Multimodality profiling of pulmonary hypertension in a group of South African patients with congenital heart disease

Musawenkosi Msizi Fairhope Henema

Thesis submitted in fulfilment of the requirements of the degree

DOCTOR OF HEALTH SCIENCES IN CLINICAL TECHNOLOGY

(DHSCT)

Department of Health Sciences

Central University of Technology

Faculty of Health and Environmental Sciences

Bloemfontein, South Africa

Promotor: Prof. SC Brown [D Med MMed MBChB FCPaed DCH (UFS)]

Co-promotor: Dr L Botes [DTech (CUT); PhD (UFS)]

MAY 2025

DECLARATION OF INDEPENDENT WORK

I, **Musawenkosi Msizi Fairhope**, do hereby declare that this thesis:

Multimodality profiling of pulmonary hypertension in a group of South African patients with congenital heart disease

submitted to the Central University of Technology, Free State, for the degree Doctorate of Health Sciences in Clinical Technology is my own independent work, and it has not been submitted to any institution by me or any other person in fulfilment of the requirements for the attainment of any qualification.

	4 June 2025
Musawenkosi Msizi Fairhope	**Date**
Principal Investigator	

ACKNOWLEDGEMENTS

First and foremost, I extend my deepest gratitude to **God Almighty** for granting me the wisdom, strength and perseverance to complete this study.

I am profoundly grateful to my supervisor, **Prof. S.C. Brown**, for his exceptional guidance, invaluable feedback, intellectual insight, constructive criticism and unwavering encouragement throughout this project. His support has been instrumental in shaping this work.

I also sincerely appreciate my co-supervisor, **Dr L. Botes**, for her invaluable contributions, motivation and thoughtful suggestions. Working with her has been an enriching experience and her perceptive critiques continually challenged me to strive for excellence.

I am deeply thankful to **Dr P. Tinarwo**, statistician, for his time, support and expertise, which were invaluable to this study.

I also want to express my gratitude towards the **Robert W Frater Cardiovascular Research Centre**.

A debt of gratitude is also owed to **Prof. P.S. Mntla,** head of the Department, **Dr P.M. Mutati**, and my colleagues in the Department of Cardiology at Dr George Mukhari Hospital.

To **Dr L. Holm**, director of Clinical Services of Dr George Mukhari Hospital, thank you for granting permission to access patient data.

To the **participants**, thank you for participating in this study and contributing to medical science.

I am deeply grateful to my **wife and children**, whose unwavering support and inspiration carried me through every stage of this project. Their encouragement made this journey possible and I could not have completed it without them.

I would also like to extend my sincere gratitude to my **family and friends**. Your unwavering support, understanding and prayers have sustained me through this challenging time and I sincerely appreciate each and every one of you.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

%	Percentage
ASD	Atrial septal defect
AV	Atrioventricular
AVSD	Atrio-ventricular septal defect
CHD	Congenital heart disease
CI	Confidence interval
Cm	Centimetres
cm/s	Centimetres per second
CMRI	Cardiac magnetic resonance imaging
CONCOR	CONgenital CORvitia
2D-Echo	Two dimensional echocardiogram
E/A	Early to atrial filling velocity ratio
ECG	Electrocardiogram
EF	Ejection fraction
ET	Ejection time
ET-1	Endothelin 1
HIV	Human immunodeficiency virus
IVC	Inferior vena cava
LVEF	Left ventricular ejection fraction
LV	Left ventricle
MAPSE	Mitral annular plane systolic excursion
M-mode	Motion mode
mPAP	Mean pulmonary artery pressure
MPI	Myocardial performance index
MRI	Magnetic resonance imaging
M	Metres
mL	Millilitres
Mm	Millimetres
mmHg	Millimetres mercury

mL/m²	Millilitres per metre square
m²	Metres square
6MWT	Six-minute walk test
NTproBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
O_2	Oxygen
PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PH	Pulmonary hypertension
PDA	Patent ductus arteriosus
PH-CHD	Pulmonary hypertension associated with congenital heart disease
PVR	Pulmonary vascular resistance
RA	Right atrium
REVEAL	Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management
RVMPI	Right ventricular myocardial performance index
RHC	Right heart catheterization
RV	Right ventricle
RVEF	Right ventricular ejection fraction
Sm	Systolic maximal
Sm VTI	Systolic maximal velocity time integral
S’	Tricuspid annular velocity
TAPSE	Tricuspid annular plane systolic excursion
TR	Tricuspid regurgitation
TDI	Tissue Doppler imaging
TOPP	Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension Registry
VSD	Ventricular septal defect
V/Q	Ventilation/perfusion
WHO	World Health Organization

LIST OF DEFINITIONS

Body mass index	The key index for relating weight to height was calculated as body weight in kilograms divided by height squared in meters (Nuttall, 2015).
Inferior vena cava measurements	Performed in a subcostal long-axis view perpendicular to the inferior vena cava with the patient supine at 1.0 to 2.0 cm from the junction with the right atrium (Kusner and Krasuski, 2023).
Left atrial enlargement	P-wave duration ≥ 0.12 secs in lead II. Notched P-wave ≥ 0.04 secs in lead V1 (Allison et al., 2017).
Left ventricle ejection fraction	The fraction of chamber volume ejected in systole compared to the amount of blood in the ventricle at the end of diastole (Kosaraju et al., 2023).
Left ventricular end-diastole diameter as per Teicholz method	Measured using M-mode echocardiography in parasternal long-axis view. The LV dimension measurement was taken when the time cursor was placed before the peak R-wave in the ventricular depolarisation complex (Chengode, 2016).
Left ventricular hypertrophy	Sokolow and Lyon index S wave in V1+R wave in V5|V6 ≥ 35 mm < 20 years, Cornell Criteria R wave in aVL+5V3 > 28 mm in men > 20 mm in women > 20 years (Bonderman et al., 2011).
Myocardial performance index	The sum of the isovolumetric contraction time and isovolumetric relaxation time divided by the ejection time (Askin et al., 2023).
Mitral annular plane systolic excursion	The displacement of the mitral valvular plane in the z-direction, reflecting left ventricular contraction or shortening (Cirin et al., 2024).
New York Heart Association classification	Classification provides a simple way of classifying the extent of heart failure (Ford et al., 2015).

Pulmonary regurgitant fraction	Regurgitant fraction = Jet width/Right ventricle outflow tract diameter X 100%. Regurgitant fraction was classified as mild < 20%, moderate 20–40%, severe > 40% (Mercer-Rosa et al., 2012).
Pulmonary vascular resistance	Calculated using mean pulmonary artery pressure – mean left atrium OR left ventricle end-diastolic pressure OR wedge/pulmonary circulation (Widrich and Shetty, 2024).
Right atrium enlargement	P-wave in lead II > 2.5 mm and or > 1.5 mm in V1 (Sun et al., 2012).
Right ventricular systolic pressure	Diagnosed using echocardiographic measurement of peak tricuspid regurgitation velocity and modified Bernoulli equation (Parasuraman et al., 2016). Patients are sent for cardiac catheterisation if right ventricular peak systolic pressure is ≥ 40 mmHg. Pulmonary hypertension is classified as mild (40−50 mmHg), moderate (51–60 mmHg), or severe pulmonary hypertension (≥ 60 mmHg) (Skinner, 2017). In adults, the inferior vena cava is dilated if it measures more than 21 mm, is distended, has a collapsibility of less than 50%, and 10 mmHg was added. In children under 12 years, the inferior vena cava is dilated if it measures more than 14 mm, is distended, has a collapsibility of less than 50%, and 10 mmHg was added.
Right ventricle free wall strain	Calculated using tissue Doppler imaging on the RV free wall in the apical four-chamber view to measure the tricuspid annular systolic myocardial (Sm) velocity. The maximum Sm velocity and velocity time integral of Sm (SmVTI) are then measured. Sm velocity < 12 cm/s and SmVTI < 2.5 are indicators of excessive pulmonary artery systolic pressure (Parasuraman et al., 2016).
Right ventricular hypertrophy	Dominant R-wave in V1 > 7 mm tall**,** Dominant S wave in V5 or V6 > 7 mm deep (Bonderman et al., 2011).
Tricuspid annular plane systolic excursion	Pertains to the systolic longitudinal displacement of the lateral tricuspid annulus towards the apex (Giusca et al., 2010).

Tricuspid annulus peak systolic velocity (S')	The maximum velocity at which the lateral tricuspid annulus may expand in systole (Kurnicka et al., 2020).
Tricuspid regurgitation volume on cardiac magnetic resonance imaging	Calculated as the difference between right ventricular stroke volume and pulmonary forward flow. Tricuspid regurgitation was classified as mild < 30 mL, moderate 30–59 mL, and severe ≥ 60 mL (Vermes et al., 2022).
E/E' and E'/A' ratios	Doppler inflow of the tricuspid valve (Zaidi et al., 2020).

EXECUTIVE SUMMARY

INTRODUCTION

Pulmonary hypertension (PH) associated with congenital heart disease (CHD) is a serious condition that can cause significant disability and death. Around 80% of the global disease burden occurs in low- and middle-income countries, where PH is strongly associated with CHD. Unoperated but potentially operable patients face a high risk of developing PH. In sub-Saharan Africa, patients often present late, which contributes to high mortality rates. Imaging is fundamental for determining the causes and severity of PH, particularly in evaluating both right and left cardiac function, which are key predictors of morbidity and mortality. To our knowledge, limited data exist on the evaluation of imaging modalities in patients with secondary PH due to left-to-right shunts, particularly in South Africa, where data on functional impairment in children are scarce. This study describes the clinical and imaging characteristics of PH resulting from congenital heart lesions with a left-to-right shunt in a group of South African patients.

METHODS

The study was conducted at Dr George Mukhari Hospital, Gauteng, South Africa, using a prospective observational design to investigate PH resulting from CHD. Demographic and anthropometric data were collected. A 12-lead electrocardiogram (ECG) was conducted using a Nihon Kohden Cardiofax ECG apparatus. A detailed echocardiographic study was performed using GE Medical Vivid E9 ultrasound equipment with an M5SC phased array transducer. A 6-minute walk test was performed according to American Thoracic Society guidelines. Patients were referred for cardiac catheterisation if the screening echocardiogram right ventricular systolic pressure was ≥ 25 mmHg. Cardiac magnetic resonance imaging was performed on all patients at rest using a 1.5 T Magnetom Symphony Siemens system. Nuclear ventriculography was conducted with an Intevo scanner, Siemens Medical Solution, and Syngo MI application software, using a Technetium-99m labelled diethylenetriamine pentaacetate injection at rest. Standard statistical software was used for data analysis.

RESULTS

Most patients (73%) were aged 6–17 years, with a median age of 9.98 years. The most common congenital abnormality associated with PH was simple ventricular septal defect (41%). The pulmonary valve annulus was dilated in all patients (z-score 4.23). Prolonged right ventricular (RV) myocardial performance index (MPI), reduced tricuspid annular velocity, decreased tricuspid annular plane systolic excursion (TAPSE), and impaired calculated RV free wall strain confirmed RV dysfunction in all patients. The right heart was dilated, likely resulting in tricuspid regurgitation and a dilated tricuspid valve annulus with a median z-score of 2.44. The median six-minute walking distance was diminished in all patients. The combination of RV systolic pressure > 50 mmHg plus pulmonary annulus z-score > 3 to predict pulmonary vascular resistance > 3 Wood unit.m² had a sensitivity of 82.4% but a low specificity of 14.3%. RV end-diastolic indexed volumes were at least double the normal reference ranges in most patients (median 240:165–268 mL/m²) on cardiac magnetic resonance imaging (CMRI). Interestingly, CMRI showed that 70% of male patients had normal RV systolic function, compared to only 45% of female patients ($p < 0.05$). Echocardiographic markers of RV function correlated poorly with CMRI RV ejection fraction. Echocardiography and isotopes left ventricular (LV) ejection fraction correlated strongly with CMRI LV ejection fraction ($r = 0.90$).

CONCLUSION

Patients in South Africa with simple, potentially operable lesions suffer from severe PH. These patients exhibited significant right-sided dilation, particularly in the pulmonary arteries, which could be an early warning sign of PH. Additionally, all patients demonstrated substantial functional impairment and right heart dysfunction. Both echocardiography and CMRI consistently revealed right heart dilation in patients with PH associated with left-to-right shunts. Right heart dimensions measured by transthoracic echocardiography and CMRI showed a strong correlation. This study's echocardiographic markers of RV function aligned well with clinical functional assessments. However, these echocardiographic markers exhibited poor correlation with RV ejection fraction measured by CMRI. Furthermore, a subset of patients presented with reduced LV ejection fraction.

CHAPTER 1 – INTRODUCTION

Congenital heart disease (CHD) is one of the most common birth abnormalities and affects approximately one in every 100 children (Ossa Galvis et al., 2023). Early detection and treatment of congenital cardiac defects can prevent pulmonary vascular disease developing (Lüscher and Deanfield, 2023). Thus, pulmonary vascular disease associated with CHD is uncommon in children in countries with well-organised referral systems, early detection and timely surgical intervention. However, pulmonary vascular disease often occurs in individuals with CHD in developing countries with restricted resources (Abman et al., 2015). It is estimated that around 80% of the global burden of the disease occurs in low- and middle-income countries where pulmonary hypertension (PH) is strongly associated with CHD (Mocumbi et al., 2015). Unoperated but potentially operable lesions with severe PH and left-to-right shunting (Van der Bom et al., 2012).

In Africa, limited data are available to accurately estimate the number of children with CHD who are at risk of developing pulmonary vascular disease. Congenital heart disease that is not surgically repaired is a significant cause of PH. Surgical correction of CHD in early infancy is often not feasible in resource-limited settings, for various reasons, including delayed detection due to a shortage of paediatric cardiology specialists and inadequate infrastructure, such as operating rooms and catheterisation laboratories, which are needed for corrective procedures (Yankah et al., 2014). A Tanzanian study reports that 6.3% of children were inoperable at first diagnosis, with 3% deemed inoperable due to severe PH (Zuechner et al., 2019). Essentially, these were simple lesions that could have been operated on easily, but which had progressed to severe PH due to late presentation. In a Ugandan CHD registry, all lesions had been diagnosed after infancy and left untreated for up to five years due to limited resources (Namuyonga et al., 2020).

Various imaging modalities are available to assess PH, but cardiac catheterisation remains the gold standard for diagnosing PH, because it measures pulmonary artery pressure (PAP) directly (Mani and Chaudhari, 2023). Echocardiography is the primary imaging technique for screening PH and assessing right ventricular (RV) and left ventricular (LV) function (Grünig et al., 2015). The New York Heart Association (NYHA) classification and six-minute walk test (6MWT)

are commonly used for functional assessments of PH (Yap et al., 2015). Cardiac magnetic resonance imaging is considered the gold standard for evaluating RV and LV function (Peacock and Vonk Noordegraaf, 2013). Additionally, radionuclide ventriculography is often used for the differential diagnosis of PH (Bodar and Modi, 2023).

It is noteworthy that most published studies focused on primary PH; consequently, there is limited data on the evaluation of imaging modalities for patients presenting with secondary PH due to left-to-right shunts. To our knowledge, there is no published literature on secondary PH due to left-to-right shunts in South Africa. Therefore, this study aimed to describe the clinical and imaging characteristics of PH resulting from congenital heart lesions with a left-to-right shunt in a group of South African patients.

1.1 OBJECTIVES

The objectives of this study were as follows:

1. To describe clinical and demographic parameters of patients with PH with left-to-right shunts and underlying CHD **[Paper I]**.
2. To correlate right heart catheterisation (RHC) with clinical, functional measurement tools, such as 6MWT and the NYHA **[Paper I]**.
3. To correlate RHC with specialised investigations such as echocardiography, cardiac magnetic resonance imaging (CMRI) and isotopes in PH **[Paper I, II]**.
4. To compare echocardiography measurements of RV function with CMR volume and function and functional assessment **[Paper I, II]**.
5. To evaluate the left hearts of patients with PH using echocardiography, CMRI and nuclear ventriculography **[Paper II]**.

1.2 LAYOUT OF THE THESIS

This thesis is structured into five chapters, each addressing a specific aspect of PH associated with CHD, with a particular emphasis on the South African context.

- **Chapter 1 – Introduction:** Provides the background and rationale for the study, outlines the research objectives and introduces the structure of the thesis.
- **Chapter 2 – Literature review:** Offers a comprehensive overview of PH in the context of CHD as the cause. This chapter discusses the complications and underlying pathophysiology of PH, including its classification and histological features. It also

explores the global and local (South African) epidemiology of PH, diagnostic approaches and the unique challenges faced in diagnosing PH in low- and middle-income countries.

- **Chapter 3 – Paper I:** Presents the findings of a clinical and echocardiographic analysis of patients with PH secondary to CHD. The study characterises patient presentations and explores key diagnostic parameters.

  Paper 1, which was prepared according to the author guidelines of the *Cardiovascular Journal of Africa*, had been submitted and was under review at the time of finalising this thesis.
- **Chapter 4 – Paper II:** Describes a study that evaluated various imaging modalities that are used to assess right and left heart volumes and function in patients with PH due to left-to-right shunts. This chapter highlights the strengths and limitations of each modality in the local context.

  Paper II, prepared according to the author guidelines of the *South African Heart Journal*, had been submitted and was under review at the time of finalising this thesis.
- **Chapter 5 – General conclusion:** Summarises the main findings of the thesis, discusses their clinical implications and offers recommendations for future research aimed at improving diagnosis and management of PH in CHD, particularly in resource-limited settings.

CHAPTER 2 – LITERATURE REVIEW

2.1 CONGENITAL HEART DISEASE

Around one in every 100 infants born worldwide is affected by CHD, which makes it one of the most prevalent congenital disabilities (Chan et al., 2020). The lesions of CHD range from simple septal wall abnormalities to complicated cardiac lesions caused by single-ventricle disease. Improvements in surgical repair or palliation and advanced CHD defect identification have increased survival into adulthood (Oldroyd et al., 2024). The emergence of PH presents novel issues in the management of CHD (Van der Bom et al., 2012).

2.2 PULMONARY VASCULAR DISEASE AS A COMPLICATION OF CONGENITAL HEART DISEASE

Pulmonary vascular disease can exacerbate untreated CHDs by increasing PAP, blood flow, or both (Van der Feen et al., 2017). Typical lesions that predispose patients to the development of pulmonary vascular disease are: i) Ventricular septal defect (VSD), ii) Patent ductus arteriosus (PDA), iii) Atrial septal defect (ASD); and iv) More complex forms of CHD without congenital or acquired obstruction of pulmonary blood flow. There is currently no data available to precisely estimate the number of children with CHD and at risk of developing pulmonary vascular disease. However, globally, over 600,000 children are born each year with severe CHD, of whom 50% or more die from infection and heart failure (Kameny et al., 2017).

2.2.1 Lack of services in sub-Saharan Africa

Most children with congenital heart disease have a favorable prognosis with appropriate treatment; however, many in South Africa do not receive the care they need. The problem arises from insufficient early detection tools and training, along with a shortage of qualified caregivers at all levels of care. Additionally, limited operating room time and critical care facilities hinder public hospitals' ability to manage the high demand for surgeries (Hoosen et al., 2010). It is crucial to recognize that with proper management, up to 85% of children with congenital heart disease can reach adulthood (Warnes et al., 2001).

Pulmonary vascular disease is common in patients with CHD (Abman et al., 2015). However, early treatment of congenital cardiac defects usually prevents the development of pulmonary vascular disease (Lopes et al., 2014). Thus, pulmonary vascular disease associated with CHD is uncommon in children in countries that offer well-organised referral systems, early detection and surgical treatment. As much as 80% of the global population lives outside of wealthy countries, and only 2% to 15% of these people with significant intracardiac or extracardiac shunt lesions obtain curative therapy (Finegold et al., 2013). For example, while surgical therapy is available in Papua New Guinea, 20% of children are inoperable due to advanced pulmonary vascular disease. Congenital heart disease is one of the primary causes of hypertensive pulmonary vascular disease, due to limited and delayed access to specialised care (Van De Bruaene and Budts, 2016).

2.2.2 Risks of developing pulmonary hypertension due to congenital heart lesions

Increased pulmonary blood flow can lead to an overload of the pulmonary vessels, causing them to become stressed and eventually develop pulmonary hypertension. Vascular remodeling occurs when the pulmonary arteries thicken and narrow, further increasing resistance to blood flow and contributing to PH. Increased pulmonary vascular resistance is the primary hallmark of PH, characterized by heightened resistance within the pulmonary arteries, making it more difficult for the heart to pump blood through the lungs. As a result of the increased pressure in the pulmonary arteries, the heart's right ventricle must work harder to pump blood against this resistance, leading to strain on the right ventricle. If the RV cannot manage this increased workload, it can result in right heart failure (Das, 2025). Eisenmenger syndrome is a congenital heart defect that results in an open shunt from the lungs to the systemic circulation, causing increased pulmonary blood flow and pulmonary hypertension (Basit et al., 2023).

The frequency of CHD-related pulmonary vascular disease in European adults ranges from 1.6 to 12.5 instances per million individuals; 25% to 50% of these patients have Eisenmenger syndrome with shunt reversal (Pascall and Tulloh, 2018). A complex combination of environmental, genetic and socioeconomic factors causes the development of pulmonary vascular disease in association with CHD (Kalisch-Smith et al., 2020). Nonetheless, a lack of access to medical therapy is the most critical factor in the global spread of irreversible pulmonary vascular disease caused by CHD. The unsettling reality is that developed countries

carry 12% of the worldwide burden of all causes of death and disability while accounting for 90% of global healthcare spending (GBD 2019 Diseases and Injuries Collaborators, 2020).

2.3 PATHOPHYSIOLOGY OF CONGENITAL HEART DISEASE WITH INTRA- AND EXTRACARDIAC SHUNTS

The pathogenesis of CHD with intracardiac and extracardiac shunts may differ between pre- and post-tricuspid lesions (i.e., proximal or distal to the subpulmonary atrioventricular [AV] valve in the circulation) (Kozlik-Feldmann et al., 2016).

2.3.1 Pre-tricuspid shunts

Pre-tricuspid shunts, such as atrial septal defects, partial anomalous pulmonary venous return, and the levoatriocardinal vein, are low-pressure, left-to-right (or bidirectional) shunts that cause volume stress to the RV and pulmonary circulation without creating an immediate or midterm increase in PAP. Between 6 and 17% of individuals with pre-tricuspid lesions develop PH-pulmonary vascular disease/paediatric pulmonary hypertensive vascular disease after their fourth decade of life (Kozlik-Feldmann et al., 2016). Pulmonary vascular disease risk is proportional to the size of the ASD and RV compliance (left-to-right shunt size). The same principles apply to partial anomalous pulmonary venous return. Additional left heart lesions and LV failure significantly increase pulmonary circulation volume strain. However, Eisenmenger syndrome in adults with ASD is uncommon – it affects only 2% of patients (Kozlik-Feldmann et al., 2016).

2.3.2 Post-tricuspid lesions

Post-tricuspid lesions are high-pressure left-to-right shunts that cause strain on the LV and pulmonary circulation. If the post-tricuspid inadequacies are large enough, pulmonary pressure rises to systemic levels (pressure-free VSD). This results in the early and more frequent development of pulmonary hypertension (Beghetti et al., 2012). Pulmonary hypertension-pulmonary vascular disease/paediatric pulmonary hypertensive vascular disease develops in post-tricuspid lesions throughout the first several years of life. If left untreated, around half of patients with post-tricuspid lesions develop supra-systemic pulmonary vascular resistance (PVR), resulting in a right-to-left shunt via the underlying lesions, known as the Eisenmenger complex (Diller et al., 2014; Frank and Hanna, 2015). While adults with Eisenmenger-PH live longer than those with idiopathic/heritable PH, children with PH-CHD and pulmonary vascular

disease (i.e., paediatric pulmonary hypertensive vascular disease) have a five-year death rate similar to that of adults with idiopathic/heritable PH (29% vs. 25%). Adult PH with CHD is typically underestimated because of an apparent survival bias in patient selection in published registries (Barst et al., 2012; Simonneau et al., 2013).

2.4 PULMONARY HYPERTENSION

2.4.1 Introduction

According to the current guidelines, pre-capillary PH is defined as a mean PAP (mPAP) greater than 20 mmHg, measured by RHC (Simonneau et al., 2019). This study was designed before the updated definition of mPAP > 20 mmHg measured by RHC was published. Therefore, this study used the previous guidelines of mean PAP ≥ 25 mmHg to diagnose PH, because this was the definition used by the clinicians at our institution.

The World Health Organization (WHO) defines PH as pre-capillary PH with a mPAP greater than 25 mmHg and a pulmonary capillary wedge pressure less than 15 mmHg (Kovács and Olschewski, 2021).

PH is frequently associated with PVR in children, which is more than three indexed Wood units. Congenital cardiac disease is the most common co-diagnosis for paediatric patients with PH, which is classified as Group 2 and 3 by the World Health Organization (Zijlstra et al., 2016).

2.4.2 Defining pulmonary hypertension and controversies

2.4.2.1 Fourth World Symposium on Pulmonary Hypertension, 2008 and 2009

Prior to the 2008 update from the World Symposium on Pulmonary Hypertension in California, all previous international meetings on PH had concentrated on diagnosing and assessing patients with PH. The conference recommendations were included in the guidelines. The fourth World Symposium on Pulmonary Hypertension raised the pulmonary artery threshold to ⩾ 25 mmHg (Condon et al., 2019).

2.4.2.2 Fifth World Symposium on Pulmonary Hypertension, 2013

At the fifth World Symposium on Pulmonary Hypertension in Nice, France, the working group on diagnosis and evaluation did not propose revisions to previous recommendations; instead,

they urged changes only when sufficient new evidence supported new proposals (Thomas et al., 2020).

2.4.2.3 Sixth World Symposium on Pulmonary Hypertension, 2018

At the sixth World Symposium on Pulmonary Hypertension in Nice, France, a working group led by Simonneau proposed revising the haemodynamic definition of PH and lowering the threshold from ⩾ 25 mmHg to > 20 mmHg. This proposal surprised many participants and raised critical voices, who argued that the old definition was the basis of all treatment trials. Participants noted uncertainty about treating patients with mPAP of 20 to 24 mmHg. There was concern that the new classification could lead to overdiagnosis and overtreatment of PH patients (Simonneau et al., 2019).

2.4.2.4 Sixth World Symposium on Pulmonary Hypertension Task Force, 2018

In conclusion, the sixth World Symposium on Pulmonary Hypertension Task Force proposed in 2018 that the upper limit of normal mPAP should be 20 mmHg, with any result above this threshold considered abnormal. However, this cut-off figure does not inherently characterise disease. An elevated mPAP can be caused by factors such as increased cardiac output, left-to-right cardiac shunts, elevated pulmonary artery wedge pressure from left heart disease, increased blood viscosity, or, in rare cases, actual pre-capillary pulmonary vascular disease (Vachiéry et al., 2019). Simonneau et al. (2019) found that pre-capillary PH is associated with pulmonary vascular disease when mPAP exceeds 20 mmHg and PVR is ⩾ 3 Wood units.

2.5 CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary hypertension is classified into five groups based on the cause (Table 1) (Anderson and Lau, 2022).

