# OUTCOMES OF SINGLE VENTRICLE REPAIR IN CENTRAL SOUTH AFRICA

**Marius Jacobus van Jaarsveld**

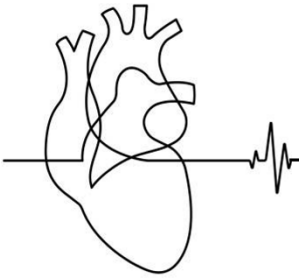
Dissertation submitted in fulfilment of the requirements for the degree

**Master of Health Science in Clinical Technology**
**M_HSCT**

Faculty of Health and Environmental Science
Central University of Technology, Free State
Bloemfontein
South Africa

Supervisor: Prof. S. Brown (DMed FCPaed DCH) Co-Supervisor: Dr L. Botes (DTech; PhD)

**August 2023**

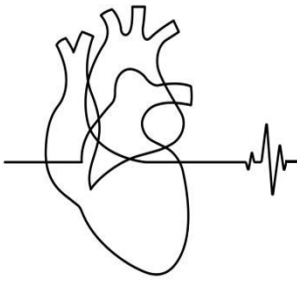


# TABLE OF CONTENTS

**DECLARATION OF INDEPENDENT WORK** ..... **v**
**ACKNOWLEDGEMENTS** ..... **vi**
**SYMBOLS, SI UNITS AND ABBREVIATIONS** ..... **vii**
**LIST OF DEFINITIONS** ..... **ix**
**LIST OF FIGURES** ..... **xi**
**LIST OF TABLES** ..... **xii**
**EXECUTIVE SUMMARY** ..... **xiii**
**CHAPTER 1 - INTRODUCTION** ..... **1**
1.1 Aim ..... 2
1.1.1 Objectives ..... 2
**CHAPTER 2 – LITERATURE REVIEW** ..... **3**
2.1. Introduction ..... 3
2.2. Epidemiology of congenital heart disease ..... 3
2.3. Single ventricle repair/treatment ..... 5
2.3.1. Stage 1: Palliative intervention ..... 7
2.3.1.1 Pulmonary circulation ..... 7
**(A) Blalock-Taussig (BT) shunt** ..... 8
**(B) Central shunt** ..... 9
**(C) Patent Ductus Arteriosus (PDA) stent** ..... 10
**(D) Pulmonary Artery Banding (PAB)** ..... 10
2.3.1.2 Systemic circulation ..... 11
**(A) Coarctectomy** ..... 11
**(B) Damus-Kaye-Stansel (DKS) repair** ..... 12
**(C) Norwood Arch repair** ..... 13
2.3.2. Stage 2: Glenn procedure ..... 14
2.3.3. Stage 3: Fontan procedure ..... 17
2.3.3.1 History of the Fontan procedure ..... 17
2.3.3.2 Physiology of the Fontan procedure ..... 18
2.3.3.3 Challenges in Fontan circulation ..... 20
2.3.3.4 Evaluation of the Fontan procedure ..... 22

**(A) Echocardiographic evaluation** ..... 22
**(B) Ross classification** ..... 26
**(C) Six-minute walk test** ..... 27
2.4. Outcomes of single ventricle repair ..... 28
2.4.1. First World countries ..... 28
2.4.2. Developing countries ..... 29
**CHAPTER 3 – ARTICLE I** ..... **31**
Abstract ..... 32
Introduction ..... 32
Methodology ..... 33
Study design and location ..... 33
Study Population ..... 34
Data Collection ..... 34
*Definitions* ..... 34
Ethics and Statistics ..... 34
Results ..... 35
Stage 1: Palliation ..... 37
Stage 2: Bidirectional Glen ..... 38
Stage 3: Fontan Procedure ..... 38
Last follow-up ..... 39
Discussion ..... 39
Limitations ..... 42
Conclusion ..... 42
**Acknowledgements** ..... 42
**Conflict of interest statement** ..... 42
**References** ..... 43
**CHAPTER 4 – CASE REPORT** ..... **46**
Abstract ..... 47
Introduction ..... 47
Methodology ..... 48
Results ..... 48
Discussion ..... 49
Conclusion ..... 50
References ..... 51
**CHAPTER 5 – GENERAL CONCLUSION** ..... **53**

**REFERENCES** ..... **54**
**APPENDIX A** ..... **66**
**Ethical clearance** ..... **66**
**APPENDIX B** ..... **67**
**Confirmation of publication** ..... **67**



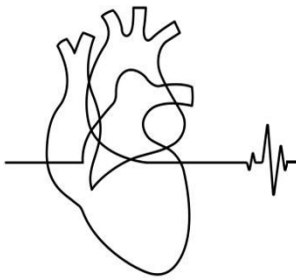
# DECLARATION OF INDEPENDENT WORK

I, Marius Jacobus van Jaarsveld, ID number _____, declare that this research project submitted to the Central University of Technology in fulfilment of the requirements for a **Master's Degree in Health Sciences in Clinical Technology** is my independent work and has not been submitted to any other institution by myself or another individual in fulfilment of my degree.

_____ 28/08/2023

**Marius Jacobus van Jaarsveld** **Date**

Principal Investigator



# ACKNOWLEDGEMENTS

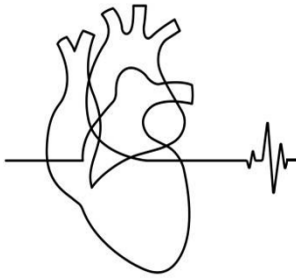
To my supervisor, ***Prof. SC Brown***, I would like to express my deepest gratitude for providing insight, guidance, and advice throughout the research study.

I thank my co-supervisor, ***Dr L Botes***, for assisting and guiding this research study.

The ***Central University of Technology***, for their financial support.

To the ***RWM Frater Cardiovascular Research Centre***, specifically ***Prof. Smit,*** for allowing me to conduct the research study within the Centre.

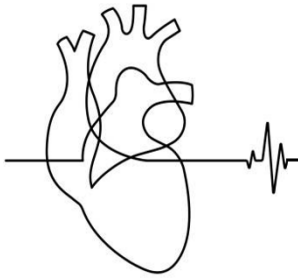
Furthermore, I would like to thank all who supported me throughout this journey.



# SYMBOLS, SI UNITS AND ABBREVIATIONS

| | |
|---|---|
| % | Percentage |
| Cm | Centimetre |
| d | Days |
| Kg | Kilogram |
| $m^2$ | meter squared |
| mmHg | Millimetres of mercury |
| msec | Milliseconds |
| Wood/ $m^2$ | Wood units per square metre |
| yrs | Years |
| A | Atrial wave inflow velocity |
| AHA | American Heart Association |
| AO | Aorta |
| ASD | Atrial septal defect |
| AVSD | Atrioventricular septal defect |
| AVV | Atrioventricular valve |
| BDG | Bidirectional Glen procedure |
| BMI | Body mass index |
| BSA | Body surface area |
| BT | Blalock-Taussig |
| CHD | Congenital heart defects |
| CoA | Coarctation of the aorta |
| CUT | Central University of Technology |
| CT | Computerized tomography |
| CV | Caval veins |
| DILV | Double inlet left ventricle |
| DIRV | Double inlet right ventricle |
| DORV | Double outlet right ventricle |
| DKS | Damus-Kaye-Stansel |
| Dr | Doctor |
| DT | Deceleration time |
| E | Early mitral inflow velocity |
| E’ | AVV annulus velocities in early diastole |
| ECG | Electrocardiography |
| EDV | End-diastolic volume |
| GLS | Global longitudinal |

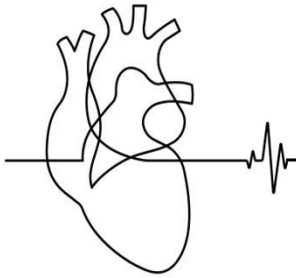
| | |
|---|---|
| GRS | Global radial strain |
| HF | Heart failure |
| HLHS | Hypoplastic left heart syndrome |
| HSREC | Health Sciences Research Ethics Committee |
| ICU | Intensive care |
| IVC | Inferior vena cava |
| IVC-PA | Inferior vena cava-pulmonary artery |
| JAMA | Journal of the American Medical Association |
| LA | Left atrium |
| LV | Left ventricle |
| MAPSE | Mitral annular plane systolic excursion |
| MBTS | Modified Blalock-Taussig shunt |
| mm | Millimetre |
| M mode | Motion Mode |
| MO | Monthly/Months |
| MPA | Main pulmonary artery |
| MPI | Myocardial performance index |
| MR | Magnetic resonance |
| N | Number |
| NT-ProBNP | N-terminal pro-B-type natriuretic peptide hormone |
| NYHA | New York Heart Association |
| PA | Pulmonary artery |
| PAB | Pulmonary artery banding |
| PA IVS | Pulmonary atresia with an intact septum |
| PDA | Patent ductus arteriosus |
| PLE | Protein-losing enteropathy |
| PTFE | Polytetrafluoroethylene |
| RA | Right atrium |
| RV | Right ventricle |
| RV-PA | Right ventricle-pulmonary artery |
| SA | Sinoatrial |
| SO2 | Oxygen saturation |
| SVC | Superior vena cava |
| SVC-PA | Superior vena cava-pulmonary artery |
| SVC-RA | Superior vena cava-right atrium |
| TA | Tricuspid atresia |
| 6MWT | Six-minute walking test |
| TAPSE | Tricuspid annular plane systolic excursion |
| TCPC | Total cavopulmonary connection |
| UAH | Universitas Academic Hospital |
| U-AVSD | Unbalanced atrioventricular septal defect |
| VSD | Ventricle septal defect |
| Y | Years |



# LIST OF DEFINITIONS

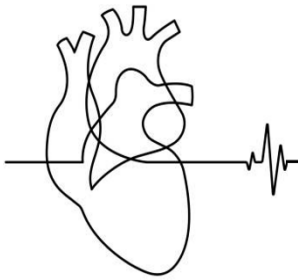
| TERM | DEFINITION |
|---|---|
| **Bidirectional Glen procedure** | A partial cavopulmonary anastomosis (Hauck et al., 2018). |
| **Blalock-Taussig shunt** | Classic end-to-side anastomosis between the subclavian and pulmonary artery (Kiran, 2017). |
| **Central shunt** | A connection between the ascending aorta and the main pulmonary artery with a short PTFE conduit (Kiran, 2017). |
| **Coarctation of the aorta** | Narrowing of the proximal descending aorta classically situated between the left subclavian artery and the ligamentum arteriosum at the aortic isthmus (Agasthi et al., 2020). |
| **Damus-Kaye-Stansel repair** | Anastomosis between the main pulmonary artery and the ascending aorta (Fujii et al., 2011). |
| **Extracardiac Fontan procedure** | A baffle to connect the inferior vena cava to the pulmonary artery without entering the right atrium, but instead is completely outside the heart (Jones, 2018). |
| **Fontan procedure** | The single ventricle pumps oxygenated blood to the systemic circulation and de-oxygenated blood flows passively from the superior and inferior vena cava to the pulmonary arteries (Weston et al., 2016). |
| **Glenn procedure** | The superior vena cava being connected to the right pulmonary artery while the pulmonary artery is detached from the ventricle (Jones, 2018). |
| **Hemi-Fontan procedure** | An anastomosis between the SVC-RA convergence and the central and branch pulmonary arteries directs SVC blood to the pulmonary circulation (Talwar et al., 2014). |
| **McGoon ratio** | Calculated using the equation of left and right pulmonary arterial diameter summation divided by the aorta diameter at diaphragm level (Kansy et al., 2013). |
| **Modified BT shunt** | PTFE or Gore-Tex graft between the subclavian or innominate artery and the pulmonary artery (Kiran, 2017). |

| | |
|---|---|
| **Palliative intervention** | Starts early in the new-born period and usually occurs in three stages with the goal of converting the single ventricle circulation from a parallel to series circulation arrangement (Edwin et al., 2019). |
| **Ross Heart Failure Classification** | A global assessment of heart failure severity (Ross, 2012). |
| **Single-ventricle physiology** | Only one functioning ventricle instead of two well-developed ventricles (Kempny, Dimopoulos and Gatzoulis, 2014). |



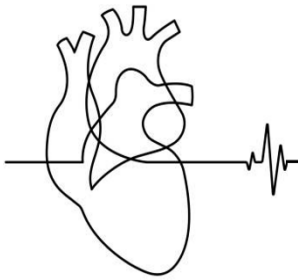
# LIST OF FIGURES


| Figure nr | Title | Page nr |
|---|---|---|
| **1** | Heterogenous group of anomalies that comprises single ventricle disorders. | 4 |
| **2** | Flow diagram of intervention stages in single ventricle repair. | 6 |
| **3** | Classic Blalock-Taussig shunts and modified Blalock-Taussig shunts. | 8 |
| **4** | Schematic presentation of a central shunt with prosthetic Graft. | 9 |
| **5** | Pulmonary artery banding technique. | 11 |
| **6** | Mayor surgical aortic coarctation techniques. | 12 |
| **7** | DKS types. | 13 |
| **8** | Norwood procedures. | 14 |
| **9** | Bidirectional Glen procedure and the hemi-Fontan Method. | 15 |
| **10** | Path lines corresponding to SVC injection for hemi-Fontan procedure and bidirectional Glenn procedure. | 16 |
| **11** | Different types of Fontan-type procedures. | 17 |
| **12** | Cardiac pressures. | 19 |
| **13** | The ten commandments for an ideal Fontan procedure. | 21 |
| **14** | Grading classification of diastolic dysfunction of Fontan Patients. | 24 |



# LIST OF TABLES


| Table nr | Title | Page nr |
|---|---|---|
| I | Prevalence of Congenital Heart Disease subtypes. | 5 |
| II | Cardiovascular system surveillance test. | 22 |
| III | Strengths and weaknesses of echocardiography used in patients with a Fontan circulation. | 23 |
| IV | Classification of TAPSE values. | 25 |
| V | NYHA and modified Ross heart failure classification for children. | 27 |



# EXECUTIVE SUMMARY


## Abstract

**Introduction:** Single ventricle physiology is a critical cardiac condition requiring early diagnosis and intervention. Surgical outcomes of Fontan procedures have improved remarkably over time.

**Objectives:** This retrospective study reports on the management and outcomes of patients diagnosed with single ventricle physiology in Central South Africa. The prospective study examined Fontan patients' functional assessment measured by echocardiography, six-minute walk test and Ross classification.

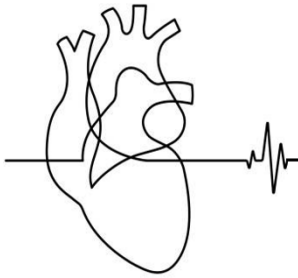
**Methods:** A retrospective observational analysis was conducted on patients presenting with single ventricle physiology at the Universitas Academic Hospital (UAH) in Central South Africa between November 1997 and June 2021. The prospective study evaluated nine Fontan patients during outpatient visits to the Department of Paediatric Cardiology Clinic at the Universitas Academic Hospital, Bloemfontein, South Africa. This evaluation included an echocardiographic examination, a six-minute walk test (according to The American Thoracic Society) and a modified Ross classification by the New York Heart Association (NYHA).

**Results:** The retrospective study reported on one hundred and fifty-four patients presenting with single ventricle physiology: 114 received interventions, and 40 were not eligible for intervention. These patients were referred from the Free State province (54%), Northern Cape (29%) and Lesotho. Overall, patients presented for the first time at a median age of 34.5 days, with patients from nearby districts presenting within a few days of birth. In contrast, patients from outlying areas presented much later. Eighty-seven patients received systemic to pulmonary artery shunting or pulmonary artery banding as a first stage. Sixty-three patients proceeded to bidirectional Glenn

procedures, and 30 patients (26%) had full palliation to Fontan. Twenty-one patients were demised after stage 1, six after the Glenn procedure and two after the Fontan procedure. Overall, 34 (29.8%) patients were lost to follow-up.

The prospective study reported a median peak E wave (Early mitral inflow velocity) of 67.7 cm/sec, and a median peak A wave (Atrial wave inflow velocity) of 52 cm/sec, with a median E/A ratio of 1.28. The median deceleration time was 231.6ms. The median E' was 15.5 cm/sec, and the median E/E' was 4.6 9 cm/sec. The median MAPSE (mitral annular plane systolic excursion) was 10.3 mm, and one TAPSE (tricuspid annular plane systolic excursion) was 15.9 mm. MPI (myocardial performance index) was prolonged with a median left ventricle MPI of 0.47 and one right ventricle MPI of 0.37. The median distance covered during the 6-minute walk tests (6MWT) was 480 metres. Four patients (44%) were classified as class I and five (56%) as class II heart failure using the Ross classification.

**Conclusion:** Patients in the retrospective study presented late, and follow-up of these patients was a challenge. The highest mortality occurs during the first stage of palliation. Outcomes from this study are comparable to other Sub-Saharan studies. Results of the prospective study demonstrated mild functional limitations in 6MWT and heart failure scores. These findings were underscored by the impairment of echocardiographic systolic function indices such as MAPSE/TAPSE and MPI.



# CHAPTER 1 - INTRODUCTION

Single ventricle physiology is a complex congenital heart lesion group requiring early detection and swift intervention (Manuel et al., 2.019). Management is divided into three stages. Stage I comprises either securing pulmonary blood flow using patent ductus arteriosus (PDA) stenting, systemic pulmonary shunting (either Ballock-Taussig (BT) or central shunting) or preventing pulmonary overflow using pulmonary artery banding (PAB). Stage II is the superior cavopulmonary connection or Glen procedure, and stage III is the total cavopulmonary connection or Fontan procedure (Manuel et al., 2019).

Outcomes for the different stages of palliation for single-ventricle physiology have improved over time, leading to better survival and quality of life. Fontan patients, however, face various complications despite their improved hemodynamics (Petit, 2011).

Edwin et al. (2019) reported that although outcomes for single ventricle intervention have improved in developed nations, the same could not be said of African countries. There needs to be more literature regarding outcomes in single ventricle intervention for Africa and especially sub-Saharan Africa; there need to be significant reports on outcomes in South Africa. There are no research results on this topic for the central region of South Africa, where the Universitas Academic Hospital is located.

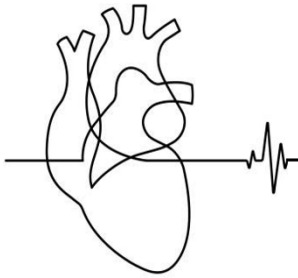
By analysing and presenting the data on outcomes of children who present with single ventricle physiology in Central South Africa, this study aims to satisfy this need. The prospective study will further supply quantitative echocardiographic and clinical data on patients palliated with a Fontan procedure.

## 1.1 Aim

This study aims to determine the long-term outcomes and survival of children who present with single ventricle physiology in Central South African and to investigate the functional status of patients who received a Fontan procedure.

### 1.1.1 Objectives

- Establish the total number of patients who present with single ventricle physiology between November 1997 and December 2019 at the Department of Paediatric Cardiology, Universitas Academic Hospital, Bloemfontein, South Africa.
- Describe the various morphological anomalies of the patients with single ventricle physiology.
- Determine the age of patients at first presentation.
- Determine the number of patients that received stage I interventions, including patent ductus arteriosus (PDA) stenting, systemic pulmonary shunting (either Ballock–Taussig (BT) or central shunt), or pulmonary artery banding (PAB), and the outcomes of these interventions.
- Determine the number of patients that survived to stage II or Glen procedure and the outcomes of these interventions.
- Determine the number of patients that survived to stage III or Fontan procedure and the outcomes of these interventions.
- To investigate the functional status of patients who received a Fontan repair through echocardiographic examinations, a six-minute walk test, and a Ross classification to evaluate heart failure.



# CHAPTER 2 – LITERATURE REVIEW

## 2.1. Introduction

Single-ventricle physiology is also described as "univentricular circulation", "common ventricle", or "functional single ventricle". It comprises several cardiac lesions, with only one functioning ventricle instead of two well-developed ventricles (Kempny et al., 2014).

Neonates with single ventricle physiology have parallel pulmonary and systemic circulations. A single functional ventricle supplies both pulmonary and systemic circulations, leading to cyanosis and ventricular volume overload (Hauck et al., 2017). Therefore, during treatment, patients with single-ventricle physiology typically undergo staged surgical palliation, usually ending in the Fontan procedure (Talwar et al., 2014). Fontan circulation completely alters blood circulation as the single ventricle pumps oxygenated blood to the systemic circulation. Deoxygenated blood flows passively from the superior and inferior vena cava to the pulmonary arteries (Weston et al., 2016).

