., *Quantification of Regional Left and Right Ventricular Deformation Indices in Healthy Neonates by Using Strain Rate and Strain Imaging.* Journal of the American Society of Echocardiography, 2009. **22**(4): p. 369-375.

40. Innelli, P., et al., *The impact of ageing on right ventricular longitudinal function in healthy subjects: a pulsed tissue Doppler study.* European Journal of Echocardiography, 2009. **10**(4): p. 491-498.
41. Gutgesell, H.P. and M. French, *Echocardiographic determination of aortic and pulmonary valve areas in subjects with normal hearts.* Am J Cardiol, 1991. **68**(8): p. 773-6.
42. Gutgesell, H.P. and M. French, *ECHOCARDIOGRAPHIC DETERMINATION OF AORTIC AND PULMONARY VALVE AREAS IN SUBJECTS WITH NORMAL HEARTS.* American Journal of Cardiology, 1991. **68**(8): p. 773-776.
43. Matsui, H.S., G. Yasukochi, S. Kaneko, S. Haseyama, K., *Evaluation of Right Ventriclar Contraction by Myocardial Strain in Children Using aTwo-Dimensional Tissue Tracking Method.* Pediatr Cardiol, 2007. **29**: p. 377-381.
44. Kampmann, C., et al., *Normal values of M mode echocardiographic measurements of more than 2000 healthy infants and children in central Europe.* Heart, 2000. **83**(6): p. 667-672.
45. Koestenberger, M., et al., *Right Ventricular Function in Infants, Children and Adolescents: Reference Values of the Tricuspid Annular Plane Systolic Excursion (TAPSE) in 640 Healthy Patients and Calculation of z Score Values.* Journal of the American Society of Echocardiography, 2009. **22**(6): p. 715-719.
46. Eidem, B.W., et al., *Impact of cardiac growth on doppler tissue imaging velocities: A study in healthy children.* Journal of the American Society of Echocardiography, 2004. **17**(3): p. 212-221.
47. Frommelt, P.C.B., J.A. Whitstone, B.N. Frommelt, M.A., *Usefulness of Doppler Tissue Imaging Analysis of Tricuspid Annular Motion for Determination of Right Ventricular Function in Normal Infants and Children.* Am J Cardiol, 2002. **89**: p. 610-613.
48. Goebel, B., et al., *Exercise tissue Doppler echocardiography with strain rate imaging in healthy young individuals: feasibility, normal values and reproducibility.* International Journal of Cardiovascular Imaging, 2007. **23**(2): p. 149-155.
49. Harada, K.O., T. Yasuoka, K. Tamura, M. Takada, G., *Tissue Doppler Imaging of Left and Right Ventricles in Normal Children.* Tohoku J. Exp. Med., 2000. **191**: p. 21-29.
50. Kapusta, L., et al., *Assessment of myocardial velocities in healthy children using tissue Doppler imaging.* Ultrasound Med Biol, 2000. **26**(2): p. 229-37.
51. Mori, K., et al., *Pulsed wave Doppler tissue echocardiography assessment of the long axis function of the right and left ventricles during the early neonatal period.* Heart, 2004. **90**(2): p. 175-180.
52. Rafeiyian, S., et al., *Pulse tissue Doppler analysis of tricuspid annular motion in Iranian children.* International Journal of Cardiovascular Imaging, 2006. **22**(3-4): p. 363-367.
53. Roberson, D.A., et al., *Annular and septal Doppler tissue imaging in children: Normal Z-score tables and effects of age, heart rate, and body surface area.* Journal of the American Society of Echocardiography, 2007. **20**(11): p. 1276-1284.
54. Ganguly, N.K., et al., *Frequency of D8/17 B lymphocyte alloantigen in north Indian patients with rheumatic heart disease.* Immunol Cell Biol, 1992. **70 (Pt 1)**: p. 9-14.
55. Mosteller, R.D., *Simplified calculation of Body Surface Area.* N. Engl J Med, 1987. **317**(17): p. 1098 (letter).
56. Clark, S.J., C.W. Yoxall, and N.V. Subhedar, *Measurement of right ventricular volume in healthy term and preterm neonates.* Archives of Disease in Childhood, 2002. **87**(2): p. F89-F93.
57. Lester, L.A., et al., *M-mode echocardiography in normal children and adolescents: some new perspectives.* Pediatr Cardiol, 1987. **8**(1): p. 27-33.
58. Chambers, J. *Stellenbosch University Echocardiography Course*. in *SUN echo course*. 2009. Zevenwacht, Kuilsriver, Cape Town, South Africa: Dept. Cardiology, Tygerberg Hospital; British Society of Echocardiography.
59. Lee, A., et al., *Superior vena cava flow: feasibility and reliability of the off-line analyses.* Arch Dis Child Fetal Neonatal Ed. **95**(2): p. F121-5.