Table 1: Classification of pulmonary hypertension according to cause

Classification	Causes
Group 1	▪ Unknown cause (idiopathic pulmonary hypertension) ▪ A genetic mutation passed down through families (heritable pulmonary arterial hypertension) ▪ Use of some prescription diet drugs or illegal substances such as methamphetamines and other drugs ▪ Heart problems present at birth (congenital heart disease) ▪ Other conditions such as connective tissue disorders (scleroderma, lupus, others), human immunodeficiency virus (HIV) infection or chronic liver disease (cirrhosis) (George et al., 2014)
Group 2	▪ Left-sided heart valve diseases, such as mitral valve or aortic valve disease ▪ Failure of the lower-left heart chamber (left ventricle) (Guazzi and Galiè, 2012)
Group 3	▪ Chronic obstructive pulmonary disease ▪ Pulmonary fibrosis, a condition that causes scarring in the tissue between the lungs air sacs (interstitium) ▪ Obstructive sleep apnoea ▪ Long-term exposure to high altitude in people who may be at higher risk of pulmonary hypertension (Igarashi et al., 2013)
Group 4	▪ Chronic blood clots in the lungs (pulmonary emboli) ▪ Other clotting disorders (Kim, 2016)
Group 5	▪ Blood disorders, including polycythaemia vera and essential thrombocythaemia ▪ Inflammatory disorders such as sarcoidosis and vasculitis ▪ Metabolic disorders, including glycogen storage disease ▪ Kidney disease ▪ Tumours pressing against pulmonary arteries (Kalantari and Gomberg-Maitland, 2016)

2.6 PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION

2.6.1 Endothelin-1 receptor

The presence of endothelin 1 (ET-1) receptors in the lungs and dysregulation of the endothelin system are likely to contribute to the beginning and progression of PVR and pulmonary vascular remodelling (Kamiyama et al., 2014). Compared to normal lungs, PH muscle arteries and vascular endothelial cells have increased levels of ET-1 and preproendothelin-1. The increased levels of PVR have been linked to ET-1 expression. The observation that PH patients have greater circulating levels of ET-1 and higher ET-1 levels exiting the lung relative to those entering the lung suggests that the lungs have improved their ability to release ET-1 (Lan et al., 2018). This effect is likely to be the result of increased output and reduced clearance. Plasma ET-1 levels are higher in people with PH-related conditions, such as congenital heart defects and pulmonary fibrosis (without connective tissue disease) and with left-to-right shunts. ET-1

interacts with ligands on the bone morphogenetic protein receptor Type 2 (Chester and Yacoub, 2014).

2.6.2 Angiotensin II

Angiotensin II stimulates the angiotensin Type 1 receptor, causing a vasoconstrictor response and stimulating aldosterone synthesis in the adrenal gland. Aldosterone then acts on the renal tubules to induce sodium and water retention, which increases circulating blood volume. It is now acknowledged that the angiotensin arm of this hormonal pathway is significantly more complex than was previously believed (Fountain et al., 2023). Alternative mechanisms for angiotensin II production exist, as do several vasoactive angiotensin cleavage peptides and other angiotensin receptors that control circulatory haemodynamics and remodelling. Angiotensin II can be produced by chymase, a protease in mast cells and skeletal muscle, or cathepsin G, a protein in inflammatory cells. Angiotensin II predominantly binds to and activates the angiotensin Type 1 and Type 2 receptors to modify vascular tone. Angiotensin Type 1 receptor activation causes a vasoconstrictor response, whereas angiotensin Type 2 receptor signalling promotes vasodilation (Maron and Leopold, 2014).

The complexity of the angiotensin pathway suggests that the pathophysiological consequences of renin-angiotensin system activation may result in PH because of an imbalance between angiotensin and other vasculoprotective angiotensin cleavage peptides, causing vasoconstriction and impaired vascular reactivity. These angiotensin-signalling peptides have opposing effects on other vascular smooth muscle cell functions required for vessel remodelling in PH (Kamiyama et al., 2014). Patients with pre-capillary PH, which is characterised by a common pulmonary angio-proliferative vasculopathy that affects the pre-capillary arterioles, are included in the pulmonary arterial hypertension group (Tuder et al., 2013). Increased RV afterload leads to an increase in PVR. Pulmonary arterial hypertension patients die from right heart failure if they do not receive proper treatment (Hussain et al., 2024).

2.7 HISTOLOGY OF PULMONARY HYPERTENSION

The functional state of the pulmonary circulation, as well as PVR and PAP, are all critical aspects of the treatment and prognosis of PH patients (Sakao et al., 2015). Furthermore, the histology and pathology of PH can help determine whether the disease is mild, moderate or severe. It can be divided into two classes – reversible and irreversible – and muscular

hypertrophy (Stage I), intimal proliferation (Stage II), concentric laminar intimal fibrosis (Stage III), necrotising vasculitis (Stage IV), plexiform lesions (Stage V), and dilatation and angiomatoid lesions (Stage VI), as explained in Table 2 (Sakao et al., 2015).

Table 2: Heath-Edwards classification (Sakao et al., 2015)

Classification	Stage
Reversible	Stage I: Medial hypertrophy (reversible) Stage II: Cellular intimal hyperplasia in an abnormally muscular artery (reversible) Stage III: Lumen occlusion from intimal hyperplasia of fibro-elastic tissue (partially reversible)
Irreversible	Stage IV: Arteriolar dilation and medial thinning (irreversible) Stage V: Plexiform lesion, which is an angiomatoid formation (terminal and irreversible) Stage VI: Fibrinoid/necrotising arteritis (terminal and irreversible)

2.8 GLOBAL EPIDEMIOLOGY OF PULMONARY HYPERTENSION IN CONGENITAL HEART DISEASE

The global prevalence of pulmonary arterial hypertension resulting from CHD varies by region: 35% in Africa, 40% in Asia, 11% in Australia, 11% in Europe, 11% in North America, and 10% in South America. These figures are based on data from populations at risk of PH and echocardiography studies, and not population-based research involving RHC (Hoeper et al., 2016). Patients with CHD-related pulmonary arterial hypertension have a better prognosis than those with idiopathic pulmonary arterial hypertension (Benza et al., 2012). Patients with CHD and pulmonary arterial hypertension, in turn, are more symptomatic and face a mortality risk that is at least twice as high as patients with CHD alone (Gu et al., 2020).

Natural history research and recent studies using PH registries have provided valuable epidemiological data on PH-CHD and Eisenmenger syndrome. However, the absolute number of paediatric and adult PH-CHD patients is still being determined because many patients are lost to follow-up, particularly after repair. Nonetheless, the prevalence of PH-CHD is differerent for adult and child populations (Dinarti et al., 2020).

Studies show that 10% of CHD patients develop PH. According to data from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL), the French PH registry, the Dutch PH registry (CONCOR), the Scottish Morbidity Record, and a group of tertiary European PH centres (Euro Heart Survey), PH-CHD accounts for 10%, 11%, 4%, 23%, and 28% of all PH cases, respectively. The slight variation is most

likely attributable to differences in inclusion criteria and patient recruitment capacity (Ling et al., 2012).

According to the CONCOR registry, Euro Heart Survey, and REVEAL registry, the prevalence of the most severe form of PH-CHD, Eisenmenger syndrome, is 1.1%, 12.3%, and 7.6%, respectively (Barst et al., 2014). This prevalence has dropped by 50% since the 1950s. Figures reported from a single centre are frequently much higher due to referral bias (Bonello et al., 2014).

Paediatric PH-CHD is substantially more common than adult PH-CHD. The prevalence ranges between 24% and 75% in the Dutch paediatric PH registry, the French paediatric PH registry, REVEAL, and the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry (Takatsuki and Ivy, 2013).

2.8.1 Lesions identified in pulmonary hypertension due to congenital heart disease

In the French paediatric PH registry with limited patient numbers, the lesions consisted of ASD, PDA, transposition of great arteries, and Scimitar syndrome, with prevalences of 25%, 25%, 42% and 8%, respectively (Ivy et al., 2024). The paediatric PH registry in the Netherlands and the TOPP registry report that systemic-to-pulmonary shunt failures occur in more than 93% of children with PH-CHD (Frank and Hanna, 2015). A sub-analysis of the Dutch paediatric PH registry reveals a strong preference for post-tricuspid shunts in the paediatric population – only a few individuals receive pre-tricuspid shunts (Berger et al., 2012).

Similar lesions can be found in adult PH-CHD patients. A study of VSDs in adult patients found that up to 50% of those with large defects (> 1.5 cm in diameter) and 3% of those with smaller VSDs acquired Eisenmenger syndrome (Dakkak et al., 2024). Natural history data from the 1960s suggest that 13% of patients had Eisenmenger syndrome, a condition that is less commonly associated with larger ASD. The Euro Heart Survey found that PH occurred in 12% of closed ASDs, 34% of open ASDs, 13% of closed VSDs, and 28% of open VSDs in PH-CHD patients (Frank and Hanna, 2015).

The Dutch CONCOR registry associates PH prevalence with even more specific lesions, such as ASDs (7–8%), VSDs (11%), AVSDs (41%), PDA (3%), truncus arteriosus (6%), aorto-pulmonary window (100%), double inlet LV (7%), double outlet RV (17%), and single ventricle (11%). In this registry, VSDs are the most common defect associated with

Eisenmenger syndrome (Group 1) and non-Eisenmenger syndrome PH (Groups 2–4), followed by ASDs and atrio-ventricular septal defects (AVSDs)(Ahmed and Anjum, 2023).

2.8.2 Survival rates for pulmonary hypertension with congenital heart disease

Survival rates for Eisenmenger syndrome and PH-CHD have increased significantly since the 1950s, especially in the paediatric population. Before the discovery of contemporary PH-targeted medicines, PH was associated with survival rates of 66%, 52% and 35% at one, three and five years, respectively (Opotowsky et al., 2014). Several studies indicate that all types of PH have greatly improved survival rates, with estimates of 73–96%, 63–88%, and 60–81% for one, three, and five-year survival rates, respectively (Korsholm et al., 2015). In the first REVEAL registry study, PH-CHD-specific survival of children was not significantly different from that of idiopathic PH (90% versus 85% two-year survival). Furthermore, there was no difference in survival rates between fixed and unrepaired/partially repaired lesions (86% versus 85% two-year survival, respectively) (Takatsuki and Ivy, 2013).

2.9 LIMITATIONS FACING PULMONARY HYPERTENSION IN AFRICA

There is an urgent need for research data on PH in Africa's paediatric population. Paediatric PH is underreported; it is most commonly related to congenital cardiac dysfunction and rheumatic heart disease. There are just two paediatric PH registries in Africa and four other disease-specific registries. Limited data on pulmonary arterial hypertension is available for Africa's paediatric population. The Pan African Pulmonary Hypertension Cohort registry clinically diagnoses PH according to RV systolic pressure determined by echocardiography and evidence of RV failure (Harerimana et al., 2018).

2.10 EISENMENGER SYNDROME

Pulmonary hypertension paired with CHD can result in a wide range of diseases (D'Alto and Mahadevan, 2012). However, the most common cause of PH-CHD is a systemic-to-pulmonary shunt between the two circulatory systems. Over time, pulmonary vascular remodelling can occur through various mechanisms, resulting in reversible or permanent vaso-occlusive lesions with high PVR. Eisenmenger syndrome is defined as progressive, irreversible and severe PH linked to CHD. In Eisenmenger syndrome, severe PH causes an unrepaired congenital heart defect associated shunt to shift from left to right to right to left. Although it is more common

in adult CHD patients, pulmonary vascular alterations can occur as early as the age of two years. To avoid Eisenmenger syndrome, early detection and intervention are essential (Frank and Hanna, 2015).

Eisenmenger syndrome results from long-term systemic-to-pulmonary shunts that alter the pulmonary vasculature and raise PVR. The most common causes of Eisenmenger syndrome include large VSDs, AVSDs, ASDs, and PDAs (Basit et al., 2023). Dr Paul Wood's pioneering work in 1958 revealed that a range of lesions could contribute to the disease; he connected 12 distinct lesions to Eisenmenger syndrome, namely PDA, aorto-pulmonary septal defect, chronic truncus arteriosus, transposition of the great arteries with VSD, corrected transposition with VSD, single ventricle, VSD, AVSD, single atrium, ASD, and partial or complete aberrant pulmonary venous return.

2.11 DIAGNOSING PULMONARY HYPERTENSION

2.11.1 Overview

The criteria for the diagnostic workup of patients with a clinical suspicion of PH remain unchanged. First, any patient with unexplained dyspnoea on exertion, syncope and indications of RV dysfunction should be suspected of having PH. Second, transthoracic echocardiography remains the most significant non-invasive screening method for diagnosing PH. However, it is still necessary to confirm the diagnosis of PH with RHC. Third, a diagnosis of PH necessitates the elimination of alternative causes of PH, requires expert knowledge, and should be undertaken at specialised facilities (Figure 1) (Barrier et al., 2012).

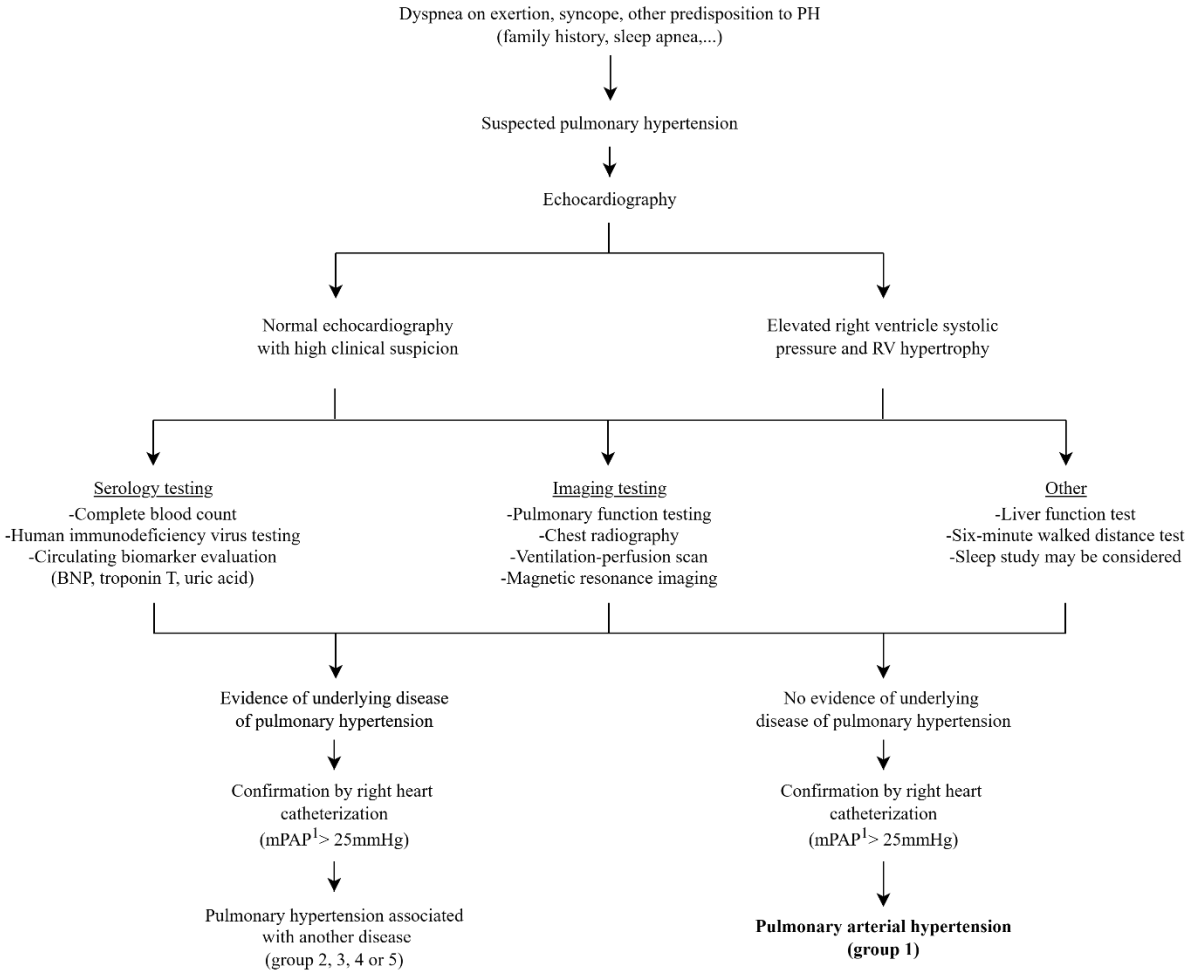

Figure 1: Investigating pulmonary hypertension (Barrier et al., 2012)

2.11.2 Clinical presentation

Patients could experience dyspnoea, chest discomfort, syncope or abrupt death (Oldroyd et al., 2024). Exercise intolerance is widespread in PH-CHD patients, with the vast majority falling into NYHA functional class II or higher (Barst et al., 2014). These findings do not generalise to both adults and children. Paediatric patients with PH-CHD have shorter six-minute walk distances and worse NYHA function categories.

2.11.2.1 New York Heart Association functional class

NYHA functional classes help to identify congestive heart failure patients based on their symptoms (Table 3) (Ford et al., 2015).

Table 3: New York Heart Association grading of symptoms in chronic heart failure

NYHA Class	Patient symptoms
Class I	No limitation on physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.
Class II	Slight limitation on physical activity.Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnoea.
Class III	Marked limitation on physical activity.Comfortable at rest but less than ordinary activity results in fatigue, palpitation or dyspnoea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

2.11.2.2 Six-minute walk test

The Borg Score should be used at the end of the 6MWT to assess the level of effort (Ekström et al., 2023). A patient's baseline six-minute walk distance predicts survival, but changes in the distance do not correlate with outcomes for PH patients (Farber et al., 2015). Gender, age, height, weight, comorbidities, oxygen need, learning curve and motivation affect the six-minute walking distance. Test results are usually published as absolute numbers rather than percentages expected. Absolute values, not fluctuations in six-minute walk distance, provide predictive information, although no single threshold applies to all patients (Savarese et al., 2012).

Peripheral O_2 measurements and heart rate response may improve prognostic relevance, although these findings must be independently validated (Matos Casano and Anjum, 2023). Several studies used six-minute walk distance with cardiac index and echocardiography to assess PH therapy response (Lahm et al., 2018). A six-minute walk distance of more than 440 m has been used to test the PH treatment response (McLaughlin et al., 2020), though the distance has yet to be extensively validated for patients with PH other than idiopathic PH (Demir and Küçükoğlu, 2015).

2.11.3 Electrocardiogram

Electrocardiography can be used to diagnose and monitor patients with PH-CHD (Sattar and Chhabra, 2023). The ECG may reveal signs of PH, although a normal ECG does not rule out the diagnosis. An abnormal ECG is more likely to indicate severe rather than mild or moderate PH (Sun et al., 2012). Abnormal ECG findings may include P-pulmonale, right axis deviation, RV hypertrophy, RV strain, right bundle branch block and corrected QT interval prolongation.

RV strain is a more sensitive screening tool than RV hypertrophy, which has low sensitivity (55% and 70% specificity). Prolongation of the ventricular depolarisation complex and corrected QT interval indicate severe disease (Bhattacharya et al., 2024).

Electrocardiography differential diagnosis includes anterolateral myocardial ischaemia. Compared to PH, ECG abnormalities in ischemia are more likely to affect the lateral and inferior leads. When leads are present in the anterior chest, they are typically associated with a Q wave in V1–V3 and rarely cause right axis deviation (Bansal et al., 2024). Supraventricular arrhythmias, notably atrial flutter and atrial fibrillation, can appear in advanced illness, with a cumulative incidence of 25% in individuals after five years. Atrial arrhythmias compromise cardiac output and almost always result in additional clinical deterioration. Ventricular arrhythmias are uncommon in patients diagnosed with PH (Olsson et al., 2013).

2.11.4 Echocardiography

Echocardiography is a non-invasive procedure to assess heart function and structures, though echocardiography cannot be used to diagnose patients with PH. It can only be used as a screening tool for patients with suspected PH, which must be confirmed by RHC (El-Korashy et al., 2014). Echocardiography is an important screening tool for symptomatic patients with PH. It offers an estimate of PAP at rest or during exercise. As an imaging modality, it has the advantages of being widely available, inexpensive and safe. It also helps to assess outcomes, monitor the efficacy of specific therapeutic interventions for PH, and diagnose the disease in its early stages (Bossone et al., 2013).

2.11.4.1 Difficulty of assessing pulmonary hypertension

The complex pyramidal shape, the retrosternal position of the RV design, and the load-dependent nature of RV functional indicators make assessment difficult (Bossone et al., 2013). The pressure gradient between the RV and right atrium (RA) is quantified using continuous wave Doppler assessment of the tricuspid regurgitation (TR) jet. The pressure difference is calculated using the simplified Bernoulli equation ($P = 4[TR_{max}]^2$) and peak TR velocity (Jang and Shin, 2020).

Right atrial pressure has traditionally been determined by adding the size and distensibility of the inferior vena cava (IVC) during inspiration at rest and forced inhalation to the peak TR velocity (Parasuraman et al., 2016). However, the most recent European Society of Cardiology

guidelines recommend using only the TR_{max} without additional right atrial pressure, as IVC assessment is prone to error (Galiè et al., 2016).

A compensated RV may have a lower TR (due to increased ventricular pressure), resulting in an underestimation of pulmonary artery systolic pressure (PASP). Similarly, high TR can cause equalisation of right atrial and ventricular pressures, resulting in a short TR Doppler envelope and an underestimation of PASP (Rudski et al., 2010). Right atrial pressure is typically overstated when IVC measures are used, leading to overestimating PASP (Augustine et al., 2018). Calculations based on the TR trace assume no pulmonary valve stenosis and may be incorrect in RV systolic failure. TR signal may be low in some lung disease patients, and TR_{max} measurement should be avoided without a good Doppler envelope (Taleb et al., 2013).

2.11.4.2 Right ventricle function

Multiple echocardiographic indices make evaluating RV systolic function more accurate, and the preferred integrative approach is to use a combination of parameters. The RV systolic function uses various measures, including tricuspid annular plane systolic excursion (TAPSE), tricuspid annular velocity, and right ventricular myocardial performance index (RVMPI) (Modin et al., 2019).

a) Tricuspid annular plane systolic excursion

The TAPSE is a simple method for assessing RV longitudinal function. It is measured using M-mode echocardiography, with the cursor placed adequately along the tricuspid lateral annulus in the apical four-chamber view. Although this index primarily measures RV longitudinal function, it correlates strongly with metrics that estimate RV global systolic function, such as radionuclide-derived RV ejection fraction (EF), 2D echocardiographic RV fractional area change, and 2D echocardiographic EF. TAPSE, as one-dimensional assessment relative to the transducer position, has the potential to over- or underestimate RV function due to cardiac translation. Often, TAPSE readings of less than 17 mm indicate RV systolic dysfunction, with slight differences depending on gender and body surface area (Sun et al., 2016). This approach is significantly associated with radionuclide angiography right ventricular ejection fraction (RVEF) but correlates poorly with magnetic resonance imaging (MRI) (Zháo et al., 2015). Although quick and easy, it is a one-dimensional method that primarily represents regional (basal) RV systolic performance. The evaluation of RV outflow tract fractional shortening may offer value to TAPSE. Right ventricular fractional area

shortening is defined as the percentage change in RV chamber area in an apical four-chamber image during the cardiac cycle, and it correlates well with MRI (Wu and Takeuchi, 2018).

b) Tricuspid annular velocity

Tricuspid annular velocity (S') is simple to measure, dependable, and reproducible. It has been shown to correlate well with other measures of global RV systolic function. The tissue Doppler imaging (TDI) of the tricuspid annulus correlates well with the RVEF measured by radionuclide angiography. A S' value of less than 9.7 cm/s indicates aberrant RV contractility and may help to make an early diagnosis of RV dysfunction. Tricuspid annular velocity is also lower in idiopathic PH patients than in healthy controls and is inversely associated with PAPs and resistance (Ryan et al., 2015). Myocardial acceleration during isovolumetric contraction is a novel global RV systolic function parameter that is determined by dividing the maximal isovolumetric myocardial velocity by the time-to-peak velocity.

Tricuspid annular velocity is less load-dependent than previous techniques. In terms of RV diastolic function, TDI may be a valuable modality when paired with pulsed wave Doppler study of the tricuspid input to quantify the early to atrial filling velocity ratio (E/A), mitral annular early diastolic velocity (E/E'), and E'/A' ratios (Zaidi et al., 2020). When corrected for heart rate, isovolumetric relaxation time is a straightforward approach to estimating systolic PAP, and it has been demonstrated to increase progressively in the presence of PH. However, results should be viewed cautiously when RV function is reduced (Meinel et al., 2020).

c) Right ventricular myocardial performance index

Right ventricular myocardial performance index (RVMPI) is a measure of global RV performance. The isovolumic contraction time, isovolumic relaxation time and ejection time intervals should all be taken from the same heartbeat. They use either pulse wave spectral Doppler or Doppler tissue imaging velocity of the lateral tricuspid annulus. When utilising pulse wave spectral Doppler to calculate RVMPI, the nonconsecutive beats must have equal RR intervals (time between 2 consecutive R waves). This constraint does not apply to Doppler tissue imaging-based RVMPI assessments. Right ventricular myocardial performance index can be deceptively low in situations linked to high RA pressures, resulting in a shorter isovolemic relaxation time. Right ventricular myocardial performance index > 0.43 on pulse wave Doppler and > 0.54 on Doppler tissue imaging indicates RV dysfunction (Modin et al., 2019). The Tei index has been found to have a significant association with RV ejection fraction

using nuclear ventriculography and to be less affected by loading conditions or heart rate (Song et al., 2015).

The Tei index was first used in the 1990s as a Doppler-derived metric of ventricular function. The combination of TR measured by PASP (≥ 35 mmHg) and Tei index (> 36 mmHg) increases echocardiographic sensitivity for diagnosing PH. The method was tested on small groups of patients but has not yet been verified in larger populations. However, the Tei index is prognostic in individuals with PH (Parasuraman et al., 2016).

2.11.4.3 Left ventricle function

Eccentric remodelling and contractile failure of the right heart in individuals with PH significantly impact the LV by impairing its geometry, structure and function (Chua et al., 2013).

The interdependence of the heart's left and right sides is determined by shared myocardium (septum) and pericardial constraint. The serial structure of the circulatory system, the RV strain, affects the LV directly.

Increased RV size and pressure cause a mechanical septal leftward shift, resulting in LV compression (Chua et al., 2013), as seen by paradoxical septal movement, a "D-shaped" LV, and an increased LV eccentricity index. Low stroke volume and cardiac output due to RV dysfunction may contribute to LV underfilling, especially during exercise (Gorter et al., 2018). Diastolic ventricular interaction is significant in PH/RV failure because right heart overload and pericardial constraint can raise left heart filling pressures even when LV preload is low and the LV is underfilled (Borlaug and Reddy, 2019). The LV function is evaluated using the parameters explained in subsections a) to c).

a) Teicholz method M-mode echocardiography

The EF measurement has historically been accomplished using the modified Simpson EF; the Teicholz formula is based on M-mode imaging or the disc approach (Bayram et al., 2018). The visual EF measurement correlates well with all previous formal approaches and has the advantage of being quick and straightforward to execute. A comparison of M-mode echocardiography with Simpson EF radionuclide ventriculography reveals that the M-mode approach had a more significant overestimation rate (10%) than the other method (Mohsen et al., 2024). In another investigation, the M-mode approach correlated well with radionuclide

ventriculography without wall motion disturbance. The M-mode had the lowest correlation and had a more significant overestimation rate than the other two techniques (Ryding, 2013).