The survival of children with critical cardiac heart disease, particularly those with single ventricle physiology, has improved drastically amongst other surgical intervention (Rychik et al., 2019; Oster et al., 2013). Data on long-term outcomes for developed countries are abundant however, short- and long-term outcomes for patients in developing countries such as South Africa are limited (Manuel et al., 2019).

## 2.2. Epidemiology of congenital heart disease

According to Weston et al., 2016, congenital disabilities are the leading cause of death in infants (less than one year of age), and the most common congenital disability is congenital heart disease (CHD), occurring in 9 out of every 1000 live births. Single ventricle physiologies have the highest mortality rates for these congenital heart

diseases. The causes of single-ventricle physiology are unknown, with no apparent genetic association and occur in about 4 to 8 out of every 10,000 live births or in about 1-2% of all congenital heart disease patients (Ezzeldin et al., 2019). Single ventricle disorders comprise a heterogeneous group of anomalies, which includes but is not limited to the following (Figure 2.1) (Rhodes and Opotowsky, 2019).

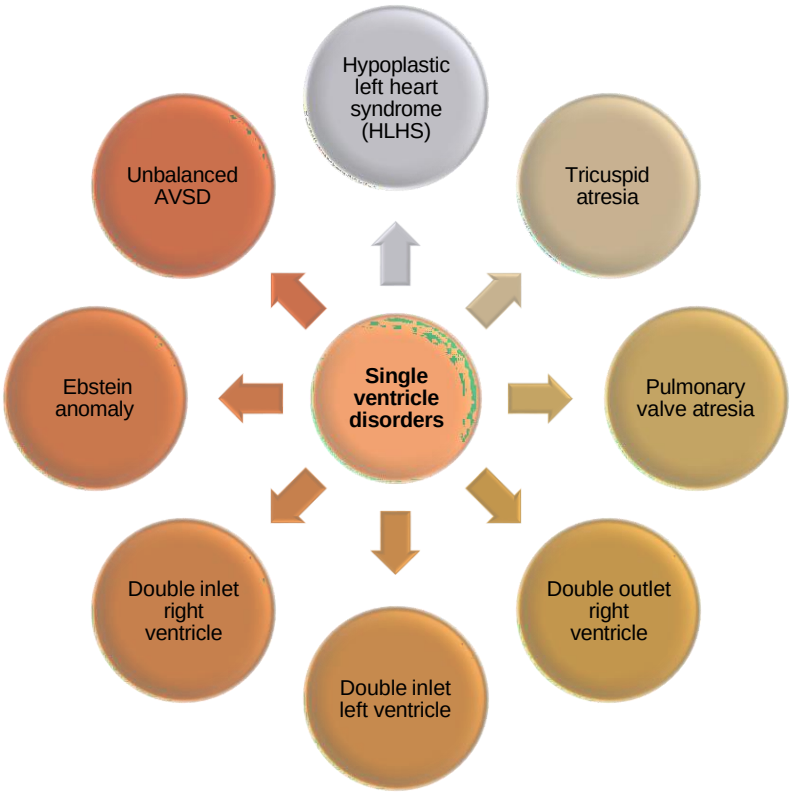



**Figure 2.1:** Heterogenous group of anomalies that comprises single ventricle disorders.

Liu et al. (2019) performed a global meta-analysis studying congenital heart defect prevalence from 1970 to 2017. The prevalence and percentages of subtypes of CHD are summarised in Table 2.1. Single ventricle physiology has a prevalence of 0.093 of CHD subtypes per thousand and accounts for 1.145% of CHD subtypes. A continued increase in the prevalence of CHD was reported globally, with evidence of severe underdiagnosis in Africa (Liu et al., 2019). Due to the higher fertility rate and growing population in developing countries, the disease burden per capita is also higher, with a rising disease prevalence (Rice et al., 2016).

**Table 2.1:** Prevalence of congenital heart disease subtypes (reproduced from Liu et al., 2019).

| CHD subtype | Prevalence of CHD subtype per thousand (95% confidence interval) | Percentage of CHD subtype (95% confidence interval) |
|---|---|---|
| Ventricular septal defect | 3.071 (2.845–3.305) | 35.568 (33.876–37.278) |
| Atrial septal defect | 1.441 (1.215–1.687) | 15.378 (13.492–17.363) |
| Patent ductus arteriosus | 1.004 (0.803–1.228) | 10.172 (8.519–11.954) |
| Pulmonary stenosis | 0.546 (0.485–0.611) | 6.233 (5.703–6.784) |
| Tetralogy of Fallot | 0.356 (0.326–0.387) | 4.422 (4.064–4.794) |
| Transposition of the great arteries | 0.295 (0.269–0.322) | 3.819 (3.446–4.210) |
| Atrioventricular septal defect | 0.290 (0.265–0.316) | 3.595 (3.302–3.900) |
| Coarctation of the aorta | 0.287 (0.261–0.314) | 3.570 (3.273–3.879) |
| Pulmonary arteriovenous aneurysm | 0.272 (0.153–0.425) | 2.975 (1.858–4.343) |
| Congenital heart block | 0.268 (0.028–0.752) | 3.223 (0.268–9.263) |
| Aortic valve insufficiency | 0.251 (0.137–0.400) | 2.318 (1.271–3.667) |
| Aortic stenosis | 0.186 (0.161–0.214) | 2.334 (2.016–2.674) |
| Hypoplastic left heart syndrome | 0.178 (0.162–0.195) | 2.564 (2.251–2.897) |
| Mitral insufficiency | 0.152 (0.097–0.220) | 1.348 (0.899–1.886) |
| Tricuspid atresia or stenosis | 0.117 (0.091–0.146) | 1.071 (0.905–1.250) |
| Double outlet right ventricle | 0.106 (0.090–0.124) | 1.303 (1.127–1.491) |
| Pulmonary atresia | 0.098 (0.085–0.112) | 1.308 (1.113–1.518) |
| Single ventricle | 0.093 (0.080–0.108) | 1.145 (0.975–1.330) |
| Dextrocardia | 0.089 (0.073–0.106) | 1.027 (0.825–1.250) |
| Total anomalous pulmonary venous return | 0.083 (0.071–0.095) | 1.501 (1.163–1.882) |
| Mitral stenosis | 0.083 (0.047–0.130) | 0.955 (0.564–1.446) |
| Truncus arteriosus | 0.078 (0.067–0.089) | 0.982 (0.849–1.124) |
| Ebstein anomaly | 0.044 (0.040–0.049) | 0.534 (0.467–0.606) |
| Coronary artery aneurysm | 0.044 (0.025–0.068) | 0.417 (0.287–0.571) |
| Interrupted aortic arch | 0.041 (0.032–0.051) | 0.609 (0.412–0.844) |
| Partial anomalous pulmonary venous return | 0.039 (0.027–0.053) | 0.314 (0.238–0.400) |
| Cor triatriatum | 0.022 (0.014–0.031) | 0.245 (0.125–0.405) |

## 2.3. Single ventricle repair/treatment

Palliative intervention starts early in the newborn period and usually involves three stages to convert the single ventricle circulation from a parallel to an “in series” circulation arrangement (Edwin et al., 2019). The first stage is generally within a few

days as a palliative intervention to ensure adequate blood flow to either the systemic or pulmonary system or to prevent lung overflow. The second step is a partial cavopulmonary anastomosis or bidirectional Glen procedure, reducing the volume load on the heart by a third. The final step involves a Fontan procedure with complete cavopulmonary anastomosis, where vena cava blood is rerouted directly to the pulmonary circulation. Figure 2.2 illustrates the three stages in treating single ventricle physiology lesions. This allows the body to receive increasing amounts of oxygen while minimising the ventricle loading to preserve ventricular function (Hauck et al., 2017).

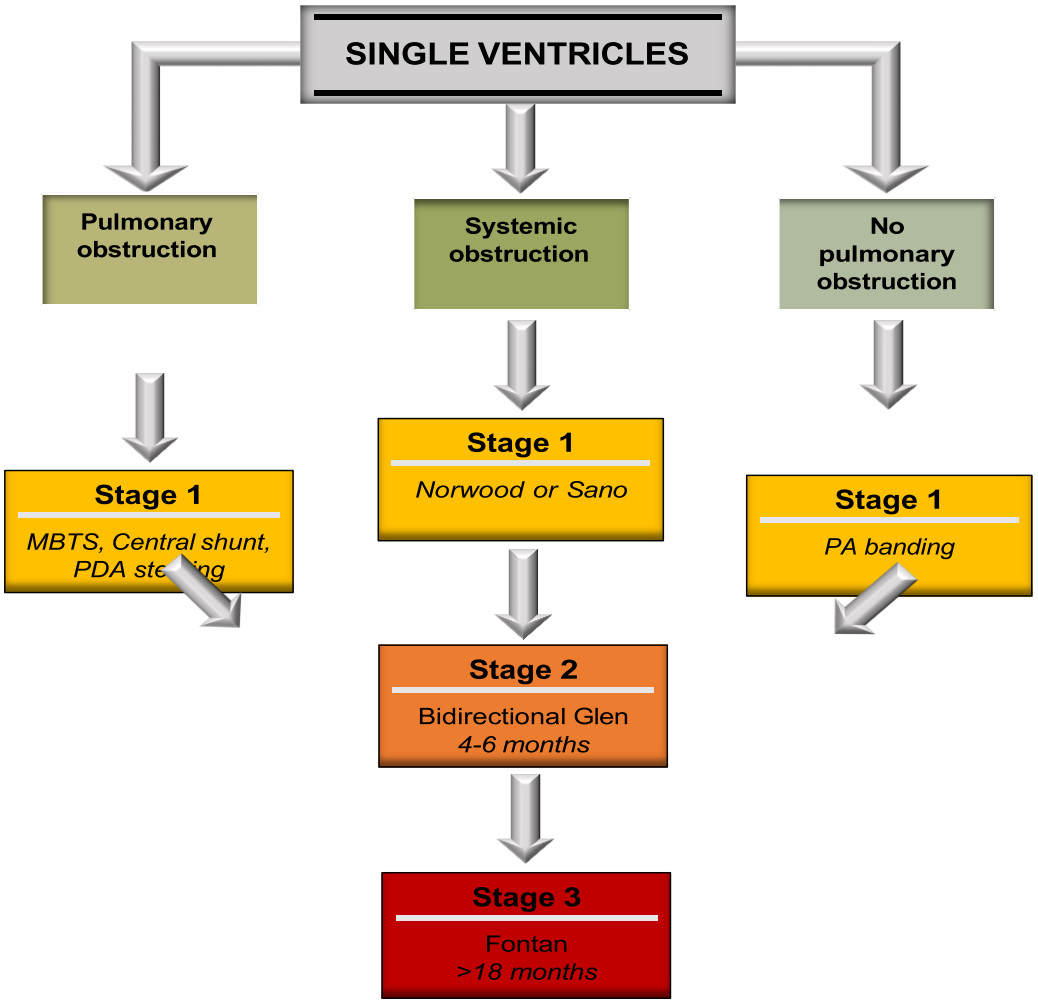



**Figure 2.2:** Flow diagram of intervention stages in single ventricle repair (Brown et al., 2010).

When the Fontan procedure is performed in a single step, it can lead to low cardiac output syndrome due to sudden changes in diastolic ventricular function caused by

the sudden loss of ventricular volume load. Therefore, the Fontan procedure is typically staged, starting with the superior vena cava to pulmonary artery (SVC-PA) connection followed by the inferior vena cava to pulmonary artery (IVC-PA) connection. This preserves initial venous return to the ventricle and allows appropriate time for the ventricle to remodel at a lower end-diastolic volume (EDV) (Stevens, 2017).

### 2.3.1. Stage 1: Palliative intervention

Stage I intervention is performed during the neonatal period, usually within the first few days after birth, to relieve cyanosis but does not resolve the parallel circulation. Notably, the systemic blood flow to the body must be guaranteed, or pulmonary blood flow must be secured (either a shunt to maintain good pulmonary flow or a band to protect from overflow) (Gewillig et al., 2019). The initial palliative intervention is essential and detrimental to the success of an ultimate successful Fontan procedure (Venna et al., 2022).

#### 2.3.1.1 Pulmonary circulation

Two scenarios are possible regarding pulmonary flow. The first is where there is a decreased flow, and the second is an increased pulmonary flow (Gewillig et al., 2019). With a reduced flow, one has to maintain adequate pulmonary flow to the lungs. Depending on the anatomy, a Blalock-Taussig (BT), central shunt or patent ductus arteriosus (PDA) stent allows increased blood flow. PDA stenting is often an emergency procedure early after birth. In patients with pulmonary blood flow obstructions, these interventions help relieve cyanosis. In addition, shunts and PDA stenting allow the pulmonary arteries to grow until the children are at a suitable age and weight for further corrective surgery (Gewillig et al., 2019).

Patients without pulmonary artery obstruction and increased pulmonary artery flow can be considered for a pulmonary artery banding procedure to prevent blood from overflowing into the lungs and prevent pulmonary hypertension (Jones, 2018).

### (A) Blalock-Taussig (BT) shunt

The Blalock-Taussig or BT shunt was named after the surgeon Alfred Blalock and paediatric cardiologist Helen Taussig and was first published in the Journal of the American Medical Association (JAMA) in 1945. Taussig observed that cyanotic patients with right heart obstruction managed better with a PDA than patients where the PDA closed (Kiran, 2017).

Blalock, with the assistance of Vivian Thomas, a surgical technologist, performed the first subclavian artery to pulmonary artery connection and changed the field of paediatric cardiology (McKenzie et al., 2013). The classical BT shunt, first performed in the 1940s, created an end-to-side anastomosis between the subclavian (or the innominate) artery and the ipsilateral pulmonary artery (Zhang et al., 2022). The procedure was performed on the opposite side of the aortic arch to minimise kinking of the subclavian artery and reduce kinking of the pulmonary artery by the longer innominate artery. The advantages of these shunts were that they grew with the patient and were easy to close during corrective surgery. However, some disadvantages included the loss of pulses in the upper limb, thrombosis, and dissection. As a result, the classical BT shunt is rarely used today (Kiran, 2017) (Figure 2.3).

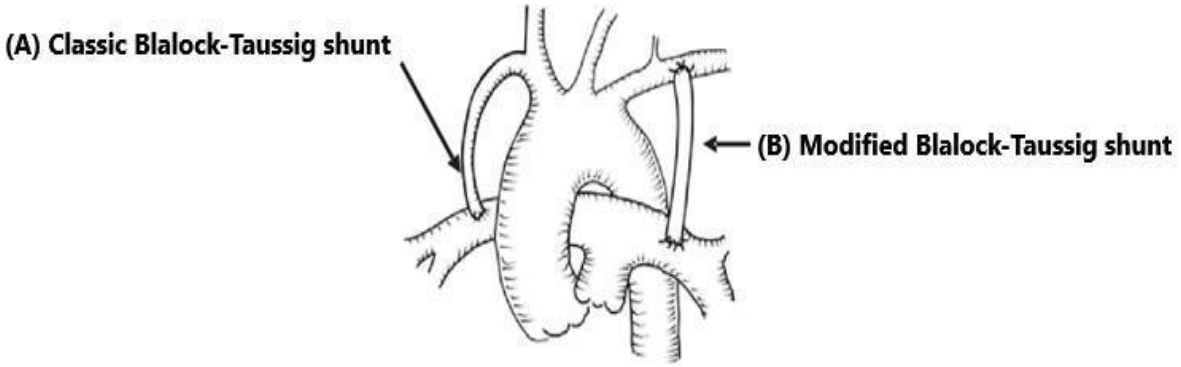



**Figure 2.3:** **(A)** Classic Blalock-Taussig shunts. **(B)** Modified Blalock-Taussig shunt (De Silva et al., 2013).

Nowadays, the modified BT shunt (MBTS) is mainly performed and consists of a Gore-Tex (PTFE) graft (3.5-5.0 mm diameter) placed between the innominate or subclavian artery and the ipsilateral pulmonary artery (Zhang et al., 2022). It is generally a non-

bypass procedure performed through a lateral thoracotomy on either the left or right side (Figure 2.1B).

The advantages of the modified BT shunt are that: (i) the subclavian artery is not sacrificed, (ii) there is less distortion of the pulmonary artery, and (iii) there is better control of blood flow to the pulmonary arteries. Thrombosis of these shunts, leakage of serous fluid into the chest through the PTFE, increased pulmonary blood flow, pleural effusion, and diaphragmatic paralysis account for the disadvantages of the modified BT shunt (AbdelMassih et al., 2021).

### (B) Central shunt

A central shunt connects the ascending aorta and the main pulmonary artery via a short PTFE conduit (Figure 2.4). It is beneficial where both the branch pulmonary arteries are small and in cases where the succeeding operative procedure requires a median sternotomy (Boa et al., 2014).

However, the central shunt has both advantages and disadvantages. The benefits include: (i) it can be performed in small children with undersized peripheral vessels, (ii) it avoids distortion of the pulmonary arteries, (iii) it provides both pulmonary arteries with equal blood flow and growth, (iv) it has a lower rate of occlusion, (v) avert subclavian artery steal, and (vi) is easily closed during the corrective repair. The disadvantages of the central shunt include: (i) it requires access into the pericardium, (ii) the risk of damage to the shunt during sternotomy, (iii) pulmonary hypertension due to over-shunting, and (iv) it requires open heart surgery and bypass (Kiran, 2017; Doshi et al., 2015).

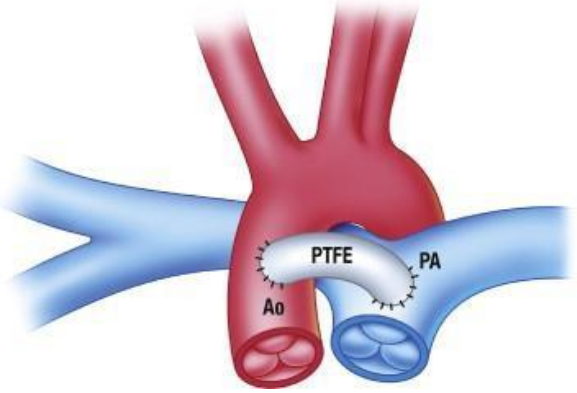



**Figure 2.4:** Schematic presentation of a central shunt with a prosthetic graft (Yuan and Jing, 2009). [AO: aorta; PA: pulmonary artery; PTFE: polytetrafluoroethylene]

### (C) Patent Ductus Arteriosus (PDA) stent

PDA stenting is a percutaneous procedure where a coronary artery stent preserves ductus arteriosus flow to the pulmonary artery (Buys et al., 2013). Surgical difficulties with systemic-pulmonary shunts include lengthy mechanical ventilation time, prolonged intensive care (ICU) stay, bleeding and transfusions, pulmonary complications, sepsis, repeated use of inotropes, and injury to adjacent structures like nerves and the lymphatic vessels (Sivakumar, 2015).

Glatz et al. (2018) performed a multicentre comparative study between BT shunts and PDA stenting as a palliation procedure for infants with ductus-dependent pulmonary blood flow. They reported no difference in the adjusted risk of death or unintended intervention. However, patients treated with a PDA stent presented with decreased risks of procedural complications, shorter ICU stays, needed fewer diuretics, and the pulmonary arteries were more prominent and more symmetric before their later surgical repair. Furthermore, it is a minimally invasive procedure that can be performed on critically ill premature newborns (Glatz et al., 2018).

Major complications associated with PDA stenting include: (i) stent migration, (ii) acute thrombosis, and (iii) permanent femoral vessel damage, (iv) ductal spasm, and (v) the need for repeat procedures. Therefore, PDA stent through percutaneous placement seems preferable as a nonsurgical palliative alternative to BT shunts and modified BT shunts (Eilers and Qureshi, 2020).

### (D) Pulmonary Artery Banding (PAB)

Muller and Damman first described the pulmonary artery banding technique in 1952 as a palliative surgical procedure to reduce excess pulmonary blood flow and pulmonary hypertension (Sharma, 2012). An external band is inserted around the main pulmonary artery and tightened to reduce the diameter of the pulmonary artery (Figure 2.5). The Trusler formula is used to evaluate the degree of pulmonary artery banding in infants (Devlin et al., 2020).