60. Eidem, B.W., et al., *Nongeometric quantitative assessment of right and left ventricular function: Myocardial performance index in normal children and patients with Ebstein anomaly.* Journal of the American Society of Echocardiography, 1998. **11**(9): p. 849-856.
61. Anderson, B., *Echocardiography*. 2nd ed. 2007.
62. Roberson, D.A. and W. Cui, *Right ventricular Tei index in children: Effect of method, age, body surface area, and heart rate.* Journal of the American Society of Echocardiography, 2007. **20**(6): p. 764-770.
63. Ishii, M., et al., *Quantitation of the global right ventricular function in children with normal heart and congenital heart disease: a right ventricular myocardial performance index.* Pediatr Cardiol, 2000. **21**(5): p. 416-21.
64. Rafeiyian, S., et al., *Pulse tissue Doppler analysis of tricuspid annular motion in Iranian children.* Int J Cardiovasc Imaging, 2006. **22**(3-4): p. 363-7.
65. Swaminathan, S.F., P.L. Wolff, G.S. Gomez-Martin, O. Rusconi, P.G., *Usefulness of tissue Doppler echocardiography for evaluating ventricular function in children without heart disease.* Am J Cardiol, 2003. **91**: p. 570-574.
66. Yasuoka, K.H., K. Orino, T. Takada, G., *Right Ventricular Diastolic Filling Assessed by Conventional Doppler and Tissue Doppler Imaging in Normal Children.* Tohoku J. Exp. Med., 1999. **189**: p. 283-294.
67. Pena, J.L., et al., *Quantification of regional left and right ventricular deformation indices in healthy neonates by using strain rate and strain imaging.* J Am Soc Echocardiogr, 2009. **22**(4): p. 369-75.
68. Barth, J.H., *Reference ranges still need further clarity.* Annals of Clinical Biochemistry., 2009. **46**: p. 1-2.

9 Appendices

9.1 Appendix A: Search strategy

1. ECHOCARDIOGRA* [Title/Abstract]
2. ("NORMAL VALUES"[Title/Abstract]) OR ("NORMAL RANGES"[Title/Abstract]) OR ("REFERENCE VALUES"[Title/Abstract]) OR ("REFERENCE RANGE"[Title/Abstract]) OR ("REFERENCE INTERVAL"[Title/Abstract])
3. #1 AND #2
4. #3 Limits: Humans

9.2 Appendix B: Inferior vena cava collapsibility index

Estimating right atrial pressure	
Collapse in inspiration	**Pressure estimate**
50 – 100 %	0 – 5 mmHg
50 %	10 mmHg
25 – 50 %	15 mmHg
< 25 %	20 mmHg

According to the collapsibility index, collapse of 50-100% suggests a normal right atrial (RA) pressure of 0-5 mmHg. For calculations of participants that fall within this range, we used an estimated RA pressure of 5 mmHg.

Collapse of 50% suggests an RA pressure range of approximately 10 mmHg. For calculations of participants that fall within this range, we used an estimated RA pressure value of 10mmHg.

For collapse of 25-49%, an RA pressure value of 15 mmHg was used in the calculations.

For collapse less than 25% an RA pressure value of 20mmHg was used.

9.4 Appendix D: Echocardiographic Equations

Variable	**Equation**	Description
RV % fractional area change	**[(RVAd – RVAs) / RVAd] X 100**	RVAd: RV end-diastolic area RVAs: RV end-systolic area
RV myocardial performance index	**(a-b) / b**	a: tricuspid valve closing time b: pulmonary valve ejection time
RV volume	**0.85 (A^2/L)**	A: area of the RV L: long-axis length of the RV
RV ejection fraction	**[RVEDV – RVESV) / RVEDV] X 100**	RVEDV: RV end-diastolic volume RVESV: RV end-systolic volume
RV systolic pressure	**$4v^2$**	v: tricuspid regurgitation peak systolic velocity
Pulmonary artery systolic pressure	**RV systolic pressure + estimated RAP**	RV systolic pressure: see previous equation RAP: right atrial pressure

The references for the equations are available in section 4.5 *Echocardiographic evaluation of the right heart: methods, technique and variables* of this document.