Another study compared the visual EF and Simpson EF to radionuclide ventriculography and found that the visual EF had a stronger correlation. However, if echogenicity is low and the ventricular wall contours cannot be detected, the Simpson EF may need to be adjusted. Furthermore, while the Simpson EF demonstrated a stronger connection with radionuclide ventriculography than the visual EF assessment, it proved disadvantageous because of picture quality and ventricular measurement failure for some patients. Nonetheless, the Simpson EF had the strongest association with the strain parameter (Kalam et al., 2014).

b) Mitral annular plane systolic excursion LV function

Zidan and Helmy (2016) found that mitral annular plane systolic excursion detection is a more efficient and time-saving method for determining left ventricular ejection fraction (LVEF) in obese mechanically ventilated patients than the eyeball method. It can also evaluate diastolic function, such as in obese adults with normal LVEF. Furthermore, even when done by an unskilled observer, MAPSE assessments proved to be a reliable predictor of EF (Matos et al., 2012). Other investigations found good relationships between MAPSE and other LV assessment methods, including three-dimensional echocardiography or MRI (Cirin et al., 2024). A fully automatic approach for detecting LV failure using MAPSE measures was recently published (Grue et al., 2018). Furthermore, cardiac biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP), galectin-3, and high-sensitivity troponin T and I correspond to cardiac MRI-derived MAPSE (Kim et al., 2016). Finally, MAPSE was demonstrated to be a useful prediction method (Agha et al., 2016).

c) Left ventricle myocardial performance index

Doppler echocardiography measures Doppler time intervals, which are the sum of isovolumic contraction time and isovolumic relaxation time. The “a” interval, which represents the period between the end of outflow tract flow and the start of AV valve inflow, equals the total of isovolumic contraction time, ejection time (ET), and isovolumic relaxation time. The “b” interval, representing the ET, is calculated using the ventricular outflow Doppler velocity profile. The sum of isovolumic contraction time and isovolumic relaxation time will be obtained by subtracting ET (b) from the “a” interval (Goroshi and Chand, 2016). Patients with PH, in particular, experience impairments in LV systolic and diastolic functions. This impairment is independently associated with PASP and RVMPI (Perez et al., 2012).

2.11.4.4 Haemodynamic effects on the left ventricles in children with pulmonary hypertension

In patients with severe PH, there are notable changes, such as a leftward shift of the septum and prolonged RV systole, which are known to affect LV diastole. These changes were found to be exacerbated in this patient group. Notably, no significant differences in diastolic measures of patients with and without shunts are reported. However, slight differences were observed for patients with and without CHD. Several echocardiographic LV diastolic measures indicate a weak to moderate relationship with the severity of PH as determined through invasive methods, as well as with the leftward septal shift and prolonged RV systole. Invasive haemodynamics, the leftward shift of the septum and prolonged RV systole are linked to LV diastolic dysfunction in paediatric patients with PH. This is most consistent with findings of poor relaxation and reduced myocardial deformation (Burkett et al., 2016).

2.11.4.5 Assessment of pulmonary artery pressure

a) Pulmonary artery systolic pressure by tricuspid regurgitation peak velocity

The RV and RA pressure difference is measured using continuous wave Doppler on the TR trace. The simplified Bernoulli equation ($P = 4[TR_{max}]^2$) is used to compute the pressure difference using peak TR velocity. This approach corresponds well with PASP during right cardiac catheterisation. A maximum TR velocity of ≤ 2.8 m/s is deemed normal (Parasuraman et al., 2016).

b) Right ventricular free wall strain systolic maximal velocity

This approach corresponds well with TR-measured PASP. It has yet to be validated entirely against the gold standard, which is invasive RHC. Although the approach aids in identifying people with PH, it cannot correctly assess the amount of PAP. The sector width must be reduced to achieve the highest possible TDI frame rate. An RV-focused apical four-chamber view may decrease the incident angle on the tissue Doppler. An enormous pulse gate could offer a more comprehensive signal by capturing some myocardium during annular descent (Parasuraman et al., 2016).

2.11.5 Right heart catheterisation

Right heart catheterisation is used to diagnose and monitor PAP (El-Korashy et al., 2014). The mPAP of ≥ 25 mmHg during RHC confirms the diagnosis of PH. Haemodynamic evaluation with cardiac catheterisation and acute vasodilator testing is a critical component and the gold standard in the PH patient's initial diagnosis, with the added benefit of serial disease assessment. Cardiac catheterisation can be utilised to identify the severity of the PH. It can also be used to evaluate the operability of heart defects and whether a transplant is required (Frank and Hanna, 2015).

During RHC, the hemodynamic measurements include blood gas analysis with venous and arterial oxygen saturations, systemic and PAP, pulmonary capillary wedge pressure or left atrial pressure and RA pressure, and pulmonary blood flow computation using Fick's equation or a thermodilution catheter (Rosenkranz and Preston, 2015). Acute vasoreactivity testing is crucial for predicting patient response to vasodilator medication; however, calcium channel blockers are rarely effective in PH-CHD patients. Tests should involve the delivery of oxygen, nitric oxide and/or prostacyclins (Frank and Hanna, 2015).

Although cardiac catheterisation represents an anaesthetic and procedural risk for all PH patients, the incidence of catastrophic events has decreased in recent years, as most catheterisations are performed at specialised facilities. A recent single-centre study reports an overall complication rate of 5.7%, a major complication rate of only 1.2% and a catheterisation-related death rate of 0.2% (Zuckerman et al., 2013).

Right heart catheterisation in patients with PH can be technically challenging and carries inherent risks. It has been associated with severe and, at times, fatal complications. These complications may include bruising, bleeding, heart attacks, strokes, damage to the pulmonary artery or heart and injury at the site where the catheter was inserted. Additionally, patients may experience irregular heart rhythms (arrhythmias), allergic reactions to the dye or medication used, kidney damage, infections and blood clots. As a result, this invasive diagnostic method should only be conducted by specialists (Rosenkranz and Preston, 2015).

2.11.6 Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging offers characteristics that make it ideal for capturing the anatomical complexity of the RV. It is the gold standard for determining ventricular volume, mass, shape and function. It is non-invasive, uses non-toxic contrast chemicals, and does not

use ionising radiation. Furthermore, CMRI produces high-resolution, three-dimensional pictures, which reduces the geometrical assumptions required in specific echocardiography calculations (Peacock et al., 2013). However, CMRI has some drawbacks, including a higher cost, limited availability compared to other approaches, more comprehensive and time-consuming investigation, and the need for extensive technical support and experience. Furthermore, CMRI is incompatible with pacemakers and infusion pumps, and PH patients may have difficulty holding their breath. However, considering the importance of the right heart in PH, the benefits of monitoring patients with established PH and evaluating treatment response in clinical trials may exceed the drawbacks (Fagiry et al., 2021).

Cardiac magnetic resonance imaging is a relatively new imaging tool that is used instead of echocardiography to diagnose and assess PH. As procedures improve and new markers emerge, it is expected that CMRI will become an important monitoring tool for clinicians in clinical practice. However, to increase the application of CMRI in PH patients, CMRI variables must be standardised and validated, and treatment time and cost need to be reduced (Aryal et al., 2020).

2.11.6.1 Right ventricular ejection fraction as a prognostic factor

Right ventricular ejection fraction is emerging as an important CMRI-based prognostic measure for PH patients (Peacock et al., 2013). Van de Veerdonk et al. (2011) state that RVEF predicts death more accurately than PVR. According to this investigation, changes in PVR after therapy were only modestly linked with changes in RVEF and had no effect on the outcome, whereas RVEF changes were independently associated with death. Overall, 25% of individuals in this study who had lower PVR after treatment showed a decline in RVEF, which demonstrates that medication-induced PVR changes do not always influence RV function. Despite improvements in PVR, patients with worsening RVEF had a poor prognosis, which emphasises the significance of monitoring RV function throughout the disease (Van de Veerdonk et al., 2011).

2.11.6.2 Comparison of echocardiography, right heart catheterisation, and cardiac magnetic resonance imaging in pulmonary hypertension

It has been found that MRI offers the highest sensitivity and specificity for diagnosing conditions related to PH, with values of 0.92 (95% confidence interval (CI) 0.88–0.96) and 0.86 (95% CI 0.77–0.95), respectively. In comparison, computerised tomography has values

of 0.79 (95% CI, 0.72–0.89) and 0.82 (95% CI, 0.76–0.92), while transthoracic echocardiography has values of 0.85 (95% CI, 0.83–0.91) and 0.71 (95% CI, 0.61–0.84). Magnetic resonance imaging has the potential to function as a surrogate technology for RHC in the diagnosis of PH (Ullah et al., 2020).

2.11.7 Nuclear ventriculography

Nuclear technologies offer several benefits, including eliminating geometric assumptions for count-based RVEF measurement methods, a high contrast-to-noise ratio, and the ability to simultaneously assess pulmonary ventilation and perfusion (V/Q scan). The main disadvantages include low spatial resolution, relatively long imaging periods, and the necessity for radioisotopes. Many facilities now use alternate modalities for RV evaluation, such as echocardiography or MRI, which do not require ionising radiation and have higher resolution (Sanz et al., 2010). First-pass radionuclide ventriculography uses a gamma camera to detect and quantify the passage of a tracer bolus through the RV. The chosen agent is technetium-99mTc-diethylenetriaminepentaacetic acid, which has a high renal clearance rate, requires less patient irradiation, and enables faster study repeat, if necessary. A good bolus injection is essential for obtaining adequate RV counts, which influences the proper determination of RV ejection percentage. The usual percentage used is 52%, with a lower limit of 40 % (Bodar and Modi, 2023).

Although nuclear ventriculography is limited by imaging in a single plane, it offers good separation of the RV and RA, correlates well with right cardiac catheterisation and MRI (although with significant limitations of agreement), and is recognised as the optimum nuclear technique for RV assessment (Das et al., 2023).

2.11.7.1 Tricuspid annular motion

As evaluated by radionuclide angiography, TAPSE strongly correlates with RVEF. It serves as an echocardiographic measure of RV function and has been proposed to overcome the difficulty of distinguishing the RV endocardium while avoiding geometric assumptions. It is defined as the distance of systolic excursion of the RV annular segment along its longitudinal plane as measured from the tricuspid lateral annulus. Multiple investigations have confirmed the link between TAPSE and RVEF in echocardiography and cardiac MRI. According to the findings, indices obtained from tricuspid annular motion appear to be valuable tools for monitoring RV systolic function (Eldamanhory et al., 2023).

2.11.7.2 Myocardial performance index

Relationship between RV systolic function and LVEF in hypertensive heart failure patients. Right ventricular MPI has been shown to correlate with RVEF derived from radionuclide studies. It strongly predicts clinical status and survival in patients with PH (Atendi et al., 2023). The LV Tei index has also been extensively studied in patients with heart failure (Ogunmola et al., 2013). These measurements primarily relate to RV systolic function, while the MPI combines systolic and diastolic functional measurements.

2.11.7.3 Right ventricular diastolic function

Routine echocardiograms should assess RV diastolic function, particularly when diastolic failure could decrease systolic function, such as pulmonary arterial hypertension (Shiina et al., 2009).

Diastolic dysfunction in patients with tetralogy of Fallot is associated with a higher risk of re-interventions, including RV dilation (Maskatia et al., 2015).

Right ventricular diastolic function can be assessed using several techniques. Doppler interrogation of tricuspid inflow, tissue Doppler analysis of the lateral tricuspid valve annulus, Doppler examination of the hepatic veins, evaluation of the RA, and measurement of the size and collapsibility of the IVC. Given the different diastole phases, evaluating diastolic function using multiple criteria is essential. Doppler signals should, ideally, be obtained at the end of exhalation during quiet breathing, although this can be challenging for children. As an alternative, measuring five to seven beats can help account for the effects of breathing on inflow velocities (DiLorenzo et al., 2015).

Right ventricular diastolic dysfunction can result in increased pressures in the RA. Consequently, the IVC may become less collapsible or may even appear to disappear entirely. This condition can be easily diagnosed using two-dimensional imaging or M-mode assessment of the caval vein. Impaired compliance of the RV and elevated end-diastolic pressures may lead to flow reversal in the hepatic and/or IVC due to atrial contraction (Hussain et al., 2024).

2.12 DIAGNOSTIC CHALLENGES OF PULMONARY HYPERTENSION IN SOUTH AFRICA

2.12.1 Shortage of resources in sub-Saharan Africa

Right heart catheterisation is invasive, costly, time-consuming, and necessitates specialist knowledge. Consequently, it is only available in a few African countries. Given these challenges, transthoracic echocardiography has been advocated as the primary diagnostic tool for PH in middle- and low-income countries (Hasan et al., 2020). The recently updated paediatric PH guidelines prioritise clinical diagnosis. Pulmonary hypertension is associated with fatigue, body oedema, dyspnoea and clinical symptoms such as hypoxia, cyanosis, RV heave and an enhanced pulmonary component (Myers et al., 2014). In addition, 2D echocardiography, ECG, chest radiography and lung function tests may be used.

Unfortunately, in Africa, invasive procedures such as RHC, ventilation/perfusion scan, advanced high-resonance computerised tomography and CMRI are not always routinely available (Hansmann et al., 2019).

Unrepaired CHD is a leading cause of PH. Correction of CHD in early infancy is not possible in resource-constrained settings, for a variety of reasons, including delayed detection due to a scarcity of paediatric cardiology specialists on the African continent and a lack of infrastructure such as operating rooms and catheterisation laboratories, which are required to perform lesion correction (Zuechner et al., 2019). The majority of lesions in the Ugandan CHD registry were only discovered after infancy and remained untreated for five years due to limited resources for diagnosis and surgery (Namuyonga et al., 2020). Uganda has only one cardiovascular centre that offers open-heart surgery and cardiac catheterisation. Lesions such as ASDs, VSDs, and PDAs were among those diagnosed after the age of one year, with some cases presenting with complications, such as PH caused by delayed referral. Complex CHD usually necessitates international referral (Aliku et al., 2017).

2.12.2 Challenges related to access to genetic testing in Africa

Asymptomatic first-degree relatives of children with a genetic type of PH should be checked and monitored regularly using echocardiography (Hansmann et al., 2016). In general, several chromosomal defects increase the likelihood of PH developing. Children with Down syndrome, for example, are more prone to develop obstructive sleep apnoea and upper airway

obstruction, which exacerbate PH regardless of CHD, though it is primarily caused by lung parenchymal hypodevelopment. Unfortunately, genetic screening is not widely available in Africa, with only a few northern and southern African facilities providing this service. Hassan and colleagues conducted a study in Lebanon to investigate the genetic causes of PH and revealed bone morphogenetic protein receptor Type 2 gene mutations in 26% of idiopathic and CHD-PH patients (Hassan et al., 2018).

CHAPTER 3 – PAPER I

CLINICAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS OF PATIENTS PRESENTING WITH PULMONARY HYPERTENSION DUE TO CONGENITAL HEART DISEASE

MMF Henema[1,2] (MHSc), FE Smit[3] (PhD), SC Brown[4] (DMed), L Botes[2] (PhD)

[1]Department of Cardiology, Dr George Mukhari Academic Hospital, Pretoria, South Africa

[2]Department of Health Sciences, Faculty of Health and Environment Sciences, Central University of Technology, Bloemfontein, South Africa

[3]Department of Cardiothoracic Surgery, School of Medicine, Faculty of Health Science, University of the Free State, Bloemfontein, South Africa

[4]Division Pediatric & Congenital Cardiology, School of Medicine, Faculty of Health Science, University of the Free State, Bloemfontein, South Africa

ABSTRACT

Background: This study aimed to assess patients' clinical and echocardiographic features related to pulmonary hypertension resulting from congenital heart disease.

Methods: The main inclusion criterion was a mean pulmonary arterial pressure ≥ 25 mmHg measured at right heart catheterisation. All patients underwent clinical examination, electrocardiography, transthoracic echocardiogram and a six-minute walk test.

Results: In total 75 patients with a median age of 9.98 years (IQR 7.97–17.1 years) were included in the study. Simple ventricular septal defect was the most common lesion. The

median mean pulmonary artery pressure on right heart catheterisation was 52 mmHg (IQR 49−67 mmHg). Right ventricle dysfunction was observed in all patients and confirmed by prolonged right ventricular myocardial performance index, reduced tricuspid annular velocity, decreased tricuspid annular plane systolic excursion, and impaired calculated right ventricular free wall strain. The pulmonary valve annulus was markedly dilated in all patients, evidenced by a median z-score of 4.23. The combination of using the right ventricular systolic pressure (RVSP) of more than 50 mmHg plus a pulmonary annulus z-score of more than 3 to predict pulmonary vascular resistance of more than 3 Wood units.m² had a high sensitivity of 82.4% but a low specificity of 14.3%.

Conclusion: Our patients exhibited dilation on the right side, especially the pulmonary arteries, which could be an early warning for pulmonary hypertension. An elevated peak RVSP and a dilated pulmonary artery should alert physicians to the possibility of pulmonary hypertension. An echocardiogram should only be used as a screening tool for diagnosing pulmonary hypertension.

Keywords: Pulmonary hypertension, congenital heart disease, echocardiography, right heart catheterisation

INTRODUCTION

Congenital heart disease (CHD) is one of the most common birth abnormalities; it affects around one in every 100 children.[1] Early treatment of congenital cardiac defects usually prevents the development of pulmonary vascular disease.[2] Thus, pulmonary vascular disease associated with CHD is uncommon in children in nations with well-organised referral systems, early detection and timely surgical intervention. However, pulmonary vascular disease often occurs in individuals with CHD.[3] In total 80% of the world population lives outside wealthy countries; of these people, only 2% to 15% of those with significant intracardiac or extracardiac shunt lesions receive curative therapy.[4] Unoperated patients who are potentially operable face a high risk of developing pulmonary hypertension (PH).[5]

In high-income countries, and as reported by registries of France and Scotland, the frequency of CHD-related pulmonary vascular disease in European adults ranges between 1.6 and 12.5 cases per million individuals, with 25% to 50% of these patients being diagnosed with Eisenmenger syndrome with shunt reversal.[6] A complex combination of environmental, genetic and socioeconomic factors causes the development of pulmonary vascular disease

associated with CHD. The most critical factor in the global distribution of irreversible pulmonary vascular disease due to CHD is a lack of access to medical treatment. The unsettling reality is that developed countries carry only 12% of the global burden of all causes of death and disability, yet account for 90% of global healthcare spending.[7]

There is currently no data available for Africa that accurately estimate the number of children with CHD who are at risk of developing pulmonary vascular disease. Unrepaired CHD is a significant cause of PH. Correction of CHD in early infancy is often not feasible in resource-limited settings, for various reasons, including delayed detection due to a shortage of paediatric cardiology specialists and a lack of infrastructure, such as operating rooms and catheterisation laboratories, to perform corrective procedures.

A Ugandan CHD registry reports on all lesions that were diagnosed and detected after infancy and left untreated for up to five years due to limited resources for diagnosis and surgery.[8,9] Congenital cardiac conditions, such as ventricular septal defects (VSDs), atrial septal defects (ASDs), and patent ductus arteriosus (PDA) were among the conditions detected after one year of age.[8] Some patients experience complications from delayed surgery, such as PH; complicated CHD cases often require transfer abroad for treatment.[9] Children with large shunts, such as ASDs, VSDs, PDA, and cyanotic heart lesions that increase pulmonary blood flow, are more likely to develop PH if not treated early on; this, in turn, can trigger a cascade of events leading to increased pulmonary vascular resistance (PVR).[10] Shunt lesions increase pulmonary blood flow, causing shear stresses, inflammation, thrombosis, endothelial dysfunction, vascular remodelling, pulmonary hyperreactivity and fibrosis. Pulmonary hypertension is more likely to develop in people with VSDs, followed by those with large ASDs. In Africa's Pan African Pulmonary Hypertension Cohort trial, more than half the children developed PH secondary to CHD.[11]

To the best of our knowledge, limited data exist that demonstrate right heart function in patients with PH because of CHD. Furthermore, there is limited data available in South Africa regarding assessment of functional impairment of groups of children. Therefore, this study aimed to assess the clinical and echocardiographic features of a group of patients who presented with PH due to CHD.

METHODS

Study design, setting and population

This prospective, observational study of patients older than 6 years with PH resulting from CHD was conducted at the cardiology unit of Dr George Mukhari Hospital, Gauteng, South Africa, from 1 December 2022 to 30 November 2023.

Inclusion and exclusion criteria for the study participants were as follows:

- The main inclusion criterion was that patients had to have a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at cardiac catheterisation.
- Cardiac patients with cyanotic CHD and those with PH not related to CHD (e.g., rheumatic heart disease, chronic obstructive pulmonary disease, primary PH were excluded, as were critically ill and unstable patients with PH. Patients with poor echocardiographic images or incomplete data sets were also excluded.

Data collection

Demographic (age in years, sex, ethnicity, geographical location) and anthropometric data (height in cm and weight in kg) were recorded, as were the types of congenital lesions and New York Heart Association (NYHA) functional class.

A standard 12-lead electrocardiogram (ECG) was done using a Nihon Kohden Cardiofax ECG apparatus. A detailed echocardiographic study was performed using GE Medical Vivid E9 ultrasound equipment with an M5SC phased array transducer. Patients were referred for cardiac catheterisation if the screening echocardiogram's right ventricular systolic pressure (RVSP) was ≥ 25 mmHg. The techniques and measurements used were according to the British Society of Echocardiography guidelines and the European Association of Cardiovascular Imaging for adults and paediatric patients.[12,13] Three cardiac technologists performed the echocardiographic examinations. Before the study commenced, interobserver variability was addressed by retraining all echocardiographers. The attending cardiologist reviewed each echocardiographic report.

The six-minute walk test (6MWT) was performed according to the American Thoracic Society guidelines.[14] Cardiac catheterisation was done according to the Accreditation for Cardiovascular Excellence Standards for Pediatric and/or Congenital Cardiac Catheterisation Laboratory Accreditation.[15] Catheterisation was conducted under general anaesthesia.

Patients were intubated and received room air, and the following drugs were administered as per standard operating procedure: Ketamine 1–2 mg/kg, Isoflurane, Midazolam 0.05 mg/kg and Dexmedetomidine hydrochloride 0.2–0.7 µg/kg.[16] Pulmonary vasoreactivity testing was done by giving 100% oxygen for 10 minutes.[17]

Definitions

Body mass index (BMI): BMI represented the key index for relating weight to height and was calculated as body weight in kilograms divided by height squared in meters.[18]

NHYA classification: This classification system provides a simple way of classifying the extent of heart failure.[19]

Right ventricular hypertrophy: Dominant R-wave in V1 > 7 mm tall**,** dominant S wave in V5 or V6 > 7 mm deep.[20]

Left ventricular hypertrophy: Sokolow and Lyon index SV1 + RV5|V6 ≥ 35 mm < 20 yrs**,** Cornell criteria RaVL + 5V3 > 28 mm in men > 20 mm in women > 20 yrs.[20]

Right atrium enlargement: P-wave in lead II > 2.5 mm and or > 1.5 mm in V1.[21]

Left atrium enlargement: P-wave duration ≥ 0.12 sec in lead II. Notched P-wave ≥ 0.04 sec in lead V1.[22]

Right ventricular systolic pressure: Diagnosed using echocardiographic measurement of peak tricuspid regurgitation velocity and modified Bernoulli equation.[23] In adults, the inferior vena cava (IVC) was considered dilated if it measured more than 21 mm, was distended, had a collapsibility of less than 50%, and 10 mmHg was added. In children under 12 years, the IVC was considered dilated if it measured more than 14 mm, was distended, had a collapsibility of less than 50%, and 10 mmHg was added. Patients were sent for cardiac catheterisation if right ventricular peak systolic pressure was ≥ 40 mmHg. Pulmonary hypertension was classified as mild (40–50 mmHg), moderate (51–60 mmHg) or severe PH (≥ 60 mmHg).[24]

Inferior vena cava measurements: Measurement was performed in a subcostal long-axis view perpendicular to the IVC with the patient supine at 1.0 to 2.0 cm from the junction with the right atrium.[25]

Pulmonary regurgitant fraction: Regurgitant fraction = Jet width/Right ventricle outflow tract diameter × 100%. Regurgitant fraction was classified as mild < 20%, moderate 20–40% or severe > 40%.[26]

Tricuspid annular plane systolic excursion (TAPSE): Pertains to the systolic longitudinal displacement of the lateral tricuspid annulus towards the apex.[27]

Pulmonary vascular resistance (PVR): Calculated using mean pulmonary artery pressure (PAP) - mean left atrium pressure OR left ventricle end-diastolic pressure OR wedge/ pulmonary circulation.[28]

Right ventricle free wall strain: Calculated using tissue Doppler imaging on the right ventricle free wall in the apical four-chamber view to measure the tricuspid annular systolic myocardial (Sm) velocity. The maximum systolic myocardial velocity and systolic myocardial velocity time (SmVTI) are then measured. Systolic velocity <12 cm/s and SmVTI < 2.5 are indicators of excessive pulmonary artery systolic pressure (PASP).[29]

Ethics and statistical analysis

Ethics approval was obtained from the Health Sciences Research Ethics Committee of the University of the Free State (UFS-HSD2022/0300/3008-0005) and the Gauteng Department of Health. Only patients who provided informed consent and assent by the patient themselves or their guardians were included in the study.

Data analysis was performed by a biostatistician using R Statistical computing software of the R Core Team 2020, version 3.6.3. Raw data were captured on Excel spreadsheets. A *t*-test was conducted to compare normally distributed data. Nonparametric data were compared using a Mann-Whitney U test. Where required, a chi-square test or Fisher's exact test was utilised for comparisons. A *p*-value of less than .05 was considered to be statistically significant.

RESULTS

Demographic, anthropometric and geographical location

A summary of the demographic and anthropometric data is presented in Table 1. We screened 85 patients, though n = 10 were excluded because of poor echocardiography images or incomplete datasets. Based on the inclusion criteria, only 75 patients could be included. The majority of the patients (73%) were between the ages of 6 and 17 years. Sex distribution was almost similar for male and female participants; they were predominantly African (75%). The median BMI for the population tended to be normal but low (18.9 kg/m^2). Thirty-one (41.3%) participants were undernourished with a BMI of less than 18.5 kg/m^2 (Table 1).

Table 1. Demographic and anthropometric data

Variable	n (%)	Median age (years)	Q1–Q3
Age (years)			
Total population	75	9.98	7.97–17.1
6–17 years	55 (73.3%)	8.69	7.21–11.4
18+ years	20 (26.7%)	18.6	17.9–20.2
Sex n (%)			
Total population	75		
Female	40 (53.3%)	10.9	7.99–17.3
Male	35 (46.7%)	9.98	8.00–16.1
Ethnicity n (%)			
Total population	75		
African	56 (75%)	11.0	8.23–17.2
Caucasian	9 (12.0%)	9.62	8.11–13.2
Mixed race	10 (13%)	7.97	6.96–11.8
BMI (kg/m^2)	75	18.9	16.7–20.9

[n, number of patients; %, percentage; Q1, 25th percentile; Q3, 75th percentile; BMI, body mass index]

The median distance travelled by patients to the treating facility (Dr George Mukhari hospital) was 17 km (Q1–Q3, 15.2–56.3 km). Almost two-thirds (n = 48) of the participants travelled less than 50 km, but some (n = 27) travelled up to 277 km from Polokwane to the treating facility.

Clinical data

Congenital heart defects

In the total study population, the most common congenital abnormality in combination with PH was simple VSD (41%) (Table 2). Atrioventricular septal defects (AVSD) and PDA were diagnosed at younger ages, while ASD tended to be present in older participants.