PAB is usually used in cardiac lesions where there are left to right shunts, such as ventricular septal defects (VSD), atrioventricular septal defects (AVSD), and patent

ductus arteriosus (PDA) (Devlin et al., 2020). Figure 2.5 illustrates the placement of a pulmonary artery band.

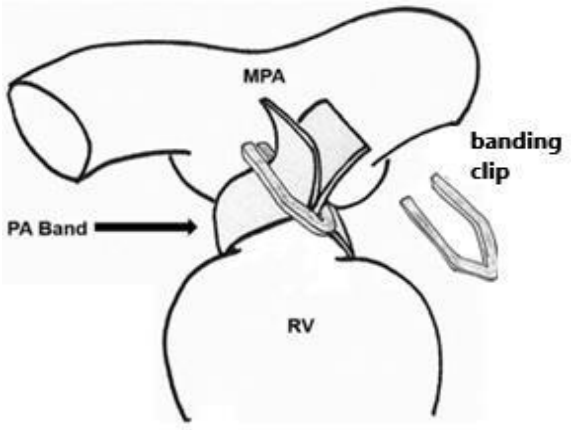



**Figure 2.5:** Pulmonary artery banding technique (Zareef et al., 2022). [RV, right ventricle; MPA, Main pulmonary artery; PA, Pulmonary artery].

However, assessing the band's optimal tightness during PAB may be difficult, and minimal changes to the diameter can drastically affect vascular resistance and blood flow. However, adjustable implantable pulmonary artery banding is available, allowing the band size to be adjusted without further surgery (Assad, 2007). The pulmonary band can also migrate and obstruct the left and right pulmonary arteries. In addition, it can cause calcification, which leads to stenosis; therefore, follow-up interventions are needed to adjust band tightness in about one-third of patients. The pulmonary artery band can also erode through the pulmonary artery leading to clotting and can also cause right ventricle hypertrophy. Pulmonary artery banding is limited due to surgical advancements but still has clinical use (Sharma, 2012).

#### 2.3.1.2 Systemic circulation

Surgical interventions such as a coarctectomy, Damus-Kaye-Stansel, or Norwood arch surgical repair might be performed to maintain adequate systemic blood flow to the body. These surgical procedures are performed in patients with hypoplastic left heart syndrome (HLHS) or mitral valve atresia (Gewillig et al., 2019).

##### (A) Coarctectomy

Coarctation of the aorta (CoA) was traditionally classified as pre-ductal, juxta-ductal, and post-ductal according to its relation to the ductus arteriosus (Agasthi et al., 2020).

The most common surgical techniques for the correction of aortic coarctation include the resection of the narrowed aortic segment and end-to-end anastomosis (Rao, 2020). If long segments are affected, an augmenting technique utilising a patch is used. The primary surgical aortic coarctation repair techniques are illustrated in Figure 2.6. Extra-anatomical correction is when a prosthetic conduit bypasses the coarcted segment from the ascending to the descending aorta (Delmo Walter et al., 2017).

Transcatheter treatment includes stent implantation with an expandable balloon stent and balloon angioplasty, which is relatively safe and effective and is rapidly becoming the treatment of choice in older children (Agasthi et al., 2020).

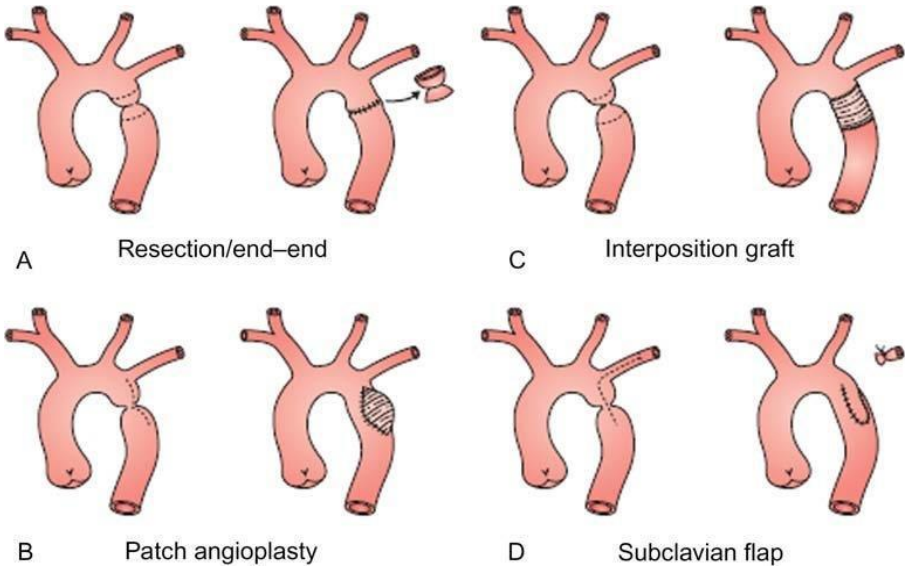



**Figure 2.6:** Major surgical aortic coarctation repair techniques (Suradi and Hijazi, 2015).

### (B) Damus-Kaye-Stansel (DKS) repair

Paul Dames, Michael Kaye, and H.C. Stansel independently described an end-to-side anastomosis between the main pulmonary artery and the ascending aorta (end-to-side DKS) in a patient with d-transposition of the great arteries in the 1970s (Figure 2.7). Pulmonary blood flow is supplied via a systemic-pulmonary shunt (Bykov et al., 2019).

The simpler and technically easier double-barrel DKS that uses no patch was reported by Waldman and colleagues (1988) in which the ascending aorta was sewed onto a new bivalve single aorta, known as the "double-barrel method" (double-barrel DKS) (Figure 2.7). With this new method, the posterior wall of the ascending aorta is left

intact to prevent bleeding and seems to provide a smoother systemic ventricular outflow tract (Fujii et al., 2011).

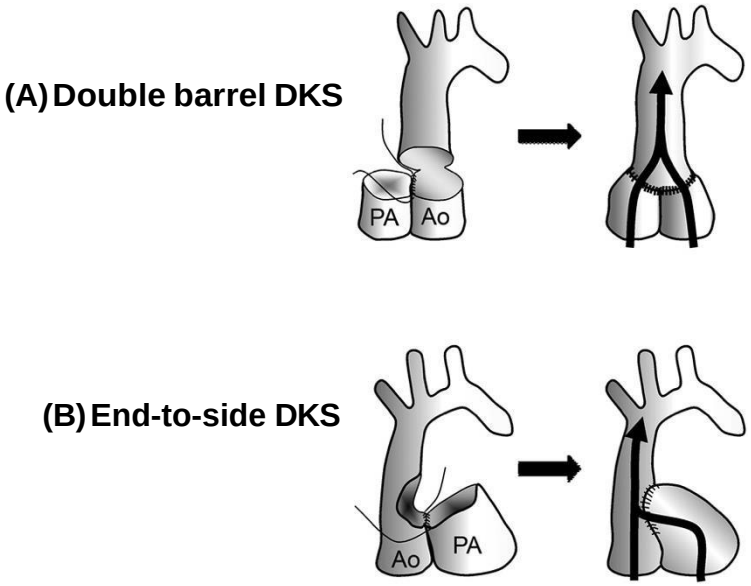



**Figure 2.7:** DKS types. Above: **(A)** Double barrel DKS. **(B)** End-to-side DKS (Fujii et al., 2011).

DKS effectively addresses obstructions of the systemic blood flow, allows for aortic arch reconstruction, and has a low risk of an emerging heart block (Bykov et al., 2019). However, DKS may lead to the alteration of the semilunar valves, causing valvular regurgitation and increased volume load on the single ventricle, typical in end-to-side anastomosis (Bykov et al., 2019).

### (C) Norwood Arch repair

The Norwood procedure is used in single ventricle patients with systemic outflow obstruction, such as hypoplastic left heart syndrome (HLHS), as the first of three surgical stage interventions (Juaneda et al., 2022).

The Norwood procedure connects the right ventricle to a reconstructed aorta where the proximal main pulmonary artery is used for systemic outflow. A shunt controls blood flow to the pulmonary artery. A significant ASD is created for unobstructed pulmonary venous return to the right atrium (Sano et al., 2022).

In the classic Norwood procedure, a modified MBT supplies pulmonary blood flow via tube grafting by connecting the subclavian or innominate artery to the pulmonary

artery. This shunt provides pulmonary artery flow during both systole and diastole. However, this may lead to "coronary steal" as coronary blood flow occurs primarily during diastole leading to myocardial ischemia, circulatory instability and ultimately, death (Ohye et al., 2010).

The modified Norwood procedure with a right ventricle–pulmonary artery (RV-PA) shunt or Sano shunt eliminates "coronary steal", contributing to lower mortality. It may, however, cause right ventricular dysfunction, arrhythmias, aneurysms, and an increased volume load due to regurgitation (Ohye et al., 2010). Figure 2.8 illustrates the difference between the classic Norwood procedure with an MBT shunt and the modified Norwood procedure with an RV-PA conduit or Sano shunt.

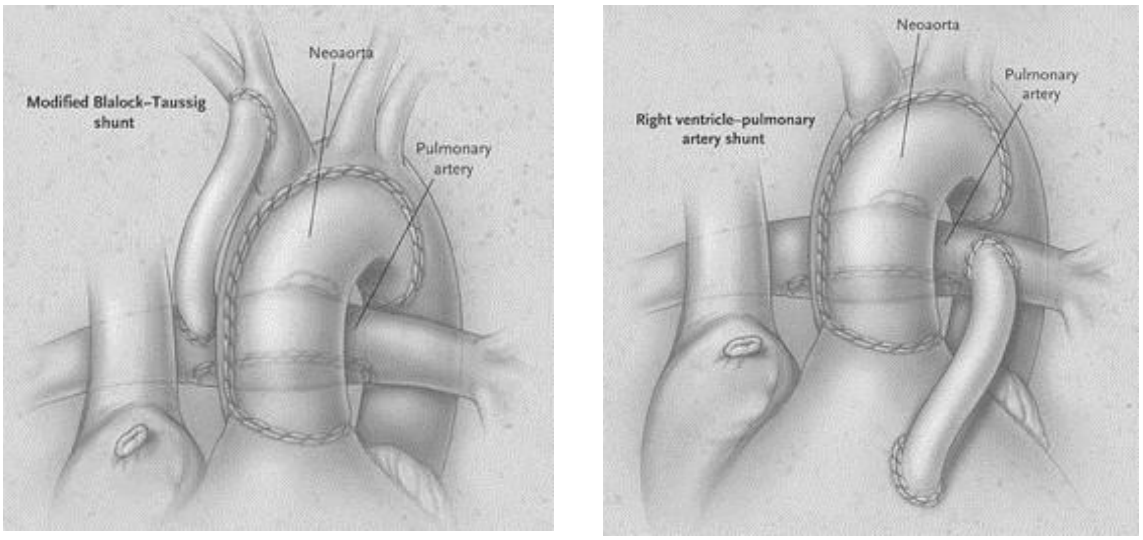



**Figure 2.8:** Norwood procedures. **Left:** Classic Norwood procedure with an MBT shunt. **Right:** Modified Norwood procedure with an RV-PA or Sano shunts (Ohye et al., 2010).

### 2.3.2. Stage 2: Glenn procedure

William Glenn introduced the Glenn procedure in 1958. It is also called a partial cavopulmonary anastomosis, bidirectional Glen procedure or a hemi-Fontan (Figure 2.9A & B). It is usually performed in late infancy, at around four to six months of age. It involves the superior vena cava being connected to the right pulmonary artery while the pulmonary artery is detached from the ventricle. The procedure is done through a median sternotomy, and if a left-sided SVC is present, the procedure is repeated on the left (bilateral bidirectional Glen) (Jones, 2018).

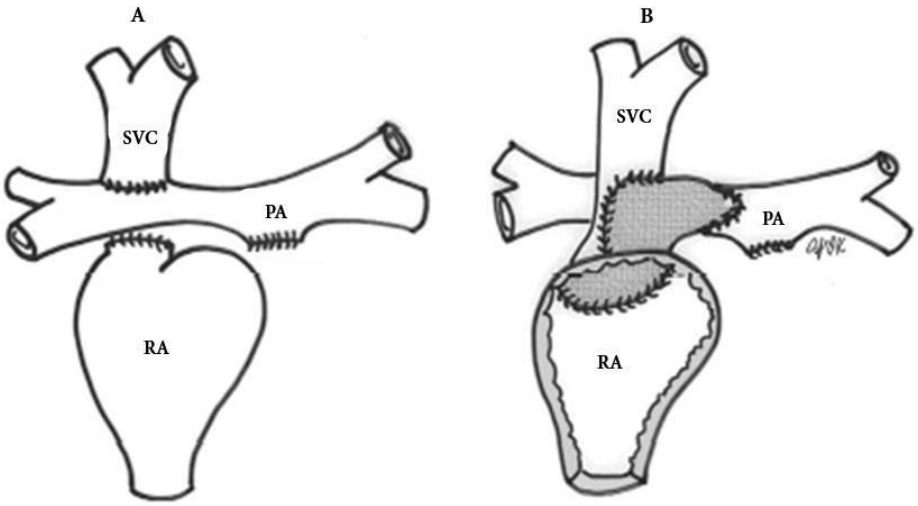



**Figure 2.9:** **(A)** Bidirectional Glen procedure and **(B)** Hemi-Fontan method. (https://radiologykey.com/glossary-of-pediatric-cardiovascular-surgical-procedures/).

The bidirectional Glenn (Figure 2.9A) is technically more straightforward than the Hemi-Fontan procedure and may even be performed without a cardiopulmonary bypass. Blood from the SVC flows into the pulmonary artery via an end-to-side anastomosis and is bidirectional to both the right and left lungs. Therefore, it is called a bidirectional Glenn procedure (Rotta et al., 2011). The bidirectional Glenn procedure may be performed with preserved antegrade pulmonary flow or the interruption of antegrade pulmonary flow. The bidirectional Glenn does not address pulmonary artery stenosis or distortion. It also does not maintain the natural connection of the right atrium to the SVC preferred for a lateral tunnel Fontan completion. The bidirectional Glenn is therefore selected as the surgical method if the extra-cardiac conduit style Fontan is chosen. In addition, the bidirectional Glenn reduces the volume load on the ventricle (Naik et al., 2021).

The hemi-Fontan procedure (Figure 2.9B) is performed through a median sternotomy during cardiopulmonary bypass. An anastomosis between the SVC-RA convergence and the central and branch pulmonary arteries directs SVC blood to the pulmonary circulation. A homograft patch enlargement of the main and branch pulmonary arteries follows this. Finally, a homograft dam (Figure 2.10) is created to prevent SVC blood from entering the right atrium, and the main pulmonary artery is disconnected. All other sources of pulmonary blood flow are ligated (Talwar et al., 2014).

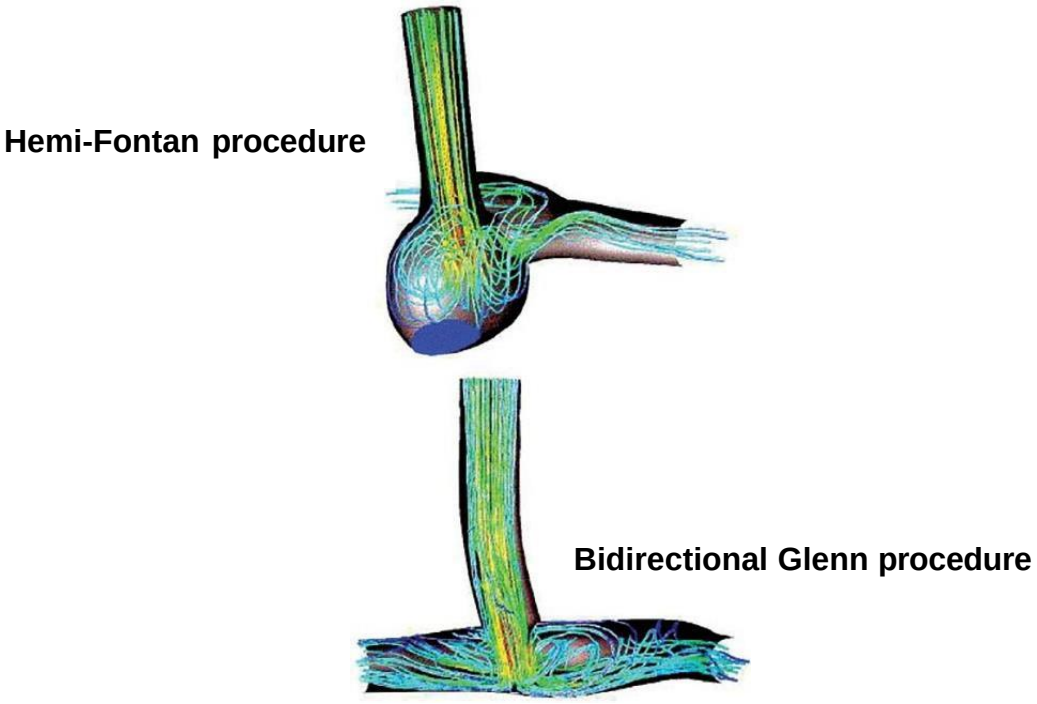



**Figure 2.10:** Path lines corresponding to SVC injection for the hemi-Fontan procedure (Upper) and bidirectional Glenn procedure (lower) (Bove et al., 2003).

Advantages of the hemi-Fontan procedure include: a better caval offset, ease of a future lateral funnel Fontan procedure, expansion of the pulmonary arteries, protection of the phrenic nerve and superior hemodynamics (Talwar et al., 2014). Disadvantages associated with a hemi-Fontan approach are that it is more difficult to perform compared to the bi-directional Glenn procedure, the follow-up extra-cardiac Fontan procedure is challenging to complete, and the sinoatrial (SA) node can be damaged, resulting in arrhythmias (Spray, 2013).

After the Glenn procedure, the ventricle no longer assists in the pulmonary blood flow; unobstructed flow to the pulmonary arteries and healthy pulmonary microvasculature is essential (Weston et al., 2016). The Glen procedure reduces the volume load on the single ventricle with improved diastolic function and partially relieves the parallel circulation and cyanosis as some blood mixing still occurs (Jones, 2018). The Glenn procedure is usually between initial palliation and the eventual Fontan procedure (Talwar et al., 2014).

### 2.3.3. Stage 3: Fontan procedure

Stage III surgery, also called total cavopulmonary anastomosis or the Fontan procedure, is usually performed in children between two to four years of age and involves the inferior vena cava connected to the pulmonary artery (Aurora et al., 2022). This converts the parallel circulation to series. Cyanosis is relieved as no mixing of blood occurs and reduces ventricle workload (volume load), as the ventricle is only responsible for systemic circulation (Weston et al., 2016).

#### 2.3.3.1 History of the Fontan procedure

Dr Francois Marie Fontan from Bordeaux, France, initially performed the Fontan procedure in 1968. He published the results of three patients with tricuspid atresia receiving a Fontan procedure in 1971 (d'Udekem et al., 2007). There are three types of Fontan procedures, namely the (i) classic atriopulmonary connection, (ii) Lateral-Tunnel connection and (iii) extra-cardiac conduct (Angelini et al., 2020) (Figure 2.11).

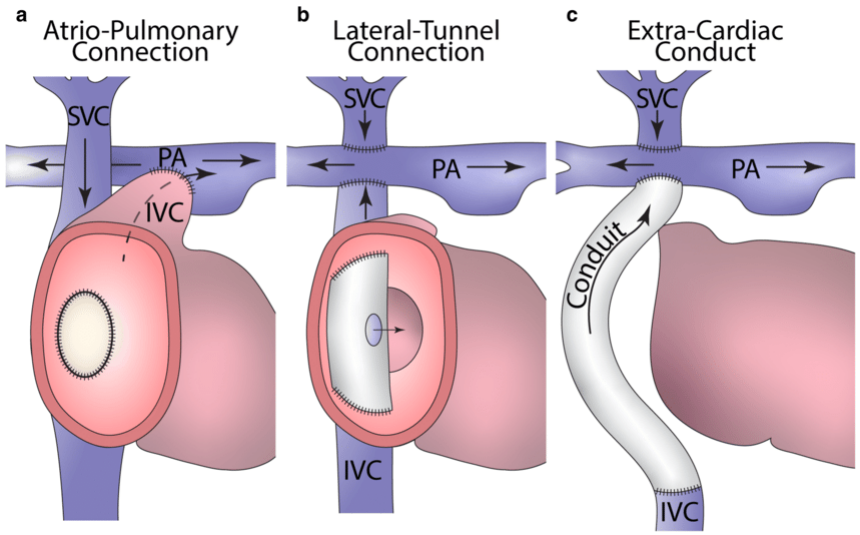



**Figure 2.11:** The different types of Fontan-type procedures, grouped in main patterns **(a–c)**. Direct atriopulmonary connection without the interposition of conduits **(a)**. Intracardiac lateral tunnel draining the IVC into the pulmonary circulation bypassing the right ventricle **(b)**. Extra-cardiac conduit draining the IVC blood into the pulmonary arteries **(c)**. In **(b)** and **(c)**, a bidirectional Glenn anastomosis drains SVC blood to the right pulmonary artery (Angelini et al., 2020).

The initial classic (atriopulmonary) procedure is not performed anymore (d'Udekem et al., 2007). It involves the superior vena cava being connected to the right pulmonary artery and a connection between the right atrium and the proximal end of the left

pulmonary artery. Pulsation of the right atrium was used to direct blood from the inferior vena cava to the left pulmonary artery (Said et al., 2012) (Figure 2.11A). Dr Guilermo Kreutzer performed a similar procedure in 1973. However, problems with the procedure involved right atrial dilatation with decreased pulmonary blood flow, stasis, and thrombosis (Jones, 2018).

A total cavopulmonary connection (TCPC) can be created through either an internal conduit (lateral tunnel procedure) or an external conduit (extra-cardiac procedure) (Lee et al., 2007). This lateral tunnel procedure (Figure 2.11b) is advantageous as it reduces arrhythmias, blood stasis and thrombosis and keeps the coronary sinus in a low-pressure atrium, allowing good myocardial venous drainage (Jones, 2018).

In 1990 the extra-cardiac Fontan procedure was described by Marcelletti and colleagues using a baffle to connect the inferior vena cava to the pulmonary artery without entering the right atrium but instead, entirely outside the heart (Figure 2.11c) (Jones, 2018). This had the advantage of better cavopulmonary blood flow, reduced risk of arrhythmias and thrombosis, and can be performed without cardio-pulmonary bypass as there is no incision into the right atrium. This procedure is also suitable for larger children, that can accept an adequate-size graft, allowing for adult IVC flow (Khairy and Poirier, 2012).

The most recent modification to the Fontan procedure is the intracardiac or extra-cardiac conduit with a fenestration involving a connection between the baffle and the left side of the heart (Figure 2.11c). The fenestration aids in decompressing high Fontan pressures, serves as a pop-off valve, enhances preload of the systemic ventricle, and increases cardiac output. However, it may lead to cyanosis due to right-to-left shunting (Jones, 2018).

#### 2.3.3.2 Physiology of the Fontan procedure

In Fontan circulation, the circulation of blood flow is changed (Figure 2.12). The single ventricle pumps oxygenated blood to the systemic circulation. Deoxygenated blood is not pumped to the lungs via the ventricle but instead flows passively from the superior and inferior vena cava to the pulmonary arteries. Pressure changes caused by normal

breathing and higher pressure in the veins help blood flow to the pulmonary arteries (Mazza et al., 2021).

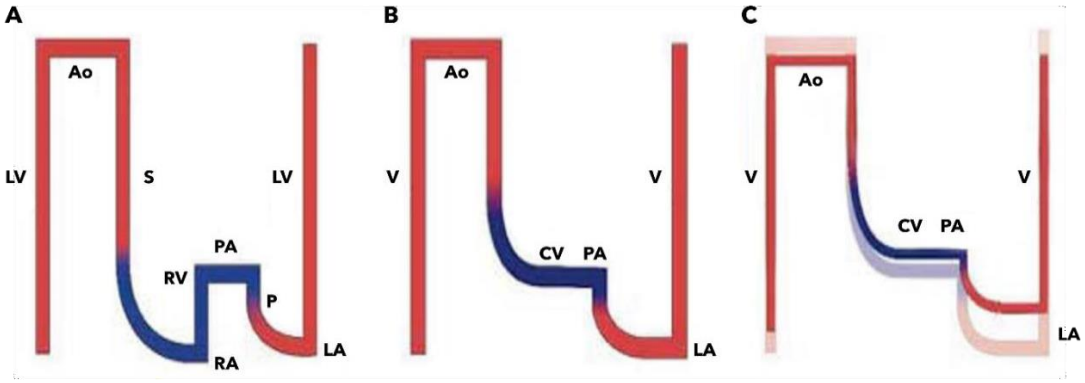



**Figure 2.12:** Cardiac pressures. **(A)** Normal biventricular heart. **(B)** Early Fontan circulation. **(C)** Late Fontan circulation (Rychik et al., 2019).

According to Gewillig and Brown (2016), a system comprising the venous connection and pulmonary arteries is created outside the heart, controlling the degree of congestion and overflow. The ventricle still acts as a pump for the system but no longer controls the blood flow and only pumps the reduced blood it receives. There are three essential resistance factors in the Fontan circulation:

(i) the pulmonary vascular resistance or the bottleneck,

(ii) the venous pressure just before the bottleneck, and

(iii) the left atrial pressure as determined by ventricular end-diastolic pressure (in the absence of mitral stenosis) just after the bottleneck (Gewillig and Brown, 2016).

The advantages of the Fontan circulation are increased arterial saturation and a decreased volume overload on the single ventricle (van der Ven et al., 2018). However, disadvantages include: (i) systemic venous hypertension and congestion and (ii) decreased cardiac output. The reason is that the heart no longer determines cardiac output or the degree of systemic vein congestion but is controlled by transpulmonary flow (Gewillig and Brown, 2016). Future innovations may combine surgical and interventional catheterisation (hybrid procedures) for Fontan completion (Galantowicz, 2020).

#### 2.3.3.3 Challenges in Fontan circulation

A significant problem with Fontan procedures is congestive cardiomyopathy caused by impaired muscle function. Theoretically, cardiac flow can be increased by enhancing contractility, increasing filling pressure or decreasing afterload (Gewillig et al., 2019). However, as the ventricle does not control flow, additional treatments that address heart rate, contractility, and afterload have a minimal hemodynamic impact (Gewillig and Brown, 2016).

A second problem is primary pulmonary hypertension. Flow can be increased with pulmonary vasodilators or decreased left atrial pressure. Pulmonary blood flow significantly increases during peak exercise as pulmonary vascular resistance decreases (Naeije and Chesler, 2012). Nakano et al. (2000) found that pulsatile flow increased the release of nitrogen oxide from the endothelium and decreased pulmonary vascular resistance. Over time the ventricular end-diastolic pressure and pulmonary vascular resistance increase, resulting in increased caval vein pressure and congestion with overall decreased flow (Gewillig et al., 2019).

Fenestration of the Fontan circulation was first described in 1990 and contributed to decreased venous congestion and increased cardiac output. The right-to-left shunting increased the preload of the systemic ventricle. Still, there are disadvantages, like lower systemic saturation, embolism risk, and the potential need to close the fenestration later (Gewillig et al., 2019).

The ten commandments for an ideal Fontan procedure are summarised in Figure 2.13 and were formulated by Choussat in 1977 (Stern, 2010).

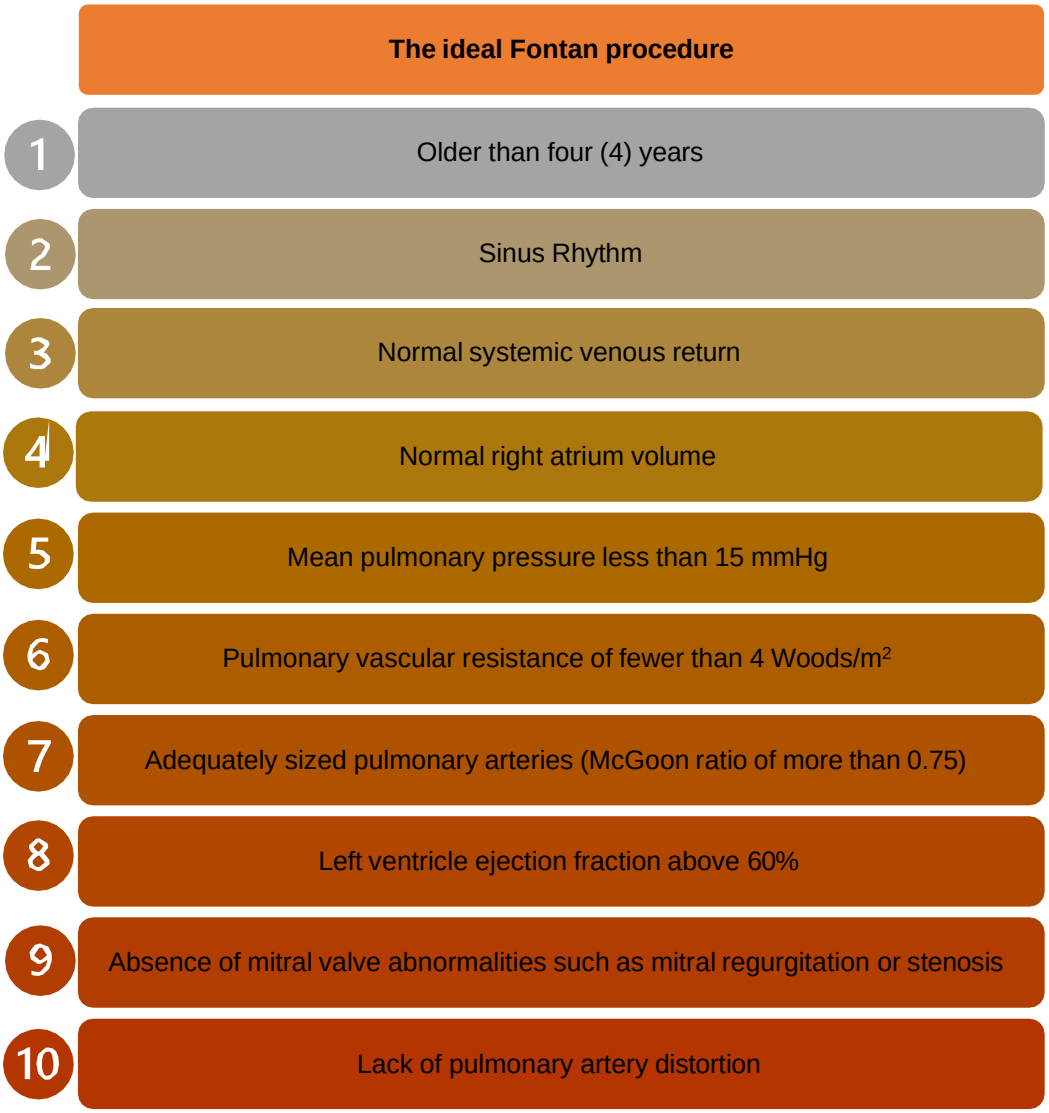



**Figure 2.13:** The ten commandments for an ideal Fontan procedure.

Ma (2022) suggests that presurgical N-terminal B-type natriuretic peptide (NT-BNP) levels, as an indicator of post-surgical long-term outcomes, could be the 11$^{th}$ commandment, but it will require further prospective validation.

Some of these factors are considered modifiable in the current era. In contrast others, such as chronic lung disease with pulmonary hypertension, pulmonary vein stenosis, and severe ventricular systolic or diastolic dysfunction, are seen as unmodifiable characteristics not fitting a Fontan procedure (Rychik et al., 2019).

Although many aspects of treating Fontan patients have been optimised, the future may entail inserting mechanical pumps into the circuit to drive blood forward (Gewillig et al., 2019).

#### 2.3.3.4 Evaluation of the Fontan procedure

Despite significant improvement in the survival of patients after the Fontan surgical procedure, satisfactory quality of life and life expectation is not currently experienced. Clinical symptoms affecting patients are cardiac and non-cardiac, including fatigue, heart failure, arrhythmias, and complications affecting multiple organ systems, including the lungs, liver, bones, brain, and lymphatic system (D'Angelo et al., 2022).

The American Heart Association (AHA) proposed using a Fontan Circulation Surveillance Testing Toolkit for the follow-up and treatment of patients with Fontan circulation (Rychik et al., 2019) (Table 2.2).

**Table 2.2:** Cardiovascular system surveillance test (Rychik et al., 2019).

| Test | Child | Adolescent | Adult |
|---|---|---|---|
| Outpatient visits, including physical examination | Every 6-12mo | Every 6-12mo | Every 6-12mo |
| ECG | Every 6-12mo | Every 6-12mo | Every 6-12mo |
| Echocardiogram | Yearly | Yearly | Yearly |
| Holter 24-hour monitor | Every 2-3yrs | Every 1-2yrs | Every 1-2yrs |
| Exercise stress test | Every 2-3yrs | Every 1-3yrs | Every 1-3yrs |
| Serum BNP or NT-probnp | Once in childhood | Every 1-3yrs | Every 1-3yrs |
| Cardiac MR | Once every 3yrs | Every 2-3yrs | Every 2-3yrs |
| CT angiography | As clinically indicated | As clinically indicated | As clinically indicated |
| Cardiac catheterisation | As clinically indicated | Once every 10yrs | Once every 10yrs |

**(A) Echocardiographic evaluation**

According to Hauser et al. (2017), a complete echocardiographic study should be performed on Fontan patients at every outpatient visit at least once a year. Functional assessment of the right ventricle remains challenging, but ongoing examination may reveal deterioration over time using M-mode or tissue Doppler imaging. In addition, echocardiography can demonstrate venous to pulmonary pathway obstruction,

atrioventricular valve regurgitation, and systolic and diastolic dysfunction (Ciliberti et al., 2023).

During the first decades following the Fontan procedure, the systolic ventricular function was preserved but declined as time progressed, and 40% to 60% of patients presented with systolic ventricular dysfunction (Rychik et al., 2019). In Fontan patients with no systemic (left) ventricle, the single right ventricle assessment is complex due to normal reference values needing to be readily available and agreed upon (Ohuchi, 2016). The strengths and weaknesses of an echocardiographic evaluation are summarised in Table 2.3.

**Table 2.3:** Strengths and weaknesses of echocardiography used in patients with Fontan circulation (Cordina et al., 2015).

| **Strengths** |
|---|
| Availability, low cost, relative ease of use, bedside compatibility. |
| Lack of invasiveness and ionising radiation, no contraindications. |
| High temporal and spatial resolution. |
| Relatively robust to arrhythmia. |
| Good characterisation of valve function. |
| **Weaknesses** |
| Inter- and intra-observer variability. |
| Often times poor acoustic window secondary to surgery. |
| No myocardial tissue characterisation. |
| Limited use for assessment of ventricular volume and function, especially in the systemic rv. |
| Unsuitable for shunt estimation and visualisation of collaterals. |
| Certain structures may be difficult to visualise (pulmonary veins, conduit). |

### i) Diastolic dysfunction

Diastolic dysfunction is a vital concern in Fontan patients, and non-invasive diagnosis remains challenging. Echocardiographic indicators do not usually comply with normal biventricular heart values but, over time, may reveal progressive dysfunction (Hauser et al., 2017).

Diastolic assessment is based on Doppler parameters of the atrioventricular valve (AVV), where the E/A ratio and deceleration time (DT) is calculated. (E) represents early mitral inflow velocity and (A) atrial wave inflow velocity (Henein and Lindqvist,

2020). Tissue Doppler assessment of peak AVV annulus velocities in early diastole (E') uses M-mode colour Doppler across the AVV inflow. For E' values, the values used are the average velocities of the two walls bounding the systemic ventricle (Margossian et al., 2016).

Margossian et al. (2016) used the following grading classification of diastolic dysfunction for Fontan patients (Figure 2.14).

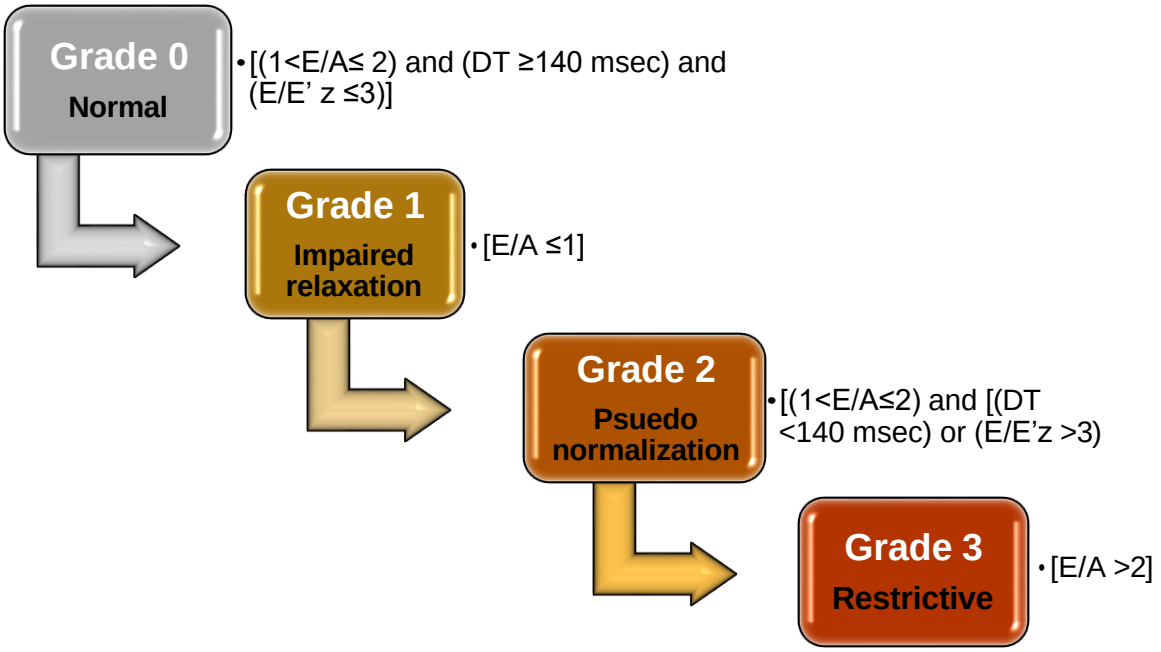



**Figure 2.14:** Grading classification of diastolic dysfunction of Fontan patients (Margossian et al., 2016). An E/E' z-score of 3 was used as the equivalent of an E/E' of 10 in adults.

The findings were then classified as having a restrictive pattern present or absent, and a restrictive pattern present was considered if E/A>2 or if 1<E/A<2 and DT<140 msec. The diastolic dysfunction grading excluded E/A ratios with complete E and A wave fusion. However, partial E and A wave fusion can still be used in grading diastolic dysfunction (Margossian et al., 2016).

When the mitral E-A fusion is partial, it is still possible to measure peak E and A velocities and demonstrate E/A reversal, suggesting left ventricular diastolic dysfunction. But when there is complete E-A fusion, it is impossible to calculate the E/A ratio to assess diastolic function (Sohn et al., 1999).

The atriums of patients with single ventricle physiology are dilated, with decreased compliance, decreased early diastolic emptying (E wave) and increased atrial contraction (A wave) for ventricular filling (Khoo et al., 2013).

### ii) Tricuspid annular plane systolic excursion or mitral annular plane systolic excursion (TAPSE/MAPSE)

Tricuspid annular plane systolic excursion (TAPSE) is a simple, reliable manner to assess right ventricular systolic function using echocardiographic measurements (López-Candales and Vallurupalli, 2022). Koetsenberger et al. (2009) published normal TAPSE values from infancy to adolescence (Table 2.4) used for RV and LV dysfunction. However, TAPSE values increase with age and body surface area (BSA) non-linearly. Therefore, it is best to reference TAPSE to an indexed age and BSA value (Koestenberger et al., 2009).