New York Heart Association functional class

All the patients were symptomatic: almost two-thirds (60%) were in NYHA functional class III, and 40% were in NYHA functional class II. Among those with VSD (41%), 29% were classified as NYHA functional class II, and 71% were in functional class III. In contrast, all patients with AVSD were classified as NYHA functional class III. In this study group, the younger and older patients were almost equally distributed (see Table 2).

Table 2. Congenital heart lesions

Variable	n (%)	Median age (years)	Q1-Q3	Lesions/age group		NYHA	
				Age 6–17 n (%)	Age 18+ n (%)	Class II n (%)	Class III n (%)
ASD	16 (21.3%)	17.1	14.2-18.1	7 (43.8%)	9 (56.3%)	10 (62.5%)	6 (37.5%)
AVSD	11 (14.7%)	13.7	9.92-17.1	8 (72.7%)	3 (27.3%)	-	11 (100%)
PDA	17 (22.7%)	8.11	6.87-9.62	16 (94.1%)	1 (5.9%)	11 (64.0%)	6 (35.2%)
VSD	31 (41.3%)	9.57	6.01-17.0	24 (77.4%)	7 (22.6%)	9 (29.0%)	22 (71.0%)
TOTAL	75 (100%)	-	-	55 (73%)	20 (27%)	-	-

[n, number of patients; %, percentage; Q1, 25th percentile; Q3, 75th percentile; ASD, atrial septal defect; AVSD, artiroventricular septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect; NYHA, New York Heart Association]

Electrocardiogram

The ECG results for all participants confirmed the presence of PH. All participants presented with right ventricular hypertrophy, a right ventricular strain pattern and P-pulmonale.

Transthoracic echocardiography

Right heart

The pulmonary valve annulus was markedly dilated in all participants, evidenced by a z-score of 4.23. Prolonged right ventricle myocardial performance index, reduced S', decreased tricuspid annular plane systolic excursion (TAPSE), and impaired calculated right ventricle free wall strain confirmed right ventricle dysfunction in all patients. The median RVSP/pulmonary artery systolic pressure by tricuspic regurgitation peak velocity was 75.0 mmHg (Table 3). In total 15 patients (20%) had moderate pulmonary regurgitation, and 60 patients (80%) had severe pulmonary regurgitation. The right heart was dilated, probably resulting in tricuspid regurgitation and a dilated tricuspid valve annulus with a median z-score of 2.44 (Table 3).

Table 3. Right heart echocardiographic characteristics of pulmonary hypertension due to congenital heart disease

Variable	Median	Q1–Q3
IVC (mm)	23.0	23.0–24.0
RA minor (mm)	28.0	26.0–29.0
RA minor width (BSA)	23.5	17.3–26.0
RA major (mm)	29.0	28.0–31.0
RA major length (BSA)	25.8	18.4–27.9
Tricuspid annulus (mm)	37.0	35.0–42.0
Tricuspid annulus in systole (z-score)	2.44	2.31–2.67
PA annulus (mm)	32.0	29.0–39.0
PA annulus (z-score)	4.23	3.60–4.75
RVSP/PASP by TR peak velocity (mmHg)	75.0	70.0–79.0
RVSP/PASP by TR mean velocity (mmHg)	38.0	36.0–39.0
TDI longitudinal right ventricle free wall strain SmVTI in (cm/sec) (< 2.5 cm/s, suggestive of elevated pulmonary artery systolic pressure)	1.48	1.43–1.58
TAPSE right ventricle function (mm)	9.00	8.00–10.0
TDI tricuspid annular velocity S' right ventricle function (cm/sec)	7.00	7.00–8.00
TDI MPI RV function	0.75	0.74–0.77

[n, number of patients; %, percentage; mm, millimeters; cm/s, centimetres per second; Q1, 25th percentile; Q3, 75th percentile ; IVC, inferior vena cava ;RA, right atrium; BSA, body surface area; RV ,right ventricle; PA, pulmonary artery; PR, pulmonary regurgitation; RVSP, right ventricular systolic pressure; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation; TDI, tissue Doppler imaging; TAPSE, tricuspid annular plane systolic excursion; S', lateral tricuspid annulus peak systolic velocity; MPI, myocardial performance index]

Six-minute walk test

The median six-minute walking distance was diminished in all patients. For patients aged 6−17 years, it was 248 m (Q1–Q3, 241–250 m); for those over 18 years, it was 290 m (Q1–Q3, 281−298 m).

Right heart catheterisation

The hemodynamic data for right heart catheterisation (RHC) indicated that the median mean pulmonary artery pressure (PAP) was 52 mmHg. The median aortic saturation was 95% on room air during cardiac catheterisation (Table 4). Even though the participants had significant pulmonary arterial hypertension, the vast majority of them still had a left–right shunt.

The median mean PAP decreased to 45 mmHg on oxygen after 10 minutes. The vasoreactivity test performed indicated that 70 participants (93%) had a vasoreactivity response (Table 4). After oxygen administration, the mean PAP was reduced by 10–20 mmHg, and the PVR decreased by 2–3 Wood unit.m². Five participants demonstrated no vasoreactivity; these

participants included AVSDs (n = 2), PVR of 6 and 5.5 Wood units.m², VSDs (n = 2) PVR of 5.7 and 6 Wood unit.m² and an ASD (n = 1) PVR of 6.2 Wood unit.m².

Table 4. Haemodynamic data from right heart catheterisation of pulmonary hypertension due to congenital heart disease

Variable	Room air			100% oxygen		
	n (%)	Median	Q1–Q3	n (%)	Median	Q1–Q3
mPAP (mmHg)	-	52.0	49.0–67.0	-	45.0	38.0–57.0
PAWP (mmHg)	-	13.0	12.0–16.0	-	6.00	5.00–7.00
Cardiac output (body surface area)	-	3.13	2.82–4.69	-	-	-
PVR (Wood unit .m²)						
< 4	8 (10.7%)	3.00	3.00–3.00	-	-	-
4–6	40 (53.3%)	4.70	4.00–5.00	-	-	-
> 6	27 (36.0%)	8.20	8.00-8.70	-	-	-
Qp:Qs	-	1.70	1.50–1.80	-	-	-
Aorta saturation (%)	-	95.0	95.0–96.0	-	100	-
Vasoreactivity test						
Vasoreactive	-	-	-	70 (93%)	-	-
Non-vasoreactive	-	-	-	5 (7%)	-	-

[n, number of patients; %, percentage; Q1, 25th percentile; Q3, 75th percentile; BSA, body surface area; RA, right atrium; RV, right ventricle; PAP, pulmonary artery pressure; Ao, aorta; PAWP, Pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; Qp:Qs: ratio of pulmonary blood flow (Qp) to systemic blood flow (Q)]

Correlation between echocardiographic and right heart catheterisation measurements

As expected, peak RVSP on the echocardiogram showed a strong positive correlation with systolic PAP on the RHC ($r = 0.9305$, $p < 0.001$, $r^2 = 86.5\%$). However, mean RVSP on the echocardiogram demonstrated a weak correlation with mean PAP on the RHC ($r = 0.1634$, $p = 0.161$, 95% CI = -0.066:0.3764). Both systolic and mean PAP on the RHC showed a good correlation with PVR ($r = 0.8929$, $p < 0.001$, 95% CI = 0.8351:0.9311), which is to be expected. Of note is that the specificity and sensitivity of predicting a PVR of more than 5 Wood unit.m² were low (59,7% and 66.7%, respectively).

The combination of using the RVSP of more than 50 mmHg plus pulmonary annulus z-score of more than 3 to predict PVR of more than 3 Wood unit.m² had a sensitivity of 82.4% but a low specificity, of 14.3%.

Lesion distribution and pulmonary vascular resistance Wood unit.m² room air

In total 36% of the participants had PVR of more than 6 Wood unit.m². In these patients, the most common lesions were VSD (n = 13, 48.1%), followed by PDA (n = 7, 25.9%) and ASD (n = 5, 18.5%) (Figure 1).

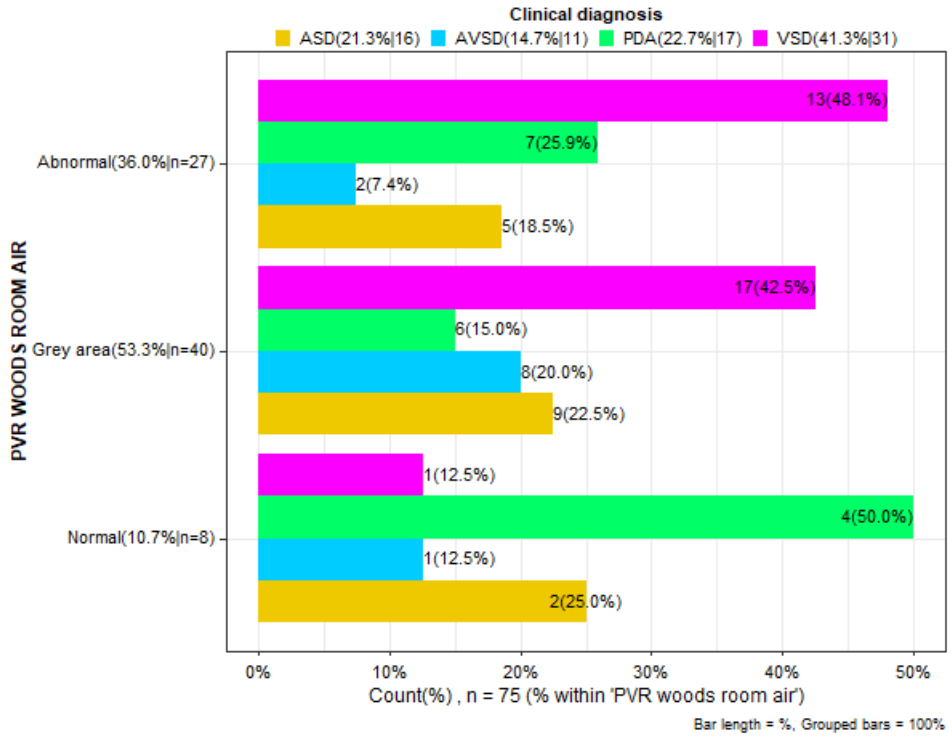

Fig. 1. Lesion distribution and pulmonary vascular resistance Wood unit.m² room air

DISCUSSION

To the best of our knowledge, limited data exist that describe the demographics of patients presenting with PH due to CHD in northern Gauteng.

Almost half the patients (41.3%) were undernourished (BMI ≤ 18.5 kg/m²), which suggests chronic PH and/or long-standing disease. This is concerning because other studies report that CHD is associated with high morbidity and mortality, especially among undernourished people.[30,31] Similar findings are described by Murni et al. who demonstrated in Indonesia that undernutrition was associated with PH.[32] Owing to our patients being undernourished, their growth and development might be impeded.

Our results show that the most common congenital abnormality that caused PH in almost half the patients was simple VSD, followed by PDA and ASD. These patients were being seen

for the first time and were over 6 years old – they should have been diagnosed much earlier. This is in contrast to the findings of a PH registry in Indonesia, where the predominant lesion (73.3%) was primarily in women aged 21–40 years.[33] Similarly, the Compera-CHD registry of 11 European countries reports that ASDs were the second-most-common condition in PH patients, who tended to be older (44 years).[34] Furthermore, a similar study on adults with PH found that VSD (29.3%) was the most common lesion, mostly in older patients (27.19 years).[35]

All our patients had functional impairment. In our cohort, patients with AVSDs and PH tended to be younger than the other groups and were all in NYHA functional class III, which suggests they became symptomatic early in childhood. In contrast, PH in patients with ASDs occurred at a notably older age compared to the other lesions. The older age of ASD patients with PH may indicate that they were missed during earlier screenings or were initially asymptomatic and only presented once they became symptomatic. Similarly, Vijarnsorn et al. report that ASDs with PH presented in late childhood and adolescence.[36] In the clinical pathophysiology of ASD, pulmonary hypercirculation and right heart volume overload induce PH after a longer time.

Dinarti et al. report that 43% of patients were in NYHA functional class II and were symptomatic.[33] Thienemann et al. concluded in the Pan African Pulmonary Hypertension Cohort registry for sub-Saharan Africa of 220 consecutive patients that 11 children (66%) were in NYHA functional class III–IV.[11] Our findings are supported further by the results of a study on PH in adults: Evaldsson et al. found that 87% of the patients were in NYHA functional class II–III.[37] These findings indicate that once PH is established in CHD, the majority of patients will present with signs of heart failure.[38]

Functional impairment in our patients was supported further by the fact that the walk test distance of the participants in our cohort was observably shorter than normal (400–700 m). This concurs with the results of Mansour et al., who report that adults with PH walked less than 300 m in six minutes.[35] Similarly, Thienemann et al. reported a median 6MWT distance of 252 m.[11] In contrast to McLaughlin et al.,[39] who used a six-minute walk distance of more than 440 m to test the PH treatment response, all our patients demonstrated functional impairment. Effort intolerance is a cardinal PH feature and strongly correlates with disease severity.[40]

Right heart catheterisation and pulmonary artery vasoreactivity testing

Pulmonary artery pressures in our PH groups B and C were substantially elevated; more than a third of the patients (36%) had a PVR > 6 Wood unit.m². In total 7% of participants

demonstrated no vasoreactivity response to oxygen administration, probably because of long-standing disease.[41] Not surprisingly, the systolic and mPAP during RHC correlated excellently with PVR during right heart catheterisation. However, the sensitivity/specificity of systolic and mPAP to predict PVR > 5 Woods unit.m^2 was not clinically helpful. Using a combination of pulmonary annular dilatation and RVSP was sensitive but not specific enough to predict a PVR of more than 3 Woods units.m^2.

Bobhate et al. conducted a similar study on catheterisation data in children with pulmonary hypertensive vascular disease, demonstrating that, at presentation, the mPAP was 43 mmHg and the mean PVR was 9.7 Wood unit.m^2.[42] Similarly, Ozek et al. revealed that the mPAP of children in Thailand with pulmonary arterial hypertension associated with CHD was 55.4 mmHg, and the median PVR was 9.1 Wood unit.m^2.[43] However, their group of patients already had Eisenmenger syndrome, unlike ours, which had aortic saturations of over 95% and lower PVR (Rp). It is evident that delayed diagnosis of PH will sentence children to irreversible PH,[44] emphasising the need to detect easily treatable conditions early on.

Correlation between echocardiographic and right catheterisation measurements

The peak RVSP, as determined by echocardiography, correlated strongly with systolic pulmonary artery pressure measured during right heart catheterisation, which indicates it can be used as a screening tool to predict systolic pulmonary pressure in patients with PH. Amelia et al. report on the role of echocardiography in evaluating patients with PH secondary to CHD and found a moderate correlation between the results of the two tests (r = 0.38, p =0.007).[45] However, they conclude that echocardiography remained inferior to cardiac catheterisation and should only be considered as an alternative method to screening for PH. In addition, Sonaglioni et al. report a moderate correlation between systolic and mPAPs estimated by transthoracic echocardiography and those evaluated by RHC (r = 0.65 and r = 0.60, respectively).[46]

Furthermore, in the first systematic and meta-analysis addressing the accuracy of echocardiograms, Janda et al. concluded that the correlation of systolic pulmonary artery pressure by echocardiogram compared with systolic pulmonary artery pressure by RHC was good (r = 0.70, 95% CI 0.67:0.73).[47] El-Korashy et al. conclude that, while RHC is performed to diagnose and follow up on PAP cases, an echocardiogram is a cheap, simple and non-invasive way to screen patients with suspected PH.[48] Therefore, based on our results and the findings of other investigators, an echocardiogram can be recommended for screening purposes only and not for diagnosis of patients with PH.

Echocardiogram

Right heart

In our group, all the measurable parameters indicated that the participants had dilated right heart chambers. However, the pulmonary arteries were considerably dilated – almost four times the normal diameter in the majority of our patients. Humbert et al. report on pulmonary artery dilation because of pressure or volume overload in CHD, that main pulmonary artery dilatation in PH could be considered diagnostic for the presence of PH.[49]

This finding contrasts with that of Kaldararova et al., who found that severe main pulmonary artery dilatation (> 50 mm) was present in only 16.7% of patients with PH-CHD.[50] The pulmonary artery might have a thinner wall structure than the right ventricle, which has a muscle, and which explains why the pulmonary arteries in our group were more than double the size of the tricuspid valve.

It is concerning that all of our participants with PH had impaired right ventricle function. Melek et al. conducted a similar study on tissue Doppler evaluation of the tricuspid annulus to estimate PAP; all our patients had impaired calculated right ventricle wall strain less than 2.5, suggesting elevated PASP.[29] Puwanant et al. report that right ventricular dysfunction diagnosed by echocardiography was present in > 80% of patients, regardless of the measure used (S', tricuspid annular motion).[51] In contrast, in a series of 120 PH patients with heart failure symptoms, Berkowitz et al. report that right ventricle dilatation was present in 42% of patients.[52]

In PH, right ventricle dysfunction develops when the right ventricle fails to adapt to the increasing pressure. Ventricular adaptation to pressure overload is the process of maintaining stroke volume without increasing right ventricle filling pressures.[53] Initially, the right ventricle responds to increased pulmonary arterial load by increasing muscular contractility and wall thickness (i.e., right ventricle hypertrophy) to reduce wall stress (Laplace's law).[54] This initial inotropic reaction is a process known as homeometric adaptation, in which the ventricle increases myocardial inotropy, restoring stroke volume without changing chamber shape.[55]

However, if systolic function cannot be improved further, right ventricle dilation remains the only response to increased afterload. This process is known as heteromeric adaptation, in which an increase in right ventricle end-diastolic volume results in an equal increase in stroke volume, restoring stroke volume and securing cardiac output. As the disease progresses,

increasing right ventricle dilation gives rise to leftward septal bowing, thereby impairing left ventricle function and filling and lowering stroke volume.[56]

LIMITATIONS OF THE STUDY

This was a voluntary, prospective study rather than a randomised clinical trial. This study enrolled consecutive patients on a prospective basis and used control methods to ensure data quality. Nonetheless, missing values constitutes a significant limitation of our investigation. The sample size was small, which can be attributed to the recruitment period and the use of only a single centre for recruitment.

We did not use the recent definition of mPAP > 20 mmHg measured by RHC.[57] This study used the previous guidelines of mPAP ≥ 25 mmHg to diagnose PH because this was the definition used by our institution's treating physicians.

The only strain utilised was a calculated strain, which was impaired in all patients. We did not have the strain package available on our echocardiography apparatus.

CONCLUSION

Our results show that simple lesions that can potentially be operated on are still present with severe PH in South Africa. Our participants with PH exhibited dilation on the right side, especially the pulmonary arteries, which could serve as an early warning for PH. Additionally, there was significant functional impairment and right heart dysfunction in all our participants. Based on the results of our study, we recommend that elevated peak RVSP and dilated pulmonary artery should alert physicians to the possibility of PH. An echocardiogram should only be used as a screening tool for diagnosing PH.

Conflict of interest

The authors declare that there are no conflicts of interest relating to this study.

Acknowledgements

The authors acknowledge the support of the Robert W M Frater Cardiovascular Research Centre.

Abbreviations

ASD	Atrial septal defect
Ao	Aorta
ASVD	Atrioventricular septal defect
BMI	Body mass index
CI	Confidence interval
CHD	Congenital heart disease
ECG	Electrocardiogram
IVC	Inferior vena cava
mPAP	Mean pulmonary artery pressure
6MWT	Six-minute walk test
NYHA	New York Heart Association
PH	Pulmonary hypertension
PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PDA	Patent ductus arteriosus
PVR	Pulmonary vascular resistance
RA	Right atrium
RF	Regurgitant fraction
RHC	Right heart catheterisation
RVSP	Right ventricular systolic pressure
S’	Tricuspid annulus peak systolic velocity
Sm	Tricuspid annular systolic myocardial velocity
SmVTI	Velocity time integral of Sm
SV	Stroke volume
TAPSE	Tricuspid annular plane systolic excursion
TR	Tricuspid regurgitation
VSD	Ventricular septal defect

REFERENCES

1. Van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg, JJM et al. Birth prevalence of congenital heart disease worldwide: a systematic review

and meta-analysis. J Am Coll Cardiol 2011; 58(21): 2241–7. https://doi.org/10.1016/j.jacc.2011.08.025.

2. Tefuarani N, Hawker R, Vince J, Sleigh A, Williams GM. Surgical programme at Royal Alexandra Hospital, Sydney, for Papua New Guinea children with congenital heart disease. J Paediatr Child Health 2002; 38(2): 178-82. https://doi.org/10.1046/j.1440-1754.2002.00757.x.

3. Abman SH, Hansmann G, Archer LS, Ivy DD, Adatia I, Chung WL et al. Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation 2015; 132(21): 2037-99. https://doi.org/10.1161/CIR.0000000000000329.

4. Adatia I, Kothari SS, Feinstein JA. Pulmonary hypertension associated with congenital heart disease pulmonary vascular disease: The global perspective. Chest 2010; 137(6): 52S-61S. https://doi.org/10.1378/chest.09-2861.

5. Van der Bom T, Bouma BJ, Meijboom FJ, Zwinderman AH, Mulder BJ. The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation. American Heart Journal 2012; 164(4): 568–75. https://doi.org/10.1016/j.ahj.2012.07.023.

6. Galiè N, Rubin L, Hoeper M, Jansa MD, Al-Hiti H, Meyer GMB et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): A double-blind, randomized controlled trial. The Lancet 2008; 371(9630): 2093–100. https://doi.org/10.1016/S0140-6736(08)60919-8.

7. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L., Hoffman JIE et al. Task force 1: The changing profile of congenital heart disease in adult life. J Am Coll Cardiol 2001; 37(5): 1170–5. https://doi.org/10.1016/s0735-1097(01)01272-4.

8. Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JSR et al.. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med 2012; 186(8): 90-6. https://doi.org/10.1164/rccm.201203-0383OC.

9. Hoeper MM, Boggard JM, Condliffe R, Frantz R, Khanna D, Kurzyna M et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013; 62(25): D42-50. https://doi.org/10.1016/j.jacc.2013.10.032.

10. McGoon M, Benza RL, Escribano-Subias P, Jian X, Miller DP, Peacock AJ et al. Pulmonary arterial hypertension: Epidemiology and registries. J Am Coll Cardiol 2013; 62(25Suppl): D51-9. https://doi.org/10.1016/j.jacc.2013.10.023.

11. Thienemann F, Dzudie A, Mocumbi AO, Blauwet L, Sani MU, Karaye KM et al.. The causes, treatment, and outcome of pulmonary hypertension in Africa: insights from the pan African pulmonary hypertension cohort (PAPUCO) registry. Int J Cardiol 2016; 221: 205-11. https://doi.org/10.1016/j.ijcard.2016.06.242.

12. Wharton G, Steeds R, Allen J, Phillips H, Jones R, Kanagala P et al. A minimum dataset for a standard adult transthoracic echocardiogram: a guideline protocol from the British Society of Echocardiography. Echocardiography Research and Practice 2015; 2(1): G9-24. https://doi.org/10.1530/ERP-15-0024.

13. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imag 2017; 18(12): 1301-10. https://doi.org/10.1093/ehjci/jex244.

14. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002). ATS statement: guidelines for the six-minute walk test. American Journal of Respiratory and Critical Care Medicine 2002; 166(1): 111–117. https://doi.org/10.1164/ajrccm.166.1.at1102

15. Wilkinson JL. Haemodynamic calculations in the catheter laboratory. Heart 2001; 85(1): 113-20. https://doi.org/10.1136/heart.85.1.113.

16. Accreditation for Cardiovascular Excellence (ACE). The ACE Congenital Heart Disease (CHD) Standards for Pediatric and Congenital Cardiac Catheterization Laboratory (PCCL) accreditation. New Standard Establish Comprehensive Guidelines for Congenital Heart Disease (2015); http://www.hmgoballearningnetwork.com [Accessed April 2021].

17. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AH, Provencher S et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005; 111(23). https://doi.org/10.1161/CIRCULATIONAHA.104.488486.

18. Nuttall FQ. Body mass index: Obesity, BMI, and health: a critical review. Nutr Today 2015; 50(3): 117–28. https://doi.org/10.1097/NT.0000000000000092.

19. Raphael C, Briscoe C, Davies J, Whinnett ZI, Manisty C, Sutton R, Mayet J, Francis DP. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart 2007; 93(4): 476-82. https://doi.org/10.1136/hrt.2006.089656.

20. Bonderman D, Wexberg D, Martischnig AM, Heinzl H. A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. European Respiratory Journal (2011); 37(5): 1096-103. https://doi.org/10.1183/09031936.00089610.

21. Sun KL, Lu Y, Yang K, Li S. ECG Analysis using multiple instance learning for myocardial infarction detection. IEEE Transactions on Biomedical Engineering 2012; 59(12): 3348-56. https://doi.org/10.1109/TBME.2012.2213597.

22. Allison DJ, Macedo FY, Hamzeh IR, Birnbaum Y. Correlation of right atrial enlargement on ECG to right atrial volume by echocardiography in patients with pulmonary hypertension. J Electrocardiol 2017; 50(5): 555-60. https://doi.org/10.1016/j.jelectrocard.2017.04.012.

23. Parasuraman S, Walker S, Loudon BL, Gollop ND, Wilson AM, Lowery C et al.. Assessment of pulmonary artery pressure by echocardiography- A comprehensive review. Int J Cardiol Heart Vasc 2016; 12: 45-51. https://doi.org/10.1016/j.ijcha.2016.05.011.

24. Skinner GJ. Echocardiographic assessment of pulmonary arterial hypertension for pediatricians and neonatologists. Frontiers in Pediatrics (2017); 5: 168. https://doi.org/10.3389/fped.2017.00168.

25. Kusner J, Krasuski RA. Echocardiographic Evaluation of the Right Heart in Pulmonary Hypertension. Advances in Pulmonary Hypertension 2023; 22(3): 122-9. https://doi.org/10.21693/1933-088X-22.3.122.

26. Mercer-Rosa L, Yang W, Kutty S, Rychik J, Fogel M, Goldmuntz E. Quantifying pulmonary regurgitation and right ventricular function in surgically repaired Tetralogy

of Fallot. Circ Cardiovasc Imaging 2012; 5(5): 637-43. https://doi.org/10.1161/CIRCIMAGING.112.972588.

27. Giusca S, Dambrauskaite V, Scheurwegs C, D'hooge J, Claus P, Herbots L et al. Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring. Heart 2010; 96(4): 81-8. https://doi.org/10.1136/hrt.2009.171728.

28. Wilkinson JL. Haemodynamic calculations in the catheter laboratory. Heart 2001; 85(1): 113-20. https://doi.org/10.1136/heart.85.1.113.

29. Melek M, Esen O, Esen AM, Barutcu I, Fidan F Onrat E et al. Tissue Doppler evaluation of tricuspid annulus for estimation of pulmonary artery pressure in patients with COPD. Lung 2006; 184(3): 121-31. https://doi.org/10.1007/s00408-005-2571-2.

30. Okoromah CAN, Ekure EN, Lesi FEA, Okunowo WO, Tijani BO, Okeiyi JC. Prevelance, profile and predictors of malnutrition in children with congenital heart defects: a case–control observational. Arch Dis Child 2011; 96(4): 354-60. https://doi.org/10.1136/adc.2009.176644.

31. Hassan BA, Albanna EA, Morsy SM, Siam AG, Al Shafie MM, Elsaadany HF et al. Nutritional status in children with unoperated congenital heart disease: an Egyptian center experience. Frontal Pediatr 2015; 3(4): 53. https://doi.org/10.3389/fped.2015.00053. eCollection 2015.