**Table 2.4:** Classification of TAPSE values (Koestenberger et al., 2009)

| Age | Mean TAPSE (cm) | Mean BSA ($m^2$) | Indexed mean TAPSE/ mean BSA |
|---|---|---|---|
| 0-30 D | 0.91 | 0.22 | 4.13 |
| 1-3 Mo | 1.14 | 0.29 | 3.93 |
| 4-6 Mo | 1.31 | 0.34 | 3.85 |
| 7-12 Mo | 1.44 | 0.40 | 3.60 |
| 1Y | 1.55 | 0.47 | 3.29 |
| 2Y | 1.65 | 0.53 | 3.11 |
| 3Y | 1.74 | 0.63 | 2.76 |
| 4Y | 1.82 | 0.70 | 2.60 |
| 5Y | 1.87 | 0.77 | 2.42 |
| 6Y | 1.90 | 0.82 | 2.31 |
| 7Y | 1.94 | 0.94 | 2.06 |
| 8Y | 1.97 | 0.97 | 2.03 |
| 9Y | 2.01 | 1.00 | 2.01 |
| 10Y | 2.05 | 1.15 | 1.78 |
| 11Y | 2.10 | 1.28 | 1.64 |
| 12Y | 2.14 | 1.39 | 1.53 |
| 13Y | 2.20 | 1.48 | 1.48 |
| 14Y | 2.26 | 1.55 | 1.45 |
| 15Y | 2.33 | 1.59 | 1.46 |
| 16Y | 2.39 | 1.66 | 1.43 |
| 17Y | 2.45 | 1.77 | 1.38 |
| 18Y | 2.47 | 1.79 | 1.37 |

[D: days; Mo: months; Y: years; TAPSE: Tricuspid annular plane systolic excursion; MAPSE Mitral annular plane systolic excursion; BSA: Body surface area]RV

### iii) Myocardial performance index (MPI)

Evaluation of ventricular function in patients with single ventricle physiology is complex (Koestenberger et al., 2009). However, the Doppler myocardial performance index (MPI/Tei index) may provide a method that includes both systolic and diastolic time intervals to evaluate global cardiac dysfunction (Eidem et al., 2000).

The MPI is higher in patients with single ventricles than those with normal ventricles. However, patients with a bidirectional Glenn procedure before one year of age demonstrate lower MPI values after surgery, suggesting improvement in ventricular function (Koestenberger et al., 2009).

### iv) Global strain – speckle tracking

Two-dimensional speckle tracking is an effective and sensitive method for the early detection of subclinical ventricular dysfunction, which can be incorporated into routine echocardiographic examinations and is reproducible (Ginde et al., 2017).
Myocardial deformation is a strain representing the fractional or percentage change from its original dimension (change in length between two points). Strain is obtained in three different directions (longitudinal, radial, and circumferential) due to the physiologically complex myocardial fibre construction. Therefore, strain is considered a relative load-independent measure of myocardial function, and strain rate represents deformation velocity (Huntgeburth et al., 2019).

Two-dimensional speckle tracking is highly reproducible and has been validated for cardiac function in several patients with single ventricle physiology cohorts (Steflik et al., 2017). Global strain parameters, such as global longitudinal (GLS) and global radial strain (GRS), are more reliable measures of ventricular performance than regional strain parameters. The reliability of strain measurements is affected by frame rate, the nature of strain (longitudinal, circumferential, radial), and even ventricular geometry, suggesting that a dedicated echocardiographic protocol for single ventricle patients is recommended (Huntgeburth et al., 2019).

## (B) Ross classification

In patients with single ventricle physiology, the dominant ventricle will eventually fail due to increased pressure from the systemic and pulmonary circulation (Ezzeldin et

al., 2019). The Ross Heart Failure Classification provides a global assessment of heart

failure severity in infants and has been modified to apply to all paediatric ages (Ross, 2012). The modified Ross classification encompasses feeding difficulties, growth problems, and exercise intolerance symptoms into a numeric score equivalent to the New York Heart Association (NYHA) classification for adults (Table 2.5).

**Table 2.5** NYHA and modified Ross heart failure classification for children (Etoile, 2016)

| | NYHA | ROSS |
|---|---|---|
| **CLASS I** | No limitations of physical activity | No limitations or symptoms |
| **CLASS II** | May experience fatigue, palpitations, dyspnea, or angina during moderate exercise but not during rest | *Infants:* Mild tachypnea or diaphoresis with feeding<br>*Older children:* Mild to moderate dyspnea on exertion |
| **CLASS III** | Symptoms with minimal exertion that interfere with normal daily activity | *Infants:* Growth failure and marked tachypnea or diaphoresis with feeding<br>*Older children:* Marked dyspnea on exertion |
| **CLASS IV** | Unable to carry out any physical activity because they typically have symptoms of HF at rest that worsen with any exertion | Symptoms at rest, such as tachypnea, retractions, grunting, or diaphoresis |

[HF: Heart failure; NYHA: New York Heart Association].

### (C) Six-minute walk test

The American Thoracic Society introduced the six-minute walking test (6MWT) in 2002 (Fell et al., 2022). The 6MWT measures the reaction to medical interventions in heart or lung disease patients. It is a one-time measurement of functional status and a predictor of morbidity and mortality (Feltez et al., 2015).

Fontan patients have a reduced exercise capacity compared to healthy peers (Myers et al., 2002). In addition, Fontan patients do not seem to have a better exercise capacity than patients who only received a Glenn operation (Sen et al., 2012). Feltez et al. (2015) concluded that children and adolescents with cyanotic heart disease have low submaximal exercise capacity even after surgical repair.

Kempny et al. (2013) reported that the six-minute walk test and resting oxygen saturation ($SO_2$) predicted outcomes in Eisenmenger patients. Therefore, it was proposed to be incorporated into these patients' risk stratification and management.

## 2.4. Outcomes of single ventricle repair

### 2.4.1. First World countries

According to the Centre for Disease Control and Prevention (2019), babies born with non-critical cardiac heart disease have a 97% 1-year survival rate and a 95% 18-year survival rate. In comparison, babies born with a critical cardiac heart disease have a 75% 1-year survival rate and a 69% 18-year survival rate (Centre for Disease Control and Prevention, 2019). The survival rate for critical cardiac heart disease has improved from 67% between 1979 and 1993 to 83% between 1994 and 2005 (Rychik et al., 2019; Oster et al., 2013).

The mortality rate in staged surgical palliation for single ventricle physiology is highest in the four and six-month periods between stage I and II, known as the interstage. It can be as high as 22% (Weston et al., 2016).

It is more than five decades since the first Fontan procedure was performed, and it is estimated that up to 70 000 patients worldwide live with Fontan circulation (Rychik et al., 2019). Nowadays, outcomes of Fontan procedures are remarkable, with operative mortality approaching 1%. The five and ten-year transplantation-free survival rate is 95% and 90%, respectively, and 20-year survival rates vary between 61% and 85% (Rychik et al., 2019). The 30-year survival rate is estimated at 85%, and in a 35 year study the Australian and New Zealand Fontan Registry reported a 62% survival rate (Schilling et al., 2016). The survival rate, especially amongst patients with a Fontan procedure, improved due to early detection, technical improvements, advanced patient selection and improved perioperative management (Rychik et al., 2019; Oster et al., 2013).

Rychik et al. (2019) reported a decreased survival rate in older patients that received a Fontan operation, patients with a common atrioventricular valve, male sex, elevated pulmonary artery pressures pre- and postoperative, and sustained pleural effusions after the Fontan procedure. In addition, patients with complications such as protein-losing enteropathy (PLE), arrhythmias, thromboembolic events, and pacemakers also have inferior survival outcomes.

International data shows a decline in the age at which Fontan procedures are performed (Kverneland et al., 2018). A five-decade review study by Kverneland et al. (2018) showed that Fontan procedures had been performed in recent years from as young as 2.0 to 5.6 years (median) in high-income countries. Dayle and d'Udekem (2019) found that Fontan operations done at an earlier age showed better survival and fewer unfavourable outcomes. Akintoye et al. (2019) stated that although Fontan operations were mainly performed at two years of age in the United States, the optimum age is three. This was evident from a lower in-hospital mortality rate and fewer related complications.

Oster et al. (2018) reported that infants presenting with a systemic right ventricle (RV), as opposed to a systemic left ventricle (LV), have significantly poorer long-term transplant-free survival rates. This was attributed to worsening heart failure in those with RV morphology. In a comprehensive study by Oster et al. (2018), which included 44 centres, 42% of patients had a systemic RV, 37% had a systemic LV, and 20% were unclassifiable. The survival after 20 years transplant-free was 52% for those with systemic RV, 72% for systemic LV, and 64% for non-classifiable ventricles. In-hospital survival of patients receiving a Fontan procedure according to systemic ventricular morphology showed no statistically significant difference.

Patients with severe cardiac lesions require lifelong follow-up, but in a Canadian study, 21% of patients with severe cardiac lesions were lost to follow-up after the age of 18 years (Mackie et al., 2009).

### 2.4.2. Developing countries

Limited data on the outcomes of single ventricle repair for sub-Saharan countries are available. However, in one of the few studies performed in a developing country, Manuel et al. (2019) reported on 83 patients with single ventricle physiology between 2011 and 2017 in Angola. Sixty-five patients underwent stage I surgery, and of these, 34 patients received pulmonary artery banding with a peri-operative mortality rate (deaths during hospitalisation) of 12%. Thirty-one per cent of the patients received BT shunts, with an operative mortality rate of 45%. Thirty patients underwent stage II surgery, 18 (60%) received a Glenn procedure as primary surgery, and 12 (40%) had previous stage I palliative surgery. Stage II patients had an operative mortality of 17

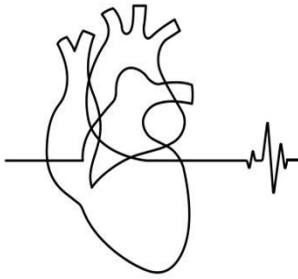
%. Of the five patients that underwent stage III Fontan surgery, one died with a mortality rate of 20%.

However, in a recent South African study, Meyer et al. (2022) reported on 61 patients who underwent BDG surgery at Red Cross War Memorial Children's Hospital over eight years. Nearly a third of the patients (n=20) had no prior intervention before the bidirectional Glen procedures. Thirty-seven per cent of patients completed single-ventricle palliation, with a mortality rate of 3.3% (Meyer et al., 2022).

Bidirectional Glenn procedures were performed in an Angolan study at a median age of 1.1 years (Manual et al., 2019). However, in a South African study (Meyer et al., 2022) and an Egyptian study (Samir et al., 2010), the median age was much older at 2.5 years and 2.3 years, respectively. In the Angolan study, the median age for Fontan procedures was 3.8 years (Manual et al., 2019) vs. a median age of 8.5 years in the South African study (Meyer et al., 2022).

In developing countries such as South Africa, determining patient outcomes is difficult because patients need more follow-up support. In a study by Smit, R. 2017) performed in Central South Africa, the reasons for the loss of follow-up could be attributed to long distances combined with unreliable transport, challenging communication, and a lack of understanding by parents. Similar trends were observed in another South African study performed at the Red Cross War Memorial Children's Hospital for patients receiving bidirectional Glenn shunts, where 30.5% of patients were also lost to follow-up (Meyer et al., 2022). In an Angolan study, other African countries faced even more challenges and almost two-thirds of their patients were lost to follow-up (Manual et al., 2019).

Therefore, there is a need for long-term survival rates in developing countries, and any such data is almost entirely deficient for developing countries such as South Africa.



# CHAPTER 3 – ARTICLE I

***Note:***

*The article is accepted for publication in Cardiovascular Journal of Africa (Appendix B)*

# Outcomes of patients presenting with single ventricle physiology in Central South Africa

**Van Jaarsveld MJ** (BTech)[1], Botes L (DTech; PhD)[1], Smit FE (PhD)[2], Brown SC (DMed)[3]

[1]*Department of Health Sciences, Central University of Technology, Bloemfontein, South Africa*

[2]*Department of Cardiothoracic Surgery, University of the Free State, Bloemfontein, South Africa*

[3] *Division Paediatric & Congenital Cardiology, University of the Free State, Bloemfontein, South Africa*

**Institution at which work was performed:** Universitas Academic Hospital, South Africa

**Corresponding author:** Prof. Stephen C. Brown [3]

**Tel:** + 27 (0)51 405 3241 **Fax:** + 27 (0)51 444 3230
**e-mail:** Gnpdscb@ufs.ac.za

**Word count: abstract:** 215 **text (excl references): 3319**
**Figures:** 2 **Tables:** 2
**Pages:** 15

**Keywords:** single ventricle, Glenn, Fontan, shunt, banding

**Short title:** Outcomes of patients with single ventricle physiology

## Abstract

**Introduction:** Single ventricle physiology is a critical cardiac condition requiring early diagnosis and intervention.

**Objectives:** To report on the management and outcomes of patients diagnosed with single ventricle physiology in Central South Africa.

**Methods:** A retrospective observational analysis included patients presenting with single ventricle physiology at the Universitas Academic Hospital (UAH) in Central South Africa between November 1997 and June 2021.

**Results:** Patients were referred from the Free State province (54%), Northern Cape province (29%) and Lesotho. One hundred and fifty-four patients presented with single ventricle physiology: 114 received interventions, and 40 were not eligible for intervention. Patients presented for the first time at a median age of 34.5 days, while patients from nearby districts presented within a few days after birth. However, patients from outlying areas presented much later. Eighty-seven patients received systemic to pulmonary artery shunting or pulmonary artery banding. Sixty-three patients proceeded to bidirectional Glenn procedures, and 30 patients (26%) had full palliation to Fontan. Twenty-one patients were demised after stage 1, six after the Glenn procedure and two after the Fontan procedure. Overall, 34 (29.8%) patients were lost to follow-up.

**Conclusion:** Patients in our study presented late, and follow-up of these patients was a challenge. The highest mortality occurs during the first stage of palliation. Outcomes from this study are comparable to other Sub-Saharan studies.

## Introduction

Lesions with single ventricle physiology occur in 4-8 out of 10,000 live births or 1-2% of patients with congenital cardiac abnormalities.[1] Single ventricle physiology encompasses a heterogenous group of complex cyanotic cardiac lesions, usually requiring early diagnosis and intervention at a congenital cardiac centre.[2] Infants born with non-critical cardiac heart disease have a 97% 1-year survival rate. In contrast, babies with critical cardiac heart disease only have a 75% 1-year survival rate.[3] This emphasises the need for early detection and treatment of these infants.

Newborns with functional single ventricle physiology have parallel pulmonary and systemic circulations resulting in cyanosis and ventricular volume overload.[4] Treatment consists of staged intervention, with the first stage involving palliative interventions such as patent ductus arteriosus (PDA) stenting, Blalock – Taussig shunts (BTS), central shunts and pulmonary artery banding (PAB) to regulate pulmonary arterial flow. The following stages consist of partial cavopulmonary

connection, e.g., bidirectional Glenn procedure, and eventually total cavopulmonary connection - the Fontan operation.[5] Surgery aims to change from a parallel circulation to circulation in series.

Outcomes for single ventricle treatments have improved in high-income countries with declining mortality rates. Kverneland et al. (2017) meta-review study of Fontan operations reported that mortality rates decreased from as high as 20.1% in the early decades to as low as 0.5% in recent years. In these, 15-year survival rates improved from 52% to 82% in the early years to 95% currently.[6]

There needs to be more data regarding the outcomes of single ventricle interventions for Africa and especially sub-Saharan Africa. Furthermore, there needs to be documentation for the central region of South Africa, which is the geographical area wherein the Universitas Academic Hospital is located. However, in middle to low-income countries like South Africa, outcomes tend to lag behind that of high-income countries, although improvements were observed.[7] A recent sub-Saharan study reported a 29% mortality rate in the early stages and a 17% late mortality rate.[2]

The objective of this study was to analyse data on the management and outcomes of children who presented with single ventricle physiology in Central South Africa over the last two decades.

## Methodology

### Study design and location

The retrospective observational analysis included all patients presenting with single ventricle physiology between November 1997 and June 2021 at the Departments of Paediatric Cardiology and Cardio-Thoracic Surgery at Universitas Academic Hospital (UAH). Universitas Academic Hospital is the only tertiary referral hospital in central South Africa and renders services to patients from the Free State, Northern Cape, and Lesotho (estimated population of 6.5 million).

**Study Population**

The main inclusion criterion consisted of patients at the central hospital diagnosed with lesions considered as single ventricle physiology presenting for the first time. Patients with hypoplastic left heart syndrome (HLHS) and biventricular physiology treated with single ventricle palliation were excluded from the study. One hundred and fifty-four patients met the inclusion criteria.

**Data Collection**

Data were retrieved from a Paediatric Cardiology database, patient folders, and the hospital information system. Data recorded included demographic [age (years), gender, ethnicity, geographical location], anthropometric [height (cm), weight (kg), and BMI (kg/m$^2$)] and clinical data [ventricle dominance, palliative intervention, palliation stage, other associated lesions, and operative mortality].

***Definitions***

*Perioperative mortality* was defined as deaths occurring during the first 30 days postoperatively, whether in a hospital or discharged, regardless of the cause.

*Late mortality* was defined as all deaths after the first 30-day postoperative period, whether at home or during subsequent hospitalisation.

*Stages of palliation:* Stage I palliation consisted of one of the following procedures: Surgical systemic-pulmonary shunt (BTS, central or Sano shunt), Pulmonary artery banding (PAB), or percutaneous implantation of a PDA stent. Stage II involved the Glenn procedure, while stage III involved the Fontan procedure.

**Ethics and Statistics**

Ethical approval was obtained from the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State (UFS-HSD2020/1823/2505) and the Free State Department of Health.

Raw data was captured on Excel spreadsheets. Continuous variables, when asymmetrically distributed, are expressed as median and interquartile ranges 25 and 75, otherwise as mean ± standard deviation. P-values of < 0,05 was considered statistically significant. A t-test was used to compare normally distributed data. Non-parametric data were compared using a Mann-Whitney U test. A Chi$^2$ or Fisher's exact

test was utilised for comparisons where required. Analysis was done using standard Statistical Analysis Software.

## Results

Over the study period, 154 infants with single ventricle physiology were included. There was a male preponderance, with almost two-thirds of the children being male (n=98, 63,6%). Tricuspid atresia (56%) was the most common lesion, followed by pulmonary valve atresia with the intact ventricular septum (29%). Other lesions included double inlet left ventricle (5%), double inlet right ventricle (3%), unbalanced AVSD (5%) and double outlet right ventricle (1%). Most patients (88%) had lesions with left ventricle dominance. As expected, most patients were referred from the Free State region (54%); interestingly, a considerable number of patients came from outside the provincial borders - Northern Cape (29%) and Lesotho (13%) (Figure 1).

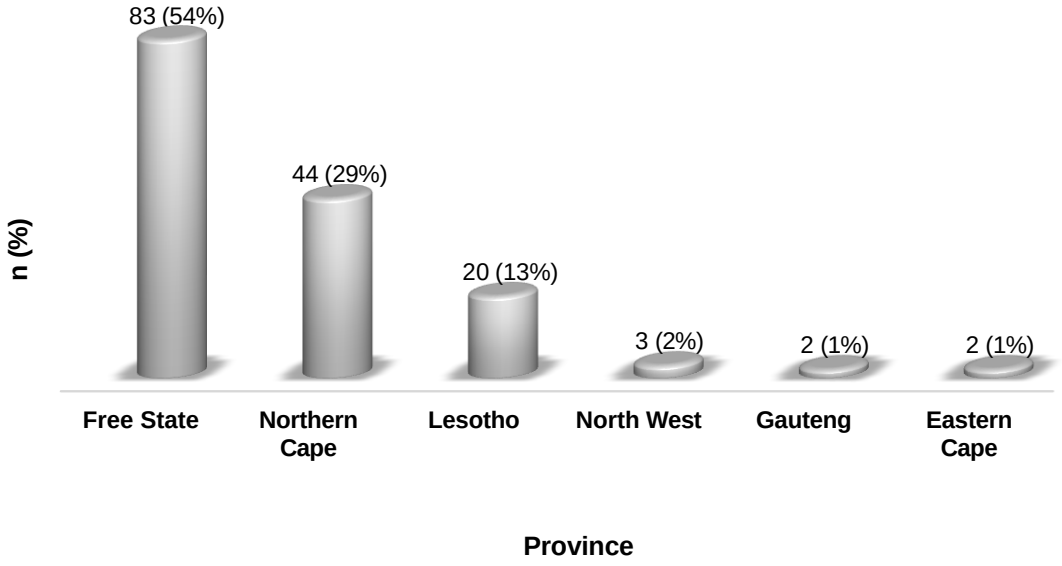



**Figure 1:** Single ventricle physiology per province of residence (n=154).

The Free State province is divided into five districts. It is the third largest province (129.8 square kilometres) in South Africa with a population of 2.8 million people, making it the province with the second lowest population density; the Northern Cape is the largest (372.9 square kilometres) province with a population of 1.3 million people making it the province with the lowest population density. Although Lesotho is a small country (30.3 square kilometres), it has a population of 2.18 million, and most of the

terrain is mountainous. Figure 2 illustrates the percentage of patients referred from each district and the population per district (P/D) for children aged 0–4 years as per the 2016 census (green). Most infants came from the Mangaung district (40%), almost double the number of patients compared to the Thabo Mafutsanyane districts (18%), although they have similar population numbers.