32. Murni IK, Patmasari L, Wirawan MT, Arafuri N, Nurani N, Sativa ER et al. Outcome and factors associated with undernutrition among children with congenital heart disease. PLoS One 2023; 18(2): e0281753. https://doi.org/10.1371/journal.pone.0281753.

33. Dinarti LK, Hartopo AB, Kusuma AD, Satwiko MG, Hadwiono MR, Pradana AD et al. The COngenital HeARt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry: a descriptive study from single-center hospital registry of adult congenital heart disease and pulmonary hypertension in Indonesia. BMC Cardiovasc Disord 2020; 20(1): 163. https://doi.org/10.1186/s12872-020-01434-z.

34. Kaemmerer H, Gorenflo M, Huscher D, Pittrow D, Apitz C, Baumgartner H et al. Pulmonary hypertension in adults with congenital heart disease: Real-world data from

the international COMPERA-CHD Registry. J Clin Med 2020; 9(5): 456. https://doi.org/10.3390/jcm9051456.

35. Mansour A, Roushdy A, Harb B, Attia H. Noninvasive predictors of functional capacity in patients with pulmonary hypertension due to congenital heart disease. Journal of Cardiovascular Echography 2020; 30(4): 193-200. https://doi.org/10.4103/jcecho.jcecho_41_20

36. Vijarnsorn C, Durongpisitkul K, Chungsomprasong P, Bositthipichet D, Ketsara S, Titaram Y, et al. Contemporary survival of patients with pulmonary arterial hypertension and congenital systemic to pulmonary shunts. PLoS One 2018; 13(4): e0195092. https://doi.org/10.1371/journal.pone.0195092.

37. Evaldsson AW, Lindholm A, Jumatate R, Ingvarsson A, Smith GJ. Right ventricular function parameters in pulmonary hypertension: echocardiography vs. cardiac magnetic resonance. BMC Cardiovascular Disorders 2020; 20(1): 259. https://doi.org/10.1186/s12872-020-01548-4.

38. Rosenkranz S, Gibbs JSR, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry J. Left ventricular heart failure and pulmonary hypertension. Eur Heart J 2016; 37(12): 942-54. https://doi.org/10.1093/eurheartj/ehv512.

39. McLaughlin VV, Channick R, de Marco T, Farber HW, Gaine S, Galiè N et al.. Results of an expert consensus survey on the treatment of pulmonary arterial hypertension with oral prostacyclin pathway agents. Chest 2020; 157(4): 955–65. https://doi.org/10.1016/j.chest.2019.10.043.

40. Ferreira EVM, Ota-Arakaki JS, Ramos RP, Barbosa PB, Almeida M, Treptow EC et al. Optimizing the evaluation of excess exercise ventilation for prognosis assessment in pulmonary arterial hypertension. Eur J Prev Cardiol 2014; 21(11): 1409-19. https://doi.org/10.1177/2047487313494293.

41. Frank DB, Hanna BD. Pulmonary arterial hypertension associated with congenital heart disease and Eisenmenger syndrome: Current practice in pediatrics. Minerva Pediatr 2015; 67(2): 169-85.

42. Bobhate P, Guo L, Jain S, Haugen R, Coe, Cave D et al. Cardiac catheterization in children with pulmonary hypertensive vascular disease. Pediatr Cardiol 2015; 36(4): 873-9. https://doi.org/10.1007/s00246-015-1100-1.

43. Ozek J, Saprungruang A, Khongphatthanayothin A. Survival of patients with high-risk pulmonary arterial hypertension associated with congenital heart disease. J Med Assoc Thai 2021; 104(6): 895-901. https://doi.org/10.35755/jmedassocthai.2021.06.12404.

44. Van Loon RLE, Roofthooft MTR, Hillege HL, ten Harkel ADJ, van Osch-Gevers M, Delhaas T et al. Pediatric pulmonary hypertension in the Netherlands. Circulation 2011; 124(16): 1755-64. https://doi.org/10.1161/CIRCULATIONAHA.110.969584.

45. Amelia P, Djer MM, Advani N, Sukardi R, Waworuntu DS. Role of echocardiography in evaluating patients with pulmonary hypertension secondary to congenital heart diseases in economically developing countries. Progress in Pediatric Cardiology 2022; 64: 101449. https://doi.org/10.1016/j.ppedcard.2021.101449.

46. Sonaglioni A, Cassandro R, Luisi F, Ferrante D, Nicolosi GL, Anzà C et al. Correlation Between Doppler echocardiography and right heart catheterisation-derived systolic and mean pulmonary artery pressures: Determinants of discrepancies between the two methods. Heart Lung Circ 2021; 30(5): 656-64. https://doi.org/10.1016/j.hlc.2020.10.009.

47. Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systemic review and meta-analysis. Heart 2011; 97(8): 612-22. https://doi.org/10.1136/hrt.2010.212084.

48. El-Korashy RIM, Amin YM, Eissa AI, Thabet TS. Echocardiography versus right heart catheterization in class I pulmonary hypertension. Egypt J Chest Di Tuberc 2014; 63(2): 419-22. https://doi.org/10.1016/j.ejcdt.2013.12.005.

49. Humbert M, Kovács G, Hoeper MM, Badagliacca R, Berger RM, Brida M et al. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur.Heart J 2022; 43(38): 3618-731. https://doi.org/10.1093/eurheartj/ehac237.

50. Kaldararova M, Bobocka K, Kantorova A, Drangova E, Mistinova JP, Klauco F et al. Pulmonary artery dilatation due to pressure or volume overload in congenital heart disease. J. Clin. Med 2024; 13(6): 1576. https://doi.org/10.3390/jcm13061567.

51. Puwanant S, Priester TC, Mookadam F, Bruce CJ, Redfield MM, Chandrasekaran K. Right ventricular function in patients with preserved and reduced ejection fraction heart failure. Eur J Echocardiogr 2009; 10(6): 733-7. https://doi.org/10.1093/ejechocard/jep052.

52. Berkowitz R, Alhaj E, Manchikalapudi RB, Satka L. Dadfarmay S, Zakir R. Determinants of right ventricular failure in patients admitted with acute left heart failure. Congest Heart Fail 2010; 16(6): 243-8. https://doi.org/10.1111/j.1751-7133.2010.00184.x.

53. Bellofiore A, Chesler NC. Methods for measuring right ventricular function and hemodynamic coupling with the pulmonary vasculature. Ann Biomed Eng 2013; 41(7): 1384-98. https://doi.org/10.1007/s10439-013-0752-3.

54. Wang Z, Chesler NC. Pulmonary vascular wall stiffness: An important contributor to the increased right ventricular afterload with pulmonary hypertension. Pulm Circ 2011; 1(2): 212-23. https://doi.org/10.4103/2045-8932.83453.

55. Cingolani HE, Perez NG, Cingolani OH, Ennis IL. The Anrep effect: 100 years later. Am J Physiol Heart Circ Physiol 2013; 304(2): H175-82. https://doi.org/10.1152/ajpheart.00508.2012.

56. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The relationship between the right ventricle and its load in pulmonary hypertension. J Am Coll Cardiol 2017; 69(2): 236-43. https://doi.org/10.1016/j.jacc.2016.10.047.

57. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Williams PG et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53(1): 1801913. https://doi.org/10.1183/13993003.01913-2018.

CHAPTER 4 – PAPER II

AN ANALYSIS OF IMAGING MODALITIES TO ASSESS THE RIGHT AND LEFT HEART IN PULMONARY HYPERTENSION WITH LEFT-TO-RIGHT SHUNTS

MMF Henema[1,2] (MHSc), SC Brown[4] (DMed), FE Smit[3] (PhD), L Botes[2] (PhD)

[1]Department of Cardiology, Dr George Mukhari Academic Hospital, Pretoria, South Africa

[2]Department of Health Sciences, Faculty of Health and Environment Sciences, Central University of Technology, Bloemfontein, South Africa

[3]Department of Cardiothoracic Surgery, School of Medicine, Faculty of Health Science, University of the Free State, Bloemfontein, South Africa

[4]Division Pediatric & Congenital Cardiology, School of Medicine, Faculty of Health Science, University of the Free State, Bloemfontein, South Africa

ABSTRACT

Background: Pulmonary hypertension (PH) as a result of congenital left-to-right shunts has serious consequences for people in sub-Saharan Africa. This study used various imaging modalities to assess right and left heart dimensions and function in patients with secondary PH.

Methods: Patients with a mean pulmonary artery pressure ≥ 25 mmHg during right heart catheterisation underwent transthoracic echocardiography, cardiac magnetic resonance imaging (CMRI), and nuclear ventriculography.

Results: The study involved 75 patients (aged median 9.98: 6.01–40.9 years). Right heart dilation was observed in all participants; increased tricuspid valve annular diameter (median z-score 2.44) on echocardiography was recorded. Similarly, right ventricular end-diastolic indexed volumes were at least double the normal reference ranges for most participants

(median 240: 165–268 mL/m²) on CMRI. The median normal right ventricular systolic function was 49% for male (IQ1–IQ3, 48.0–50.0%) and 49% for female participants (IQ1−IQ3, 47.3–49.8%). CMRI showed that 70% of male participants had normal right ventricular systolic function, compared to only 45% of female participants ($p < 0.05$). Echocardiographic markers of right ventricular function correlated poorly with CMRI right ventricular ejection fraction, with correlation coefficients of r =-0.28, r = -0.10, and r = -0.04. Interestingly, 80% of our participants demonstrated left heart dilation, and 35% had impaired left ventricular ejection fraction on echocardiography, isotopes and CMRI.

Conclusion: Echocardiography and CMRI consistently revealed right heart dilation but correlated poorly with right heart function. The evaluation of the left heart function should not be neglected, as some patients exhibited decreased left ejection fraction. A holistic approach incorporating multiple modalities and clinical assessment is recommended, as the pathophysiology of PH may differ in patients with left-to-right shunts.

Keywords: Pulmonary hypertension; congenital heart disease; echocardiography; right heart catheterisation; cardiac magnetic resonance imaging

INTRODUCTION

Pulmonary hypertension (PH) associated with congenital heart disease associated (CHD) is a serious condition that can result in significant disability and even death.(1) The global prevalence of CHD associated with PH is estimated to be approximately 15.6 cases per million people, with an incidence rate of 2.2 cases per million. Therefore, PH is an important concern for individuals with congenital heart defects, particularly those with ventricular septal defects (VSD), which are the most common.(2)

The prevalence of PH in Africa ranges between 10% and 68%, which is higher than in high-income countries, although its epidemiology is poorly understood.(3) It is estimated that around 80% of the global burden of the disease occurs in low and middle-income countries, where PH is strongly associated with CHD.(4) A study in Tanzania indicated that 6.3% of children were inoperable at first diagnosis, and 3% were inoperable because of severe PH.(5) Essentially, children had simple lesions that could have been operated on but, because of late presentation, they had already developed severe PH.

Low and middle-income countries have limited resources for diagnosing and treating medical conditions, including PH.(6) Pulmonary hypertension has devastating symptoms and, if left

untreated, has poor survival rates and shortens life expectancy.[7] In sub-Saharan Africa, patients often present at the hospital only when they become symptomatic during the late stages of the disease, which contributes to a high mortality rate.[4]

Imaging is fundamental to determining the underlying causes and extent of PH. It evaluates both right and left heart function, which are significant predictors of morbidity and mortality.[8] Right cardiac catheterisation is the gold standard for diagnosing PH, because it measures pulmonary artery pressure (PAP) directly.[9] Echocardiography is the primary imaging technique for screening PH and assessing right ventricular and left ventricular function.[10] Cardiac magnetic resonance imaging (CMRI) is considered the gold standard for evaluating right ventricular and left ventricular function.[11] Additionally, radionuclide ventriculography is often utilised for the differential diagnosis of PH.[12]

To our knowledge, limited data are available on the evaluation of imaging modalities in CHD patients with PH in South Africa. Consequently, this study aimed to provide an analysis using various imaging modalities to assess the right and left heart of patients with PH with left-to-right shunts.

METHODS

Study design, settings and population

This prospective observational study included patients over the age of 6 years and was conducted at the cardiology unit of Dr George Mukhari Hospital, Gauteng, South Africa, from 1 December 2022 to 30 November 2023. We screened 85 patients, but 10 patients were excluded because of poor echocardiography images or incomplete datasets.

Inclusion and exclusion criteria were as follows:

- Patients were only included if the mean PAP was ≥25 mmHg during right heart catheterisation (RHC).
- Cardiac patients diagnosed with cyanotic CHD (e.g., Tetralogy of Fallot, tricuspid atresia, truncus arteriosus) or primary PH were excluded, as were children who required full general anaesthetic for CMRI.

Data collection

Standard demographic and anthropometric data were collected. Detailed echocardiography was performed using a GE Medical Vivid E9 ultrasound machine with an M5SC phased array

transducer. The techniques and measurements were done according to the British Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines for adults and paediatric patients.[13,14] Right and left heart variables were measured as described in Paper 1 (submitted for publication). Right heart catheterisation was performed according to Accreditation for Cardiovascular Excellence Standards for Paediatric and/or Congenital Cardiac Catheterization Laboratory Accreditation.[15]

A CMRI investigation was performed on all patients at rest using a 1.5 T Magnetom Symphony, Siemens system. The approach of the European Association of Cardiovascular Imaging and the Society for Cardiovascular Magnetic Resonance was used with Segment Version 2.2 software.[14,16] In a cine magnetic resonance imaging sequence in a short-axis view, right and left ventricular end-diastolic and end-systolic volumes were quantified and used to calculate right and left ejection fraction and stroke volume. Interpretations were analysed by a single radiologist. Sedation was only used for younger children. The drugs administered per standard operating procedure were Ketamine 1–2 mg/kg, Midazolam 0.05 mg/kg and Dexmedetomidine hydrochloride 0.2–0.7 µg/kg.

Nuclear ventriculography was performed using an Intevo scanner, Siemens Medical Solution, and Syngo MI application software, by injecting a Technetium-99m labelled diethylenetriamine pentaacetate at rest, R-wave gated limit of agreement imaging and obtaining a cardiac chamber image with a gamma camera. Heart rate, electrocardiogram and blood pressure were monitored during the entire examination. The left ventricular end-diastolic and end-systolic volumes and left ventricular ejection fraction were measured. The left ventricular function was assessed according to the European Society of Cardiology guidelines.[17] If sedation was required for uncooperative children, the following drugs were administered according to standard operating procedure: Ketamine 1–2 mg/kg, Midazolam 0.05 mg/kg.

Definitions

Tricuspid annular plane systolic excursion (TAPSE): TAPSE pertains to the systolic longitudinal displacement of the lateral tricuspid annulus towards the apex.[18]

Tricuspid annulus peak systolic velocity (S'): The maximum velocity at which the lateral tricuspid annulus may expand in systole.[19]

Myocardial performance index (MPI): The sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time.[20]

Mitral annular plane systolic excursion (MAPSE): The displacement of the mitral valvular plane in the z-direction, reflecting left ventricular contraction or shortening.[21]

Left ventricle ejection fraction: The fraction of chamber volume ejected in systole compared to the amount of blood in the ventricle at the end of diastole.[22]

Left ventricular end-diastole (LVED) diameter, according to Teicholz method: Diameter was measured using M-mode echocardiography in parasternal long-axis view. The left ventricular dimension measurement was taken when the time cursor was placed before the peak R-wave in the ventricular depolarisation complex.[23]

CMRI ventricular reference ranges: Ranges for women's and men's cardiac structure and function using CMRI were from the Biobank population cohort in the United Kingdom.[24]

Tricuspid regurgitation volume on CMRI: Calculated as the difference between right ventricular stroke volume and pulmonary forward flow. Tricuspid regurgitation was classified as mild < 30 mL, moderate 30–59 mL, and severe ≥ 60 mL.[25]

Ethics and statistical analysis

Ethics approval was obtained from the Health Sciences Research Ethics Committee of the University of the Free State (UFS-HSD2022/0300/3008-0005) and the Gauteng Department of Health. Only patients who provided informed consent and assent, either themselves or their guardians, were included in the study.

Data analysis was performed in collaboration with a biostatistician using R Statistical computing software of the R Core Team 2020, Version 3.6.3. Raw data were captured on Excel spreadsheets. A *t*-test was conducted to compare normally distributed data. Nonparametric data were compared using a Mann-Whitney U test. Where required, a chi-square test or Fisher's exact test was utilised for comparisons. A *p*-value of less than .05 was considered to be statistically significant.

RESULTS

Clinical characteristics of PH patients

In total 75 patients met the study's inclusion criteria; they had a median age of 9.98 years (min–max, 6.01–40.9 years). During RHC, the median mean arterial pulmonary pressure on room air was 52 mmHg (min–max, 41.0–91.0) and pulmonary vascular resistance of 5 Wood units.m^2 (min–max, 2.30–10.0) (Table I). The most common underlying lesions were ventricular septal

defects, in 31 patients (52.5%), followed by patent ductus arteriosus (PDA) in 17 patients (28.8%) and atrioventricular septal defects (AVSD) in 11 patients (18.6%). For more details, see Paper I (submitted for publication).

Table I: Main clinical characteristics of pulmonary hypertension patients

	PH patients (n=75)		
	n (%)	**Median**	**IQ1–IQ3**
Age (years)	75	9.98	7.97–17.10
Sex			
Male	35 (46.7)	9.98	8.00–16.1
Female	40 (53.3)	10.98	7.99–17.3
**BMI (kg/m²)*	75	18.9	16.7–20.9
Functional class, NYHA			
Class II	30 (40)	-	-
Class III	45 (60)	-	-
*6 MWT (m)**			
6–17 years	55 (73.3)	248	241–250
18+ years	20 (26.7)	290	281–298
CI (L/min/m²)	75	3.13	2.82–4.69
mPAP (mmHg)	75	52.0	49.0–67.0
PAWP (mmHg)	75	13.0	12.0–16.0
PVR (Wood unit.m²)	75	5.00	4.00–8.00

[n, number of patients; IQ1, 25th percentile; IQ3, 75th percentile; 6MWT, 6-min walking test; BMI, body mass index; NYHA, New York Heart Association; CI, cardiac index; PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; * see paper I, submitted for publication].

Dimensions

Right heart: Transthoracic echocardiography

Right heart dilation was observed in all participants, as evidenced by an increased tricuspid valve annular diameter (median z-score of 2.44; IQ1–IQ3, 2.31–2.67). This dilation was accompanied by considerable tricuspid regurgitation and marked pulmonary artery dilation, demonstrated by a median z-score of 4.23 (IQI–IQ3, 3.60–4.75). Of the group of patients, 15 (20%) exhibited moderate pulmonary regurgitation, while 60 patients (80%) had severe pulmonary regurgitation (see Paper I, submitted for publication).

Right heart: Cardiac magnetic resonance imaging

As shown in Table II, both indexed right ventricle end-diastolic and right ventricle end-systolic volumes were markedly increased in male and female patients (at least double the normal reference ranges), which emphasises the extent of right heart dilation. Similar to the echocardiographic findings, tricuspid regurgitation was severe in all the participants (≥ 60 mL). Almost all participants (95%) had severe pulmonary regurgitation with a median pulmonary regurgitant volume of 68.0 mL (IQ1–IQ3, 58.0–77.0 mL). Four patients had moderate regurgitation, with a median pulmonary regurgitant volume of 52.5 mL (IQ1–IQ3, 50.8−55.3 mL).

Left heart: Transthoracic echocardiography

In almost 80% of participants, the left ventricle was dilated, as shown by a high left ventricular end-diastolic dimension median z-score of more than 2 (IQ1–1Q3, 2.3–3.3) (Table II). In these participants, a normal left ventricular end-diastolic dimension z-score was observed in those with atrial septal defects (ASD) (n = 16, 100%). Dilated left ventricular end-diastolic dimension z-score was noted in participants with VSD (n=31, 52.5%), followed by PDA (n = 17, 28.8%) and AVSD (n = 11, 18.6%).

Left heart: Cardiac magnetic resonance imaging

Similar to the echocardiographic findings, the left ventricular end-diastolic indexed volume showed dilation in 81.3% of the participants, regardless of gender.

Interestingly, all of the female participants (100%) exhibited a significant increase in left ventricular mass compared to 69% of the male participants ($p < 0.001$) (Table II). In these participants, normal left ventricular end-diastolic indexed volume was observed primarily in patients with ASD (n = 13, 92.9%), followed by AVSD (n = 1, 7.1%). The dilated left ventricular end-diastolic indexed volume was most commonly found in patients with VSD (n = 31, 50.8%), followed by PDA (n = 17, 27.9%), AVSD (n = 10, 16.4%), and ASD (n = 3, 4.9%).

Left heart: Nuclear ventriculography

Nuclear ventriculography demonstrated left heart dilation, where the left ventricular end-diastolic indexed volumes were increased in 89.3% of patients.

Table II: Cardiac dimensions as measured by echocardiography, cardiac magnetic resonance imaging, and nuclear ventriculography

Cardiac dimension variables	n (%)	Median	IQ1-IQ3
Echocardiography			
LA (mm)	75	26.0	23-36
LVED M-mode (mm)	75	55.0	51-61
LVED M-mode (z-score)	75	2.78	2.3-3.3
Ao annulus (mm)	75	20.0	17-22
Ao annulus (z-score)	75	0.95	0.6-1.3
Cardiac magnetic resonance imaging			
RVED volume (indexed [mL/m²])	75	240	165–268
Female above 99 mL/m^2	40 (100)	238	162–259
Male above 125mL/m^2	35 (100)	241	177–272
RVES volume (indexed [mL/m²])	75	128	88–137
Female above 46 mL/m^2	40 (100)	126	88–138
Male above 63 mL/m^2	35 (100)	128	93–137
LVED volume (indexed [mL/m²])	75	218	144–252
Female >94 mL/m^2	33 (83)	233	162–256
Male >110 mL/m^2	28 (80)	228	175–253
LVES volume (indexed [mL/m²])	75	100	67.3–113
Female >40 mL/m^2	40 (100)	99	66–114
Male >49 mL/m^2	34 (97)	101	71–109
TR volume (mL)	75	75	70–79
LV mass (g)	75	147	140–152
Female >44 g	40 (100)	147	140–154
Male >56 g	24 (69)	149	148–152
Nuclear ventriculography			
LVED volume [indexed (mL/m²)]	75	230	154–260
Female >106 mL/m^2	40 (100)	228	152–266
Male >157 mL/m^2	27 (77)	240	213–259
LVES volume [indexed (mL/m²)]	75	115	76–133
Female >47 mL/m^2	34 (85)	124	81–136
Male >78 mL/m^2	35 (100)	115	77–127

[n, number of patients; IQ1, 25th percentile; IQ3, 75th percentile; Ao, aorta; LVED, left ventricular end-diastolic; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RVEDV, right ventricle end-diastolic volume; RVESV, right ventricle end-systolic volume; LV, left ventricle; TR, tricuspid regurgitation; TR volume mild < 30 mL, moderate 30–59 mL, and severe ≥ 60 mL. Reference ranges: CMRI: RVESV female, 17–46 mL/m^2, male, 25–63mL/m^2; LVEDV female, > 94 mL/m^2, male >110 mL/m^2; LVESV female > 40 mL/m^2, male > 49 mL/m^2; LV mass female > 44 g, male > 56 g; Nuclear ventriculography LVEDV female, > 106 mL/m^2, male, > 157 mL/m^2; LVESV female, > 47 mL/m^2, male > 78 mL/m^2]

There was a strong correlation between LVED indexed volume on CMRI and LVED indexed volume on nuclear ventriculography (Table IV). A similar, moderate correlation was noted for the comparison on LVED indexed volume on CMRI and LVED dimension on echocardiography (Table IV).

Functions

Right heart: Transthoracic echocardiography

Right ventricular systolic dysfunction was present in all participants, which was confirmed by conventional echocardiographic parameters of right ventricular function such as Doppler and

M-mode echocardiography (prolonged right ventricle myocardial performance index, reduced S', decreased TAPSE, and impaired calculated right ventricular free wall strain) (see Paper I, submitted for publication).

Right heart: Cardiac magnetic resonance imaging

The median normal right ventricular systolic function was 49% for male (IQ1–IQ3, 48.0−50.0%) and 49% for female participants (IQ1–IQ3, 47.3–49.8%). Interestingly, CMRI showed that 70% of male participants had a normal right ventricular systolic function, compared to only 45% of female participants ($p < 0.05$).

Left heart: Transthoracic echocardiography

In total 65% of male participants exhibited normal function according to the Teicholz ejection fraction method; however, the overall median left ventricular ejection fraction was in the low normal range. Nearly three-quarters of the patients showed evidence of impaired left ventricular function when assessed using more subtle markers, such as MAPSE and MPI (see Table III). Mitral annular plane systolic excursion was decreased in significantly more patients than Teicholz left ventricular systolic function ($p < 0.001$).

Left heart: Cardiac magnetic resonance imaging

Reminiscent of echocardiography findings, significantly more male (97%) had normal left ventricular ejection fraction on CMRI compared to female particpants (45%, $p < 0.05$). Even though left ventricular ejection fraction was decreased in 55% of female participants, it was only a mild impairment with a median ejection fraction of 49% (Table III).

Left heart: Nuclear ventriculography

Isotopes showed that 70% of male participants had a normal left ventricular ejection fraction. However, similar to CMRI findings, fewer female participants (47%) had a normal ejection fraction. In these, the median left ventricular ejection fraction was 52.0% for male (IQ1–IQ3, 50.0–62.3%) and 55% for female participants (IQ1–IQ3, 51.5–61.0%). Using isotopes, significantly more female than male participants had impaired left ventricular ejection fraction (left ventricular ejection fraction, $p < 0.05$) (Table III).

Table III: Cardiac functional measurements by echocardiography, cardiac magnetic resonance imaging and nuclear ventriculography

Cardiac functional variables	n (%)	Median	IQ1–IQ3
Echocardiography			
LVSF (M-mode Teicholz) (mm)	75	25	24–28
LVEF (%)	75	50	49–54
Female <50%	14 (35)	48	47–49
Male <50%	12 (34)	49	48–49
MAPSE LV (mm)	75	9.3	9–10.2
Female <12 mm	30 (75)	9.0	8.8–9.6
Male <12 mm	27 (77)	9.0	8.7–9.3
TDI MPI LV	75	0.73	0.6–0.7
Female >0.54	29 (72)	0.74	0.73–0.74
Male >0.54	27 (77)	0.74	0.72–0.74
CMRI			
RVEF (%)	75	47	42–49
Female <45%	22 (55)	42	40–43
Male <40%	11 (31.0)	41	40–43
LVEF (%)	75	51	49–57
Female <50%	22 (55)	49	48–50
Male <47%	1 (3)	45	45–45
Nuclear Ventriculography			
LVEF (%)	75	50	48–55
Female <50%	21 (53)	48	47–49
Male <50%	11 (31)	48	47–49

[n, number of patients; IQ1, 25th percentile; IQ3, 75th percentile; MPI, myocardial performance index; MAPSE, mitral annular systolic excursion; LVSF, left ventricular shortening fraction; LVEF, left ventricular ejection fraction; TDI, tissue Doppler imaging; TDI MPI LV, tissue Doppler imaging myocardial performance index left ventricle; MAPSE LV, mitral annular systolic excursion left ventricle; Reference ranges used: Echocardiography: LVEF female and male < 50%; MAPSE LV female and male < 12 mm; TDI MPI LV male and female > 0.54; CMRI: RVEF female < 45%, male < 40%; LVEF female < 50%, male < 47%; nuclear ventriculography, female and male < 50%]

Table IV: Correlation of dimensional measurements from echocardiographic, cardiac magnetic resonance imaging and nuclear ventriculography

Variable	Median (IQ1–IQ3)	CMRI LVEDV indexed, *r*-value	CMRI LVESV indexed, *r*-value
CMRI			
LVEDV indexed (mL/m²)	218 (144-252)	-	-
Female	222 (141-252)	-	-
Male	216 (147-249)	-	-
LVESV indexed (mL/m²)	100 (67-113)	-	-
Female	100 (66-114)	-	-
Male	100 (70-109)	-	-
Echocardiography			
LVED z-score (%)	2.78 (2.3–3.3)	0.73	-
Nuclear ventriculography			
LVEDV indexed (mL/m²)	230 (154–260)	0.96	-
Female	228 (152–266)	0.97	-
Male	230 (160–257)	0.95	-
LVESV indexed (mL/m²)	115 (76–133)	-	0.97
Female	114 (75–135)	-	0.95
Male	115 (77–127)	-	0.97

[%, percentage; CMRI, cardiac magnetic resonance imaging; left ventricular end-diastolic volume ; IQ1, 25th percentile; IQ3, 75th percentile; LVESV, left ventricular end-systolic volume; LVED, left ventricular end-diastolic]

There was a poor correlation between CMRI right ventricular ejection fraction and all the echocardiographic right ventricular function markers. Cardiac magnetic resonance imaging left ventricular systolic function had a strong positive correlation with left ventricular systolic function on echocardiogram, as had MAPSE on echocardiogram, and there was a strong negative correlation with left ventricular MPI on echocardiography (Table V).