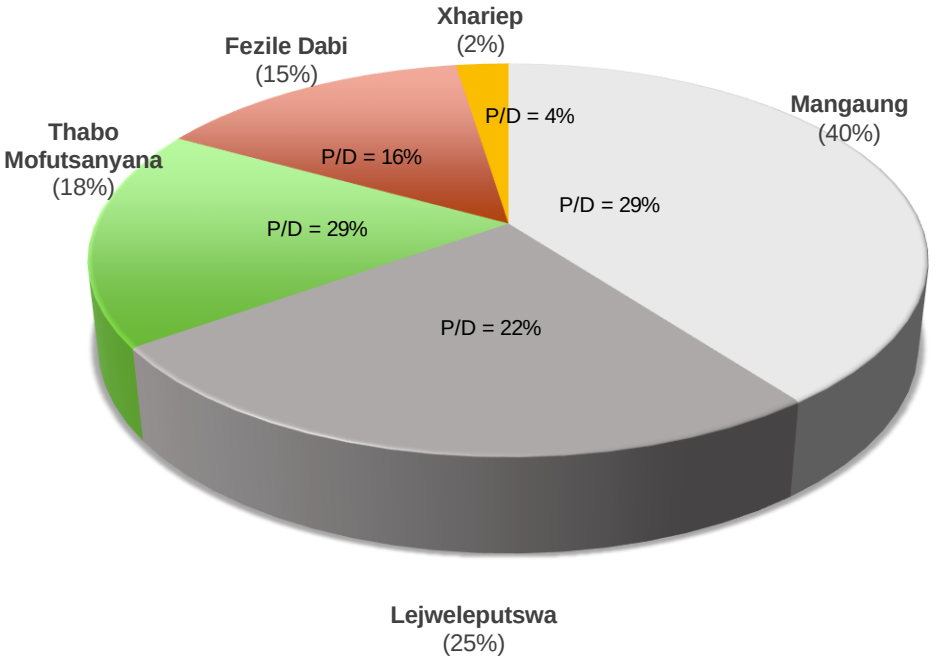



**Figure 2:** Patient referral per Free State districts. [P/D, Population per District].

Patients were seen for the first time at just over one month of age (median: 34.5 days; IQR: 2.2,156.1). In the Free State, patients from the Fezile Dabi district (median three days; IQR: 1.3:134.1) and Mangaung districts (4.1 days; IQR: 1.0:83.1) presented earliest (within a few days), whereas patients from the Thabo Mofutsanyane district (30.4 days; IQR: 2.0:221.1) and the Lejweleputswa district (38.5 days; IQR: 2.5:148.5) only presented after a median of a month. The Xhariep district only had two patients presenting at age four days and seven months respectively. Mangaung and Fezile Dabi districts are the two smallest geographical districts with high population densities, whereas the Xhariep District has the largest surface area but low population density. In contrast, patients from the Northern Cape presented after almost two months (56.8 days; IQR: 3.3:155.4) and Lesotho even later at almost six months (178.4 days; IQR: 3.3:517.7) of age.

Forty patients received no intervention. The reasons were poor presentation conditions, significantly associated lesions, lethal syndromes, and other lethal conditions. Forty-five per cent of these patients (18/40) demised, and almost half (42%) occurred within seven days, emphasising the severity of co-morbidities. Eighteen of these patients were lost to follow-up, and four were still alive at the conclusion of the study. Table 1 presents the procedural data of the 114 patients.

**Table 1:** Clinical data of patients with single ventricle physiology.

| Variable | STAGE 1 | | | | | STAGE 2 | STAGE 3 |
|---|---|---|---|---|---|---|---|
| | **PDA stents** (n=24) | **BT shunts** (n=34) | **Central shunts** (n=18) | **PAB** (n=9) | **SANO** (n=2) | **Glen procedure** (n=63) | **Fontan procedure** (n=30) |
| **Age (median)** | 4.6 d | 24.3 d | 201.8 d | 110.5 d | 1.5yrs | 1.3 y | 5.9 y |
| **Weight (kg)** | 3.0 | 3.0 | 6.6 | 5 | 4.85 | 9.3 | 17.3 |
| **BSA ($m^2$)** | 0.17 | 0.20 | 0.33 | 0.27 | 0.27 | 0.4 | 0.7 |
| **Diagnosis:** | | | | | | | |
| TA | 6 | 23 | 11 | 4 | 1 | 34 | 18 |
| PA IVS | 17 | 9 | 6 | 0 | 0 | 10 | 6 |
| DILV | 0 | 0 | 0 | 3 | 0 | 5 | 1 |
| U-AVSD | 0 | 0 | 0 | 0 | 0 | 7 | 1 |
| DIRV | 0 | 1 | 0 | 0 | 1 | 3 | 1 |
| DORV | 0 | 0 | 1 | 1 | 0 | 2 | 1 |
| **Others** | 1 | 1 | 0 | 1 | 0 | 2 | 2 |

[TA: tricuspid atresia, PA IVS: pulmonary atresia with an intact septum, DILV: double inlet left ventricle, u-AVSD: unbalanced atrioventricular septal defect, DIRV: double inlet right ventricle, PDA: patent ductus arteriosus, BT: Blalock-Taussig, PAB: pulmonary artery banding d: days, y: years].

### Stage 1: Palliation

Eighty-seven patients underwent first-stage palliation consisting of mostly mBTS (39%), followed by PDA stents and central shunts (28% and 21%). PDA stents (n=24) were percutaneously implanted at an early age with a median of 4.6 days (IQR:2.2:20.8), compared to BTS, which was performed at a median age of 24.3 days (IQR:6.1:111.5), and central shunts even later at a median age of 201.8 days (IQR:69.1:584.5). PAB (n=9) and central shunts (n=18) were performed at a markedly older median age of 110.5 days (IQR:53.2:217.5) and 201.8 days (IQR:69.5:584.5), respectively. The median weights for PDA and BTS were also noticeably less (3 kg)

than that of PAB and central shunts, with median weights of 5 kg and 6.6 kg, respectively.

The highest mortality was observed in this group, with 21 deaths (24%) in stage I; perioperative mortalities were similar for patients with PDA stents (13%), BT shunts (12%) and central shunts (17%). There were no deaths in the PAB and Sano shunt groups (Table 2). Sixteen patients in stage 1 were lost to follow-up, and 13 are still alive and awaiting further intervention.

**Table 2.** Intervention outcome

| Variable | PDA Stents (n=24) | BT Shunts (n=34) | CENTRAL Shunts (n=18) | PAB (n=9) | SANO (n=2) | GLEN Procedure (n=63) | FONTAN Procedure (n=30) |
|---|---|---|---|---|---|---|---|
| Perioperative % | 13 | 12 | 17 | 11 | 0 | 3 | 0 |
| Death > 30 days | 3 | 4 | 3 | 1 | 1 | 2 | 0 |
| Total death | 7 | 10 | 3 | 1 | 1 | 6 | 2 |
| Lost to follow-up | 1 | 10 | 2 | 3 | 1 | 12 | 6 |

### Stage 2: Bidirectional Glen

Sixty-three (n = 63) patients underwent a bidirectional Glenn operation at a median age of 1.33 years (IQR:0.9:2.3). Twenty-six had no prior stage I intervention. The primary lesion for these patients was tricuspid atresia (n = 33) in more than 50% of children. These patients presented for the first time at a much later median age of 146 days versus the median age of 91 days of the group that received prior stage 1 interventions. Six patients were demised during stage II intervention, two within 30 days (perioperative mortality of 3%). Twelve stage II intervention patients were lost to follow-up, and 16 patients are still alive and being followed up with the aim of Fontan operation (Table 2).

### Stage 3: Fontan Procedure

At the conclusion of the study, 30/114 (26%) completed single ventricle palliation to Fontan. The median age at Fontan was 5.9 years (IQR: 5.2:6.9). Stage III suffered two deaths, of which none were within 30 days; six (n= 6) stage III patients were lost to follow-up, and 22 patients are still alive (Table 2).

### Last follow-up

At the cessation of the study, 29 of the total group of 114 patients had demised, 35 were lost to follow-up, whilst 50 are in follow-up and at various management stages. The treatment outcomes of the 114 patients are summarised in Figure 3.

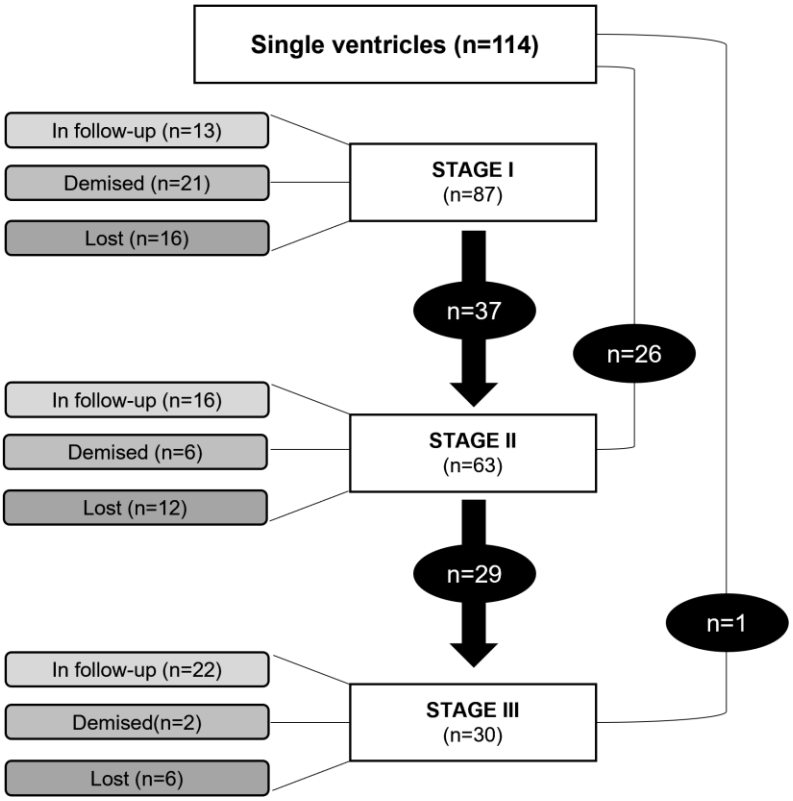



**Figure 3:** Treatment outcomes of patients presenting with single ventricle physiology.

## Discussion

This study reports the outcomes of single ventricle patients spanning more than two decades in a Sub-Saharan country and is the first report on outcomes in the Free State region. This study's key findings were that patients in this region presented late and that single ventricle physiology in central SA is a severe cardiac condition. The highest mortality occurs during the first palliative procedures. It is of concern that a substantial number of patients (almost a third) are lost to follow-up.

Tricuspid atresia was the most common lesion diagnosed in more than half of the cases. A similar trend was observed in an Angolan study.[2] However, in a Cape Town report, only a third of patients presented with tricuspid atresia, and two-thirds had

dominant left ventricles. In this study, however, most patients (88%) presented with lesions exhibiting dominant left ventricles.[8] It should be noted that the Meyer study analysed all lesions undergoing BDG procedures. [8]

Although more than half of the patients came from the Free State, the rest were mainly from the bordering Northern Cape (almost a third) and Lesotho (13%). The data shows that patients presented late, except for two Free State districts, namely Mangaung and Fezile Dabi, that presented within days. In contrast, outlying areas took weeks to months to present at our clinic for the first time. The Mangaung district's early referral can be explained by the fact that it is the smallest geographical district, has the largest population density, is closest to the central referral hospital, and has three well-staffed and large functional regional hospitals. Access to healthcare facilities is challenging in rural districts because of smaller regional hospitals, larger patient-to-doctor ratios, and extensive travelling. This may partially explain why patients were referred much later. These findings emphasise the need for early detection and educational programs in rural areas. The authors speculate that long distances, rugged terrain, limited primary care facilities and inadequate referral systems contribute to the late presentation of these infants. Late referral contributed to poor condition at presentation and explained why several patients could not be offered palliation.

Stage 1 palliation was offered to many of the patients, with more than three-quarters of eligible patients receiving initial interventions. PDA stenting was the palliative intervention performed earliest (within a few days), followed by BT shunts within a few weeks. Other palliative interventions were only performed much later. Stage I had the highest mortality rate of the three stages. This is in line with developed countries where up to 22% of patients demise during the early stages.[9] These findings illustrate that ductal stenting may be a good option in resource-limited settings like ours - it can be performed early with results comparable to surgical systemic pulmonary artery shunts. [10,11,12]

Forty-three per cent of patients receiving stage 1 palliative interventions proceeded to bidirectional Glenn operations. Many of these patients (41%) had no prior intervention(s). This is similar to findings in the Cape Town study, where a third of patients had had no previous intervention before bidirectional Glen procedures.[8] In

our study, bidirectional Glenn procedures were performed relatively young, with a median age of 1.3 years. This is similar to an Angolan study where the median age was 1.1 years.[2] However, in another South African[8] and a sizeable Egyptian study,[13] it was found that the median age was much older at 2,5 years and 2.3 years, respectively, for bidirectional Glenn procedures. The operative mortality for Glenn procedures was 3%, similar to the Cape Town study[8] and acceptable compared to the operative mortality of 17% in the Angolan study.[2] In our study, almost half of the patients receiving a bidirectional Glen operation proceeded to a Fontan procedure, which compares favourably to the Cape Town results.[8]

For bidirectional Glenn procedures, the median age was much older at 2,5 years and 2.3 years, respectively. The operative mortality for Glenn procedures was 3%, similar to the Cape Town study[8] and acceptable compared to the operative mortality of 17% in the Angolan study.[2] In our study, almost half of the patients receiving a bidirectional Glen operation proceeded to a Fontan procedure, which compares favourably with the Cape town results.[8]

Fontan procedures were performed at a median age of 5.9 years. This is in line with international data that shows a decline in the age at which Fontan procedures are performed. A five-decade review study by Kverneland et al. (2017) showed that Fontan procedures are performed as young as 2.0 to 5.6 years (median) in recent years in high-income countries.[6] In the Angolan study,[2] the median age for Fontan procedures was 3.8 years vs. a median age of 8.5 years in the Cape Town study.[8] In our study, no operative mortalities (within 30 days) were observed after the Fontan procedure, which compares favourably with an Angolan study,[2] which reported operative mortality of 20%.

Patients lost to follow-up are a concern in our setting as almost a third of patients (35/114) in this study was lost to follow-up. In a study by Smit et al. (2017), the reasons for the loss to follow-up were attributed to the long distances combined with unreliable transport, challenging communication, and a lack of understanding by parents.[14] Analogous trends were observed in another South African study[8] performed at the Red Cross War Memorial Children's Hospital for patients receiving bidirectional Glenn shunts, where 30.5% of patients were also lost to follow-up. Other African

countries face even more challenges, and in an Angolan study, almost two-thirds of their patients were lost to follow-up.[2] Patients with severe cardiac lesions require lifelong follow-up. Still, even in a Canadian study,[15] 21% of patients with severe cardiac lesions were lost to follow-up after the age of 18 years. The authors speculate that most of our patients lost to follow-up can be attributed to the large migratory population, cultural barriers, or being deceased.

## Limitations

The main limitation is the retrospective nature of this study with its inherent challenges. Mortality rates should be interpreted with caution, bearing in mind that many patients were lost to follow-up, treatments may have changed over the two-decade period of the study, and only patients with single ventricular physiology were included in this study. Because of its design, it is essential to note that this study does not reflect all Glenn and Fontan procedures performed at our institution. A considerable number of patients still have to proceed to the next stage.

## Conclusion

Treatment of single ventricle physiology at our institution, as in other Sub-Saharan countries, faces various challenges. These include large distances from the cardiac centre, late presentation and many patients needing more support for follow-up. Outcomes of interventions compare favourably with other Sub-Saharan countries. The highest mortality rate occurs during stage I, and patients who progress to Glenn and Fontan procedures have a low mortality rate. This study highlights the need to detect patients with single ventricle physiology early. A new strategy is also needed for the follow-up of patients.

## Acknowledgements

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

## Conflict of interest statement

The authors have no disclosures of any nature.

## References


1. Ezzeldin DA, Shouman K, Atteya H. Impact of ventricular morphology on myocardial deformation in patients with single ventricle. Journal of The Indian Academy of Echocardiography & Cardiovascular Imaging. 2019;3(3):127.

2. Manuel V, Morais H, Turquetto AL, Miguel G, Miana LA, Pedro A, Nunes MA, Leon G, Magalhães MP, Martins T, Júnior AP. Single ventricle palliation in a developing sub-Saharan African country: what should be improved? World Journal for Pediatric and Congenital Heart Surgery. 2019;10(2):164-70.

3. Centre for disease control and prevention. 2019. Congenital heart defects: Data and statistics on congenital heart defects. Available at: https://www.cdc.gov/ncbddd/heartdefects/data.html (Assessed 15 March 2023).

4. Hauck A, Porta N, Lestrud S, Berger S. The pulmonary circulation in the single ventricle patient. Children. 2017;4(8):71.

5. Talwar S, Nair VV, Choudhary SK, Airan B. The Hemi-Fontan operation: A critical overview. Annals of pediatric cardiology. 2014;7(2):120.

6. Kverneland LS, Kramer P, Ovroutski S. Five decades of the Fontan operation: a systematic review of international reports on outcomes after univentricular palliation. Congenital heart disease. 2018;13(2):181-93.

7. Edwin F, Elgamal MA, Dorra A, Reddy D, Entsua-Mensah K, Adzamli I, Yao NA, Tettey M, Tamatey M, Vosloo S, Kinsley R. Challenges of caring for functionally single ventricle patients in Africa. World Journal for Pediatric and Congenital Heart Surgery. 2019;10(3):338-42.

8. Meyer HM, Marange-Chikuni D, Zühlke L, Roussow B, Human P, Brooks A. Outcomes After Bidirectional Glenn Shunt in a Tertiary-Care Pediatric Hospital in South Africa. Journal of Cardiothoracic and Vascular Anesthesia. 2022;36(6):1573-81.

9. Weston C, Husain SA, Curzon CL, Neish S, Kennedy GT, Bonagurio K, Gosselin K. Improving outcomes for infants with single ventricle physiology through standardised feeding during the interstage. Nursing Research and Practice. 2016; 1:e9505629.

10. Benson L, Arsdell GV. Comparisons between ductal stenting and Blalock-Taussig shunts for infants with ductal-dependent pulmonary circulation. Circulation. 2018;137(6):602-4.

11. Glatz AC, Petit CJ, Goldstein BH, Kelleman MS, McCracken CE, McDonnell A, Buckey T, Mascio CE, Shashidharan S, Ligon RA, Ao J. Comparison between patent ductus arteriosus stent and modified Blalock-Taussig shunt as palliation for infants with ductal-dependent pulmonary blood flow: insights from the congenital catheterisation research collaborative. Circulation. 2018;137(6):589-601.

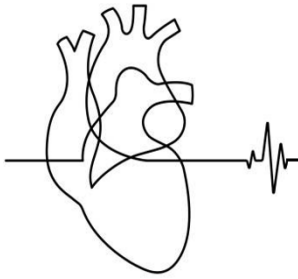
12. AbdelMassih AF, Menshawey R, Menshawey E, El-Maghraby AE, Sabry AO, Kamel A, Seyam MY, Elshawarbi P, Ahmed SN, Salem SS, Ragab S. Blalock-Taussig shunt versus ductal stent in the palliation of duct dependent pulmonary circulation; a systematic review and metanalysis. Current Problems in Cardiology. 2021; 8:100885.

13. Samir R, Diab OA, Morttada A, Aboulmaaty M. Permanent pacing in infants and children: A single centre experience in implantation and follow up. The Egyptian Heart Journal. 2011; 63(3-4):183-9.

14. Smith R. *Neurodevelopment, quality of life and burden of care of young children who have undergone cardiac interventions in central South Africa: Three-month and six-month post cardiac intervention outcomes* (Doctoral dissertation, PhD

dissertation. Johannesburg: University of the Witwatersrand). https://wiredspace.wits.ac.za/bitstreams/5c86fbbb-a28c-40d3-af1b-54105c2d8c53/download. (Assessed 30 March 2023).

15. Mackie AS, Ionescu-Ittu R, Therrien J, Pilote L, Abrahamowicz M, Marelli AJ. Children and adults with congenital heart disease lost to follow-up: who and when? Circulation. 2009;120(4):302-9.



# CHAPTER 4 – CASE REPORT

## Functional evaluation of a small group of Fontan patients

**Van Jaarsveld MJ** (BTech)[1], Botes L (DTech; PhD)[1], Smit FE (PhD)[2], Brown SC (DMed)[3]

*[1]Department of Health Sciences, Central University of Technology, Bloemfontein, South Africa*

*[2]Department of Cardiothoracic Surgery, University of the Free State, Bloemfontein, South Africa*

*[3] Division Paediatric & Congenital Cardiology, University of the Free State, Bloemfontein, South Africa*

**Institution at which work was performed:** Universitas Academic Hospital, South Africa

**Corresponding author:** Prof. Stephen C. Brown [3]

**Tel:** + 27 (0)51 405 3241 **Fax:** + 27 (0)51 444 3230

**e-mail:** Gnpdscb@ufs.ac.za

**Word count: abstract: 224 text (excluding references): 1273**

**Pages: 8**

**Keywords:** Fontan, echocardiography, six-minute walk test, Ross classification

**Short title:** Functional Evaluation of Fontan Patients

## Abstract

**Introduction:** Outcomes of Fontan procedures have improved remarkably over time.

**Objectives:** The functional assessment of Fontan patients measured by echocardiogram examinations, six-minute walk test and Ross classification.

**Methods:** Nine Fontan patients were evaluated during their outpatient visits to the Department of Paediatric Cardiology clinic at the Universitas Academic Hospital, Bloemfontein, South Africa. An echocardiographic study included the global and systolic assessment. The six-minute walk test was performed according to The American Thoracic Society and a modified Ross classification by the New York Heart Association (NYHA).

**Results:** The peak E wave median was 67.7 cm/sec, and the peak A wave median was 52 cm/sec, with a median E/A ratio of 1.28. The median deceleration time was 231.6ms. The median E' was 15.5 cm/sec, and the median E/E' was 4.6 9 cm/sec. The median mitral annular plane systolic excursion (MAPSE) was 10.3 mm, and one tricuspid annular plane systolic excursion (TAPSE) was 15.9 mm. Myocardial performance index (MPI) was prolonged with a median left ventricle MPI of 0.47 and one right ventricle (RV) MPI of 0.37. The median distance covered during the 6-minute walk tests was 480 metres. Four patients were classified as class I and five as class II heart failure using the Ross classification.

**Conclusion:** Results of our study demonstrated mild functional limitations in the six-minute walk test (6MWT) and heart failure scores. These findings were underscored by the impairment of echocardiographic systolic function indices such as MAPSE/TAPSE and MPI.

## Introduction

Over time, outcomes of Fontan procedures have improved remarkably, with operative mortality approaching 1%. The five and ten-year transplantation-free survival rate is now 95% and 90%, respectively, and 20-year survival rates vary between 61% and 85% (Rychik et al., 2019). Therefore, the American Heart Association (AHA) proposed using a Fontan Circulation Surveillance Testing Toolkit for the follow-up and treatment of patients with Fontan circulation, including annual outpatient visits, electrocardiography, and echocardiogram examinations (Rychik et al., 2019).

In patients with single ventricle physiology, the dominant ventricle will eventually fail due to increased resistance from the systemic and pulmonary circulation (Ezzeldin et al., 2019). A complete echocardiographic evaluation on Fontan patients at every outpatient visit at least once a year is recommended to control for systolic and diastolic functional deterioration over time, assessing venous to pulmonary pathway obstruction and atrioventricular valve regurgitation (Hauser et al., 2017). The six-

minute walk test is a one-time measurement of functional status and a predictor of morbidity and mortality, especially in patients with pulmonary hypertension (Feltez et al., 2015). The Ross heart failure classification provides a global clinical assessment of heart failure severity in infants and has been modified to apply to all paediatric ages (Ross, 2012).

## Methodology

Nine Fontan patients were evaluated during their outpatient visits to the Department of Paediatric Cardiology clinic at the Universitas Academic Hospital, Bloemfontein, South Africa.

An echocardiographic study was performed, which included the diastolic assessment of the ventricle. This measured the peak E and A velocity, the E/A ratio, deceleration time, and the E' and E/E' ratio. In addition, tricuspid annular plane systolic excursion (TAPSE) or mitral annular plane systolic excursion (MAPSE) and myocardial performance index (MPI) were also determined. Three measurements were taken, and the average was calculated. One technologist performed all echocardiographic studies to prevent inter-observer variability.

The six-minute walk test was performed according to The American Thoracic Society and included total distance patients could walk, oxygenation and blood pressure measurements before and after the examination (Feltez et al., 2015).

The modified Ross classification by the New York Heart Association (NYHA) was used to grade the presence and severity of heart failure by a paediatric cardiologist (Ross, 2012).

## Results

There were four males and five females with a median age of 15.1 years ranging from 8.1 to 22.7 years.

The peak E wave median was 67.7 cm/sec (range: 56.7 cm/sec to 100.7 cm/sec), and the peak A wave median was 52 cm/sec (range: 45.1 cm/sec to 84.6 cm/sec), with a median E/A ratio of 1.28 (range: 1.04 to 2.06). The median deceleration time was

231.6ms (range: 173ms to 263ms). The median E' was 15.5 cm/sec, and the median E/E' was 4.6 9 cm/sec (n=3).

Seven patients presented with single left ventricles, and two with single right ventricles. The median MAPSE was 10.3 mm, ranging from 8.8 mm to 12.1 mm. TAPSE was 15.9 mm in a patient with a dominant RV, and in the second patient, TAPSE could not be measured due to difficult/poor quality images.

The MPI of the study group was prolonged with a median left ventricle MPI of 0.47 (range; 0.34 to 1.1) and one RV MPI of 0.37. This is prolonged when compared to the normal range of 0.28 ±+-0.04.

The median distance covered during the 6-minute walk tests was 480 metres (420 to 728 metres, average 508 metres). The median for males was 476 metres (average: 483 metres), and the median for females was 480 metres (average: 495 metres). The median blood pressures before and after the 6-minute walk tests were unchanged. The median saturation before the 6-minute walk tests was 94% compared to 92.5% after the test. The median heart rate before the 6-minute walk tests was 95 bpm compared to 107 bpm afterwards. One person reported dyspnoea, and three patients reported fatigue after the 6-minute walk tests. Four patients were classified as class I and five as class II heart failure using the Ross classification.

## Discussion

During the first decades following the Fontan procedure, systolic ventricular function is preserved but declines as time progress (Rychik et al., 2019). There is evidence in Fontan patients that diastolic function is impaired even in the presence of normal systolic function, and this further decreases over time. (Panesar and Burch, 2017). However, echocardiographic data on diastolic dysfunction in Fontan patients are limited, and both MAPSE and TAPSE in our study were low even after age was considered, indicating systolic dysfunction. A prolonged MPI further confirmed this, indicating global dysfunction (both systolic and diastolic). Di Maria et al. (2018) also indicated prolonged MPI in Fontan patients, attributed to ventricular relaxation abnormalities and lower pulmonary venous return. In our study, patients displayed

mostly normal diastolic functioning. The young age can partially explain this in our patients (average age of 15,2 years).

In a study by Gazzoletti et al. (2022), the average walking distance for healthy adult individuals was 581 metres (range: 383 to 800 metres) for females and 608 metres (range 410 to 875 metres) for males. The average walking distance in our study was much lower but is similar to a study conducted in our department among children with heart failure, who also had a median distance of 480 metres (Mofokeng et al., 2021). Although this indicates a lower functional exercise capacity, it is noteworthy that our study population was much younger and that our average age of 15,2 years is much younger than their average age of 46.4 and 47.1 for males and females, respectively, in the study conducted by Gazzoletti et al. (2022). The six-minute walk test is an inexpensive, non-invasive, and easy investigation to assess exercise tolerance and functional capacity in Fontan patients over time. Nystoriak and Bhatnagar (2018) showed that heart rate and mean arterial pressure increased during exercise. However, in our study, heart rate only increased moderately, and saturation demonstrated a slight decrease after the 6-minute walk test, as expected in Fontan patients. Eroglu et al. (2017) reported decreased saturation in athletes after exercise from 97.3% to 96.2%. Moreira et al. (2014), in a study of saturation in COPD patients after a 6-minute walk test, suggest a decrease of more than 4% to be significant.

## Conclusion

The results of our study demonstrated mild functional limitations in 6MWT and heart failure scores. These findings were underscored by the impairment of echocardiographic systolic function indices such as MAPSE/TAPSE and MPI.

## References

Cazzoletti, L., Zanolin, M.E., Dorelli, G., Ferrari, P., Dalle Carbonare, L.G., Crisafulli, E., Alemayohu, M.A., Olivieri, M., Verlato, G. and Ferrari, M. 2022. Six-minute walk distance in healthy subjects: reference standards from a general population sample. *Respiratory Research*, 23(1): 1-9.

Di Maria, M.V., Lopez, C., Landeck, B., Younoszai, A., Friedberg, M., Hunter, K. and Mertens, L. 2017. Abnormalities in Myocardial Performance Index in single left ventricles after Fontan are driven by abnormal relaxation. *Circulation*, 136(1):14011.

Eroglu, H., Okyaz, B. and Türkçapar, Ü. 2018. The effect of acute aerobic exercise on arterial blood oxygen saturation of athletes. *Journal of Education and Training Studies*, 6(9): 74-79.

Ezzeldin, D.A., Shouman, K. and Atteya, H. 2019. Impact of ventricular morphology on myocardial deformation in patients with single ventricle. *Journal of The Indian Academy of Echocardiography & Cardiovascular Imaging*, 3(3):127-134.

Feltez, G., Coronel, C.C., Pellanda, L.C. and Lukrafka, J.L. 2015. Exercise capacity in children and adolescents with corrected congenital heart disease. *Pediatric Cardiology*, 36(5):1075-1082.

Hauser, J.A., Taylor, A.M. and Pandya, B. 2017. How to image the adult patient with Fontan circulation. *Circulation: Cardiovascular Imaging,* 10(5): e004273.

Mofokeng, M., Botes, L., Brown, S.C., and Smit, F. 2021. Echocardiographic and clinical correlation in children with dilated cardiomyopathy in central South Africa. *South African Heart, Journal,* 18(3):*178.*

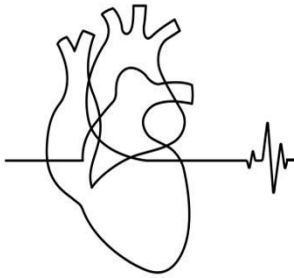
Moreira, M.Â.F., Medeiros, G.A.D., Boeno, F.P., Sanches, P.R.S., Silva Júnior, D.P.D. and M Müller, A.F. 2014. Oxygen desaturation during the six-minute walk test in COPD patients. *Jornal Brasileiro de Pneumologia*, 40: 222-228.

Nystoriak, M.A. and Bhatnagar, A. 2018. Cardiovascular effects and benefits of exercise. *Frontiers in Cardiovascular Medicine*, 5(135): PMID: 30324108.

Panesar, D.K. and Burch, M. 2017. Assessment of diastolic function in congenital heart disease. *Frontiers in Cardiovascular Medicine*, 4(5): PMID: 28261582.

Ross, R.D. 2012. The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. *Pediatric Cardiology*, 33(8):1295-1300.

Rychik, J., Atz, A.M., Celermajer, D.S., Deal, B.J., Gatzoulis, M.A., Gewillig, M.H., Hisa, T.Y., Hsu, D.T., Kovacs, A.H., McCrindle, B.W. and Newburger, J.W. 2019. Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American Heart Association. *Circulation*, 140(6): 234-284.



# CHAPTER 5 – GENERAL CONCLUSION

This study reports the outcomes of single ventricle patients spanning more than two decades in a Sub-Saharan country and is the first report on outcomes in the Free State region. Treatment of single ventricle physiology at our institution, as in other Sub-Saharan countries, faces various challenges.

Patients in our region presented late, and the study shows that single ventricle physiology in central SA is a severe cardiac condition. The late presentation can be attributed to challenging access to healthcare facilities in rural districts because of smaller regional hospitals, larger patient-to-doctor ratios, and extensive travelling.

The highest mortality rate is observed during stage I, with PDA stenting being the earliest intervention. These findings illustrate that ductal stenting may be a good option in resource-limited settings like ours - it can be performed early with results comparable to surgical systemic pulmonary artery shunts.

Patients who progress to Glenn and Fontan procedures have a low mortality rate. Outcomes of interventions compare favourably with other Sub-Saharan countries. It is of concern that a substantial number of patients are lost to follow-up. Late referral contributed to poor condition at presentation and explained why several patients could not be offered palliation.

The results of the echocardiographic examinations, the 6MWT test and the Ross classification, demonstrated mild functional limitations. Therefore, this study highlights the need for early detection and educational programs in rural areas to detect patients with single ventricle physiology. A new strategy is also needed for the follow-up of patients.

# REFERENCES


AbdelMassih, A.F., Menshawey, R., Menshawey, E., El-Maghraby, A.E., Sabry, A.O., Kamel, A., Seyam, M.Y., Elshawarbi, P., Ahmed, S.N., Salem, S.S. and Ragab, S. 2021. Blalock-Taussig shunt versus ductal stent in the palliation of duct dependent pulmonary circulation; a systematic review and metanalysis. *Current Problems in Cardiology*, 47(9):100885.

Agasthi, P., Pujari, S.H., Tseng, A., Graziano, J.N., Marcotte, F., Majdalany, D., Mookadam, F., Hagler, D.J. and Arsanjani, R. 2020. Management of adults with coarctation of the aorta. *World Journal of Cardiology*, 12(5):167-191.

Akintoye, E., Veldtman, G.R., Miranda, W.R., Connolly, H.M. and Egbe, A.C. 2019. Optimum age for performing Fontan operation in patients with univentricular heart. *Congenital Heart Disease*, 14*(*2):138-139.

Angelini, A., di Gioia, C., Doran, H., Fedrigo, M., Henriques de Gouveia, R., Ho, S.Y., Leone, O., Sheppard, M.N., Thiene, G., Dimopoulos, K. and Mulder, B. 2020. Autopsy in adults with congenital heart disease (ACHD). *European Journal of Pathology*, 476: 797-820.

Assadi, R.S., Zamith, M.M., Silva, M.F., Thomaz, P.G., Miana, L.A., Guerra, V.C., Pedra, C.A.C. and Barbero-Marcial, M. 2007. A novel adjustable pulmonary artery banding system for hypoplastic left heart syndrome. *Brazilian Journal of Cardiovascular Surgery*, 22: 41-48.

Aurora, R.G., Prakoso, R., Fakhri, D., Sakidjan, I., Siagian, S.N., Almazini, P. and Lilyasari, O. 2022. Impact of older age at Fontan completion on mid-term survival. *The Egyptian Heart Journal*, 74(1): 1-8.

Bao, M., Li, H., Pan, G., Xu, Z. and Wu, Q. 2014. Central shunt procedures for complex congenital heart diseases. *Journal of Cardiac Surgery: Including Mechanical and Biological Support for the Heart and Lungs*, 29(4):537-541.

Bove, E.L., de Leval, M.R., Migliavacca, F., Guadagni, G. and Dubini, G. 2003. Computational fluid dynamics in the evaluation of hemodynamic performance of cavopulmonary connections after the Norwood procedure for hypoplastic left heart syndrome. *The Journal of Thoracic and Cardiovascular Surgery*, *126*(4): 1040-1047.

Brown, D.W., Powell, A.J. and Geva, T. 2010. Imaging complex congenital heart disease - functional single ventricle, the Glenn circulation and the Fontan circulation: a multimodality approach. *Progress in Pediatric Cardiology*, 28(1-2):45-58.

Buys, D.G., Brown, S.C. and Greig, C. 2013. Stenting the arterial duct: practical aspects and review of outcomes: PDA stenting. *SA Heart*, 10(3):514-519.

Bykov, S.E., Kovalev, S.A., Gryaznov, D.Y., Korosan, E.I. and Novick, W.M. 2019. Surgical treatment for the single ventricle with subaortic obstruction. Clinical case of the Damus-Kaye-Stansel procedure. *Almanac of Clinical Medicine*, 47(4):376-379.

Centre for disease control and prevention. 2019. Congenital heart defects: Data and statistics on congenital heart defects. Available at: https://www.cdc.gov/ncbddd/heartdefects/data.html (Assessed 15 March 2023).

Ciliberti, P., Ciancarella, P., Bruno, P., Curione, D., Bordonaro, V., Lisignoli, V., Panebianco, M., Chinali, M., Secinaro, A., Galletti, L. and Guccione, P. 2023. Cardiac Imaging in Patients After Fontan Palliation: Which Test and When? *Insights in Pediatric Cardiology,* 10: 16648714.

Cordina, R., von Klemperer, K., Kempny, A., Senior, R., Celermajer, D.S., Babu-Narayan, S., Gatzoulis, M. and Li, W. 2015. Echocardiographic predictors of mortality in adults with a Fontan circulation. *Circulation*, 132(3):10259-10259.

Daley, M. and d'Udekem, Y. 2019. In patients undergoing Fontan completion, does a younger age at operation result in better long-term exercise capacity and prognosis? *Interactive CardioVascular and Thoracic Surgery*, 28(2):301-305.

D'Angelo, E.C., Ciuca, C. and Assenza, G.E. 2022. Management of Fontan failure. *Heart*, 108(22):1822-1831.

Delmo Walter, E.M., Javier, M.F.D.M. and Hetzer, R. 2017. Extra-anatomical bypass in complex and recurrent aortic coarctation and hypoplastic arch. *Interactive CardioVascular and Thoracic Surgery*, 25(3):400-406.

De Silva, D.C.L., Perera, S.N., Wijemanne, I., Perera, L.A.P., Mahalekamge, R. and Fernando, J. 2013. Perigraft seroma following Right Modified Blalock Taussig shunt in a child with complex cyanotic heart disease. *Galle Medical Journal*, 18(2):25-27.

Devlin, P.J., Jegatheeswaran, A., McCrindle, B.W., Karamlou, T., Blackstone, E.H., Williams, W.G., DeCampli, W.M., Mertens, L., Fackoury, C.T., Eghtesady, P. and Jacobs, J.P. 2020. Pulmonary artery banding in complete atrioventricular septal defect. *The Journal of Thoracic and Cardiovascular Surgery*, 159(4):1493-1503.

Doshi, S.R., Gupta, H. and Ramakrishnan, S. 2015. Central (Garland) aortopulmonary shunt. *Heart Asia*, 7(1):8-9.

d'Udekem, Y., Iyengar, A.J., Cochrane, A.D., Grigg, L.E., Ramsay, J.M., Wheaton, G.R., Penny, D.J. and Brizard, C.P. 2007. The Fontan procedure: contemporary techniques have improved long-term outcomes. *Circulation*, 116(11):157-164.

Edwin, F., Elgamal, M.A., Dorra, A., Reddy, D., Entsua-Mensah, K., Adzamli, I., Yao, N.A., Tettey, M., Tamatey, M., Vosloo, S. and Kinsley, R. 2019. Challenges of caring for functionally single ventricle patients in Africa. *World Journal for Pediatric and Congenital Heart Surgery*, 10(3):338-342.

Eidem, B.W., O'Leary, P.W., Tei, C. and Seward, J.B. 2000. Usefulness of the myocardial performance index for assessing right ventricular function in congenital heart disease. *The American Journal of Cardiology*, 86(6):654-658.

Eilers, L. and Qureshi, A.M. 2020. Advances in Pediatric Ductal Intervention: an Open or Shut Case? *Current Cardiology Reports*, 22(14):1-7.