Table V: Correlation of functional measurements from echocardiography, cardiac magnetic resonance, and nuclear ventriculography

Variable	Median (IQ1–IQ3)	CMRI RVEF, r-value	ECHO LVEF, r-value	CMRI LVEF, r-value
CMRI				
RVEF (%)	47.0 (42.0–49.0)	-	-	-
Female	44.5 (42.0–48.3)	-	-	-
Male	48.0 (43.5–49.0)	-	-	-
LVEF (%)	51.0 (49.0–57.0)	-	-	-
Female	50.0 (49.0–59.8)	-	-	-
Male	52.0 (50.0–54.5)	-	-	-
Echocardiography				
TAPSE (mm)	9.00 (8.00–10.0)	-0.28	-	-
S'(cm/s)	7.00 (7.00–8.00)	-0.10	-	-
RVMPI echo	0.75 (0.74–0.77)	-0.04	-	-
LVEF (%)	50.0 (49.0–54.5)	-	-	0.90
Female	50.5 (48.8–54.3)	-	-	0.89
Male	50.0 (49.0–54.0)	-	-	0.94
MAPSE (mm)	9.33 (9.00–10.2)	-	0.91	0.89
Female	9.33 (9.00–10.8)	-	0.89	0.86
Male	9.00 (8.83–10.0)	-	0.94	0.93
LVMPI	0.73 (0.57–0.74)	-	-0.87	-0.87
Female	0.73 (0.44–0.74)	-	-0.82	-0.81
Male	0.73 (0.69–0.74)	-	-0.95	-0.96
Nuclear ventriculography				
LVEF (%)	50.0 (48.0–55.0)	-	0.90	0.89
Female	49.0 (48.0–52.8)	-	0.92	0.88
Male	50.0 (49.0–55.5)	-	0.91	0.91

[%, percentage; CMRI, cardiac magnetic resonance imaging; LVEF, left ventricular ejection fraction; IQ1, 25th percentile; IQ3, 75th percentile; RVEF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; S', tricuspid annulus peak systolic velocity; MAPSE, mitral annular plane systolic excursion; RV and LV MPI, right and left myocardial performance index]

DISCUSSION

Limited data are available regarding the use of various imaging modalities to assess right and left heart function of patients in northern Gauteng who have PH secondary to congenital left-to-right shunts. Imaging of these patients demonstrated marked right heart chamber dilation, right ventricular dysfunction and, occasionally, left ventricular dilation. Notably, right ventricular ejection fraction measured by CMRI showed a poor correlation with transthoracic echocardiography and functional estimates of right ventricular function.

Dimensions

Right heart

Both echocardiography and CMRI showed a markedly dilated right heart, characterised by secondary tricuspid and pulmonary regurgitation. A study with an older patient group (mean age 34.7 years) in Indonesia found that most patients with PH due to CHD demonstrated a dilated right atrium and right ventricle, with mean diameters of 45.6 mm and 42.1 mm, respectively.[26] Mottaghi et al. found that younger patients (mean age 6.49 years) with primary PH exhibited dilated right atrium and right ventricle on echocardiogram.[27] A CMRI study reports that all patients presented with dilated right hearts, and 85% exhibited noteworthy pulmonary regurgitation.[28] It should be noted that this group consisted primarily of younger patients (mean age 12.5 years) with PH due to CHD.

In our study, CMRI demonstrated the considerable extent of right heart dilation by using indexed right ventricular end-diastolic volume volume and right ventriclar end-diastolic volume – values were nearly double the normal ranges. This finding aligns with the findings of Wald et al., namely that a dilated right ventricle of more than 170 mL/m² was associated with pulmonary regurgitation, particularly for older patients.[29] An increase in right ventricular end-diastolic volume indicates progressive right ventricle failure.[30] A high right ventricular end-diastolic volume index is a CMRI parameter independently associated with poor long-term outcomes, treatment failure and mortality in patients with PH.[8]

In cases of chronically increased afterload, the right ventricular pressure–volume relationship changes from a trapezoidal shape, reflecting high efficiency and low impedance, to a square or rectangular shape. This transformation features well-developed periods of isovolumetric contraction and relaxation that resemble the normal left ventricle pressure–volume loop.[31] However, as the condition progresses, the right ventricle eventually fails, leading to further right ventricular dilation, a rightwards shift in the pressure–volume curve, a reduction in end-systolic elastance and decreased cardiac output.[32]

The systemic right ventricle demonstrates enhanced circumferential contraction and decreased longitudinal shortening, similar to the normal left ventricle. Interestingly, diffusion tensor magnetic resonance imaging has revealed that right ventricle hypertrophy does not alter fibre orientation.[31]

Left heart

Almost 80% of our patients exhibited increased left ventricular end-diastolic and end-systolic volumes, as indicated by echocardiogram, CMRI and isotopes. These markers are commonly associated with heart failure, with elevated left ventricular end-systolic volume being strongly linked to a higher risk of mortality.[33] In contrast, Evaldsson et al. report on right ventricular functional parameters and demonstrate lower-left ventricular end-diastolic volumes in patients with PH, particularly in cases of primary PH.[34] Sjögren et al. analysed the left ventricles of 39 patients with primary PH (mean age of 61 years) and found that, while the left ventricle volume decreased across groups, left ventricular ejection fraction was preserved.[35] Therefore, in contrast to patients with primary PH, the authors of this paper speculate that the increased left ventricular end-diastolic volumes and end-systolic volumes observed in our group of patients reflect a different pathophysiological process, because a left-to-right shunt was still present in most patients (Paper I, submitted for publication). Since few studies report on left ventricle dimensions in PH with CHD, further investigation is warranted, to shed light on pathophysiological differences between primary PH patients and PH associated with CHD, because of the combination of volume and pressure overload.

We found a strong correlation between the isotopes and CMRI methods in evaluating left heart volumes, suggesting that either modality can effectively measure these parameters. However, radionuclide ventriculography has limitations, such as low resolution, the need for background adjustments and the potential for inaccuracies caused by overlapping structures. Additionally, the interpretation of radionuclide ventriculography results can vary between centres.[12] In contrast, CMRI provides high-resolution tomographic images that do not rely on geometric assumptions and avoid the use of ionising radiation.[36]

Similarly, Yanagi et al. demonstrated that CMRI is accurate and reproducible for assessing normal and dilated hearts, including determining left and right heart volumes.[37] Moreover, given the limitations of echocardiography and radionuclide ventriculography, CMRI is recommended as the preferred method for evaluating left ventricular volumes, particularly in cases involving dilated hearts.[38] Although isotopes offer valuable information regarding the volume of the left heart, CMRI remains the gold standard for these measurements.[38]

Left ventricular mass

Interestingly, in our study, female patients exhibited a higher left ventricular mass as measured by CMRI. This is unusual because Escudero et al. report that, in their study, male patients

presented with a higher left ventricular mass than female patients.[39] In a study by Hardziyenka et al., patients with chronic thromboembolic pulmonary hypertension reported an impaired six-minute walking time and decreased left ventricular mass.[40] They reasoned that left ventricular free wall mass reflected left ventricular remodelling better than the interventricular septum (IVS) does, because the IVS consists of both left ventricular and right ventriculum fibres, and IVS hypertrophy may be explained mainly by right ventricular hypertrophy.[41] It is interesting that left ventricular mass was reduced in rats with right ventricular failure, which was linked to left ventricular myocyte shrinkage because of atrophic remodelling.[42] Our study's higher left ventricular mass in female patients is unusual, but a possible explanation is that many male participants in our study were severely undernourished, with a body mass index (BMI) < 18 kg/m². This could account for the decreased left ventricular mass of male participants.

Functions

Right ventricular function

Cardiac magnetic resonance indicated that right ventricular systolic function was impaired in almost two-thirds of our patients, and significantly more frequently in female than male participants. This contrasts with the findings of Ventetuolo et al., who report that older women with PH tended to display better right ventricular systolic function and higher survival rates than older men.[43] Sex hormones may influence this disparity, as the female sex is a recognised risk factor for developing PH.[44]

In our study, all measured echocardiographic right ventrical functional parameters were impaired and corresponded with clinical functional measurements, such as the six-minute walking test (Paper I, submitted for publication).

The right ventricular ejection fraction on CMRI measures the systolic function of the right ventricle. It is a significant predictor of adverse cardiovascular outcomes and mortality in patients with CHD.[45] The right ventricle has a complex geometric shape and prominent trabeculations, which makes it difficult to define its borders clearly when precise endocardial outlines are needed for specific calculations.[46] The right ventricle contraction occurs primarily longitudinally, with shortening arising from the inlet towards the apex and from the apex towards the outlet. Additionally, the left ventricle contributes 20% to 30% of the contractile performance of the right ventricle through the movement of the shared septal fibres.[47] While pressure overload affects the right ventricle uniformly, understanding the mechanical characteristics of a volume-overloaded right ventricle is more complicated. In addition to

contractility, both preload and afterload play critical roles in determining right ventricular function. Moreover, it is essential to consider the effect of pericardial constraint.[48]

Consequently, the contraction pattern of the right ventricle is characterised by a bellow-like movement of the free wall towards the septum, a longitudinal motion of the base towards the apex, and a bulging of the ventricular septum into the right ventricular cavity. However, in disease states, the right ventricle may deviate from this primarily longitudinal contraction pattern, even when it is not the most severely affected chamber.[49]

Our findings also demonstrate that clinical echocardiography corresponded more effectively with clinical functional impairment, such as the six-minute walking test and New York Heart Association classifications, than right ventricular ejection fraction measurements obtained from CMRI for this specific group of patients with PH associated with CHD. Similarly, Shang et al. report that, for a group of 36 PH patients, mostly older (mean age 32.81 years), there was no correlation between right ventricular ejection fraction on CMRI and New York Heart Association Classes I/II and III.[50] It should be noted that CMRI has been mostly evaluated in patients with primary PH, rather than in younger patients with secondary PH because of CHD.[8]

Furthermore, Smiseth et al. report that modern echocardiographic modalities are more sensitive in detecting mild right ventricular systolic dysfunction.[51] Therefore, we emphasise the importance of combining echocardiographic measurements such as TAPSE, S', MPI and calculated right ventricular free wall strain with right ventricular ejection fraction from CMRI for a comprehensive right ventricular functional assessment.

A poor correlation was observed in our study between right ventricular systolic function assessed by CMRI and echocardiographic markers. Similarly, Avitabile et al. report a weak correlation between tricuspid annular systolic plane excursion and ejection fraction measured by CMRI.[52] While tricuspid annular systolic plane excursion is valuable for adults with heart failure and PH, it may not correlate well with ejection fraction in right ventricular volume overload of children. Tricuspid annular plane systolic excursion should, ideally, be reserved for individual longitudinal follow-up of these cases. This discrepancy possibly arises from the intricate geometry of the right ventricle and the complex mechanics involved in right ventricular contraction.[53] Additionally, the poor correlation between longitudinal measurements of right ventricular function and right ventricular ejection fraction in CMRI may

be because right ventricular ejection fraction is more closely related to fractional transverse movements than longitudinal movements in patients with PH.[54]

In contrast to the findings of Evaldsson et al., who found a strong correlation between tricuspid annular systolic plane excursion and right ventricular systolic function on CMRI, we observed no correlation.[34]

Left ventricular function

In total 65% of our patients had a normal left ventricular ejection fraction, while 35% exhibited impaired left ventricular function on echocardiogram, isotopes and CMRI. Notably, significantly more female than male patients had impaired left ventricular systolic function on CMRI and isotopes. Manders et al. report that, in primary PH patients who were mostly older (mean age 45 years), there was decreased left ventricular systolic function in the late stages of PH because of abnormal left ventricular mechanics caused by ventricular interdependence.[55]

Similarly, Rajagopalan et al. reported that 96% of PH patients had left ventricular dysfunction, evidenced by a prolonged left ventricular MPI (0.62 mean left ventricular MPI), despite preserved ejection fraction. However, the mean age of their cohort (53 years) was considerably higher than ours.[56]

Elevated right ventricular pressure and volume lead to the leftward displacement of the IVS, resulting in compression of the left ventricle,[57] causing paradoxical septal movement, a "D-shaped" left ventricle, and an increased left ventricle eccentricity index.[58] Furthermore, the increased volume of the right ventricle leads to structural remodelling of the chamber. This remodelling occurs because of the elongation of cardiac myocytes when newly synthesised sarcomeres assemble in series. As dilation of the right ventricle progresses, the chamber gradually adopts a more spherical shape, increasing its cross-sectional area and flattening the interventricular septum and contributing to left ventricular dysfunction.[59]

Our results show a strong correlation between the isotope and CMRI methods for evaluating the function of the left heart, with limitations similar to those discussed in the previous section.

Ejection fraction, calculated using the Teicholz formula from a parasternal long-axis view, assesses cardiac function in the radial and circumferential directions. However, it does not specifically evaluate longitudinal function. Since diastolic and systolic performances are closely interconnected, the reduced MAPSE observed in patients with diastolic dysfunction is likely a consequence of decreased systolic function.[60] In cases of PH, relying solely on

ejection fraction may lead to underlying left ventricle dysfunction being overlooked, thereby emphasising the need for additional measurements.

In our patients, the left ventricular ejection fraction determined by echocardiogram and isotopes showed a strong correlation with CMRI. Additionally, there was a significant but negative correlation between the mitral annular plane excursion and the MPI. Kosaraju et al. suggest that, given the variability in ejection fraction estimates (e.g., a 40% ejection fraction could range from 20 to 60%), a second method, such as radionuclide ventriculography, could be applied to improve reliability.[22]

Similarly, Mohsen et al. report that the M-mode approach demonstrated a good correlation with radionuclide ventriculography, even in cases without wall motion disturbances.[61] Furthermore, MAPSE assessments are reliable predictors of ejection fraction, even when conducted by inexperienced observers.[62]

LIMITATIONS OF THE STUDY

The number of patients included in the study was limited. However, compared to similar studies, most of which involved fewer than 30 patients, our cohort represents a substantial sample size. Importantly, our study did not include parameters of advanced echocardiographic techniques, such as strain, strain rate, speckle tracking and 3D echocardiography of the right and left ventricular functions. The reason is that the echocardiographic machine in our unit does not have these software functionalities. We did not evaluate right ventricular fractional area change or diastolic function using echocardiography, as these assessments are not routinely performed at our institution. Based on our findings, it is clear that further studies are required to evaluate the clinical significance of detailed characterisation of right ventricular and left ventricular mechanics, especially in PH associated with CHD. It would be interesting to examine gene expression in primary PH and secondary PH with CHD, which could possibly explain some of the differences observed in this study.

CONCLUSION

Our results demonstrate that both echocardiography and CMRI consistently revealed right heart dilation in patients with PH associated with left-to-right shunts. Right heart dimensions measured by transthoracic echocardiography and CMRI showed a strong correlation. In this study, echocardiographic markers of right ventricular function correlated well with clinical assessment of functional status. However, echocardiographic markers showed a weak

correlation with right ventricular ejection fraction as assessed by CMRI. Moreover, a subset of patients exhibited reduced left ventricular ejection fraction. Therefore, we recommend a comprehensive approach to integrating multiple imaging modalities with clinical evaluation, because the underlying pathophysiology may vary for patients with PH secondary to left-to-right shunts.

Conflict of Interest

The authors declare that there are no conflicts of interest relating to this study.

Acknowledgement

The authors acknowledge the support of the Robert WM Frater Cardiovascular Research Centre.

Abbreviations

ASD	Atrial septal defect
Ao	Aorta
ASVD	Atrioventricular septal defect
BMI	Body mass index
CI	Cardiac index
CHD	Congenital heart disease
CMRI	Cardiac magnetic resonance imaging
IQ1	25th quartile
IQ3	75th quartile
IVS	Interventricular septum
LA	Left atrium
LV	Left ventricle
LVED	Left ventricular end-diastolic
LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
LVEF	Left ventricular ejection fraction
LVSF	Left ventricular systolic function
MAPSE	Mitral annular plane systolic excursion
PAP	Pulmonary artery pressure
mPAP	Mean pulmonary artery pressure
mL	Mililitre

MPI	Myocardial performance index
NYHA	New York Heart Association
PAWP	Pulmonary artery wedge pressure
PH	Pulmonary hypertension
PDA	Patent ductus arteriosus
PVR	Pulmonary vascular resistance
RHC	Right heart catheterisation
RV	Right ventricle
RVEF	Right ventricular ejection fraction
RVEDV	Right ventricular end-diastolic volume
RVESV	Right ventricular end-systolic volume
RVSP	Right ventricular systolic pressure
RVMPI	Right ventricle myocardial performance index
S’	Tricuspid annulus peak systolic velocity
TAPSE	Tricuspid annular plane systolic excursion
TR	Tricuspid regurgitation
TDI	Tissue Doppler imaging
VSD	Ventricular septal defect
3D	Three dimensional

REFERENCES

1. Zhao M, Liu J, Xin M et al. Pulmonary arterial hypertension associated with congenital heart disease: An omics study. *Front Cardiovasc Med* 2023;10(10):1037357. https://doi.org/10.3389/fcvm.2023.1037357.
2. Pascall E, Tulloh RM. Pulmonary hypertension in congenital heart disease. *Future Cardiol* 2018;14(4):343-53. https://doi.org/10.2217/fca-2017-0065.
3. Maarman GJ, A philosophical perspective on pulmonary hypertension: What is 'rare'?. *S Afr J Sci* 2020;116:5-6. https://doi.org/10.17159/sajs.2020/7939.
4. Mocumbi AO, Thienemann F, Sliwa K. A global perspective on the epidemiology of pulmonary hypertension. *Can J Cardiol* 2015;31(4):375–81. https://doi.org/10.1016/j.cjca.2015.01.030.
5. Zuechner A, Mhada T, Majani NG et al. Spectrum of heart diseases in children presenting to a paediatric cardiac echocardiography clinic in the Lake Zone of Tanzania: A 7 years overview. *BMC Cardiovascular Disorders* 2019;19(1):291. https://doi.org/10.1186/s12872-019-01292-4.
6. Dzudie A, Dzekem BS, Ojji DB et al. Pulmonary hypertension in low- and middle-income countries with focus on sub-Saharan Africa. *Cardiovasc Diagn Ther* (2020); 10(2):316-324. https://doi.org/10.21037/cdt.2019.07.06.
7. Thienemann F, Dzudie A, Mocumbi AO et al. Rationale and design of the Pan African Pulmonary hypertension Cohort (PAPUCO) study: implementing a contemporary registry on pulmonary hypertension in Africa. *BMJ Open* 2014;4(10):e005950. https://doi.org/10.1136/bmjopen-2014-005950.
8. Aryal SR, Sharifov OF, Lloyd SG. Emerging role of cardiovascular magnetic resonance imaging in the management of pulmonary hypertension. *Eur Respir Rev* 2020;29(156):190138. https://doi.org/10.1183/16000617.0138-2019.
9. Mani CB, Chaudhari SS. *Right Heart Cardiac Catheterization*. StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK557404/.
10. Grünig E, Peacock AJ. Imaging the heart in pulmonary hypertension: an update. *European Respiratory Review* 2015;24(138):653-64. https://doi.org/10.1183/16000617.0058-2015.
11. Singh RP, Singh P, Kler TS et al. Diagnostic value of cardiac magnetic resonance imaging (CMRI) in the evaluation of arrhythmia and cardiomyopathy. *Cureus* 2024;16(10):e72675. https://doi.org/10.7759/cureus.72675.

12. Bodar V, Modi K. *Radionuclide ventriculography*. StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK562164/.
13. Wharton G, Steeds R, Allen J et al. A minimum dataset for a standard adult transthoracic echocardiogram: a guideline protocol from the British Society of Echocardiography. *Echo Res Pract* 2015;2(1):G9-24. https://doi.org/10.1530/ERP-15-0024.
14. Galderisi M, Cosyns B, Edvardsen T et al. 2016-2018 EACVI Scientific Documents Committee; 2016–2018. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovas Imaging* 2017;18(12):1301-10. https://doi.org/10.1093/ehjci/jex244.
15. Accreditation for Cardiovascular Excellence (ACE). ACE Congenital Heart Disease (CHD) Standards for Pediatric and Congenital Cardiac Catheterization Laboratory (PCCL) accreditation. New Standard Establish Comprehensive Guidelines for Congenital Heart Disease; 2015; Retrieved April 2021: https://www.cvexcel.org/pccl.aspx
16. Fogel MA, Anwar S, Broberg C et al. Society for Cardiovascular Magnetic Resonance/European Society of Cardiovascular Imaging/American Society of Echocardiography/Society for Pediatric Radiology/North American Society for Cardiovascular Imaging Guidelines for the use of cardiovascular magnetic resonance in pediatric congenital and acquired heart disease: Endorsed by The American Heart Association. *J Cardiovasc Magn Reson* 2022;24(1):37. https://doi.org/10.1186/s12968-022-00843-7.
17. Das GK, Ng CS, Abdul Manap M. Left ventricular ejection fraction by multigated acquisition scan using planar sodium iodide and cadmium-zinc-telluride cameras: a comparison with two-dimensional echocardiography. *Asia Ocean J Nucl Med Biol* 2023;11(1):55-70. https://doi.org/10.22038/AOJNMB.2022.60392.1424.
18. Sun X, Zhang H, Aike B et al.Tricuspid annular plane systolic excursion (TAPSE) can predict the outcome of isolated tricuspid valve surgery in patients with previous cardiac surgery? *J Thorac Dis* 2016;8(3):369-74. https://doi.org/10.21037/jtd.2016.02.38.
19. Kurnicka K, Lichodziejewska B, Ciurzyński M et al. Peak systolic velocity of tricuspid annulus is inferior to tricuspid annular plane systolic excursion for 30 days prediction of adverse outcome in acute pulmonary embolism. *Cardiol J* 2020;27(5):558-65. https://doi.org/10.5603/CJ.a2018.0145.

20. Askin L, Yuce Eİ, Tanriverdi O. Myocardial performance index and cardiovascular diseases. *Echocardiography* 2023 4 (7):720-5. https://doi.org/10.1111/echo.15628.
21. Cirin L, Crișan S, Luca CT et al. Mitral annular plane systolic excursion (MAPSE): A review of a simple and forgotten parameter for assessing left ventricle function. *J Clin Med* 2024;13(17):5265. https://doi.org/10.3390/jcm13175265.
22. Kosaraju A, Goyal A, Grigorova Y. Left ventricular ejection fraction. StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK459131/.
23. Chengode S. Left ventricular global systolic function assessment by echocardiography. *Ann Card Anaesth* 2016;19:S26-34. https://doi.org/10.4103/0971-9784.192617.
24. Petersen SE, Aung N, Sanghvi MM et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. *J Cardiovasc Magn Reson* 2017;19(1):18. https://doi.org/10.1186/s12968-017-0327-9.
25. Vermes E, Iacuzio L, Levy F et al. Role of cardiovascular magnetic resonance in native valvular regurgitation: A comprehensive review of protocols, grading of severity, and prediction of valve surgery. *Front Cardiovasc Med* 2022;9:881141. https://doi.org/10.3389/fcvm.2022.881141.
26. Dinarti LK, Hartopo AB, Kusuma AD et al. The COngenital HeARt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry: A descriptive study from single-center hospital registry of adult congenital heart disease and pulmonary hypertension in Indonesia. *BMC Cardiovasc Dis* 2020;20(1):163. https://doi.org/10.1186/s12872-020-01434-z.
27. Mottaghi H, Ghofrani M, Alizadeh B et al. The predictability of echocardiography in children with primary pulmonary hypertension and its comparison with cardiac catheterization parameters. *Zahedan J Res Med Sci* 2022;24(4):e115130. http://dx.doi.org/10.5812/zjrms-115130.
28. Mercer-Rosa L, Yang W, Kutty S et al. Quantifying pulmonary regurgitation and right ventricular function in surgically repaired tetralogy of Fallot: A comparative analysis of echocardiography and magnetic resonance imaging. *Circ Cardiovasc Imaging* 2012;5(5):637-43. https://doi.org/10.1161/CIRCIMAGING.112.972588.
29. Wald RM, Valente AM, Gauvreau K et al. Cardiac magnetic resonance markers of progressive RV dilation and dysfunction after tetralogy of Fallot repair. *Tal Geva Heart* 2015;101(21):1724-30 https://doi.org/10.1136/heartjnl-2015-308014.

30. Hussain K, Mandras SA, Desai S. Right heart failure. StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK459381/
31. Richter MJ, Hsu S, Yogeswaran A et al. Right ventricular pressure-volume loop shape and systolic pressure change in pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2021;320(5):L715-25. https://doi.org/10.1152/ajplung.00583.2020.
32. Brener MI, Masoumi A, Vivian G et al. Invasive right ventricular pressure-volume analysis: Basic principles, clinical applications, and practical recommendations. *Circ Heart Fail* 2022;15(1):e009101. https://doi.org/10.1161/CIRCHEARTFAILURE.121.009101.
33. Kato M, Kitada S, Kawada Y et al. Left ventricular end-systolic volume is a reliable predictor of new-onset heart failure with preserved left ventricular ejection fraction. *Cardiol Res Pract* 2020;3:1-7. https://doi.org/10.1155/2020/3106012.
34. Evaldsson AW, Lindholm A, Jumatate R et al. Right ventricular function parameters in pulmonary hypertension: echocardiography vs. cardiac magnetic resonance. *BMC Cardiovasc Dis* 2020) 20(1):259. https://doi.org/10.1186/s12872-020-01548-4.
35. Sjögren H, Kjellström B, Bredfelt A. Underfilling decreases left ventricular function in pulmonary arterial hypertension. *Int J Cardiovasc Imaging* 2021;37(5):1745–55. https://doi.org/10.1007/s10554-020-02143-6.
36. Alenezi F, Covington TA, Mukherjee M et al. Novel approaches to imaging the pulmonary vasculature and right heart. *Circ Res* 2022;130(9):1445-65. https://doi.org/10.1161/CIRCRESAHA.121.319990.
37. Yanagi Y, Amano M, Tamai Y et al. Accuracy of shunt volume measured by three-dimensional echocardiography and cardiac magnetic resonance in patients with an atrial septal defect and a dilated right ventricle. *J Am Soc Echocardiogr* 2024;37(8):797-805. https://doi.org/10.1016/j.echo.2024.04.016.
38. Cankaya B Y, Kantarci M, Gundogdu F. Evaluation and comparison of left ventricular functions by cardiac MRI and 2D transthoracic echocardiography. *Eurasian J Med* 2021;53(1):28-33. https://doi.org/10.5152/eurasianjmed.2021.20038.
39. Escudero EM, Orlowski A, Díaz A et al. Gender differences in cardiac left ventricular mass and function: Clinical and experimental observations. *Cardiol J* 2014;21(1):53-9. https://doi.org/10.5603/CJ.a2013.0105.
40. Hardziyenka M, Campian ME, Reesink HJ et al. Right ventricular failure following chronic pressure overload is associated with reduction in left ventricular mass. *JACC* 2011;57(8):921-8. https://doi.org/10.1016/j.jacc.2010.08.648.

41. Triposkiadis F, Xanthopoulos A, Boudoulas KD et al. The interventricular septum: Structure, function, dysfunction, and diseases. *J Clin Med* 2022;11(11):3227. https://doi.org/10.3390/jcm11113227.
42. Stoppel WL, Hu D, Ibrahim J et al. Anisotropic silk biomaterials containing cardiac extracellular matrix for cardiac tissue engineering. *Biomed Mater* 2016;10(3):034105. https://doi.org/10.1088/1748-6041/10/3/034105.
43. Ventetuolo CE, Ouyang P, Bluemke DA et al. Sex hormones are associated with right ventricular structure and function: The MESA-right ventricle study. *Am J Respir Crit Care Med* 2011;183(5):659-67. https://doi.org/10.1164/rccm.201007-1027OC.
44. Keen J, Prisco SZ, Prins KW. Sex differences in right ventricular dysfunction: Insights from the bench to bedside. *Front Physiol* 2021;11:623129. https://doi.org/10.3389/fphys.2020.623129.
45. Lee JS, Jung JM, Choi J et al. Major adverse cardiovascular events in Korean congenital heart disease patients: A nationwide age- and sex-matched case-control study. *Yonsei Med J* 2022;63(12):1069-77. https://doi.org/10.3349/ymj.2022.0111.
46. Dawes TJW, de Marvao A, Shi W et al. Machine learning of three-dimensional right ventricular motion enables outcome prediction in pulmonary hypertension: A cardiac MR imaging study. Radiology 2017; 283(2):381-90. https://doi.org/10.1148/radiol.2016161315.
47. Bernal-Ramirez J, Díaz-Vesga MC, Talamilla M et al. Exploring functional differences between the right and left ventricles to better understand right ventricular dysfunction. *Oxid Med Cell Long* 2021;1:21. https://doi.org/10.1155/2021/9993060.
48. Molnar AA, Kovacs A, Lakatos BK et al. Sinus of Valsalva aneurysm protruding intramurally into right ventricle: does size really matter? *Eur Heart J Cardiovasc Imaging* 2018;19(2):234. https://doi.org/10.1093/ehjci/jex227.
49. Kovács A, Lakatos B, Tokodi, M. Right ventricular mechanical pattern in health and disease: beyond longitudinal shortening. *Heart Fail Rev* 2019;24:511-20. https://doi.org/10.1007/s10741-019-09778-1.
50. Shang X, Xiao S, Dong N et al. Assessing right ventricular function in pulmonary hypertension patients and the correlation with the New York Heart Association (NYHA) classification. *Oncotarget* 2017;8(52):90421-9. https://doi.org/10.18632/oncotarget.19026.

51. Smiseth OA, Donal E, Boe E et al. Phenotyping heart failure by echocardiography: Imaging of ventricular function and haemodynamics at rest and exercise. *Eur Heart J Cardiovasc Imaging* 2023;24(10):1329-42. https://doi.org/10.1093/ehjci/jead196.
52. Avitabile CM, Whitehead K, Fogel M et al. Tricuspid annular plane systolic excursion does not correlate with right ventricular ejection fraction in patients with hypoplastic left heart syndrome after Fontan palliation. *Pediatr Cardiol* 2014;35(7):1253–8. https://doi.org/10.1007/s00246-014-0924-4.
53. Mercer-Rosa L, Parnell A, Forfia PR et al. Tricuspid annular plane systolic excursion in the assessment of right ventricular function in children and adolescents after repair of tetralogy of Fallot. *J Am Soc Echocardiogr* 2013;26(11):1322-9. https://doi.org/10.1016/j.echo.2013.06.022.
54. Hoette S, Creuzé N, Günther SRV. Fractional area change and TAPSE as predictors of severe right ventricular dysfunction in pulmonary hypertension: A CMR study. *Lung* 2018;196(2):157–164. https://doi.org/10.1007/s00408-018-0089-7.
55. Manders E, Bogaard HJ, Handoko ML et al. Contractile dysfunction of left ventricular cardiomyocytes in patients with pulmonary arterial hypertension. *J Am Coll Cardiol* 2014;64(1):28-37. https://doi.org/10.1016/j.jacc.2014.04.031.
56. Rajagopalan N, Simon MA, Edelman K et al. Identifying left ventricular dysfunction in pulmonary hypertension. *Congest Heart Fail* 2009;15(5):218-21. https://doi.org/10.1111/j.1751-7133.2009.00105.x.
57. Gorter TM, van Veldhuisen DJ, Bauersachs J et al.Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;20(1):16-37. https://doi.org/10.1002/ejhf.1029.
58. Triposkiadis F, Xanthopoulos A, Boudoulas KD et al. The interventricular septum: Structure, function, dysfunction, and diseases. *J Clin Med* 2022;11(11):3227. https://doi.org/10.3390/jcm11113227.
59. Bhattacharya PT, Shams P, Ellison MB. Right ventricular hypertrophy. StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK499876/
60. Taşolar H, Mete T, Çetin M et al. Mitral annular plane systolic excursion in the assessment of left ventricular diastolic dysfunction in obese adults. *Anatol J Cardiol* 2015;15(7):558-64. https://doi.org/10.5152/akd.2014.5561.
61. Mohsen S, Naderi M, Abbasi M et al. Correlation of equilibrium radionuclide ventriculography scan with two-dimensional transthoracic echocardiography for early

evaluation of the left ventricular ejection fraction after anthracycline treatment in patients with acute lymphoid leukemia. *JMRO* 2024;4(2):22-9. https://doi.org/10.53011/JMRO.2024.02.03.

62. Shah A, Nanjayya V, Ihle J. Mitral annular plane systolic excursion as a predictor of left ventricular ejection fraction in mechanically ventilated patients. *Australas J Ultrasound Med* 2019;22(2):138-42. https://doi.org/10.1002/ajum.12131.

CHAPTER 5 – GENERAL CONCLUSION

5.1 INTRODUCTION

Congenital heart disease is one of the most common birth abnormalities and affects approximately one in every 100 children. Timely treatment of congenital cardiac defects typically prevents the progression of pulmonary vascular disease. In sub-Saharan Africa, patients often present to hospital only once they become symptomatic in the late stages of the disease, which contributes to high mortality rates and PH. Little data are available to accurately estimate the number of children with CHD who are at risk of developing pulmonary vascular disease. Uncorrected CHD is a significant cause of PH. Furthermore, surgical correction of CHD in early infancy is often not possible in resource-limited settings. This shortcoming is the result of various factors, including delayed diagnosis caused by a shortage of paediatric cardiology specialists and inadequate infrastructure, such as operating rooms and catheterisation laboratories, required for corrective procedures.

5.2 PAPER I

There is a shortage of demographic data and limited information on right heart features of patients with PH due to CHD. Furthermore, data reporting on functional impairment in children with CHD-associated PH in South Africa is scarce. This study aimed to assess the clinical and echocardiographic features of a group of patients who presented with PH due to CHD.

In this study, most patients (73%) were between the ages of 6 and 17 years, with a median of 9.98 years (range: 7.97–17.7 years). Our results show that the most common congenital abnormality associated with PH was simple VSD (41%). All the patients were symptomatic: almost two-thirds (60%) were in NYHA functional class III, and 40% were in NYHA functional class II. Right-sided dilation was observed in all patients, evidenced by an increased tricuspid valve annular diameter (median z-score: 2.44 [2.31–2.67]). This dilation was associated with significant TR and marked pulmonary artery dilation (median z-score: 4.23 [3.60–4.75]). Right ventricular systolic dysfunction was confirmed for all patients by conventional echocardiographic parameters, including decreased TAPSE, reduced S', prolonged RVMPI and impaired calculated RV free wall strain. The median 6-minute walking distance was reduced for all patients. Haemodynamic data from RHC show that the median

mPAP was 52 mmHg. The median aortic saturation was 95% on room air during cardiac catheterisation. Even though our patients had significant pulmonary arterial hypertension, the vast majority of them still had a left–right shunt. The combination of RVSP > 50 mmHg plus pulmonary annulus z-score > 3 to predict PVR > 3Wood unit.m² showed a sensitivity of 82.4% but a low specificity of 14.3%**.** Based on our findings, echocardiography should be used primarily as a screening tool for diagnosing PH; we suggest that elevated peak RVSP and dilated pulmonary artery should prompt further investigation for PH.

5.3 PAPER II

Imaging is fundamental to determining the underlying causes and extent of PH, as it evaluates both right and left heart function as key predictors of morbidity and mortality. However, limited data are available on the use of imaging modalities in CHD patients with PH in South Africa. This study aimed to analyse various imaging modalities to assess the right and left heart function of patients with PH secondary to left-to-right shunts.

For most patients in this study, right ventricular end-diastolic indexed volumes were at least double the normal reference range (median: 240 mL/m²; range: 165–268) on CMRI. Interestingly, CMRI showed that 70% of male participants had normal right ventricular systolic function, compared to only 45% of female participants (p <0.05). Echocardiographic markers of right ventricular function (TAPSE, S', RVMPI) correlated poorly with CMRI RVEF, with correlation coefficients of r = -0.28, r = -0.10 and r = -0.04. However, these echocardiographic markers aligned well with clinical functional assessments (NYHA and 6MWT). LVEF on echocardiography and isotope correlated strongly with CMRI LVEF (r = 0.90). Therefore, we recommend a comprehensive approach that integrates multiple imaging modalities with clinical evaluation, as the underlying pathophysiology may vary among patients with PH secondary to left-to-right shunts.

5.4 CONCLUSION

Our results indicate that, in South Africa, simple lesions that are potentially operable still present with severe PH. According to the NYHA classification and 6MWT, significant functional impairment was observed in all participants. Both echocardiography and CMRI consistently revealed right heart dilation in patients with PH that was associated with congenital left-to-right shunts. Right heart dimensions measured by transthoracic echocardiography and CMRI showed a strong correlation. Echocardiographic markers of right ventricular function

used in this study corresponded well with clinical functional assessments. However, these echocardiographic markers correlated poorly with RVEF measured by CMRI. Additionally, a subset of patients presented with reduced LVEF.

There was a discrepancy between the echocardiographic markers of RV function and CMRI RVEF. Echocardiography tends to perform better in reflecting functional impairments than CMRI RVEF. Based on our results, echocardiography can be used as a screening and continuing assessment tool for diagnosing PH; we recommend a holistic approach that integrates multiple imaging modalities with clinical evaluation. Further studies are required to define the roles of these different techniques.

South Africa can cut late referrals and improve outcomes for children with PH due to CHD by formalising hub-and-spoke referral pathways, equipping district/regional hospitals with handheld echocardiogram plus tele-mentorship, designating regional centres of excellence with protected imaging/cardiac catheterisation capacity, and building a national registry that turns routine care data into actionable insights. Parallel investment in targeted training, retention incentives, and maintenance-backed procurement will stabilise the workforce and infrastructure, while digital eReferral, virtual multidisciplinary team meetings, and patient-centred supports (transport/data subsidies) ensure timely access and continuity of care even in rural settings.

BIBLIOGRAPHY

Abman, S.H., Hansmann, G., Archer, L.S., Ivy, D.D., Adatia, I., Chung, WL et al. (2015). Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. *Circulation,* **132**(21):2037–2099. https://doi.org/10.1530/ERP-17-0071

Augustine, D.X., Coates-Bradshaw, L.D., Willis, J., Harkness, A., Ring, L., Grapsa, J. et al. (2018). Echocardiographic assessment of pulmonary hypertension: a guideline protocol from the British Society of Echocardiography. *Echo Res Pract*, **5**(3):G11-G24.

Agha, H., Shalaby, L., Attia, W., Abdelmohsen, G., Aziz, O.A., Rahman, M.Y.A. (2016). Early ventricular dysfunction after anthracycline chemotherapy in children. *Pediatric Cardiology,* **37**(3):537–544. https://doi.org/10.1007/s00246-015-1311-5

Ahmed, I., Anjum, F. (2023). *Atrioventricular septal defect*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK562194/

Aliku, T. O., Lubega, S., Namuyonga, J. Mwambu, T., Oketcho, M., Omagino, J.O. et al. (2017). Pediatric cardiovascular care in Uganda: current status, challenges, and opportunities for the future. *Annals of Pediatric Cardiology*, **10**(1):50–57. https://doi.org/10.4103/0974-2069.197069

Allison, D.J., Macedo, F.Y. Hamzeh, I.R., Birnbaum, Y. (2017). Correlation of right atrial enlargement on ECG to right atrial volume by echocardiography in patients with pulmonary hypertension. *Journal of Electrocardiology*, **50**(5):555–560. https://doi.org/10.1016/j.jelectrocard.2017.04.012

Anderson, J.J., Lau, E.M. (2022). Pulmonary hypertension definition, classification, and epidemiology in Asia. *JACC Asia*, **2**(5):538–546. https://doi.org/10.1016/j.jacasi.2022.04.008

Askin, L., Yuce, E.İ., Tanriverdi, O. (2023). Myocardial performance index and cardiovascular diseases. *Journal of Echocardiography*, **40(7)**:720–725. https://doi.org/10.1111/echo.15628

Atendi, A.B., Ogunyemi, A.S., Adebayo, R.A., Akintomide, A.P., Ayayi, O.E.,Balogun, M.O. (2023). Relationship between right ventricular systolic function, mean pulmonary arterial pressure and left ventricular ejection fraction in hypertensive heart failure patients seen at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife. *Clinical Cardiology Journal*, **7**(1):1–8.

Aryal, S.R., Sharifov, O.F., Lloyd, S.G. (2020). Emerging role of cardiovascular magnetic resonance imaging in the management of pulmonary hypertension. *European Respiratory Review*, **29**(156):190138. https://doi.org/10.1183/16000617.0138-2019

Bansal, K., Gore, M., Afzal, M., Shams, P., Nalabothu, P. (2024). *Anterior myocardial infarction*. StatPearls; https://www.ncbi.nlm.nih.gov/books/NBK562234/

Barrier, M., Meloche, J., Jacob, M.H., Courboulin, A., Provencher, S., Bonnet, S. (2012). Today's and tomorrow's imaging and circulating biomarkers for pulmonary arterial hypertension. *Cellular and Molecular Life Sciences,* **69**(17):2805–2831. https://doi.org/10.1007/s00018-012-0950-4

Barst, R.J., Ivy, D.D., Foreman, A.J., McGoon, M.D., Rosenzweig, E.B. (2014). Four- and seven-year outcomes of patients with congenital heart disease-associated pulmonary arterial hypertension (from the REVEAL Registry). *American Journal of Cardiology,* **113(1)**:147−155. https://doi.org/10.1016/j.amjcard.2013.09.032

Barst, R.J., McGoon, M.D., Elliott, C.G., Foreman, A.J., Miller, D.P., Ivy, D.D. (2012). Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. *Circulation,* **125**(1):113–122. https://doi.org/10.1161/circulationaha.111.026591

Basit, H., Wallen, T.J., Sergent, B.N. (2023). *Eisenmenger syndrome*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK507800/

Bayram, E., Gülcu, O., Aksu, U., Aksakal, E., Birdal, O., Kalkan, K., (2018). Evaluating the Association Between the Three Different Ejection Fraction Measurement Techniques and Left Ventricle Global Strain. *The Eurasian Journal of Medicine*, **50**(3):173–177. https://doi.org/10.5152/eurasianjmed.2018.17409

Beghetti, M., Galiè, N., Bonnet, D. (2012). Can "inoperable" congenital heart defects become operable in patients with pulmonary arterial hypertension? Dream or reality? *Congenit Heart Dis,* **7**(1) :3-11. https://doi.org/10.1111/j.1747-0803.2011.00611.x

Benza, R.L., Miller, D.P., Barst, R.J., Badesch, D.B., Frost, A.E., McGoon, M.D. (2012). An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest*, **142**(2):448–456. https://doi.org/10.1378/chest.11-1460

Berger, R.M., Beghetti, M., Humpl, T., Raskob, G.E., Ivy, D.D., Jung, Z.-C. et al. (2012). Clinical features of paediatric pulmonary hypertension: A registry study. *The Lancet*, **379**(9815):537-546. https://doi.org/10.1016/s0140-6736(11)61621-8

Bhattacharya, P.T., Shams, P., Ellison, M.B. (2024). *Right ventricular hypertrophy*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK499876/

Bodar, V., Modi, K. (2023). *Radionuclide ventriculography*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK562164/

Bonderman, D., Wexberg, D., Martischnig, A.M., Heinzl, H., Lang, M.-B., Sadushi, R. et al. (2011). A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. *European Respiratory Journal*, **37**(5):1096−1103. https://doi.org/10.1183/09031936.00089610

Bonello, B., Renard, S., Mancini, J., Hubert, S., Habib, G., Fraisse, A. (2014). Life span of patients with Eisenmenger syndrome is not superior to that of patients with other causes of pulmonary hypertension. *Cardiovascular Diagnosis & Therapy*, **4**(5):341–349. https://doi.org/10.3978/j.issn.2223-3652.2014.10.03

Borlaug, B.A., Reddy, Y.N.V. (2019). The role of the pericardium in heart failure: Implications for pathophysiology and treatment. *JACC Heart Failure*, **7**(7):574–585. https://doi.org/10.1016/j.jchf.2019.03.021

Bossone, E., D'Andrea, A., D'Alto, M., Citro, R., Argiento, P., Ferrara, F. et al. (2013). Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. *Journal of the American Society of Echocardiography*, **26**(1):1-14. https://doi.org/10.1016/j.echo.2012.10.009

Burkett, D.A., Slorach, C., Patel, S.S., Redington, A.N. Ivy, D.D., Mertens, L. et al. (2016). Impact of pulmonary hemodynamics and ventricular interdependence on left ventricular

diastolic function in children with pulmonary hypertension. *Circulation: Cardiovascular Imaging*, **9**(9):10. https://doi.org/10.1161/circimaging.116.004612

Condon, D.F., Nickel, N.P., Anderson, R., Mirza, S., de Jesus Perez, V.A. (2019). The 6th World Symposium on Pulmonary Hypertension: What's old is new. *F1000Res*, **8**:F1000 Faculty Rev-888. https://doi.org/10.12688/f1000research.18811.1

Cirin, L., Crișan, S., Luca, C.T., Buzaș, R., Lighezan, D.F., Văcărescu, C. et al. (2024). Mitral annular plane systolic excursion (MAPSE): A review of a simple and forgotten parameter for assessing left ventricle function. *Journal of Clinical Medicine*, **13**(17):5265. https://doi.org/10.3390/jcm13175265

Chan, A., Aijaz, A., Zaidi, A.N. (2020). Surgical outcomes in complex adult congenital heart disease: a brief review. *Journal of Thoracic Disease*, **12**(3):1224–1234. https://doi.org/10.21037/jtd.2019.12.136

Chester, A.H., Yacoub, M.H. (2014). The role of endothelin-1 in pulmonary arterial hypertension. *Global Cardiology Science & Practice*, **2014**(2):62–78. https://doi.org/10.5339/gcsp.2014.29

Chua, J., Zhou, W., Ho, J.K., Patel, N.A., Mackensen, G.B., Mahajan, A. (2013). Acute right ventricular pressure overload compromises left ventricular function by altering septal strain and rotation. *Journal of Applied Physiology*, **115**(2):186–193. https://doi.org/10.1152/japplphysiol.01208.2012

Chengode, S. (2016). Left ventricular global systolic function assessment by echocardiography. *Annals of Cardiac Anaesthesia*, **19**(Suppl 1):S26–S34. https://doi.org/10.4103/0971-9784.192617

Dakkak, W., Alahmadi, M.H., Oliver, T.I. (2024). *Ventricular septal defect*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK470330/

D'Alto, M., Mahadevan, V.S. (2012) Pulmonary arterial hypertension associated with congenital heart disease. *European Respiratory Review*, **21**(126):328–337. https://doi.org/10.1183/09059180.00004712

Das, B.B. (2025). Mechanism and Treatment of Right Ventricular Failure Due to Pulmonary Hypertension in Children. *Children (Basel)*, **12**(4): 476. https://doi.org/10.3390/children12040476

Das, G.K., Ng, C.S., Abdul Manap, M. (2023). Left ventricular ejection fraction by multigated acquisition scan using planar sodium iodide and cadmium-zinc-telluride cameras: a comparison with two-dimensional echocardiography. *Asia Oceania Journal of Nuclear Medicine and Biology*, **11**(1):55–70. https://doi.org/10.22038/AOJNMB.2022.60392.1424

Demir, R., Küçükoğlu, M.S. (2015). Six-minute walk test in pulmonary arterial hypertension. *Anadolu Kardiyoloji Dergisi/The Anatolian Journal of Cardiology*, **15**(3):249–254. https://doi.org/10.5152/akd.2015.5834

Diller, G.P., Kempny, A., Inuzuka, R., Radke, R. Wort, S.J., Baumgartner, H. et al. (2014). Survival prospects of treatment naïve patients with Eisenmenger: a systematic review of the literature and report of own experience. *Heart*, **100**(17):1366–1372. https://doi.org/10.1136/heartjnl-2014-305690

DiLorenzo, M.P., Bhatt, S.M., Mercer-Rosa, L. (2015). How best to assess right ventricular function by echocardiography. *Cardiology in the Young*, **25**(8):1473–1481. https://doi.org/10.1017/s1047951115002255

Dinarti, L.K., Hartopo, A.B., Kusuma, A.D., Satwiko, M.G., Hadwiono, M.R., Pradana, A.D., et al. (2020). The COngenital HeARt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry: A descriptive study from single-center hospital registry of adult congenital heart disease and pulmonary hypertension in Indonesia. *BMC Cardiovascular Disorders*, **20**(1):163. https://doi.org/10.21203/rs.2.14688/v3

Ekström, M., Li ,P.Z., Lewthwaite, H. Bourbeau, J., Tan, W. C., & Jensen, D. (2023). The modified Borg/6-min walk distance ratio: a method to assess exertional breathlessness and leg discomfort using the 6-min walk test. *ERJ of Open Research*, **9**(5):00281. https://doi.org/10.1183/23120541.00281-2023

Eldamanhory, A.S., Mansour, K.S,. Elmaaty, M. S. A., Ghanem, I.G.A. (2023). Role of tricuspid annular plane systolic excursion in echocardiographic evaluation of right ventricular systolic function. *International Journal of Chemical and Biochemical Sciences*, **24**(10):1336−1340.

El-Korashy, R.I.M., Amin, Y. M., Eissa, A.I., Thabet, T.S. (2014). Echocardiography versus right heart catheterization in class I pulmonary hypertension. *Egyptian Journal of Chest Diseases and Tuberculosis*, **63**(2):419–422. https://doi.org/10.1016/j.ejcdt.2013.12.005

Farber, H.W., Miller, D.P., McGoon, M.D., Frost, A.E., Benton, W.W. Benza, R.L. (2015). Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. *The Journal of Heart and Lung Transplantation*, **34**(3):362–368. https://doi.org/10.1016/j.healun.2014.08.020

Fagiry, M.A., Abdelaziz, I., Davidson, R., Mahmoud, M.Z. (2021). The recent advances, drawbacks, and the future directions of CMRI in the diagnosis of IHD. *Scientific Reports*, **11**(1):14958. https://doi.org/10.1038/s41598-021-94311-4

Finegold, J.A., Asaria, P., Francis, D.P. (2013). Mortality from ischaemic heart disease by country, region, and age: Statistics from World Health Organisation and United Nations. *International Journal of Cardiology*, **168**(2):934–945. https://doi.org/10.1016/j.ijcard.2012.10.046

Ford, I., Robertson, M., Komajda, M., Böhm, M., Borer, J.S., Tavazzi, L. et al. (2015). Top ten risk factors for morbidity and mortality in patients with chronic systolic heart failure and elevated heart rate: The SHIFT Risk Model. *International Journal of Cardiology*, **184**:163–169. https://doi.org/10.1016/j.ijcard.2015.02.001

Fountain, J.H., Kaur, J., Lappin, S.L. (2023). *Physiology, renin angiotensin system*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK470410/

Frank, D.B., Hanna, B.D. (2015). Pulmonary arterial hypertension associated with congenital heart disease and Eisenmenger syndrome: current practice in pediatrics. *Minerva Pediatrica*, **67**(2):169-85.

Galiè, N., Humbert, M., Vachiéry, J., Gibbs, S., Lang, I., Torbicki, A. et al. (2016). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal*, **37**(1):67−119. https://doi.org/10.1093/eurheartj/ehv317

GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, **396**(10258):1204–1222.

George, P.M., Oliver, E., Dorfmuller, P., Dubois, O.D., Reed, D.M., Kirkby, N.S. et al. (2014). Evidence for the involvement of type I interferon in pulmonary arterial hypertension. *Circulation Research*, **114**(4):677–688. https://doi.org/10.1161/circresaha.114.302221

Giusca, S., Dambrauskaite, V., Scheurwegs, C., D'hooge, J., Claus, P., Herbots, L. et al. (2010). Deformation imaging describes right ventricular function better than longitudinal

displacement of the tricuspid ring. *Heart*, **96**(4):281–288. https://doi.org/10.1136/hrt.2009.171728

Goroshi, M., Chand, D. (2016). Myocardial Performance Index (Tei Index): A simple tool to identify cardiac dysfunction in patients with diabetes mellitus. *Indian Heart Journal*, **68**(1):83−87. https://doi.org/10.1016/j.ihj.2015.06.022

Gorter, T.M., Obokata, M., Reddy, Y.N.V., Melenovsky, V., Borlaug, B.A. (2018). Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. *European Heart Journal,* **39**:2825–2835. https://doi.org/10.1093/eurheartj/ehy331

Grue, J.F., Storve, S., Dalen, H., Salvesen, Ø., Mjølstad, O.C., Samstad, S.O., Torp, H., Haugen, B.O. (2018). Automatic measurements of mitral annular plane systolic excursion and velocities to detect left ventricular dysfunction. *Ultrasound in Medicine & Biology*, **44**(1):168−176. https://doi.org/10.1016/j.ultrasmedbio.2017.09.002

Gu, L., Li, Y.Y., Gu, L., Xie, L., Liu, H.M. (2020). Idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease in Chinese children: Similarities, differences, and prognostic factors. *Frontiers in Pediatrics*, **8**:106. https://doi.org/10.3389/fped.2020.00106

Grünig, E., Peacock, A.J. (2015). Imaging the heart in pulmonary hypertension: an update. E*uropean Respiratory Review*, **24**(138):653-664. https://doi.org/10.1183/16000617.0058-2015

Guazzi, M., Galiè, N. (2012). Pulmonary hypertension in left heart disease. *European Respiratory Review*, **21**(126):338–346. https://doi.org/10.1183/09059180.00004612

Hansmann, G., Apitz, C., Abdul-Khaliq, H., Alastalo, T.P., Beerbaum, P., Bonnet, D. et al. (2016). Executive summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK, *Heart*, **10**(2):ii86–i100. https://doi.org/10.1136/heartjnl-2015-309132

Hansmann, G., Koestenberger, M., Alastalo, T.P., Austin, E.D., Bonnet, D., Budts, W. et al. (2019). Updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. The *American Journal of*

Respiratory and Critical Care Medicine, **38**(9):879–901. https://doi.org/10.1164/ajrccm-conference.2020.201.1_meetingabstracts.a4243

Harerimana., I., Ballot, D.E., Cooper, P.A. (2018). Retrospective review of neonates with persistent pulmonary hypertension of the newborn at Charlotte Maxeke Johannesburg Academic Hospital. *South African Journal of Child Health,* **12**(1):29–33. https://doi.org/10.7196/sajch.2018.v12i1.1245

Hassan, O. K. A., Haider, W., Nemer, G., Skouri, H., Haddad, F., BouAkl, I. (2018). Clinical and genetic characteristics of pulmonary arterial hypertension in Lebanon. *BMC Medical Genetics,* **19**(1):89. https://doi.org/10.1186/s12881-018-0608-7

Hasan, B., Hansmann, G., Budts, W., Heath, A., Hoodbhoy, Z., Jing, Z.-C. et al. (2020). Challenges and special aspects of pulmonary hypertension in middle- to low-income regions. *Journal of the American College of Cardiology,* **75**(19):2463–2477. https://doi.org/10.1016/j.jacc.2020.03.047

Hoeper, M.M., Humbert, M., Souza, R., Idrees, M., Kawut, S.M., Sliwa-Hahnle, K. et al. (2016). A global view of pulmonary hypertension. *The Lancet Respiratory Medicine*, **4**(4):306-22. https://doi.org/10.1016/s2213-2600(15)00543-3

Hoosen, E.G.M., Cilliers, A.M., Hugo-Hamman, C.T., Brown, S.C., Harrisberg, J.R., Takawira, F.F. et al. (2010). Optimal paediatric cardiac services in South Africa – what do we need? *SA Heart Journal*, **7**(1):10-16. http://www.saheart.org/journal/index.php?journal=SAHJ

Hussain, K., Mandras, S.A., Desai, S. (2024). *Right heart failure*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK459381/

Igarashi, A., Sato, T., Tsujino, I., Ohira, H., Yamada, A., Watanabe, T. et al. (2013). Four cases with group 3 out of proportion pulmonary hypertension with a favorable response to vasodilators. *Respiratory Medicine Case Reports*, **9**:4–7. https://doi.org/10.1016/j.rmcr.2013.03.002

Ivy, D., Rosenzweig, E.B., Abman, S.H., Beghetti, M., Bonnet, D., Douwes, J.M. et al. (2024). Embracing the challenges of neonatal and paediatric pulmonary hypertension. *European Respiratory Journal*, **64**(4):2401345. https://doi.org/10.1183/13993003.01345-2024

Jang, A.Y., Shin, M.S. (2020). Echocardiographic screening methods for pulmonary hypertension: A practical review. *Journal of Cardiovasc Imaging*, **28**(1):1–9. https://doi.org/10.4250/jcvi.2019.0104

Kalam, K., Otahal, P., Marwick, T.H. (2014). Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart*, **100**(21):1673–1680. https://doi.org/10.1136/heartjnl-2014-305538

Kalantari, S., Gomberg-Maitland, M. (2016). Group 5 pulmonary hypertension. *Cardiology Clinics*, **34**(4):443–449. https://doi.org/10.1016/j.ccl.2016.04.004

Kalisch-Smith, J.I., Ved, N., Sparrow, D.B. (2020). Environmental Risk Factors for Congenital Heart Disease. *Cold Spring Harbour Perspectives in Biology*, **12**(3):a037234. https://doi.org/10.1101/cshperspect.a037234

Kameny, R.J., Colglazier, E., Nawaytou, H., Moore, P.. Reddy, M.V., Teitel, D. (2017). Pushing the envelope: A treat and repair strategy for patients with advanced pulmonary hypertension associated with congenital heart disease. *Pulmonary Circulation*, **7**(3):747–751. https://doi.org/10.1177/2045893217726086

Kamiyama, J., Jesmin, S., Sakuramoto, H., Shimojo, N., Islam, M.M., Khatun, T. et al. (2014). Assessment of circulatory and pulmonary endothelin-1 levels in a lavage-induced surfactant-depleted lung injury rabit model with repeated open endotracheal suctioning. *Life Sciences*, **118**(2):370–378. https://doi.org/10.1016/j.lfs.2014.04.001

Kim, N.H. (2016). Group 4 pulmonary hypertension: Chronic thromboembolic pulmonary hypertension: Epidemiology, pathophysiology, and treatment. *Cardiology Clinics*, **34**(3):435−41. https://doi.org/10.1016/j.ccl.2016.04.011

Kim, S.H., Behnes, M., Natale, M., Hoffmann, J., Reckord, N., Hoffmann, U. et al. (2016). Galectin-3 reflects mitral annular plane systolic excursion being assessed by cardiovascular magnetic resonance imaging. *Disease Marker* ,**2016**:7402784. https://doi.org/10.1155/2016/7402784

Kosaraju, A., Goyal, A., Grigorova, Y. (2023). *Left ventricular ejection fraction*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK459131/

Kozlik-Feldmann, R., Hansmann, G., Bonnet, D., Schranz, D., Apitz, C., Michel-Behnke, I. (2016). Pulmonary hypertension in children with congenital heart disease (PAH-CHD,

PPHVD-CHD). Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart,* **102**(Suppl 2):ii42-ii48. https://doi.org/10.1136/heartjnl-2015-308378

Kovacs, G., Olschewski, H. (2021). The definition of pulmonary hypertension: history, practical implications and current controversies. *Breathe (Sheffield, England)*, **17**(3):210076. https://doi.org/10.1183/20734735.0076-2021

Korsholm, K., Andersen, A., Kirkfeldt, R.E., Hansen, K.N., Mellemkjær, S., Nielsen-Kudsk, J.E. (2015). Survival in an incident cohort of patients with pulmonary arterial hypertension in Denmark. *Pulmonary Circulation*, **5**(2):364-369. https://doi.org/10.1086/681270

Kurnicka, K., Lichodziejewska, B., Ciurzyński, M., Kostrubiec, M., Goliszek, S., Zdończyk, O. et al. (2020). Peak systolic velocity of tricuspid annulus is inferior to tricuspid annular plane systolic excursion for 30 days prediction of adverse outcome in acute pulmonary embolism. *Cardiology Journal*, **27**(5):558-565. https://doi.org/10.5603/cj.a2018.0145

Kusner, J., Krasuski, R.A. (2023). Echocardiographic evaluation of the right heart in pulmonary hypertension. *Advances in Pulmonary Hypertension,* **22**(3):122–129. https://doi.org/10.21693/1933-088x-22.3.122

Lahm, T., Douglas, I.S., Archer, S.L., Bogaard, H.J., Chesler, N.C., Haddad, F. et al. (2018). Assessment of right ventricular function in the research setting: knowledge gaps and pathways forward, an official American Thoracic Society research statement. *American Journal of Respiratory and Critical Care Medicine*, **198** (4):e15−e43. https://doi.org/10.1164/rccm.201806-1160st

Lan, N.S.H., Massam, B.D., Kulkarni, S.S., Lang, C.C. (2018). Pulmonary arterial hypertension: Pathophysiology and treatment. *Diseases*, **6**(2):38. https://doi.org/10.3390/diseases6020038

Ling, Y., Johnson, M.K., Kiely, D.G., Condliffe, R., Elliot, C.A., Gibbs, J.S.R. et al. (2012). Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. *American Journal of Respiratory and Critical Care Medicine*, **186**(8):790–796. https://doi.org/10.1164/rccm.201203-0383oc

Lopes, A.A., Barst, R.J., Haworth, S.G., Rabinovitch, M., Al Dabbagh, M., Del Cerro, M.J. et al. (2014). Repair of congenital heart disease with associated pulmonary hypertension in children: What are the minimal investigative procedures? Consensus statement from the Congenital Heart Disease and Pediatric Task Forces, Pulmonary Vascular Research Institute (PVRI). *Pulmonary Circulation*, **4**(2):330-41. https://doi.org/10.1086/675995

Lüscher, T.F., Deanfield, J.E. (2023). Screening and prevention in congenital heart disease: Whom, when, and how? *International Journal of Cardiology Congenital Heart Disease*, **14**:100480. https://doi.org/10.1016/j.ijcchd.2023.100480

Mani, C.B., Chaudhari, S.S. (2023). *Right heart cardiac catheterization*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK557404/

Maron, B.A., Leopold, J.A. (2014). The role of renin-angiotensin-aldosterone system in the pathobiology of pulmonary arterial hypertension. *Pulmonary Circulation*, **4**(2):200-210. https://doi.org/10.1086/675984

Maskatia, S.A., Morris, S.A., Spinner, J.A., Krishnamurthy, R., Altman, C.A. (2015). Echocardiographic parameters of right ventricular diastolic function in repaired tetralogy of fallot are associated with important findings on magnetic resonance imaging. *Congenital Heart Disease*, **10**(3): E113–E122. https://doi.org/10.1111/chd.12265

Matos, J., Kronzon, I., Panagopoulos, G., Perk, G. (2012). Mitral annular plane systolic excursion as a surrogate for left ventricular ejection fraction. *Journal of the American Society of Echocardiography*, **25**(9):969–974. https://doi.org/10.1016/j.echo.2012.06.011

Matos Casano, H.A., Anjum, F. (2023). *Six-minute walk test.* StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK576420/

McLaughlin, V.V., Channick, R., de Marco, T., Farber, H. W., Gaine, S., Galié, N. et al. (2020). Results of an expert consensus survey on the treatment of pulmonary arterial hypertension with oral prostacyclin pathway agents. *Chest*, **157**(4):955–965. https://doi.org/10.1016/j.chest.2019.10.043

Mercer-Rosa, L., Yang, W., Kutty, S., Rychik, J., Fogel, M., Goldmuntz, E. (2012). Quantifying pulmonary regurgitation and right ventricular function in surgically repaired tetralogy of Fallot: a comparative analysis of echocardiography and magnetic resonance

imaging. *Circulation: Cardiovascular Imaging*, **5**(5):637-643. https://doi.org/10.1161/circimaging.112.972588

Meinel, K., Koestenberger, M., Sallmon, H., Hansmann, G., Pieles, G.E. (2020). Echocardiography for the Assessment of Pulmonary Hypertension and Congenital Heart Disease in the Young. *Diagnostics (Basel)*, **11**(1):49. https://doi.org/10.3390/diagnostics11010049

Mocumbi, A.O., Thienemann, F., Sliwa, K. (2015). A global perspective on the epidemiology of pulmonary hypertension. *Canadian Journal of Cardiology*, **31**(4):375–381. https://doi.org/10.1016/j.cjca.2015.01.030

Mohsen, S., Naderi, M., Abbasi, M., Etekhari, M.R., Abtahi, H., Houjaghan, A.K. (2024). Correlation of equilibrium radionuclide ventriculography scan with two-dimensional transthoracic echocardiography for early evaluation of the left ventricular ejection fraction after anthracycline treatment in patients with acute lymphoid leukemia. *Journal of Medical and Radiation Oncology*, **4**(2):22-29. https://doi.org/10.53011/jmro.2024.02.03

Modin, D., Møgelvang, R., Andersen, D.M., Biering-Sørensen, T. (2019). Right ventricular function evaluated by tricuspid annular plane systolic excursion predicts cardiovascular death in the general population. *Journal of the American Heart Association,* **8**(10):e012197. https://doi.org/10.1161/jaha.119.012197

Myers, P.O., Tissot, C., Beghetti, M. (2014). Assessment of operability of patients with pulmonary arterial hypertension associated with congenital heart disease. *Circulation Journal*, **78**(1):4–11. https://doi.org/10.1253/circj.cj-13-1263

Namuyonga, J., Lubega, S., Aliku, T., Omagino, J., Sable, C., Lwabi, P. (2020). Pattern of congenital heart disease among children presenting to the Uganda Heart Institute, Mulago Hospital: a 7-year review. *African Health Sciences*, **20**(2):745–752. https://doi.org/10.4314/ahs.v20i2.26

Nuttall, F.Q. (2015). Body mass index: Obesity, BMI, and health: a critical review. *Nutrition Today*, 50(3):117–128.

Ogunmola, O.J., Akintomide, A.O., Olamoyegun, A.M. (2013). Relationship between clinically assessed heart failure severity and the Tei index in Nigerian patients. *BMC Research Notes,* **6**:488. https://doi.org/10.1186/1756-0500-6-488

Olsson, K.M., Nickel, N.P., Tongers, J., Hoeper, M. (2013). Atrial flutter and fibrillation in patients with pulmonary hypertension. *International Journal of Cardiology*, **167**(5):2300−2305. https://doi.org/10.1016/j.ijcard.2012.06.024

Oldroyd, S.H., Manek, G., Bhardwaj, A. (2024). *Pulmonary hypertension*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK482463/

Opotowsky, A.R., Landzberg, M.J., Beghetti, M. (2014). The exceptional and far-flung manifestations of heart failure in Eisenmenger syndrome. *Heart Failure Clinics,* **10**(1):91–104. https://doi.org/10.1016/j.hfc.2013.09.005

Ossa Galvis, M.M., Bhakta, R.T., Tarmahomed, A. (2023). *Cyanotic heart disease*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK500001/

Parasuraman, S., Walker, S., Loudon, B.L., Gollop, N.D., Wilson, A.M., Lowery, C. et al. (2016). Assessment of pulmonary artery pressure by echocardiography – A comprehensive review. *International Journal of Cardiology. Heart & Vasculature*, **12**:45-51. https://doi.org/10.1016/j.ijcha.2016.05.011

Pascall, E., Tulloh, R.M. (2018). Pulmonary hypertension in congenital heart disease. *Future Cardiology*, **14**(4):343–353. https://doi.org/10.2217/fca-2017-0065

Peacock, A.J., Vonk Noordegraaf, A. (2013). Cardiac magnetic resonance imaging in pulmonary arterial hypertension. *European Respiratory Review*, **22**(130):526–534. https://doi.org/10.1183/09059180.00006313

Perez, V.A., Haddad, F., Zamanian, R.T. (2012). Diagnosis and management of pulmonary hypertension associated with left ventricular diastolic dysfunction. *Pulm Circ,* **2**(2):163-169.

Rosenkranz, S., Preston, I.R. (2015). Right heart catheterisation: best practice and pitfalls in pulmonary hypertension. *European Respiratory Review*, **24**(138):642–652. https://doi.org/10.1183/16000617.0062-2015

Rudski, L.G., Lai, W.W., Afilalo, J., Hua, L. Handschumacher, M.D., Chandrasekaran, K. et al. (2010). Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *Journal of the American*

Society of Echocardiography, **23**(7):685–713. https://doi.org/10.1016/j.echo.2010.05.010

Ryan, J.J., Huston, J., Kutty, S., Hatton, N.D., Bowman, L., Tian, L. et al. (2015). Right ventricular adaptation and failure in pulmonary arterial hypertension. *Canadian Journal of Cardiology*, **31**(4):391–406. https://doi.org/10.1016/j.cjca.2015.01.023

Ryding, A. (2013). *Essential echocardiography*. 2nd ed. Edinburgh*:* Churchill Livingstone/Elsevier.

Sakao, S., Voelkel, N.F., Tanabe, N., Tatsumi, K. (2015). Determinants of an elevated pulmonary arterial pressure in patients with pulmonary arterial hypertension. *Respiratory Research*, **16**(1):84. https://doi.org/10.1186/s12931-015-0246-y

Sanz, J., Fernandez-Friera, L., Moral, S. (2010). Imaging Techniques and the Evaluation of the right heart and the pulmonary circulation. *Revista Española de Cardiología (English Edition)*, **63**(2):209–223. https://doi.org/10.1016/s1885-5857(10)70039-6

Sattar, Y., Chhabra, L. (2023). *Electrocardiogram.* StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK549803/

Savarese, G., Paolillo, S., Costanzo, P., D'Amore, C., Cecere, M., Losco, T. et al. (2012). Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *Journal of Am Coll Cardiol*, **60**(13):1192–1201.

Simonneau, G., Gatzoulis, M.A., Adatia, I., Celermajer, D., Denton, C., Ghofrani, A. et al. (2013). Updated clinical classification of pulmonary hypertension. *Journal of American Coll Cardiology,* **62**(25 Suppl):D34–41. https://doi.org/10.1016/j.jacc.2013.10.029

Simonneau, G., Montani, D., Celermajer, D.S., Gatzoulis, M.A., Krowka, M. et al. (2019). Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *European Respiratory Journal*, **53**(1):1801913. https://doi.org/10.1183/13993003.01913-2018

Shiina, Y., Funabashi, N., Lee, K., Daimon, M., Sekine, T., Kawakubo, M. et al. (2009). Right atrium contractility and right ventricular diastolic function assessed by pulsed tissue Doppler imaging can predict brain natriuretic peptide in adults with acquired pulmonary hypertension. *International Journal of Cardiology,* **135**(1):53–59. https://doi.org/10.1016/j.ijcard.2008.03.090

Skinner, G.J. (2017). Echocardiographic assessment of pulmonary arterial hypertension for pediatricians and neonatologists. *Frontiers in Pediatrics*, **5**:168. https://doi.org/10.3389/fped.2017.00168

Song, B., Qi, Q., Liu, R., Xing, W., Tang, H., Li, Y. (2015). Clinical value of Tei index in pediatric patients with repaired tetralogy of Fallot. *International Journal of Clinical and Experimental Medicine*, **8**(5):7971–7976.

Sun, K.L., Lu, Y., Yang , K., Li, S. (2012). ECG Analysis using multiple instance learning for myocardial infarction detection. *IEEE Transactions on Biomedical Engineering*, **59**(12):3348−3356. https://doi.org/10.1109/tbme.2012.2213597

Sun, X., Zhang, H., Aike, B., Yang, S., Yang, Z., Dong, L. et al. (2016). Tricuspid annular plane systolic excursion (TAPSE) can predict the outcome of isolated tricuspid valve surgery in patients with previous cardiac surgery? *Journal of Thorac Disease*, **8**(3):369–374. https://doi.org/10.21037/jtd.2016.02.38

Takatsuki, S., Ivy, D.D. (2013). Current challenges in pediatric pulmonary hypertension. *Seminars in Respiratory and Critical Care Medicine*, **34**(5):627–644. https://doi.org/10.1055/s-0033-1356461

Taleb, M., Khuder, S., Tinkel, J., Khouri, S.J. (2013). The diagnostic accuracy of Doppler echocardiography in assessment of pulmonary artery systolic pressure: a meta-analysis. *Echocardiogram,* **30**(3):258–265. https://doi.org/10.1111/echo.12061

Thomas, C.A., Anderson, R.J., Condon, D.F., de Jesus Perez, V.A. (2020). Diagnosis and management of pulmonary hypertension in the modern era: Insights from the 6th World Symposium. *Pulmonary Therapy*, **6**(1):9–22. https://doi.org/10.1007/s41030-019-00105-5

Tuder, M.R., Archer, S.L., Dorfmuller, P., Erzurum, S. C., Guignabert, C., Michelakis, E. et al. (2013). Relevant issues in the pathology and pathobiology of pulmonary hypertension. *Journal of the American College of Cardiology*, **62**(25):D4–D12. https://doi.org/10.1016/j.jacc.2013.10.025

Ullah, W., Minalyan, A., Saleem, S., Nadeem, N., Abdulla, H.M., Abdalla, A., et al. (2020). Comparative accuracy of non-invasive imaging versus right heart catheterization for the diagnosis of pulmonary hypertension: A systematic review and meta-analysis.

International Journal of Cardiology Heart & Vasculature, **29**:100568. https://doi.org/10.1164/ajrccm-conference.2020.201.1_meetingabstracts.a2923

Vachiéry, J.L., Tedford, R.J, Rosenkranz, S., Palazzini, M., Lang, I., Guazzi, M., et al. (2019). Pulmonary hypertension due to left heart disease. *European Respiratory Journal,* **53**(1):1801897. https://doi.org/10.1183/13993003.01897-2018

Van De Bruaene, A., Budts, W. (2016). Pulmonary hypertension in the changing landscape of congenital heart disease: Global differences and a possible driver of end-stage heart failure. *Netherlands Heart Journal*, **24**(6):372–373. https://doi.org/10.1007/s12471-016-0844-4

Van der Bom, T., Bouma, B.J., Meijboom, F.J., Zwinderman, A.H., Mulder, B.J. (2012). The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation. *American Heart Journal*, **164**(4):568–575. https://doi.org/10.1016/j.ahj.2012.07.023

Van der Feen, D.E., Bartelds, B., De Boer, R.A., Berger, R.M.F. (2017). Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease. *European Heart Journal*, **38**(26):2034-2041. https://doi.org/10.1093/eurheartj/ehx034

Van de Veerdonk, M.C., Kind, T., Marcus, J.T. Mauritz, G.-J., Heymans, M.W., Bogaard, H.-J. et al. (2011). Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *Journal of the American College of Cardiology,* **58**(24):2511–2519. https://doi.org/10.1016/j.jacc.2011.06.068

Vermes, E., Iacuzio, L., Levy, F., Bohbot, Y., Renard, C., Gerber, B. et al. (2022). Role of cardiovascular magnetic resonance in native valvular regurgitation: A comprehensive review of protocols, grading of severity, and prediction of valve surgery. *Frontiers in Cardiovascular Medicine*, **9**:881141. https://doi.org/10.3389/fcvm.2022.881141

Warnes, C.A., Liberthson, R., Danielson, G.K., Dore, A., Harris, L., Hoffman, J.I. et al. (2001). Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol*, **37**(5): 1170-5. https://doi.org/ 10.1016/s0735-1097(01)01272-4

Widrich, J., Shetty, M. (2024). *Physiology, pulmonary vascular resistance*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK554380/

Wu, V.C.C., Takeuchi, M. (2018). Echocardiographic assessment of right ventricular systolic function. *Cardiovascular Diagnosis and Therapy*, **8**(1):70–79. https://doi.org/10.21037/cdt.2017.06.05

Yankah, C., Fynn-Thompson, F., Antunes, M., Edwin, F., Yuko-Jawi, C., Mendis, S. et al. (2014). Cardiac surgery capacity in sub-Saharan Africa: quo vadis? *The Thoracic and Cardiovascular Surgeon,* **62**(5):393–401. https://doi.org/10.1055/s-0034-1383723

Yap, J., Lim, F.Y., Gao, F., Teo, L.L., Lam, C.S., Yeo, K.K. (2015). Correlation of the New York Heart Association classification and the 6-minute walk distance: A systematic review. *Clinical Cardiology,* **38**(10):621–628. https://doi.org/10.1002/clc.22468

Zaidi, A., Knight, D.S., Augustine, D.X., Harkness, A., Oxborough, D., Pearce, K. et al. (2020). Education Committee of the British Society of Echocardiography. Echocardiographic assessment of the right heart in adults: a practical guideline from the British Society of Echocardiography. *Echo Research and Practice*, **7**(1):G19–G41. https://doi.org/10.1530/erp-19-0051

Zidan, D.H., Helmy, T.A. (2016). Usefulness of mitral annular plane systolic excursion in assessment of left ventricular systolic function in mechanically ventilated obese patients. *Journal of Critical Care,* **34**:74–6. https://doi.org/10.1016/j.jcrc.2016.03.022

Zijlstra, W.M., Douwes, J.M., Ploegstra, M.J., Krishnan, U., Roofthooft, M.T., Hillege, H.L. et al. (2016). Clinical classification in pediatric pulmonary arterial hypertension associated with congenital heart disease. *Pulm Circ*, **6**(3):302-12. https://doi.org/10.1086/687764

Zháo, J., Peng, M., Xu, L. (2015). Equilibrium radionuclide angiocardiography for the evaluation of right ventricular ejection fraction in patients with cardiac disorders. *International Journal of Clinical and Experimental Medicine*, **8**(10):18144–18150.

Zuckerman, W.A., Turner, M.E., Kerstein, J., Torres, A., Vincent, J.A., Krishnan, U. et al. (2013). Safety of cardiac catheterization at a center specializing in the care of patients with pulmonary arterial hypertension. *Pulmonary Circulation,* **3**(4):831–839. https://doi.org/10.1086/674752

Zuechner, A., Mhada, T., Majani, N.G., Sharau, G.G., Mahalu, W., Freund, M.W. (2019). Spectrum of heart diseases in children presenting to a paediatric cardiac

echocardiography clinic in the Lake Zone of Tanzania: A 7 years overview. *BMC Cardiovascular Disorders*, **19**(1):291. https://doi.org/10.1186/s12872-019-01292-4

APPENDICES

APPENDIX 1 – ETHICAL CLEARANCE

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

22-Aug-2022

Dear **Musawenkosi Henema**

Ethics Clearance: **Multimodality profiling of pulmonary hypertension in a group of South African patients with congenital heart disease**

Principal Investigator: **Musawenkosi Henema**

Department: **CUT - Central University of Technology**

Submission Page

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2022/0300/3008**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

Research conducted in any Department of Health facility: Researchers are required to sign and return the HSREC approval letters to the provincial Department of Health where they applied. It is also a requirement for researchers to submit electronic copies of their final research findings, and/or make a presentation of their findings and recommendations at departmental research days when and where indicated.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2020); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; International Council for Harmonisation (ICH) Harmonised Guideline, Integrated Addendum to ICH E6(R1), Guideline for Good Clinical Practice (GCP) E6(R2), 2016, SAHPRA Guidelines as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Prof. A. Sherriff
Chairperson: Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00011992; REC 230408-011; IORG 0010096; FWA 00027947
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa
www.ufs.ac.za

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

10-Aug-2023

Dear **Musawenkosi Henema**

Ethics Number: UFS-HSD2022/0300/3008-0005

Ethics Clearance: **Multimodality profiling of pulmonary hypertension in a group of South African patients with congenital heart disease**

Principal Investigator: **Musawenkosi Henema**

Department: **CUT - Central University of Technology**

Submission Page

SUBSEQUENT SUBMISSION APPROVED

With reference to your recent submission for ethical clearance from the Health Sciences Research Ethics Committee. I am pleased to inform you on behalf of the HSREC that you have been granted ethical clearance for your request as stipulated below:

- Annual re-approval: The ethical clearance of this project is extended to 07 August 2024.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2020); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; International Council for Harmonisation (ICH) Harmonised Guideline, Integrated Addendum to ICH E6(R1), Guideline for Good Clinical Practice (GCP) E6(R2), 2016, SAHPRA Guidelines as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

The Principal Investigator (PI) bears final responsibility for the RIMS application. In the event of any misconduct or improper activities perpetuated by a third party, the PI will be held vicariously liable. The HSREC will bear no responsibility or liability for any actions of a PI and/or third party or breach of confidentiality caused by the PI and/or third party.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this request for ethical clearance and we wish you continued success with your research.

Yours Sincerely

Prof. A. Sherriff
Chairperson : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00011992; REC 230408-011; IORG 0010086; FWA 00027947
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa
www.ufs.ac.za