Etoile, H.M. 2016. Special abstract issue of the 12th Annual Congress of the European Cardiac Arrhythmia Society. *Journal of Interventional Cardiac Electrophysiology*, 45: 233-333.

Ezzeldin, D.A., Shouman, K. and Atteya, H. 2019. Impact of ventricular morphology on myocardial deformation in patients with single ventricle. *Journal of The Indian Academy of Echocardiography & Cardiovascular Imaging*, 3(3):127-134.

Fell, B., Hanekom, S. and Heine, M. 2022. A modified six-minute walk test (6MWT) for low-resource settings-a cross-sectional study. *Heart & Lung*, 52:117-122.

Feltez, G., Coronel, C.C., Pellanda, L.C. and Lukrafka, J.L. 2015. Exercise capacity in children and adolescents with corrected congenital heart disease. *Pediatric Cardiology*, 36(5):1075-1082.

Fujii Y, Kasahara S, Kotani Y, Takagaki M, Arai S, Otsuki SI, Sano S. 2011. Double-barrel Damus–Kaye–Stansel operation is better than end-to-side Damus–Kaye–Stansel operation for preserving the pulmonary valve function: The importance of preserving the shape of the pulmonary sinus. *The Journal of Thoracic and Cardiovascular Surgery*, 141(1):193-199.

Galantowicz, M. 2020. Hybrid Procedures: A Surgeon's Viewpoint on the Next 10 Years. *Pediatric Cardiology*, 41(3):514-521.

Gewillig, M. and Brown, S.C. 2016. The Fontan circulation after 45 years: update in physiology. *Heart*, 102(14):1081-1086.

Gewillig, M., Brown, S.C., van de Bruaene, A. and Rychik, J. 2019. Providing a framework of principles for conceptualising the Fontan circulation. *Acta Paediatrica*, 109(4):651-658.

Ginde S, Goot BH, Frommelt PC. 2017. Imaging adult patients with Fontan circulation. *Current Opinion in Cardiology*, 32(5):521-528.

Glatz, A.C., Petit, C.J., Goldstein, B.H., Kelleman, M.S., McCracken, C.E., McDonnell, A., Buckey, T., Mascio, C.E., Shashidharan, S., Ligon, R.A. and Ao, J. 2018. Comparison between patent ductus arteriosus stent and modified Blalock-Taussig shunt as palliation for infants with ductal-dependent pulmonary blood flow: insights from the congenital catheterisation research collaborative. *Circulation*, 137(6):589-601.

Hauck, A., Porta, N., Lestrud, S. and Berger, S. 2017. The pulmonary circulation in the single ventricle patient. *Children*, *4*(8):71.

Hauser, J.A., Taylor, A.M. and Pandya, B. 2017. How to image the adult patient with Fontan circulation. *Circulation: Cardiovascular Imaging,* 10(5): e004273.

Henein, M.Y. and Lindqvist, P. 2020. Diastolic function assessment by echocardiography: A practical manual for clinical use and future applications. *Echocardiography*, 37(11):1908-1918.

Huntgeburth, M., Germund, I., Geerdink, L.M., Sreeram, N. and ten Cate, F.E.U. 2019. Emerging clinical applications of strain imaging and three-dimensional echocardiography for the assessment of ventricular function in adult congenital heart disease. *Cardiovascular Diagnosis and Therapy,* 9(2):326-345.

Jones, M.B. 2018. The fontan procedure for single-ventricle physiology. *Critical Care Nurse*, 38(1):1-10.

Juaneda, I., Chiostri, B. and Kreutzer, C. 2022. Technical aspects and common pitfalls of Norwood With Modified Blalock Taussig Shunt. *World Journal for Pediatric and Congenital Heart Surgery*, 13(5):576-580.

Kansy, A., Brzezińska-Rajszys, G., Zubrzycka, M., Mirkowicz-Małek, M., Maruszewski, P., Manowska, M. and Maruszewski, B. 2013. Pulmonary artery growth in univentricular physiology patients. *Kardiologia Polska (Polish Heart Journal)*, *71*(6):581-587.

Kempny, A., Dimopoulos, K., Alonso-Gonzalez, R., Alvarez-Barredo, M., Tutarel, O., Uebing, A., Piatek, P., Marino, P., Swan, L., Diller, G.P. and Wort, S.J. 2013. Six-

minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with Eisenmenger syndrome. *International Journal of Cardiology*, 168(5):4784-4789.

Kempny, A., Dimopoulos, K. and Gatzoulis, M.A. 2014. Single-ventricle physiology in the UK: an ongoing challenge of growing numbers and growing complexity of congenital heart disease. *Heart*, 100(7):1315-1316.

Khairy, P. and Poirier, N. 2012. Is the extracardiac conduit the preferred Fontan approach for patients with univentricular hearts? The extracardiac conduit is not the preferred Fontan approach for patients with univentricular hearts. *Circulation*, 126(21):2516-2525.

Khoo, N.S., Smallhorn, J.F., Kaneko, S., Kutty, S., Altamirano, L. and Tham, E.B. 2013. The assessment of atrial function in single ventricle hearts from birth to Fontan: a speckle-tracking study using strain and strain rate. *Journal of the American Society of Echocardiography,* 26(7):756-764.

Kiran, U., Aggarwal, S., Choudhary, A., Uma, B. and Kapoor, P.M. 2017. The Blalock and Taussig shunt revisited. *Annals of Cardiac Anaesthesia*, 20(3):323-330.

Koestenberger, M., Ravekes, W., Everett, A.D., Stueger, H.P., Heinzl, B., Gamillscheg, A., Cvirn, G., Boysen, A., Fandl, A. and Nagel, B. 2009. Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. *Journal of the American Society of Echocardiography*, 22(6):715-719.

Kverneland, L.S., Kramer, P. and Ovroutski, S. 2018. Five decades of the Fontan operation: a systematic review of international reports on outcomes after univentricular palliation. *Congenital heart disease*, 13(2):181-193.

Lee, J.R., Kwak, J., Kim, K.C., Min, S.K., Kim, W.H., Kim, Y.J. and Rho, J.R. 2007. Comparison of lateral tunnel and extracardiac conduit Fontan procedure. *Interactive CardioVascular and Thoracic Surgery*, 6(3):328-330.

Liu, Y., Chen, S., Zühlke, L., Black, G.C., Choy, M.K., Li, N. and Keavney, B.D. 2019. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. *International Journal of Epidemiology*, 48(2):455-463.

López-Candales, A. and Vallurupalli, S. 2022. Utility of the tricuspid annular tissue Doppler systolic velocity and pulmonary artery systolic pressure relationship in right ventricular systolic function assessment: A pilot study. *Echocardiography*, 39(10):1276-1283.

Ma, M. 2022. Commentary: A new Fontan commandment. *The Journal of Thoracic and Cardiovascular Surgery*, 164(3):783-784.

Mackie, A.S., Ionescu-Ittu, R., Therrien, J., Pilote, L., Abrahamowicz, M. and Marelli, A.J. 2009. Children and adults with congenital heart disease lost to follow-up: who and when? *Circulation*, 120(4):302-330.

Manuel, V., Morais, H., Turquetto, A.L., Miguel, G., Miana, L.A., Pedro, A., Nunes, M.A., Leon, G., Magalhães, M.P., Martins, T. and Júnior, A.P. 2019. Single Ventricle Palliation in a Developing Sub-Saharan African Country: What Should be Improved? *World Journal for Pediatric and Congenital Heart Surgery*, 10(2):164-170.

Margossian, R., Sleeper, L.A., Pearson, G.D., Barker, P.C., Mertens, L., Quartermain, M.D., Su, J.T., Shirali, G., Chen, S., Colan, S.D. and Pediatric Heart Network Investigators. 2016. Assessment of diastolic function in single-ventricle patients after the Fontan procedure. *Journal of the American Society of Echocardiography*, 29(11):1066-1073.

Mazza, G.A., Gribaudo, E. and Agnoletti, G. 2021. The pathophysiology and complications of Fontan circulation. *Acta BioMedica: Atenei Parmensis*, 92(5):e2021260.

McKenzie, E.D., Khan, M.S., Samayoa, A.X., Vener, D.S., Ishak, Y.M., Santos, A.B., Heinle, J.S. and Fraser Jr, C.D. 2013. The Blalock-Taussig shunt revisited: a contemporary experience. *Journal of the American College of Surgeons*, 216(4):699-704.

Meyer, H.M., Marange-Chikuni, D., Zühlke, L., Roussow, B., Human, P. and Brooks, A. 2022. Outcomes After Bidirectional Glenn Shunt in a Tertiary-Care Pediatric Hospital in South Africa. *Journal of Cardiothoracic and Vascular Anesthesia*, 36(6):1573-1581.

Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S. and Atwood, J.E. 2002. Exercise capacity and mortality among men referred for exercise testing. *New England Journal of Medicine,* 346(11):793-801.

Naeije, R. and Chesler, N. 2012. Pulmonary circulation at exercise. *Comprehensive Physiology*, 2(1):711-741.

Naik, R.B., Srivastava, C.P., Arsiwala, S., Mathur, A. and Sharma, S. 2021. Early outcomes after the on-pump bidirectional Glenn procedure: A single centre experience. *Journal of Cardiac Surgery*, 36(9):3207-3214.

Nakano, T., Tominaga, R., Nagano, I., Okabe, H. and Yasui, H. 2000. Pulsatile flow enhances endothelium-derived nitric oxide release in the peripheral vasculature. *American Journal of Physiology-Heart and Circulatory Physiology*, 278(4):1098-1104.

Ohuchi, H. 2016. Adult patients with Fontan circulation: what we know and how to manage adults with Fontan circulation? *Journal of Cardiology*, 68(3):181-189.

Ohye, R.G., Sleeper, L.A., Mahony, L., Newburger, J.W., Pearson, G.D., Lu, M., Goldberg, C.S., Tabbutt, S., Frommelt, P.C., Ghanayem, N.S. and Laussen, P.C. 2010. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *New England Journal of Medicine*, 362(21):1980-1992.

Oster, M.E., Lee, K.A., Honein, M.A., Riehle-Colarusso, T., Shin, M. and Correa, A. 2013. Temporal trends in survival among infants with critical congenital heart defects. *Paediatrics*, 131(5):1502-1508.

Oster, M.E., Knight, J.H., Suthar, D., Amin, O. and Kochilas, L.K. 2018. Long-Term Outcomes in Single-Ventricle Congenital Heart Disease: Importance of Ventricular Morphology. *Circulation*, 138(23):2718-2720.

Petit, C.J. 2011. Staged single-ventricle palliation in 2011: Outcomes and expectations. *Congenital Heart Disease*, *6*(5): 406-416.

Radiology key. Fastest radiology insight engine. Available at: https://radiologykey.com/glossary-of-pediatric-cardiovascular-surgical-rocedures (Assessed 20 March 2023).

Rao, P.S. 2020. Neonatal (and infant) coarctation of the aorta: management challenges. *Research and Reports in Neonatology*, 2020(10):11-22.

Rice, A.S., Smith, B.H. and Blyth, F.M. 2016. Pain and the global burden of disease. *Pain*, 157(4):791-796.

Rhodes, J. and Opotowsky, A.R. 2019. Fontan Circulation. *Exercise Physiology for the Pediatric and Congenital Cardiologist*: 97-115.

Ross, R.D. 2012. The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. *Pediatric Cardiology*, 33(8):1295-1300.

Rotta, A.T., Laussen, P.C. and Wessel, D.L. 2011. Critical care after surgery for congenital cardiac disease. *Pediatric Critical Care*, Mosby: 401-440.

Rychik, J., Atz, A.M., Celermajer, D.S., Deal, B.J., Gatzoulis, M.A., Gewillig, M.H., Hisa, T.Y., Hsu, D.T., Kovacs, A.H., McCrindle, B.W. and Newburger, J.W. 2019. Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American Heart Association. *Circulation*, 140(6): 234-284.

Said, S.M., Burkhart, H.M. and Dearani, J.A. 2012. The Fontan connections: past, present, and future. *World Journal for Pediatric and Congenital Heart Surgery*, 3(2):171-182.

Samir, K., Muftah, H. and Ammar, A. 2009. Bidirectional cavopulmonary shunt without cardiopulmonary bypass, the experience of Ain Shams University. *Journal of the Egyptian Society of Cardiothoracic Surgery*, 18(1-2): 79-84.

Sano, S., Kouretas, P.C., Kobayashi, Y., Kotani, Y. and Kasahara, S. 2020. How to reconstruct neo-aortic arch without patch at Norwood-Sano procedure. *Operative Techniques in Thoracic and Cardiovascular Surgery*, 25(4):221-241.

Schilling, C., Dalziel, K., Nunn, R., Du Plessis, K., Shi, W.Y., Celermajer, D., Winlaw, D., Weintraub, R.G., Grigg, L.E., Radford, D.J. and Bullock, A. 2016. The Fontan epidemic: population projections from the Australia and New Zealand Fontan registry. *International Journal of Cardiology*, 219:14-19.

Sen, S., Bandyopadhyay, B., Eriksson, P. and Chattopadhyay, A. 2012. Functional Capacity Following Univentricular Repair—Midterm Outcome. *Congenital Heart Disease*, 7(5):423-432.

Sharma, R. 2012. Pulmonary artery banding: Rationale and possible indications in the current era. *Annals of Paediatric Cardiology*, 5(1):40-43.

Sivakumar, K., 2015. PDA Stenting in Duct-Dependent Pulmonary Circulation. *Cardiac Catheterization for Congenital Heart Disease*: From Fetal Life to Adulthood: 449-478.

Smith, R. 2017. Neurodevelopment, quality of life and burden of care of young children who have undergone cardiac interventions in central South Africa: Three-month and six-month post cardiac intervention outcomes (Doctoral dissertation, PhD dissertation. Johannesburg: University of the Witwatersrand). https://wiredspace.wits.ac.za/bitstreams/5c86fbbb-a28c-40d3-af1b-54105c2d8c53/download. (Assessed 30 March 2023).

Sohn, D.W., Kim, Y.J., Kim, H.C., Chun, H.G., Park, Y.B. and Choi, Y.S. 1999. Evaluation of left ventricular diastolic function when mitral E and A waves are completely fused: role of assessing mitral annulus velocity. *Journal of the American Society of Echocardiography*, 12(3):203-208.

Spray, T.L. 2013. Hemi-Fontan Procedure. *Operative Techniques in Thoracic and Cardiovascular Surgery*, 18(2):124-137.

Steflik, D., Butts, R.J., Baker, G.H., Bandisode, V., Savage, A., Atz, A.M. and Chowdhury, S.M. 2017. A preliminary comparison of two-dimensional speckle tracking echocardiography and pressure–volume loop analysis in patients with Fontan physiology: The role of ventricular morphology. *Echocardiography*, 34(9):1353-1359.

Stern, H.J. 2010. Fontan's “Ten Commandments” revisited and revised. *Pediatric Cardiology*, 31(8):1131-1134.

Suradi, H. and Hijazi, Z.M. 2015. Current management of coarctation of the aorta. *Global Cardiology Science and Practice*, 2015(4):1-14.

Talwar, S., Nair, V.V., Choudhary, S.K. and Airan, B. 2014. The Hemi-Fontan operation: A critical overview. *Annals of Paediatric Cardiology*, 7(2):120-125.

Van der Ven, J.P., van den Bosch, E., Bogers, A.J. and Helbing, W.A. 2018. State of the art of Fontan strategy for the treatment of univentricular heart disease. *F1000Research*, (7): 1-14.

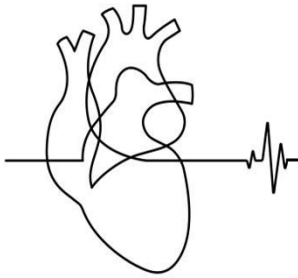
Venna, A., Cetta, F. and d'Udekem, Y. 2022. Fontan candidacy, optimising Fontan circulation, and beyond. *The Journal of Thoracic and Cardiovascular Surgery,* 9:227-232.

Weston, C., Husain, S.A., Curzon, C.L., Neish, S., Kennedy, G.T., Bonagurio, K. and Gosselin, K. 2016. Improving outcomes for infants with single ventricle physiology through standardised feeding during the interstage. *Nursing Research and Practice*, 2016:9505629.

Yuan, S.M. and Jing, H. 2009. Palliative procedures for congenital heart defects. *Archives of Cardiovascular Diseases*, 102(6-7): 549-557.

Zareef, R., Al Hassan, S., Younis, N., Tannoury, T., El Rassi, I., Bitar, F. and Arabi, M. 2022. Pulmonary artery debanding in the cath lab: Lessons learned! *Frontiers in Cardiovascular Medicine*, (9): 1-10.

Zhang, S., Bhansali, S., McKinstry, J., Ramaswamy, P., Thomas, K., Martinez, M., Mosca, R.S. and Kumar, T.S. 2022. Modified Blalock-Thomas-Taussig Shunt Using Femoral Artery Homograft. *Annals of Thoracic Surgery Short Reports*, 1(1): 94-95.



# APPENDIX A

## Ethical clearance

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

**Health Sciences Research Ethics Committee**

21-Apr-2021

Dear **Mr Marius Van Jaarsveld**

Ethics Clearance: **Outcomes of patients presenting with single ventricle physiology in Central South Africa**
Principal Investigator: **Mr Marius Van Jaarsveld**
Department: **Clinical Technology - CUT**
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-HSD2020/1823/2505**

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.

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(2006); 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

# APPENDIX B

## Confirmation of publication

**From:** em.cvjsa.0.8542ff.31937017@editorialmanager.com <em.cvjsa.0.8542ff.31937017@editorialmanager.com> on behalf of CardioVascular Journal of Africa <em@editorialmanager.com>
**Sent:** Thursday, August 10, 2023 12:49:26 PM
**To:** Stephen Brown <Gnpdscb@ufs.ac.za>
**Subject:** Your Submission

Ref.: Ms. No. CVJSA-D-23-00038R1
Outcomes of single ventricle physiology in Central South Africa
CardioVascular Journal of Africa

Dear Prof Brown,

We wish to inform you that your manuscript, Outcomes of single ventricle physiology in Central South Africa, has been accepted for publication in CardioVascular Journal of Africa.

Unfortunately, we are unable to tell you which Volume and on what pages at present as we rely on our set-out design & publishers for that information.

You will be contacted by our Production Editor when your article is ready for final proof reading before publication.

On acceptance of a manuscript an Article Processing Fee will apply before the production team can finalise the paper for publicaton.

- Article Processing/Publishing Fee: South African and International Authors: ZAR 7200. Paid on Article Acceptance for Publication in the CVJA. This fee includes the Online First (Advance Publication) within 21 working days.

Payment link : https://urldefense.com/v3/__http://www.cvja.co.za/apc-payment.php__;!!LRJdiIM!Bgau1tFqf42u1M3hYlwrP8zDMyx-4KlskAz5_0QxtuddPxltGA_tNDZQ-RrQS68-QJpdZzBExamZs8TLnw$

Please note that the online First Facility with full text availability via PubMed and the Journal's website which is accessible via Google and other search engines (https://urldefense.com/v3/__http://www.cvja.co.za__;!!LRJdiIM!Bgau1tFqf42u1M3hYlwrP8zDMyx-4KlskAz5_0QxtuddPxltGA_tNDZQ-RrQS68-QJpdZzBExamuXj_zEQ$ ). This facility is also known internationally as E-publication, ahead of print and offers authors the opportunity to publish

their research articles sooner for an international audience.

Articles published online with CVJA will be published with their unique DOI numbers, which ensures that the article can be cited using the date of the manuscript's first online posting and its DOI number. DOI's provided a persistent, permanent way to identify manuscripts in an electronic environment and are generated via our Editorial Management system and in accordance with the policy of the DOI foundation (https://urldefense.com/v3/__http://www.doi.org__;!!LRJdiIM!Bgau1tFqf42u1M3hYlwrP8zDMyx-4KlskAz5_0QxtuddPxltGA_tNDZQ-RrQS68-QJpdZzBExakA5zrNLg$ ).

We thank you for your interest and support in the Journal and we will be interested in any other material you may feel you would like to submit in this field.

Thank you for submitting your work to this journal.

With kind regards

CardioVascular Journal of Africa

Comments from the Editors and Reviewers: