RESEARCH REPORT

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Clinical presentation and Outcomes of Anomalous left coronary artery from the pulmonary artery: A retrospective study from January 1998 - August 2019 at the Department of Paediatrics Cardiology, Universitas Hospital

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Declaration

Submitted in fulfilment of the requirements in respect of the Master's Degree MMed in the Department of Paediatrics in the Faculty of Health Sciences at the University of the Free State

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Declaration of Authorship

I, Dr Ntombikayise Gladys Makhoba, declare that the coursework Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification in Paediatrics at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.

Dr. NG Makhoba

Author contributions

The contribution of each author of the article is stipulated below:

Author	Affiliation	Role in the study
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All researchers declare that they have no conflict of interest and that no other situation of real, potential, or apparent conflict of interest is known to them. They undertake to inform the University of any change in these circumstances.

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- My husband and two kids for love and support during the long nights working on this project.

Report Layout

This research report comprises of 3 parts as illustrated in Figure 1: Layout of the **report**.

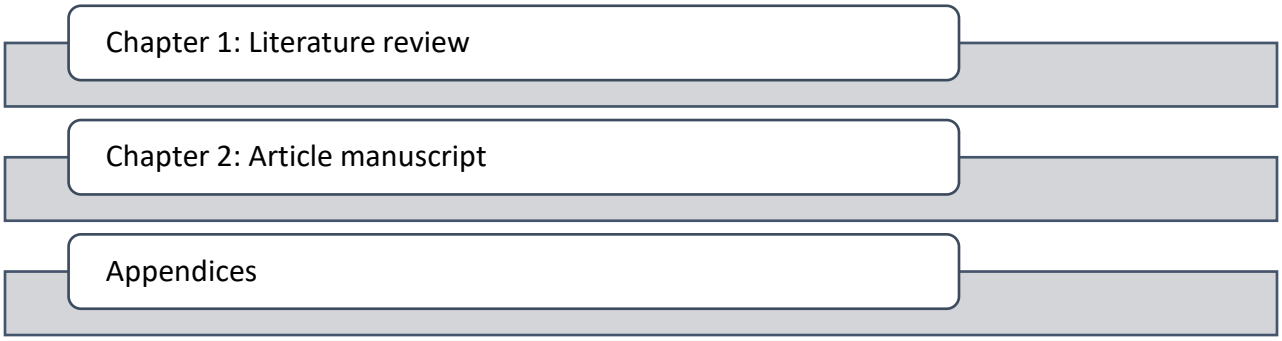

Figure 1: Layout of the report

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Abstract

BACKGROUND: Anomalous left coronary artery from the pulmonary artery (ALCAPA) or Bland-White-Garland syndrome is a rare congenital anomaly that has profound effects on heart function. Patients with ALCAPA present with non-specific symptoms like irritability, feeding difficulties and signs and symptoms of cardiac failure. If left untreated, ALCAPA has a 90% mortality rate in the first year of life, primarily due to myocardial ischemia and heart failure. It is therefore important to diagnose them in time and offer surgery.

OBJECTIVES: The primary objective of the study was to determine the clinical presentation and severity of symptoms using the Ross classification and to describe the clinical status of the patients at last follow up, including the clinical outcome (Ross classification) and survival.

METHODS: This was a retrospective descriptive study at the Department of Pediatric Cardiology between January 1998 and August 2019. All patients with the diagnosis of ALCAPA during the study period were included. Medical records of patients referred from Free State, Northern Cape and Lesotho were reviewed. Data collection included demographics of patients, clinical presentations, referral diagnosis, echocardiography before and after surgery, catheterization data, surgical data, clinical presentation at last follow up and ECHO at last follow up. Data was captured using the REDCap® online database. The researchers considered a Ross classification of more than two as clinically diagnostic of heart failure. The SF ranges were classified as follows: SF >28% = normal, SF 20-25% = mild, SF 15-20% = moderate and SF <15% =severe.

RESULTS: During the study period a total of 30 patients presented to Universitas Paediatric Cardiology Unit with the diagnosis of ALCAPA. At presentation, 89% (n=25) of patients were in cardiac failure with a Ross classification for age of more than two. The diagnosis of ALCAPA was made primarily by echocardiography in 75.8% (n=22) of patients. Most patients 83.3% (n=25) had a dilated heart at presentation, with a median LVEDD z-score of 6.4 and 37% (n=11) had severe LV dysfunction (SF <15%). About half of the patients, 43% (n=13) had severe MR. ALCAPA repair was done in 76.6% (n=23) of our patients. The median age at surgery was 35 months (range: 1 day - 73 months), with a median weight of 6kg (range: 4kg - 20kg). The median days from diagnosis to the day of surgery was 11 days (range: 1 day to 6 years). Most patients had re-implantation of the anomalous left coronary artery except for two where the left coronary artery was tied off. One child required a left ventricular assist device (LVAD) for 7 days post operatively and survived. Immediately post-surgery there was some improvement on left ventricular function with 17% (n=4) of patients demonstrating normal SF and 13% (n=3) had mild left ventricular dysfunction. Heart failure symptoms (Ross) at follow-up improved significantly from original presentation ($p < 0,01$): forty five percent, (n=8) of our patients had no symptoms of cardiac failure, with Ross

classification of two and less. At last follow a marked improvement on LV function was observed with 73% (n=11) patients having a normal SF. SF at last follow up showed a statistically significant difference compared to, at presentation with a p-value of 0.014. Seventy eight percent (n=18) of patients were alive at the end of the study and mortality post-surgery was 22% (n=5).

CONCLUSION: Our results show that most children in central South Africa present in the first year of life with clinical features of heart failure. The most common echocardiographic features at presentation are impaired systolic function, dilated left ventricles and mitral regurgitation. Furthermore, surgery results in significant clinical and echocardiographic improvement. It is of paramount importance to have a high index of suspicion based on the clinical presentation and ECHO to ensure early referral, so corrective surgery may be offered timeously.

Keywords

Anomalous left coronary artery from the pulmonary artery, Ross classification, ECHO, Cardiac failure, Mitral regurgitation

Acronyms and Abbreviations

ALCAPA	Anomalous left coronary artery from the pulmonary artery
DOB	Date of birth
ECG	Electrocardiogram
ECHO	Echocardiogram
EF	Ejection fraction
FSDoH	Free State Department of Health
HSREC	Health Sciences Research Ethics Committee
LA	Left atrium
LAD	Left anterior descending artery
LCA	Left coronary artery
LCX	Left circumflex artery
LMS	Left main stem
LVEDD	Left ventricular end diastolic diameter
LVEDP	Left ventricular end diastolic pressure
LVEF	Left ventricular ejection fraction
MR	Mitral regurgitation
RCA	Right coronary artery
SF	Fractional shortening

Definitions

Myocardium:	is the muscular tissue of the heart
Congenital:	born with it
Cardiac lesion:	heart abnormality
Myocardial ischemia:	decreased blood flow and decrease oxygen to the heart muscle
Myocardial infarction:	no blood supply to heart muscle leading to tissue damage
Desaturated blood:	low blood oxygen concentration
Cardiac output:	the amount of blood the heart pumps out in a minute
Angina pectoris:	severe chest pain, spreading to shoulders, arms and neck, all due to inadequate blood supply to the heart
Syncope:	temporary loss of consciousness caused by a fall in blood pressure
Peri-operative deaths:	deaths less than 30 days
Infant:	a child older than one month but less than one year of age

1. CHAPTER 1: LITERATURE REVIEW

1.1 Introduction to the research project

The leading cause of myocardial ischemia and infarction in infants and children is anomalous origin of left coronary artery from the pulmonary artery (ALCAPA). This is a rare congenital cardiac lesion with an incidence of 1/300 000 live births..[1,2] Infants with ALCAPA present with non-specific symptoms like irritability, feeding difficulties and signs and symptoms of ischemic cardiomyopathy.[2]

If not treated, it is estimated that 90% of patients with ALCAPA die in the first year of life.[2] It is therefore important to diagnose them in time and offer intervention, i.e. surgery. In a study done in 2014 by Aliku et al. at Uganda Heart institute, a 10-week old infant died after one week of hospital discharge whilst awaiting transfer to a center that could offer the infant surgical intervention for ALCAPA. It is thus imperative not to delay surgery.[3]

In this research project, the researcher studied the clinical presentation and outcomes of patients that presented with the diagnosis of ALCAPA to Universitas Academic Hospital.

The purpose of the study was:

- A self-audit in the Department of Pediatric Cardiology and Cardiothoracic Department
- To research and document data on ALCAPA in the Free State
- To identify geographic distribution of patients presenting with ALCAPA

The researcher conducted a retrospective review of patient files and medical records. The study collected information about outcomes of patients with ALCAPA, i.e. when did they present, what was their referral diagnosis, how soon was surgery offered to these patients and their clinical status at follow up.

The study involved the researcher, supervisor, and co-supervisor. Regulatory approval was obtained from the Health Science Research Ethics Committee (HSREC) at the University of the

Free State, as well as the Free State Department of Health (FSDoH). Permission to access clinical files was obtained from the Head of Department of Paediatrics. The Biostatistics Department from the University of the Free State analysed the data.

1.2 Background on ALCAPA

Normal anatomy of coronary arteries

The entire blood supply to the myocardium comes from two main coronary arteries which arise from the right and left aortic sinuses of Valsalva.[4] The two main coronary arteries then descend towards the cardiac apex. The left main stem comes from the left sinus of Valsalva, it then crosses between the main pulmonary artery and the left atrial appendage. LMS on average has a length of 2-40mm and normally divides into left anterior descending artery and left circumflex artery. The right coronary artery comes from the right sinus of Valsalva. The LAD extend towards the apex of the heart in the epicardial fat across the anterior interventricular sulcus. Its length ranges from 10-13mm, it then divides to diagonal and septal branches. It provides blood supply to the anterior wall, apex and large portion of the interventricular septum. The left circumflex artery measures 5-8mm and crosses the coronary sulcus on the diaphragmatic cardiac surface. The LCX divides to obtuse marginal branches and provides large blood supply to the lateral wall of the left ventricle.[5]

The RCA descends to the right between the pulmonary artery and the right auricle, then travels down across the right atrioventricular sulcus and extends posteriorly after the acute margin of the heart. It measures 12-14mm in length. During its descent it may divide into many branches, like the conus branch, sinoatrial branch, right ventricular branch, atrioventricular nodal branch, posterior descending branch and posterolateral branch. It provides major blood supply to the right side of the heart.[5]

Within the myocardium there are small arteries that divide repeatedly until they get to the endocardium. There are normally connections between coronary arterial branches measuring 25-200mm in diameter, they are called collaterals. They may be found superficial or sub endocardial and they are able to enlarge if pressure gradient develops between branches.[4]

Normal variations of coronary arteries without structural heart disease:

The right and left coronary arteries come from the right and left aortic sinuses of Valsalva. They usually originate from the middle of the sinuses but they can sometimes come from sinotubular junction or even above it. The position of the ostium does not affect the blood flow through it. The shape of the ostium may be round, oval or elliptical. The arteries are often in a perpendicular position to the aorta wall, in other words they are radially organized in relation to the center of the aorta. A different origin of the conus branch of the right coronary artery occurs more often. About 1% of patients with bicuspid aortic valve present with left side anomalies (i.e. LAD and LCX arteries). Not any of these anomalies show clinical complications.[7]

Anomalous origin of left coronary arterial branches from the right sinus Valsalva

The most common abnormality, accounting for about one third of all major coronary arterial anomalies, is the origin of left circumflex coronary artery from the right main coronary artery. The LCX artery tracks through behind the aorta to connect with its normal territory of supply. This anomaly has no general clinical importance.

Far less commonly seen is origin of left main coronary artery from the right sinus of Valsalva, accounting for 1% to 3% of major coronary arterial anomalies. This has great clinical significance.

The connection may take place in four anatomical areas: 1. posterior to the aorta; 2. anterior to the right ventricular outflow tract; 3. within the ventricular septum beneath the right ventricular infundibulum (this is the most common variant and 4. between the aorta and the right ventricular outflow tract. The first three connections have not been associated with sudden death or early myocardial ischemia. The connection that passes through the two big arteries has been associated with sudden death in children during or just after strenuous exercise. A number of these patients had had episodes of syncope or chest pain during previous exercise. In many of these patients, the ostium of the left main coronary artery was slit like, with an intramural connection within the aortic root and adherent to it for about 1.5cm.

Sometimes the left anterior descending coronary artery stems from the right sinus of Valsalva or from the right main coronary artery. This abnormality is not usually seen in the absence of congenital heart disease but is common in tetralogy of Fallot.[4]

Anomalous left coronary artery from the pulmonary artery

This is an unusual form of abnormality where babies are born with abnormal left coronary artery. There are two types of ALCAPA syndrome: one variant observed in young children less than a year of age and the other an adult type; each one of these present differently and have different outcomes. The young children present with myocardial infarction and symptoms of heart failure and about 90% of them die within the first year of life. It is unusual for ALCAPA syndrome to present in adults; if it happens, they usually present with sudden cardiac death.[6]

If ALCAPA presents in an adult, a wide range of differential diagnoses should be investigated, for example myocarditis, dilated cardiomyopathy, and coronary artery disease.[7] In this abnormality the left coronary artery originates from the pulmonary artery and it usually makes a connection at the posterior facing sinus. This abnormality was first noticed by pathologists in 1866, and by the year 1962 Fontana and Edwards had already collected 58 cases during autopsy with this abnormality; a number of these died before 13 months of age. The first case of a death was reported by Bland et al, this was proven clinically and on autopsy in a 3-month old boy. This abnormality was then called Bland-White-Garland syndrome.[4]

Tedla et al. in a mini-review done in Ethiopia, reported that ALCAPA was first reported by Alexia Vinovich Abrikosov in 1911, when he did a postmortem that he later called ‘a left ventricular aneurysm with anomalous origin of the left coronary artery from pulmonary artery in a 5-month old child’. A detailed and complete clinical account was given by three physicians, namely Adward Bland, Paul Dudley White, and Joseph Garland in 1933. Hence the name Bland-White-Garland syndrome for a typical case of ALCAPA. Nine cases of ALCAPA were presented in their pathological review.[8]

ALCAPA affects 1 out of every 300 000 babies born alive. It accounts for 0.5% of all babies born with heart defects.[9] It is usually seen as an isolated defect, but in 5% of cases it may be associated with other cardiac abnormalities such as atrial septal defect, ventricular septal defect and aortic coarctation. Aliku et al.[3], reported a much less incidence of ALCAPA at 0.02%, compared to most international literature.[6,9,10,11]

Alkhalifa et al. conducted a retrospective study in Sudanese patients to look at the overall incidence of coronary artery abnormalities. The study looked at 270 patients who had coronary angiography at Ahmed Gasim cardiac center from April 2004 to August 2005. This study found a rather higher rate of coronary anomalies at 3%, but this was not different from the incidence found in first world countries. He concluded that anomalies of origin were the most detected abnormality. He further concluded that coronary anomalies are not rare in Sudanese patients.[12]

ALCAPA may cause complications like myocardial infarction, left ventricular dysfunction and mitral regurgitation. Silent myocardial ischemia, which can result in sudden death often, occurs in patients who survive to adulthood. It is important to diagnose and treat these patients promptly, offering them surgical intervention with the aim of creating a two-coronary-artery circulation system, this provides excellent results and eventually leads to myocardial recovery.[6] The most common cause of myocardial ischemia and infarction in children is ALCAPA syndrome. Prompt treatment is required otherwise 90% of these children die in the first year of life if left untreated.[2]

1.3 Pathophysiology

ALCAPA results in abnormal left ventricular perfusion, which is the result of a left to right shunt; this is called a “coronary steal” phenomenon. The coronary steal causes profound myocardial ischemia, leading to left ventricular dysfunction and mitral regurgitation.[13] During fetal life, this abnormality has no harmful effects because pressures and oxygen saturations are the same in the aorta and pulmonary artery. Myocardial perfusion is presumed to be normal and there is nothing stimulating collateral formation.

After birth, pressures drastically drop in the pulmonary artery, which is carrying desaturated blood, to below systemic pressures. Hence the left ventricle which has a high demand for oxygen receives desaturated blood at low pressures. The left ventricular myocardial vessels enlarge to decrease their resistance and increase blood flow, but soon coronary vascular reservoir becomes exhausted and myocardial ischemia occurs. Initially there is transient ischemia which occurs during exertion such as feeding or crying. But ongoing demand of myocardial oxygen lead to infarction of the anterolateral left ventricular free wall, which results in compromise of left ventricular function. This leads to heart failure which is usually made worse by mitral regurgitation following dilated mitral valve ring or infarction and non-functioning of the anterolateral papillary muscle.[4] Initially collateral blood flow is low. When collateral vessels develop between the normal right coronary artery and the abnormal left coronary artery, there is increased blood flow. The enlarged right coronary artery and its collaterals allow retrograde flow to supply the left ventricle.[2] However because the left coronary artery is connected to the low pressure pulmonary artery, the collateral flow tends to flow into the pulmonary artery instead of the high resistance myocardial blood vessels; this called the pulmonary-coronary steal, with a left to right shunt. The shunt is often quite small in terms of cardiac output but relatively huge in terms of coronary flow. Approximately 15% of these patients make it to adulthood because myocardial blood flow can keep with myocardial function at rest or during exercise.[4]

1.4 Pathology

ALCAPA has been seen together with other heart defects like patent ductus arteriosus, ventricular septal defect, tetralogy of Fallot or coarctation of the aorta. However, in most cases it is seen as an isolated disease. Left ventricular perfusion may be adequate to prevent ischemia if there is pulmonary hypertension as often seen in patients with a large ventricular septal defect. In this situation a ventricular septal defect with decreased pulmonary arterial pressure is not to be closed as that may have fatal effects.

Normally in infancy the heart is big, the left ventricle and atrium are dilated and have thick muscle. The anterolateral papillary muscle is scarred and atrophic, and its chordae is often shortened. The poster papillary muscles may be affected similarly as reported in some studies.

The anterior mitral leaflet is commonly thickened and you may find diffuse endocardial fibro elastosis of the left ventricle. Due to infarction, thinning and scarring of the anterolateral left ventricular wall and apex mural thrombi are also often seen.[4]

Alkhalifa et al.[12] looked at the anatomical classification of coronary anomalies:

A. Anomalies of the origin

- ALCAPA
- Single coronary artery
- Origin from systemic vessels

B. Anomalies of course

- Duplication of arteries
- Coronary artery passing between the pulmonary trunk and the aorta

C. Anomalies of termination

- Abnormal termination into a cardiac chamber, great vessel, or systemic vein.

They stipulated the importance of being able to diagnose these correctly as surgery is different and difficulties are known with performing corrective surgery for each one of these. They also stated that ALCAPA is the most morbid anomaly, usually resulting in death during infancy especially if both coronary arteries are involved.

1.5 Clinical features

In infancy

Occurrence of symptoms is determined by the degree of collateral development and the related left coronary artery in ALCAPA syndrome.[2] Infants who develop early signs of cardiac failure have insufficient inter-coronary collaterals and hence poor blood supply for myocardial function.[14]

Nothing is usually noted in newborns until the 10th week of life, when the patient presents with paroxysmal episodes of acute discomfort worsened by exertion during nursing. The infant may initially look distressed as evidenced by expiratory grunting, then followed by general appearance of severe shock, severe pallor, and cold sweat. At times there may be transient loss of consciousness which comes with unusual severe attacks. Burping seemed to relieve the discomfort at times and would shorten the length of attacks which last 5-10 minutes. After this the infant might nurse without difficulty and remain without symptoms for several days. It is assumed that these paroxysmal attacks in these infants are signs of angina pectoris. Not all infants present in this way. Many of them present with signs and symptoms of cardiac failure.(4)

In 2014, Aliku et al.(3), presented a case of was a 10-week old male infant who was misdiagnosed as dilated cardiomyopathy secondary to myocarditis. This infant presented with irritability, restlessness and was inconsolably crying. Clinically in respiratory distress and was in shock. The ECG had typical features of ALCAPA with deep Q waves in lead I, aVL, V5, V6 with ST elevation in anterolateral leads, ECHO showed a dilated left ventricle LVEDd of 40mm, with severe left ventricular systolic dysfunction (FS=15%, EF=28%), left ventricle anterolateral wall echo brightness and flow reversal in the left coronary artery with its origin from the pulmonary trunk. The patient was admitted with a diagnosis of acute myocardial infarction with cardiovascular collapse. Fluid resuscitation and inotropes were given to the patient and management of heart failure instituted. Six days later he was discharged home with a plan to refer to one of the developed countries because Uganda Heart Institute still lacks the capacity to offer surgical intervention to these patients. Unfortunately, the patient died at home a week later.

Irritability and feeding difficulties when approaching second month of life should raise the suspicion of ALCAPA.(7) Another common presentation in infancy is dilated cardiomyopathy and mitral regurgitation.(13) Diagnosis of ALCAPA in severely ill infants can be difficult because ECHO findings are less visible when collateral circulation is less developed.(10)

Older children and adults

This group may present with angina, dyspnea, syncope, myocardial infarction or arrhythmia. Malignant ventricular arrhythmia is the most common presentation leading to sudden cardiac death. The few patients who survive to adulthood without surgery have well developed coronary collaterals with adequate perfusion of the left ventricle.[2] Major manifestations of ALCAPA are impaired left ventricular function and myocardial ischemia.[11]

On physical examination

ALCAPA patients have poor growth and signs of cardiac failure.[13] In children less than 1 (one) year the heart is often big, with the left ventricle being the main ventricle affected. If left ventricular failure has caused significant pulmonary hypertension, it may lead to right ventricular enlargement and loud pulmonary component of second heart sound. If there is mitral regurgitation, the first heart sound may be soft or absent. Commonly apical gallop rhythms are seen. Murmurs can be audible or no murmur auscultated, you may hear a soft continuous murmur at the upper left sternal border that is the same as the murmur of a small patent ductus arteriosus, this is due to the ongoing flow from the anomalous coronary artery into the pulmonary artery. A murmur of mitral regurgitation may also sometimes be heard.[4] Unexplained, mitral regurgitation is a clue to the diagnosis of ALCAPA.

1.6 Diagnosis

Clinicians must have a high index of suspicion while managing infants and children with global myocardial dysfunction. These patients present with subtle to severe symptoms which may mimic a number of diseases, making it a challenge to diagnose ALCAPA. The rarity of the disease also contributes enormously to reasons for missing the diagnosis. It is important to note that patients with ALCAPA usually present around 8 weeks of age with signs and symptoms of myocardial infarction and heart failure. It is usually diagnosed with non-invasive tools like ECG and ECHO, but some cases may require a coronary angiography. Literature clearly states the detrimental results of missing the diagnosis where patients die, hence the emphasis of high index of suspicion of ALCAPA.[8]

1.7 Investigations

Electrocardiography

Typically, the ECG shows abnormal Q waves in leads I and aVL as well as the precordial leads V4-V6, because there is classically an anterolateral infarct by the time the infant presents for diagnosis. There may also be abnormal R waves or R wave progression noted in the left precordial leads. If this is found, other causes of myocardial infarction should be considered. Occasionally, cardiomyopathies may cause this; R-wave abnormalities are not specific for ALCAPA and proper evaluation by other means then becomes important. Deteriorating ventricular function accompanied with signs of ischemia on ECG is suggestive of ALCAPA.[10]

Noninvasive imaging

ALCAPA is often confused with cardiomyopathy because on **CXR,** one may observe severe cardiomegaly, with prominent left atrium and left ventricle. Additionally, features suggestive of pulmonary edema may also be present.

Nuclear myocardial perfusion imaging is very sensitive, showing decrease uptake in the anterolateral ischemic region. Of note, this is not a specific finding as it has also been observed in cardiomyopathies.

The standard method of diagnosis is by means of non-invasive transthoracic **echocardiography with Doppler color flow** mapping; this has replaced cardiac catheterization. Even if the attachment of the coronary artery to the great artery is uncertain by the two-dimensional imaging, the presence of diastolic flow in the pulmonary artery is informative. Increased echogenicity of the pupillary muscle and adjacent endocardium due to fibrosis and fibro elastosis may be seen.[4]

A study done at a children's hospital with 25-year experience of treating patients with ALCAPA came up with ECHO findings suggestive of ALCAPA. In 46% of ECHOs done, the anomalous coronary artery was not visualized. However, the following seven ECHO findings were described:[15]

- 91% being flow reversal within the left coronary artery.
- 85% identification of collateral coronary artery flow.
- 81% right coronary artery dilation.
- 79% abnormal flow signals within the pulmonary artery
- 74% mitral regurgitation
- 66% left ventricular systolic dysfunction
- 57% left ventricular endocardial fibro elastosis.

The very first ECHO had more than 5 of the above findings in the patients that were studied. Left ventricular dysfunction being the most common by 90% in infants compared to 37% in older children. Instead, the older group had lots of collateral formation.[15]

Trans-esophageal echocardiography is helpful in cases where transthoracic ECHO cannot visualize the origin of left coronary artery from the pulmonary trunk.[7] Shortening fraction, ejection fraction, left ventricular end diastolic dimension, and severity of mitral regurgitation were used to assess ventricular function. All patients had normal ejection fraction and shortening fraction at last follow up.[16]

In older patients, **Computed Tomography scans** have shown high resolution in defining coronary artery anatomy and its origin. Rapid acquisition time is the main advantage of a CT-scan. ECG gating of the scans requires a slow heart rate or for the heart rate to be slowed with medication, especially in a young child. There is a lot of radiation exposure with CT-scans, but it has excellent ability to define coronary artery abnormalities.[4]

Cardiac catheterization and Angiography

Currently, cardiac catheterization and angiography is utilized only if the results of non-invasive imaging are uncertain. In the past, cardiac catheterization and angiography were used for diagnosis of congenital coronary abnormalities. In symptomatic infants, diagnostic cardiac catheterization shows low cardiac output and high filling pressures and usually pulmonary hypertension to a certain degree. Slight increase in left ventricular end diastolic pressure is all you see in asymptomatic older patients, output and pressures are normal. There may be a left to right shunt at the pulmonary arterial level, but the shunt may be small so its absence does not rule out the

diagnosis of ALCAPA. Ventriculography shows the presence and severity of mitral regurgitation, it also shows dilated left ventricle and atrium, with dysfunction of anterolateral left ventricular free wall.

Aortic root angiography shows a dilated right coronary artery and if there are large collaterals, it also shows filling of the left coronary artery and passage of contrast from the left coronary artery to the main pulmonary artery. Even though the main pulmonary artery angiography may show reflux of contrast into the origin of the left coronary artery, not this, nor left ventriculography can exclude the diagnosis of ALCAPA reliably.[4]

Dilated, tortuous right coronary artery originating from the right sinus and supplying the left coronary system draining through left coronary artery into posterior part of main pulmonary artery, with a lot of collaterals between the right and left coronary system were seen on computed tomography coronary angiography.[17]

Sasikumar et al. proved majority of infants (82%) had moderate to severe ventricular dysfunction at presentation, and none had ventricular dysfunction (defined as EF<50%) in the group older than one year. Children older than one year had significant (moderate to severe) mitral regurgitation compared to infants.[18]

In a study done by Aliku et al.[3], it was pointed out that in a setting of high infectious burden, ALCAPA may be easily misdiagnosed as myocarditis, dilated cardiomyopathy, or other common childhood disorders.

Tedla et al. describe the most common point of origin of the coronary artery in ALCAPA patients as being from the posterior facing sinus of the pulmonary artery. The other possibilities being from any part of the main pulmonary artery or its branches but the latter is rare. In very rare instances the left coronary artery may arise from the junction of the main pulmonary artery and right pulmonary artery or from the right pulmonary artery itself, literature is limited to very few reports of these cases.[8]

1.8 Natural history of ALCAPA

Approximately 87% of patients born with this unusual anomaly presents during infancy. Out of these 65% to 85% die before the age of 1 (one) year due to uncontrollable heart failure, this usually happens after 2 (two) months of age. Few children improve spontaneously. Others might never have symptoms. This could be due to a lot of collaterals and a limiting small opening between the origin of the left coronary artery and the pulmonary trunk. Having said this, these patients are still at high risk of sudden death, especially during exercise. Some present as adults with angina induced by exercise or with heart failure secondary to mitral regurgitation.[4]

1.9 Treatment

The goal of modern surgical management of ALCAPA is to establish a dual coronary system with long term patency.[14] Surgical interventions have undergone a substantial advancement since its commencement.[8] Willis J. Potts from children's Memorial Hospital in Chicago was the first surgeon to operate on an ALCAPA patient. With success he created an aortopulmonary anastomosis in two patients with an idea to create an anastomosis and increase pulmonary artery blood flow and as a result, increase left coronary artery oxygen saturation.[8] The first most effective form of surgical treatment was to prevent the steal phenomenon by ligating the left coronary artery from its origin from the pulmonary artery. A lot of older children benefit from this procedure, especially if they have severe coronary to pulmonary arterial shunting, but late sudden death may still occur. Tying of the origin of the left coronary artery and restoration of blood flow through with a subclavian arterial or saphenous venous graft has been a success, although graft thrombosis and stenosis has occurred before. Late blockage changes in saphenous vein grafts has been seen, which may complicate the patient's course because around 3 (three) years after revascularization, there is a significant reduction in collaterals from the right coronary artery. For long term survival it is better to use grafts from the internal mammary artery and this may be desirable in older children.

The standard approach which has been proven successful in many centers is the direct re-implantation of the origin of the left coronary artery into the aorta (with a button of pulmonary artery around the origin). There is an alternative approach called Takeuchi procedure, where an

aortopulmonary window is created and then a tunnel fashioned that directs blood from the aorta to the left coronary artery ostium.

Early surgical intervention to establish a dual coronary system has been shown to have important outcomes. Significant preoperative mitral insufficiency has been shown to be a risk factor for both mortality and need for late mitral valve surgery, this is because of papillary muscle infarction and dysfunction.[4]

It is not necessary to repair or replace the mitral valve at the time of ALCAPA repair, unless mitral regurgitation remains persistent and depending on the severity, management can be planned for later date.[16]

Tedla et al. share the same sentiments with most literature that early surgical intervention on diagnosis to restore a two-coronary system circulation is the endeavor of current treatment.[8] It's important to encourage very early surgical correction of ALCAPA before ischemia occurs because this makes ICU management easier should a patient complicate and require ICU, It also helps prevent the complication of mitral regurgitation, But note it does not decrease perioperative risk associated with this major surgery.[15] Early diagnosis and treatment of ALCAPA is important for faster myocardial recovery.[14]

1.10 Complications

- Patients may need respiratory support during surgery, (e.g. with ECMO). They may also need ICU management post operation.
- Other complications may be moderate to severe mitral regurgitation with left ventricular dysfunction, this usually improved in the first year of follow up.
- Mitral valve replacement if valve severely damaged.
- In small babies with severe mitral regurgitation it might be better initially to avoid mitral valve repair as it is very difficult technically.[19]
- Supravalvular pulmonary stenosis, baffle obstruction, baffle leaks and aortic regurgitation may be experienced in patients who had Takeuchi surgery. [20]

- Complications like permanent mitral valve damage following surgery, may necessitate the need for future valve surgery.[8]

1.11 Outcomes of ALCAPA

There is excellent short term and midterm outcomes of surgical treatment for ALCAPA patients. In a study performed in China (2019), by Zhang et al., 138 patients with a median age of 36 months underwent ALCAPA repair. Pre operatively <50% of these patients had a depressed LVEF, at discharge it had significantly improved from 25% to 33%. Moderately significant MR decreased from 36.2% to 5.2%. Zhang et al. then concluded that within the first 6 (six) months' post-surgery normal left ventricular function is expected.[1] A close follow up is warranted in patients with persistent mitral regurgitation and a moderate rate of late mitral valve repair.[20] A total of 92% of patients had normal left ventricular function at last follow up, moderate mitral regurgitation was seen in 3% of patients and those that required re-intervention were about 17%.[19]

Due to papillary muscle ischemia survivors after infancy have improved left ventricular function but continue to have mitral regurgitation. In all patients the follow up ECHO showed improved left ventricular ejection fraction and degree of mitral regurgitation was less. ECG is important in long term follow up to look for arrhythmias whilst ECHO looks at left ventricular function and mitral regurgitation.[13]

In most patients, ALCAPA mitral regurgitation has been shown to improve without concomitant mitral valve repair.[18] After dual coronary repair, the overall survival rate was 92%.[15]

A study done by Mohamed et al.[21], reported on the first 3 (three) cases of ALCAPA diagnosed in Senegal, which were all under 1-year old. Patients typically presented with features of heart failure. They had similar ECG findings of deep Q waves at V5 and V6, there were also ST elevation at V5 and V6, left ventricular hypertrophy and left axis deviation. Diagnosis was confirmed on ECHO for all three patients. Two patients were offered surgery immediately and the outcome was excellent. On follow up both these patients had normal ECGs and left ventricular function completely recovered.[21]

Mohamed et al. concluded that the diagnosis of ALCAPA is possible in Sub Saharan Africa, however they often do not have the surgical expertise required for surgical repair for these patients, they then refer them to developed countries.[21]

Very few patients with ALCAPA survive to adulthood, they may then present with chest pain syncope or sudden cardiac death from ventricular arrhythmias according to Aliku et al.[3]

Alkhalifa et al. had a clinical interest in coronary anomalies. As we know they are associated with sudden death and myocardial ischemia and it may cause difficulties in interpretation of coronary angiograms and hence errors in surgical approach.[12]

Tedla et al. performed a study in Ethiopia and said it is prudent to have a high index of suspicion to the diagnosis of ALCAPA so these patients can be referred to appropriate centers. They stated that ALCAPA could be operated on with good outcomes. They emphasized the importance of close follow up of these patients, to monitor persistent MR and a moderate rate of late valve repair demands. Furthermore, regular post-surgical follow ups are important because of a high risk of sudden cardiac death and arrhythmias in ALCAPA patients. According to these authors, it is extremely rare for adults to present with ALCAPA and when they do present it is usually with symptoms of heart failure. However, patients with extensive collateral circulation may survive to adulthood.[8]

1.12 References

1. Zhang C, Zhang H, Yan J, Hua Z, Song Y, Sun H, et al. Mid-Term Outcome for Anomalous Origin of the Left Coronary Artery From the Pulmonary Artery. *Heart, Lung and Circulation*, 2020 May;29(5):766–71. http://dx.doi.org/10.1016/j.hlc.2019.04.018

2. Yolcu, M., Bilal, M.S., Avsar, M.K. & Yildirim O. Case Report A patient with anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA syndrome) and 13 live births. *Cardiovascular Journal of Africa.* 2019; 30. doi: 10.5830/CVJA-2019-003

3. Aliku, T.O., Lubega, S., Lwabi, P. A case of anomalous origin of the left coronary artery presenting with acute myocardial infarction and cardiovascular collapse. *African Health Sciences* 2014;14(1): 223-227. Available from: http://dx.doi.org/10.4314/ahs.v14i1.35

4. Matherne, G. P. & Lim, D. S. Congenital anomalies of the coronary vessels and aortic root. In H. D. Allen, D. J. Driscoll, R. E. Shaddy & T. F. Feltes (Eds.). Moss and Adams'. Heart Disease in Infants, Children and Adolescents: Including the Fetus and Young Adult, 2008. vol. 1 (7th ed.). Baltimore: LWW, 702-714.

5. Kastellanos, S., Aznaouridis, K., Vlachopoulos, C., Tsiamis, E. & Tousoulis, D. Overview of coronary artery variants, aberrations and anomalies. *World Journal of Cardiology*. 2018 October 26;10(10): 127–40. doi: 10.4330/wjc.v10.i10.127

6. Exhibit E. ALCAPA Syndrome: Not Just a Pediatric Disease. 2009.

7. Saedi, S., Parsaee, M., Farrashi, M., Noohi, F. & Mohebbi, B. The role of echocardiography in anomalous origin of coronary artery from pulmonary artery (ALCAPA): Simple tool for a complex diagnosis. *Echocardiography*. 2019; 36: 177–181. https://doi.org/10.1111/echo.14236

8. Tedla, M. G. & Worku, D. K. Anomalous Left Coronary Artery from the Pulmonary Artery: Mini-Review. *ARC Journal of Cardiology*. 2017; 3(1): 13-16. http://dx.doi.org/10.20431/2455-5991.0301003

9. Zhang, H. L., Li, S.J., Wang, X., Yan, J. & Hua, Z.D. Preoperative Evaluation and Midterm Outcomes after the Surgical Correction of Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery in 50 Infants and Children. *Chinese Medical Journal*. 2017; 130(23): 2816–2822. doi: 10.4103/0366-6999.219156

10. Gonzalez, M., Tirado, A. M., Hosseinpour, R. & Santos de Soto, J. Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery: Diagnoses and Surgical Results in 12 Pediatric Patients. *Tex Heart Inst J*. 2015; 42(4): 350–356. doi: 10.14503/THIJ-13-3849

11. Zhang, C., Luo, Q., Li, Y., Wu, X., Hao, Z., Li, S., Xia, Z., Yan, F. & Sun, L. 2018. Predictors of Short-term Outcomes Following Repair of Anomalous Origin of the Left Coronary Artery From the Pulmonary Artery in Chinese Children: A Case-Control Study. *J Cardiothorac Vasc Anesth*. 2018(32): 2644-2651. doi: 10.1053/j.jvca.2018.04.008

12. Alkhalifa, M. S. & Omar, A. M. Coronary anomalies in Sudanese patients: angiographic study and brief review. *Sudan Journal of Medical Sciences*. 2006;1(1): 43-47.

13. Kamran, M., Memon, Y., Amanullah, M. & Ma, M.A. Anomalous Left Coronary Artery from Pulmonary Artery: An Important Cause of Ischemic Mitral Regurgitation in Children. *Cureus*. 2019; 11(4): e4441. doi: 10.7759/cureus.4441

14. Birk, E., Stamler, A., Katz, J., Berant, M., Dagan, O., Matitiau, A., Erez, E., Blieden, L. V. & Vidne, B. A. Anomalous origin of the left coronary artery from the pulmonary artery: Diagnosis and postoperative follow up. *Isr Med Assoc J*. 2000; 111-4.

15. Patel, S. G., Frommelt, M., Frommelt, P. & Cramer, J. Echocardiographic diagnosis, surgical treatment and outcomes of anomalous left coronary artery from the pulmonary artery: a 25-year experience. *J Am Coll Cardiol*. 2016; 67(13):969. http://dx.doi.org/10.1016/S0735-1097(16)30970-6

16. Cabrera, A. G., Chen, D. W., Pignatelli, R. H., Khan, M.S., Jeewa, A., Mery, C. M., et al. Outcomes of Anomalous Left Coronary Artery From Pulmonary Artery Repair: Beyond Normal Function. *Ann Thorac Surg*. 2015; 99(4): 1342–7. http://dx.doi.org/10.1016/j.athoracsur.2014.12.035

17. Wejner-Mik, P., Lipiec, P., Peruga, J. Z., Mozdzan, M. & Kasprzak, J. D. 2019. Transthoracic echocardiographic diagnosis of late-presentation Bland-White-Garland (ALCAPA) syndrome. *European Heart Journal - Cardiovascular Imaging*. 2019; 20(3): 306. https://doi.org/10.1093/ehjci/jey193

18. Sasikumar, D., Dharan, B. S., Arunakumar, P. & Gopalakrishnan, A. The outcome of mitral regurgitation after the repair of anomalous left coronary artery from the pulmonary artery in infants and older children. *Interactive CardioVascular and Thoracic Surgery*. 2018; 27(2): 238–242. https://doi.org/10.1093/icvts/ivy022

19. Alqathamy H., Elwy A., Ragheb A., Alfaraidi Y., Donato RM Di. Long term results of surgical management of anomalous origin of the left coronary artery from pulmonary artery (ALCAPA) and mitral

incompetence. *Journal of the Saudi Heart Association*. 2013;25(2):135. Available from: https://doi.org/10.1016/j.jsha.2013.03.084

20. Naimo, P. S., Fricke, T. A., Udekem, Y., Cochrane, A.D., Bullock, A., et al. Surgical Intervention for Anomalous Origin of Left Coronary Artery From the Pulmonary Artery. *Ann Thorac Surg*, 2016; 101(5): 1842–8. http://dx.doi.org/10.1016/j.athoracsur.2015.11.020

21. Leye, M. The Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery (ALCAPA) in Senegal. *International Journal of Cardiovascular and Thoracic Surgery*. 2017;3(2):9-13. http://dx.doi.org/10.11648/j.ijcts.20170302.12. Senegal.

2. CHAPTER 2: ARTICLE MANUSCRIPT

2.1 Abstract

BACKGROUND: Anomalous left coronary artery from the pulmonary artery (ALCAPA) or Bland-White-Garland syndrome is a rare congenital anomaly that has profound effects on heart function. Patients with ALCAPA present with non-specific symptoms like irritability, feeding difficulties and signs and symptoms of cardiac failure. If left untreated, ALCAPA has a 90% mortality rate in the first year of life, primarily due to myocardial ischemia and heart failure. It is therefore important to diagnose them in time and offer surgery.

OBJECTIVES: The primary objective of the study was to determine the clinical presentation and severity of symptoms using the Ross classification and to describe the clinical status of the patients at last follow up, including the clinical outcome (Ross classification) and survival.

METHODS: This was a retrospective descriptive study at the Department of Pediatric Cardiology between January 1998 and August 2019. All patients with the diagnosis of ALCAPA during the study period were included. Medical records of patients referred from Free State, Northern Cape and Lesotho were reviewed. Data collection included demographics of patients, clinical presentations, referral diagnosis, echocardiography before and after surgery, catheterization data, surgical data, clinical presentation at last follow up and ECHO at last follow up. Data was captured using the REDCap® online database. The researchers considered a Ross classification of more than two as clinically diagnostic of heart failure. The SF ranges were classified as follows: SF >28% = normal, SF 20-25% = mild, SF 15-20% = moderate and SF <15% =severe.

RESULTS: During the study period a total of 30 patients presented to Universitas Paediatric Cardiology Unit with the diagnosis of ALCAPA. At presentation, 89% (n=25) of patients were in cardiac failure with a Ross classification for age of more than two. The diagnosis of ALCAPA was made primarily by echocardiography in 75.8% (n=22) of patients. Most patients 83.3% (n=25) had a dilated heart at presentation, with a median LVEDD z-score of 6.4 and 37% (n=11) had severe LV dysfunction (SF <15%). About half of the patients, 43% (n=13) had severe MR. ALCAPA repair was done in 76.6% (n=23) of our patients. The median age at surgery was 35 months (range: 1 day - 73 months), with a median weight of 6kg (range: 4kg - 20kg). The median days from diagnosis to the day of surgery was 11 days (range: 1 day to 6 years). Most patients had re-implantation of the anomalous left coronary artery except for two where the left coronary artery was tied off. One child required a left ventricular assist device (LVAD) for 7 days post operatively and survived. Immediately post-surgery there was some improvement on left ventricular function with 17% (n=4) of patients demonstrating normal SF and 13% (n=3) had mild left ventricular

dysfunction. Heart failure symptoms (Ross) at follow-up improved significantly from original presentation ($p < 0,01$): forty five percent, (n=8) of our patients had no symptoms of cardiac failure, with Ross classification of two and less. At last follow a marked improvement on LV function was observed with 73% (n=11) patients having a normal SF. SF at last follow up showed a statistically significant difference compared to, at presentation with a p-value of 0.014. Seventy eight percent (n=18) of patients were alive at the end of the study and mortality post-surgery was 22% (n=5).

CONCLUSION: Our results show that most children in central South Africa present in the first year of life with clinical features of heart failure. The most common echocardiographic features at presentation are impaired systolic function, dilated left ventricles and mitral regurgitation. Furthermore, surgery results in significant clinical and echocardiographic improvement. It is of paramount importance to have a high index of suspicion based on the clinical presentation and ECHO to ensure early referral, so corrective surgery may be offered timeously.

2.2 Introduction

Anomalous origin of left coronary artery from the pulmonary artery (ALCAPA) is a rare congenital cardiac lesion with an incidence of 1/300 000 live births.[17] It is a leading cause of myocardial ischemia and infarction in infants and children.[17] Patients with ALCAPA present with non-specific symptoms like irritability, feeding difficulties and other signs and symptoms of cardiac failure. It is estimated that 90% of patients with untreated ALCAPA die in the first year of life if not detected and treated.[6] It is therefore important to diagnose them in time to offer intervention. Open heart surgery with re-implantation of the anomalous coronary artery is the treatment of choice and outcomes are good.[7]

This study was conducted with the aim to look at the profile, presentation and outcomes of patients who present with the diagnosis of ALCAPA to the Pediatric Cardiology Unit based in Universitas Academic Hospital. The purpose of this study was to determine the clinical symptoms at presentation, describe short and long-term survival and describe the clinical status of the patients at last follow up.

To the researchers' knowledge, there have not been any studies in central South Africa to assist clinicians to suspect and diagnose ALCAPA early enough to offer these patients intervention timeously. This study was prompted by the clinical impression that most patients with ALCAPA are misdiagnosed, which delay referral and result in possible demise prior to referral. Furthermore, it is known that most of these patients present with non-specific symptoms which makes it difficult to diagnose.

2.3 Method

This was a retrospective descriptive study conducted on the medical records of patients who presented to the Department of Pediatric Cardiology between January 1998 and August 2019. All patients diagnosed with ALCAPA during the study period were included. Medical records of patients referred from the Free State, Northern Cape, Eastern Cape and Lesotho were reviewed. Data collection included patient demographics, clinical presentations, referral diagnosis, echocardiography before and after surgery, cardiac catheterization data, surgical data, clinical status, and echocardiography (ECHO) at last follow up.

Data was captured using the REDCap® online database. The standardized Ross classification for age (Appendix 1) was used to classify severity of symptoms.[25] A Ross classification of more than two was considered to indicate clinically noticeable heart failure. Systolic dysfunction on ECHO was classified as follows: SF >28% = normal, SF 20-25% = mild, SF 15-20% = moderate and SF <15% =severe. Mitral regurgitation was classified based on length of colour Doppler regurgitation jet in the left atrium as mild (< 1/3), moderate (1/3-2/3) or severe (> 2/3). Left ventricular end diastolic dimension (LVEDD) was classified using z-score nomograms normalized for body surface area.

The study was approved by the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State (UFS-HSD2019/1841) and the Free State Department of Health. Statistical analysis was carried out by the Department of Biostatistics of the University of Free State.

2.4 Results

During the study period a total of 30 patients presented to Universitas Paediatric Cardiology Unit with the diagnosis of ALCAPA.

Clinical presentation at Universitas Hospital

In order to demonstrate classical presentation at the unit, the first and last patients are briefly summarized: The first patient presented in May 1998; she was a 6 year old girl from Dewetsdorp (Free State Province) presenting with symptoms of cardiac failure. She was referred with a diagnosis of suspected ventricular septal defect. Echocardiography showed mild left ventricular dysfunction (SF = 25%), moderate mitral regurgitation (MR) with a normal heart size on chest radiography. The final diagnosis of ALCAPA was made by means of cardiac catheterization and demonstrated that the patient had collateral flow from the right coronary artery. ALCAPA surgical repair was subsequently performed. The patient did very well: SF normalized to 35% immediately post-surgery and mitral regurgitation (MR) also improved to mild. Her last follow up was in 2006, where the patient had a normal left ventricular function (SF-37%) and trivial MR.

The last patient included in the study was seen in February 2019. She was a 5-month old girl from King Williamstown (Eastern Cape). She presented with symptoms of cardiac failure and was referred with the diagnosis of cardiac failure with pulmonary edema. ECHO at presentation diagnosed ALCAPA with severe left ventricular dysfunction, mild MR and a dilated heart. During cardiac catheterization the patient developed bradycardia; she was resuscitated, but unfortunately the patient demised despite optimal resuscitation.

Demographics

The gender and age distributions of patients are illustrated in Table 1. The median age of patients was 4 months (range: birth to 6 years) with a median weight of 6.2 kg (range: 4.1 kg - 20 kg). Out of the 30 patients included in the study, 53.3% (n=16) and 46.7% (n=14) were females and males, respectively. Most patients (77%, n=23) presented in the first year of life.

Table I. Gender and age distribution at presentation

	Frequency	Percentage (%)
Gender		
Female	16	53.3
Male	14	46.7
Age category		
< 1 year	23	77
> 1 year	5	17
> 6years	2	6

The median age at presentation of infants was 3 months (range: 1 day - 10 months). There were two patients (n=2) that presented late at 6 years of age. The first patient was asymptomatic and presented with an incidental murmur heard during routine examination. He was referred to the cardiology department with the diagnosis of mitral regurgitation. This patient had a normal left ventricular function (SF = 37%) and negligible mitral regurgitation but the heart was dilated on ECHO. The patient had good collaterals vessels from the right coronary artery, which explains why the patient had been asymptomatic for so many years. Sixteen days later the patient underwent surgery and did very well post ALCAPA repair.

The second patient also presented at the age of 6 years with mild cardiac failure and a cardiac murmur; referral diagnosis was for suspected VSD. First ECHO showed mild left ventricular dysfunction (SF=25%), moderate MR 2/4 and there was no cardiac chamber dilatation. A catheterization was performed and the diagnosis of ALCAPA was confirmed - of note: this patient had poor collaterals but still survived for years which is a rare phenomenon. Surgery was then performed. Patient did well post ALCAPA repair - Left ventricular function normalized and mitral regurgitation improved (<1/4 MR) with no dilatation of the heart.

Referral per Province/Country

Two thirds (n=20) of patients were from the Free State Province, 26.7% (n=8) from the Northern Cape, 3.3% (n=1) from Eastern Cape and 3.3% (n=1) from Lesotho, also shown in **Table II** .

Table II. Breakdown by Province/Country

	Frequency	Percentage (%)
Free State	20	66.7
Northern Cape	8	26.7
Eastern Cape	1	3.3
Lesotho	1	3.3

Out of the 20 patients from the Free State, 30% (n=6) of them were from Bloemfontein. Their median age was 3 months (range: 1d - 10 months). A further 30% (n=6) was from areas less than 100 kilometers from Bloemfontein e.g. Botshabelo and Dewetsdorp; median age for these patients was 2.5 months (range:1 month to 6 years). A total of 40% (n=8) of patients was from areas more than 100 kilometers from Bloemfontein e.g Betlehem and Kroonstad. Their median age was 9 months (range: 20 days to 6 years), however this was not statistically significant (p = 0.66).

Clinical presentation

During initial clinical presentation, 53.6% of patients were referred with the diagnosis of cardiac failure, 28.6% with pneumonia and 25% had non-specific symptoms e.g. acute diarrhea with incidental cardiomegaly on chest X-ray, tonsillitis, and diarrhea with respiratory distress. Clinically the vast majority, 89% (n=25) were in cardiac failure at presentation with a Ross classification for age of more than two (**Table III**).

Table III. Ross Heart failure classification at presentation

Age	Main symptoms	SF	MR	Ross
3 yr	Tachycardia	36%	Moderate	2
2 yr 8 mo	Tachycardia	10%	Trivial	3
6 yr	Tachycardia, tachypnoea	25%	Moderate	3
4 mo	Tachypnoea	15%	Mild	3
1 mo	Shortness of breath	20%	Moderate	3
1 mo	Difficulty breathing	18%	Mild	4
3 mo	Pale	23%	Severe	4
2 yr	Tachypnoea, swelling of abdomen, hepatomegaly	40%	Severe	5
6 mo	Tachypnoea	17%	Severe	5
2 mo	Tachypnoea, tachycardia	16%	Severe	6
3 mo	Poor feeding, tachypnoea	17%	Severe	6
1 d	Poor feeding, tachypnoea, tachycardia	21%	Mild	7
14 mo	Tachypnoea, tachycardia Weight loss, hepatomegaly	17%	Severe	8
2 mo	Tachypnoea, tachycardia, Increased Pro BNP	16%	Severe	9
20 d	Fast breathing, tachycardia	14%	Mild	9
12 mo	Tachypnoea, tachycardia, hepatomegaly	15%	Mild	9
3 mo	Poor feeding, fast breathing, tachycardia	17%	Severe	10
6 mo	Shortness of breath, poor feeding, tachycardia	8%	Moderate	10
10 mo	Poor feeding, Tachycardia, Tachypnea, underweight,4cm hepatomegaly, increased ProBNP	11%	Severe	13
4 mo	Poor feeding,weight loss,Tachypnoea, tachycardia, hepatomegaly, increased proBNP	8%	Moderate	17
3 mo	Poor feeding, weight loss, tachypnoea, tachycardia, hepatomegaly, Increased proBNP	13%	Severe	18
3 mo	Poor feeding, Tachypnoea, tachycardia, increased pro BNP, hepatomegaly, poor growth	13%	Moderate	18
1 mo	Poor feeding, tachypnoea, tachycardia, hepatomegaly, increased proBNP	12%	Severe	18
1 mo	Poor feeding, tachypnoea, tachycardia, hepatomegaly, increased proBNP	19%	Severe	18

Ross: Ross clinical presentation of heart failure; SF- fractional shortening; MR- mitral regurgitation; d: day; mo: month; yr: year

Echocardiogram

The diagnosis of ALCAPA was made primarily by Echocardiography in 75.8% (n=22) of patients. The remainder of patients had features suggestive of ALCAPA, e.g. left ventricular dysfunction in 16.6% (n=5) of patients, suspected congenital heart lesions e.g. VSD in 3.3% (n=1), mitral valve prolapse in 3.3%(n=1) and one patient had no report(file missing).

The majority of patients 83.3% (n=25) had a dilated left ventricle at presentation, with a median LVEDD z-score of 6.4 and only 10% (n=3) had a normal left heart dimension, median LVEDD z-score being 1.6. ECHO at first presentation demonstrated normal left ventricular function with SF between 28-44% in 10% (n=3) of patients; 13% (n=4) had mild left ventricular dysfunction (SF 15 – 20), 37% (n=11) had moderate LV dysfunction (SF 15 – 20) and 37% (n=11) had severe LV dysfunction (SF <15%). About half of the patients, 43% (n=13) had severe MR, 23% (n=7) had moderate MR and 30% (n=9) had mild MR and in one patient MR was undocumented.

Cardiac catheterization

Cardiac catheterization was performed in 76.6%, (n=23) of patients. In 95.6% (n=22) of these patients the indication for cardiac catheterization was to demonstrate origin of the left coronary artery and assessment of collateral circulation according to local surgical SOP. Collateral circulation from the right coronary artery were noted in 78% (n=18) of these patients. Twenty three percent (n=7) of our patients did not have a cardiac catheterization. Reasons being prematurity, a patient too sick, a family that refused surgery despite extensive counselling about poor outcome of ALCAPA without surgical intervention. Ten percent (n=3) did not have cardiac catheterization

done because ECHO had given enough information to diagnose ALCAPA – during the latter cohort of the study period.

Surgical repair

ALCAPA repair was done in 76.6% (n=23) of patients. The median age at surgery was 35 months (range: 1 day - 73 months), with a median weight of 6kg (range: 4kg - 20kg). The median days from diagnosis to the day of surgery was 11 days (range: 1 day to 6 years). Most patients had re-implantation of the anomalous left coronary artery except for two where the left coronary artery was tied off. One child required a left ventricular assist device (LVAD) for 7 days post operatively and survived.

First ECHO post-surgery showed some improvement of left ventricular function with 17.3% (n=4) of patients demonstrating a normal SF, 13% (n=3) had mild left ventricular dysfunction whilst 52% (n=12) remained with severe LV dysfunction. The majority of patients 60% (n=14) still had a dilated left ventricle early after surgery. Seventeen percent (n=4) of patients had trivial MR post-surgery, 30% (n=7) had mild MR, 26% (n=6) had moderate MR with severe MR observed in 13% (n=3) of patients.

Deaths

Early deaths: Thirteen percent 13% (n=4) of patients demised prior to surgery. The first patient was a premature neonate at 34 weeks gestation who demised in neonatal ICU due to septic shock. The second death was that of a 3-month old infant who was admitted to the Paediatric ICU due to pneumonia and discharged home prior to surgery. However, the patient presented in septic shock and unfortunately succumbed prior to surgery. The third case was a 2-month old who had an E. coli

urinary tract infection complicated by septic shock and demised before surgery. Last death before surgery was that of a 4-month old who died at home whilst awaiting surgery. Of these deaths before surgery, 50% had severe left ventricular dysfunction, 75% had severe MR and 75% had a markedly dilated left heart at presentation. The main cause of death in 75% of them was septic shock, see **Table IV** below.

Table IV. Deaths before surgery

Age	SF (%) at presentation	LV dysfunction	MR at presentation	Cardiac dilation (LVED z score)	Cause of death
Premature (34 weeks)	21%	Mild	Mild	1.6	Septic shock
3-months	13%	Severe	Severe	6.8	Septic shock, pneumonia
2-months	12%	Severe	Severe	9.4	Septic shock, E. coli UTI
4-months	23%	Mild	Severe	3.7	Died at home, awaiting surgery

One family refused surgery despite extensive counseling which involved the whole family including the in-laws, they still refused, having been told about all the complications and poor prognosis of ALCAPA without definitive surgery. Two patients did not have surgery for reasons unknown to us as we struggled to find records.

The peri-operative surgical mortality was 22% (n=5). Three children demised at 2, 3- and 6-months post-surgery. In all of these, the main cause of death was severe pneumonia.

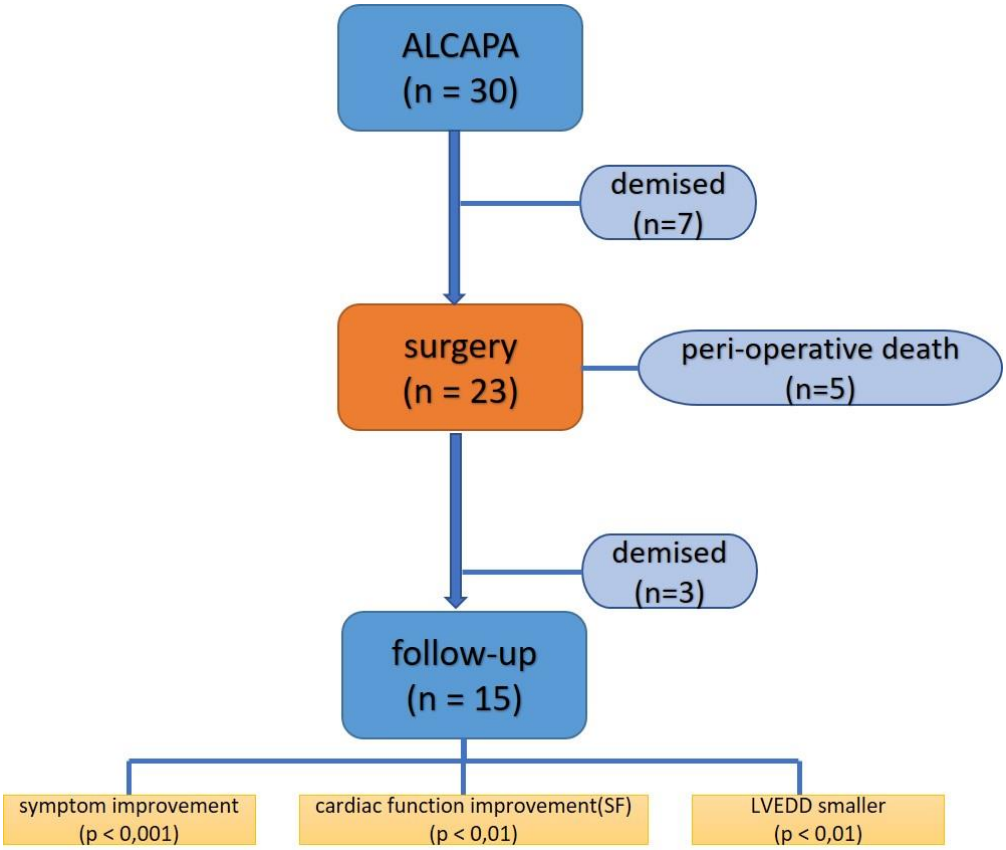

Figure 2: Diagram of study population

Follow-up

A total of 18 patients were followed up at a median period of 4.5 years post-surgery (range: 5 days to 20 years 9 months). Their median age at last follow up was 2.8 years (2 months to 20.9 years). Heart failure symptoms (Ross) at follow-up improved significantly from original presentation ($p < 0,01$): forty five percent, (n=8) of our patients had no symptoms of cardiac failure, with Ross classification of two and less and 40% (n=7) had mild heart failure with a Ross classification of three to five. Unfortunately, three (n=3) of these patients had no symptoms recorded at last follow up (Table V.).

Table V. Ross Heart failure classification at last follow up

Age	Main symptoms	SF	MR	Ross
9 yr 2 mo	Nil	45%	trivial	0
13 yr	Nil	37%	trivial	1
4 yr 9 mo	Nil	39%	trivial	1
20 yr	Nil	32%	trivial	1
4 yr 9 mo	Nil	30%	trivial	1
4 mo	Nil	29%	trivial	2
5 mo	Nil	31%	mild	2
1 yr 9 mo	Nil	24%	trivial	2
2 yr 4 mo	Nil	22%	mild	3
2 yr 4 mo	Nil	10%	mild	3
4 yr 8 mo	Tachypnoea	30%	severe	3
5 yr 8 mo	Nil	29%	moderate	4
2 yr 11 mo	Tachypnoea	38%	severe	4
8 yr	poor feeding, tachypnoea	32%	severe	5

Ross: Ross clinical presentation of heart failure; SF: fractional shortening; MR: mitral regurgitation; d: day; mo: month; yr: year

Forty percent (n=6) of the patients have not been seen in the last 5 years prior to end of study.

Echocardiography

There was a significant improvement in SF of operated children compared to their SF at presentation (p = 0,001). Most patients, seventy three percent (n=11) demonstrated a normal SF, thirteen percent (n=2) had mild left ventricular dysfunction and only one (n=1) had severe LV dysfunction. Forty six percent (n=7) of patients had trivial MR at last follow with severe MR seen in only 13% (n=2). Left ventricular end diastolic dimensions also improved significantly (p =0,01) with a mean z-score of 2.7 versus 5.6 at presentation.

Out of the 23 patients that had surgery, 13% (n=3) of them had additional surgery like mechanical valve mitral, relief of left ventricular outflow tract obstruction and mitral valve annuloplasty.

Figure 3 illustrates systolic function at presentation and at last follow up.

Of significance is that 73% (n=22) patients presented with moderate to severe LV dysfunction with SF <20 , immediately post-surgery there was still a significant number of patients with severe LV dysfunction with SF <15, i.e. 52% (n=12) patients. At last follow up we see a marked improvement on LV function with 73% (n=11) patients having a normal SF. SF at last follow up showed a statistically significant difference compared to, at presentation with a p-value of 0.014.

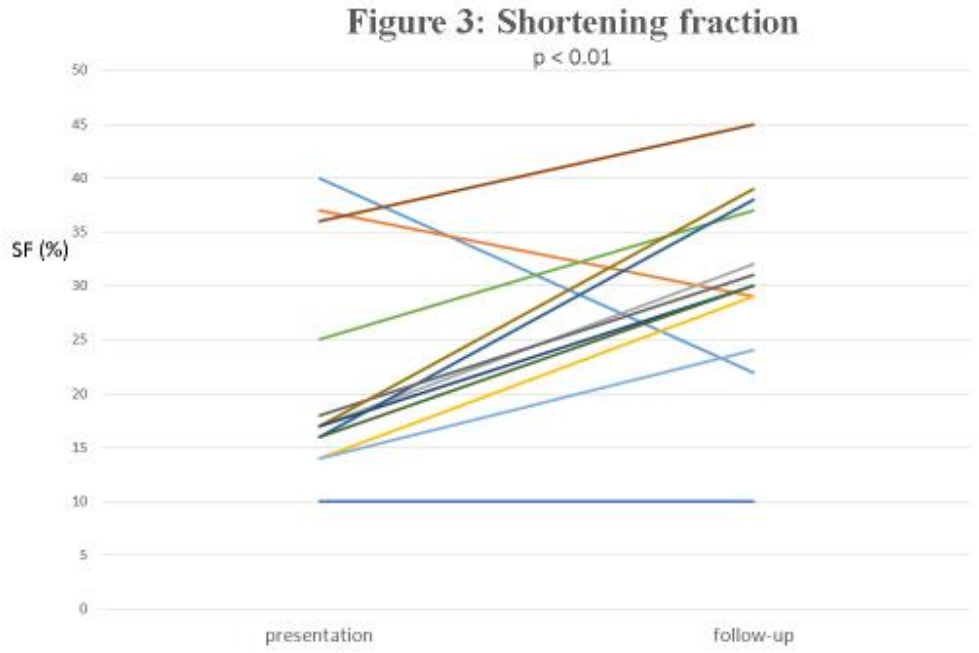

Figure 3: Systolic function (SF) at presentation and follow up

Figure 4 illustrates left ventricular end diastolic dimensions at presentation versus at last follow up. There was a statistically significant improvement on LVEDD at presentation versus at last follow up (p =0,01) with a mean z-score of 2.7 at last follow up, compared to 5.6 at presentation.

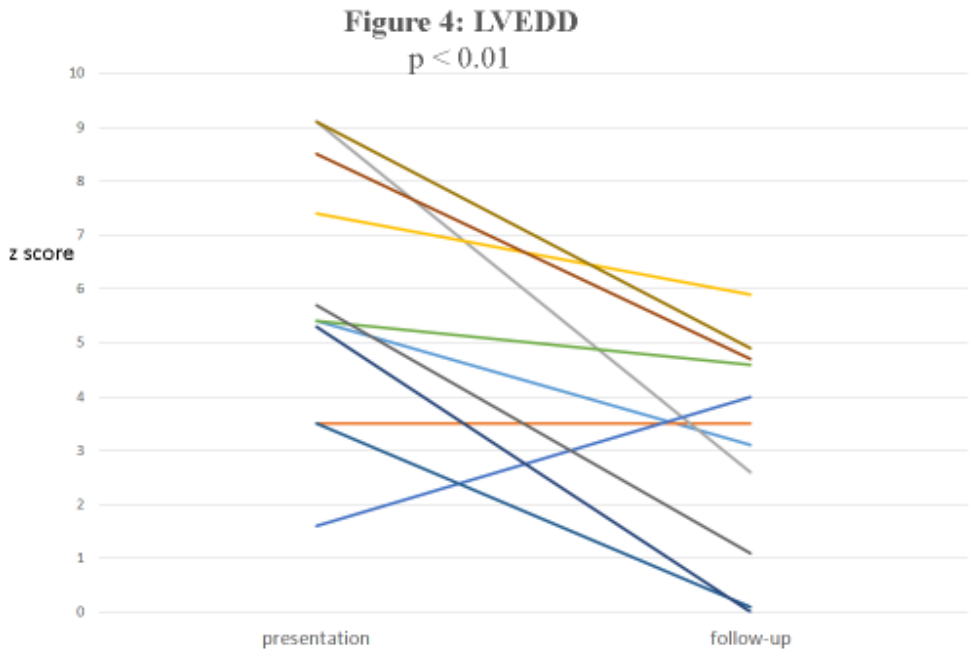

Figure 4: LVEDD at presentation and last follow up

Figure 5 shows MR at presentation, immediately post-surgery and at last follow up. Over time mitral regurgitation seemed to improve: at presentation majority of patients 43% (n=13) had severe MR, immediately post-surgery 57% (n=13) of patients had mild to moderate MR and at last follow 67% (n=10) of patients had trivial to mild MR.

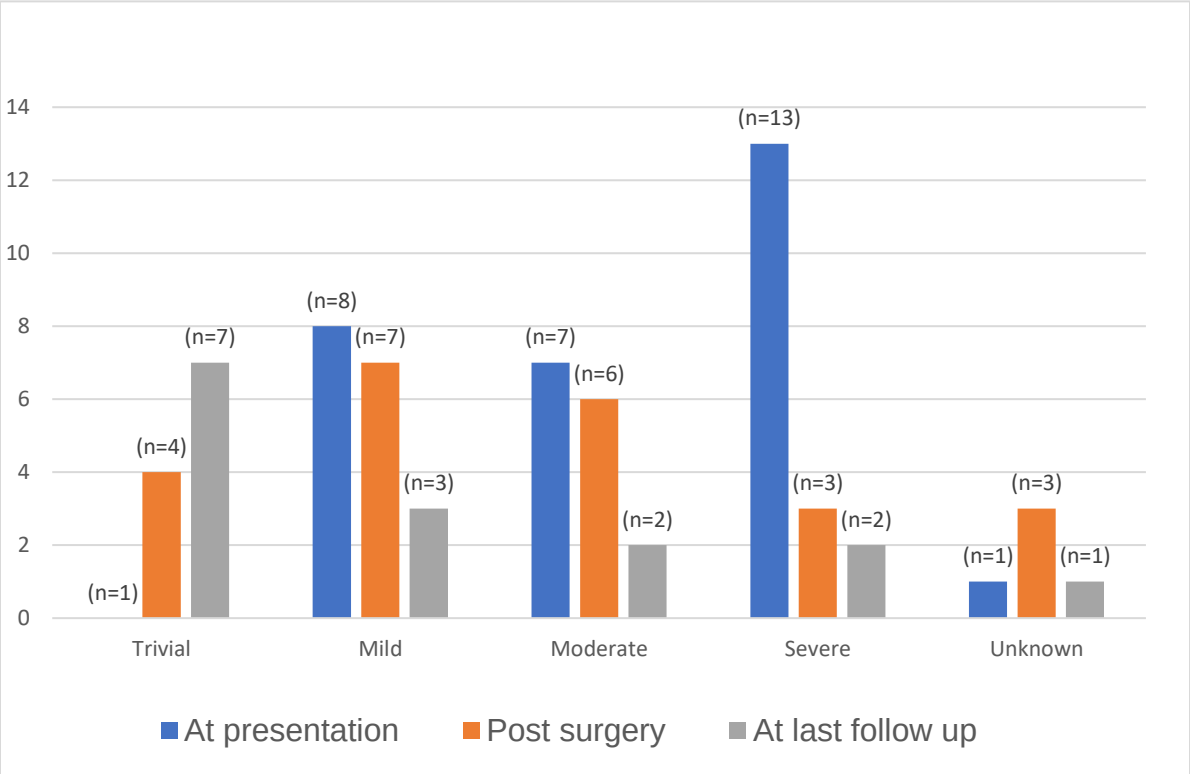

Figure 5: Mitral regurgitation at presentation, post-surgery and at follow up

Seventy eight percent (n=18) of patients were alive at the end of the study and mortality post-surgery was 22% (n=5), see Figure 6 below.

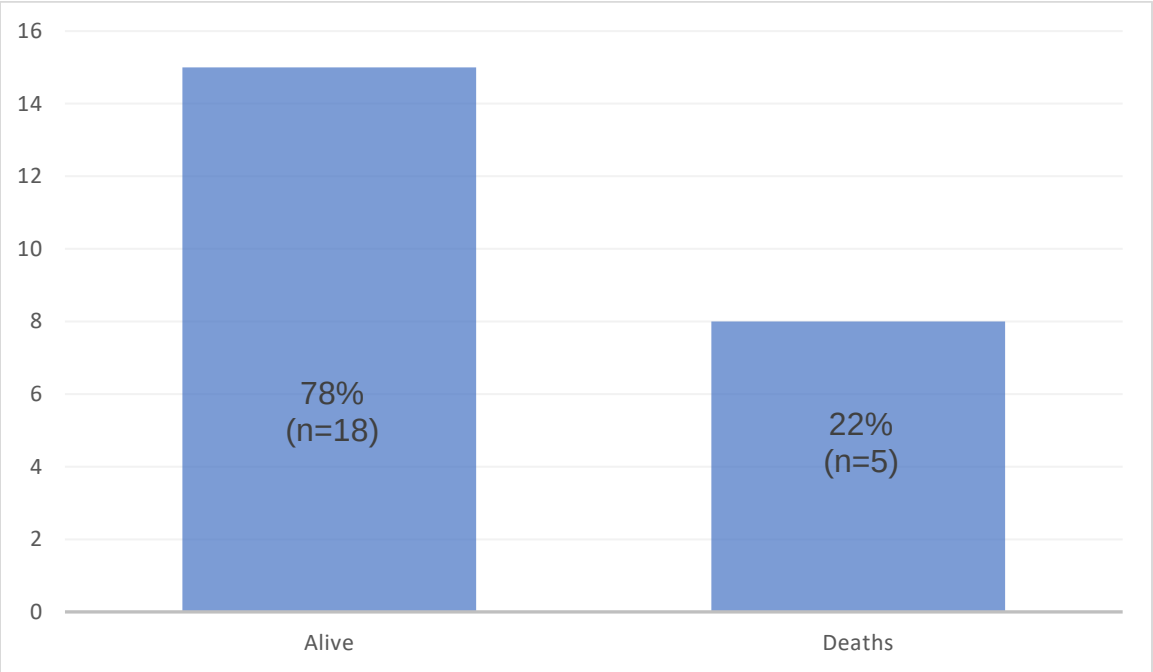

Figure 6: Survival vs Mortalities

Looking at the 78% (n=18) survivors at follow up, there was marked improvement in symptoms of heart failure where 53.3% (n=8) of them had no symptoms of heart failure and they were off anti-heart failure treatment, their Ross classification was normal at two and less. Only 13.3% (n=2) still had symptoms of heart failure, where Ross classification was more than two. Unfortunately, the medical records of 33.3% (n=5) of these patients were incomplete since their clinical symptoms at last follow up were not documented.

2.5 Discussion

The study confirms that ALCAPA is a rare congenital cardiac abnormality as we only saw 30 patients presenting to Universitas Paediatric Cardiology Unit over a period of 21 years in a database consisting of 31 554 (0.001%) patients. Gender distribution of patients with ALCAPA was roughly equal. This finding compares favorably with most literature reports as there seems to be no specific gender distribution: both males and females are affected equally.[7]

Young patients in our study presented predominantly with symptoms of cardiac failure. International literature[4,5,6,20,22], reported similar findings as in our setting, the main referral diagnosis in these patients being cardiac failure. This can be explained since, shortly after birth and during the first weeks of life, symptoms are rare as a result of the elevated pulmonary vascular resistance that persists during the neonatal period. However, when pulmonary vascular resistance drops, most infants become symptomatic as antegrade coronary artery flow changes due to the lower pressures and myocardial ischemia ensues because of a diastolic flow steal phenomenon due to the lower pressure pulmonary artery.[3,5,7,8,12]

Our patients presented at a median age of 3 months (infantile) and an older group. Dilawar et al., in a study done in Qatar, found that patients with ALCAPA classically present at 2-6 weeks of age with history of irritability and inconsolable crying during feeding and symptoms or signs of heart failure.[23] They seem to have diagnosed their patients earlier than we did in our study, this could be ascribed to the fact that it is a first world country with ECHO screening facilities readily available. However, in a study done by Lardhi et al, similar findings to our study were reported,

usually at 2 to 3 months (when pulmonary arterial resistance drops to adult level), patients with ALCAPA become symptomatic.[24]

Birk et al., conducted a study over a 6-year period where 13 infants and children (2 months to 15 years) with ALCAPA were included. Eight of these infants were diagnosed with ALCAPA in the first year of life, all were symptomatic and had severe dysfunction of LV. The five patients diagnosed at an older age had normal myocardial function.[8] Findings in our study concur with Birk et al in that 89% (n=25) of our patients had symptoms of cardiac failure at presentation with a Ross classification for age of more than two and majority of patients that presented after infancy were asymptomatic and had good collaterals.

The Ross classification was used to accurately record the severity of heart failure in our patients. Interestingly we found that 89% (n=25) of our patients were clinically in heart failure at presentation, where their Ross classification was more than two. After surgery there was a significant improvement in symptoms of heart failure over time at last follow up where 53.3% of our survivors had no symptoms of heart failure and a Ross classification of less than 2. These findings are comparable to those reported by Zhang et al.[5].

Similarly, there was also a significant improvement in LVEDD (heart size) at last follow up compared to initial presentation. In a study conducted in China in 2017, which looked at 50 patients with ALCAPA, follow up was only possible in 38 patients (24% lost to follow-up). The median age at follow up was 84.5 months (range: 49 - 216 months) and they found that patients with impaired left ventricular function and severe myocardial infarction showed a satisfactory

recovery of cardiac function.[5] Our follow-up attendance compares poorly to these as we have not seen 40% of our survivors in the past 5 years. The authors speculate that our patients may be asymptomatic and thus ignore visiting the pediatric cardiology clinic, they may have moved to the adult cardiology department or may have died or migrated to other provinces.

Our results show that a simple tool like echocardiography could help diagnose a complex disease like ALCAPA in accordance to what is reported in literature. In our study the diagnosis of ALCAPA was made primarily by Echocardiography in 75% of patients. Majority of ALCAPA cases can be diagnosed by ECHO if the diagnostic markers are carefully studied. At presentation 48% of our patients had significant MR and 68% of them had papillary muscle ischemia similar to those reported by Saedi, Sasikumar et al.[4,14]. These authors also concluded that ALCAPA should be considered as a differential diagnosis in patients with mitral regurgitation accompanied by left ventricular systolic dysfunction. A noteworthy number of patients underwent cardiac catheterization in our group – this was due to surgical SOP at local cardiothoracic department.

Two-thirds of our patients who were operated were alive at the end of the study with significant improvements in clinical symptoms and echocardiographic parameters comparable to other studies.[7,12,14,16] However, this is not as good when compared to first world countries. Phillip S, conducted a retrospective study review which included 42 patients who underwent surgical repair of ALCAPA in Royal children's hospital, Melbourne and found that there was a 98% survival rate, 20 years later. [16] Thirteen percent of our patients demised before surgery as they were too sick, often admitted in Pediatric Intensive Care Unit with severe pneumonia. In our study half of those that died prior to surgery had severe LV dysfunction with a SF <15% and 75% (n=3) had severe

MR; this concurs with findings reported by Zhang et al, that poor LV function and severe MR are risk factors for mortality in patients with ALCAPA.[17]

Our mortality rate within 30 days post surgical repair was of 22% (n=5) which is close to what is described in second world countries like China, where a recently published hospital mortality rate after surgical repair of ALCAPA ranging from 0% -16% was reported.[17]

In a study done in Sub Saharan Africa Leye et al. reported on the first three cases of ALCAPA seen in Senegal in 2017: all were infants under one year of age, they all presented with symptoms of heart failure and on ECHO all three of them had a dilated LV ventricle and LV dysfunction. Surgical repair was done in two thirds of these patients and they had good outcomes. Thirty three percent could not have surgery due to comorbid medical conditions. Their median follow up period post surgery was 3.5 years and the patients showed significant clinical improvement of symptoms and all of them had normal LV function on ECHO at last follow up.[19] Our patients had a similar clinical presentation where 89% had symptoms of heart failure, ECHO showed LV dysfunction in 87% of our patients and a dilated left heart in 83%. Median follow up period post surgery for our patients was slightly longer at 4.5 years (range: 5 days - 20 years 9 months). Seventy three percent of our patients showed marked improvement on LV function with a normal SF at last follow up. SF in our patients showed a statistically significant improvement at last follow up .

Aliku et al, in a study done in Uganda, looked at a clinical case of a 10 week old infant, who presented with symptoms of heart failure, had a dilated heart and LV systolic dysfunction on ECHO, this patient was admitted received fluid resuscitation and inotropes and heart failure treated. Patient was unfortunately discharged home six days later with a plan to refer abroad for

corrective surgery since Uganda Heart Institute still lacks capacity to operate on ALCAPA cases. [20]

Aliku et al, emphasized the importance of having a high index of suspicion of ALCAPA based on clinical symptoms and typical ECHO findings in a young infant who presents with LV dysfunction to assist with early diagnosis of ALCAPA.[20]

Our results show that there is a tendency for earlier diagnosis in patients living closer to a major center with a pediatric cardiac service and delayed diagnosis in patients further than 100km e.g. Eastern Cape children. A similar observation was made by Rossouw B et al, 2014[18], where a small percentage of patients presenting with ALCAPA were coming from the Eastern Cape, which houses 15% of childhood population in South Africa.

2.6 Limitations

Limitations to our study consist mostly of the retrospective nature and long period resulting in not all the data being available resulting in some of the archived files not being found. as the study stretched over 21 years. A significant number of our patients 40% (n=6) were not followed up in the last five years and we are uncertain of the real reasons these patients are lost to follow up, we are only left with speculations. However, this is not uncommon in developing countries.

2.7 Recommendations

1. Clinically a young child with clinical features of heart failure and a big heart warrants an early echo and early referral to a paediatric cardiology facility.

2. In any infant with the diagnosis of pneumonia and a big heart, ALCAPA should be excluded.
3. ECHO findings of poor SF and MR should raise a high index of suspicion of ALCAPA.

2.8 Conclusion

Our results show that the majority of children in central South Africa present in the first year of life with clinical features of heart failure. The Ross scoring system may aid the peripheral clinician in doubt of the diagnosis. The most common echocardiographic features are impaired systolic function, dilated left ventricles and mitral regurgitation. Furthermore, surgery results in significant clinical and echocardiographic improvement. It is of paramount importance to have a high index of suspicion based on the clinical presentation and ECHO to ensure early referral, so corrective surgery may be offered timeously.

2.9 References

1. Matherne, G. P. & Lim, D. S. Congenital anomalies of the coronary vessels and aortic root. In H. D. Allen, D. J. Driscoll, R. E. Shaddy & T. F. Feltes (Eds.). *Moss and Adams'. Heart Disease in Infants, Children and Adolescents: Including the Fetus and Young Adult*, 2008. vol. 1 (7th ed.). Baltimore: LWW, 702-714.

2. Kastellanos, S., Aznaouridis, K., Vlachopoulos, C., Tsiamis, E. & Tousoulis, D. Overview of coronary artery variants, aberrations and anomalies. *World Journal of Cardiology*, 2018 October 26;10(10): 127–40. doi: 10.4330/wjc.v10.i10.127

3. Exhibit E. ALCAPA Syndrome: Not Just a Pediatric Disease. 2009.

4. Saedi, S., Parsaee, M., Farrashi, M., Noohi, F. & Mohebbi, B. The role of echocardiography in anomalous origin of coronary artery from pulmonary artery (ALCAPA): Simple tool for a complex diagnosis. *Echocardiography* 2019; 36: 177–181. https://doi.org/10.1111/echo.14236

5. Zhang, H. L., Li, S.J., Wang, X., Yan, J. & Hua, Z.D. Preoperative Evaluation and Midterm Outcomes after the Surgical Correction of Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery in 50 Infants and Children. *Chinese Medical Journal* 2017; 130(23): 2816–2822. doi: 10.4103/0366-6999.219156

6. Yolcu, M., Bilal, M.S., Avsar, M.K. & Yildirim O. Case Report A patient with anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA syndrome) and 13 live births. *Cardiovascular Journal of Africa* 2019; 30. doi: 10.5830/CVJA-2019-003

7. Kamran, M., Memon, Y., Amanullah, M. & Ma, M.A. Anomalous Left Coronary Artery from Pulmonary Artery: An Important Cause of Ischemic Mitral Regurgitation in Children. *Cureus*, 2019; 11(4): e4441. doi: 10.7759/cureus.4441

8. Birk, E., Stamler, A., Katz, J., Berant, M., Dagan, O., Matitiau, A., Erez, E., Blieden, L. V. & Vidne, B. A. Anomalous origin of the left coronary artery from the pulmonary artery: Diagnosis and postoperative follow up. *Isr Med Assoc J* 2000; 111-4.

9. Gonzalez, M., Tirado, A. M., Hosseinpour, R. & Santos de Soto, J. Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery: Diagnoses and Surgical Results in 12 Pediatric Patients. *Tex Heart Inst J*, 2015; 42(4): 350–356. doi: 10.14503/THIJ-13-3849

10. Zhang, C., Luo, Q., Li, Y., Wu, X., Hao, Z., Li, S., Xia, Z., Yan, F. & Sun, L. 2018. Predictors of Short-term Outcomes Following Repair of Anomalous Origin of the Left Coronary Artery From the Pulmonary Artery in Chinese Children: A Case-Control Study. *J Cardiothorac Vasc Anesth*, 2018(32): 2644-2651. doi: 10.1053/j.jvca.2018.04.008

11. Patel, S. G., Frommelt, M., Frommelt, P. & Cramer, J. Echocardiographic diagnosis, surgical treatment and outcomes of anomalous left coronary artery from the pulmonary artery: a 25-year experience. *J Am Coll Cardiol*, 2016; 67(13):969. http://dx.doi.org/10.1016/S0735-1097(16)30970-6

12. Cabrera, A. G., Chen, D. W., Pignatelli, R. H., Khan, M.S., Jeewa, A., Mery, C. M., et al. Outcomes of Anomalous Left Coronary Artery From Pulmonary Artery Repair: Beyond Normal Function. *Ann Thorac Surg* 2015; 99(4): 1342–7. http://dx.doi.org/10.1016/j.athoracsur.2014.12.035

13. Wejner-Mik, P., Lipiec, P., Peruga, J. Z., Mozdzan, M. & Kasprzak, J. D. 2019. Transthoracic echocardiographic diagnosis of late-presentation Bland-White-Garland (ALCAPA) syndrome. *European Heart Journal - Cardiovascular Imaging*, 2019; 20(3): 306. https://doi.org/10.1093/ehjci/jey193

14. Sasikumar, D., Dharan, B. S., Arunakumar, P. & Gopalakrishnan, A. The outcome of mitral regurgitation after the repair of anomalous left coronary artery from the pulmonary artery in infants and older children. *Interactive CardioVascular and Thoracic Surgery* 2018; 27(2): 238–242. https://doi.org/10.1093/icvts/ivy022

15. Alqathamy H., Elwy A., Ragheb A., Alfaraidi Y., Donato RM Di. Long term results of surgical management of anomalous origin of the left coronary artery from pulmonary artery (ALCAPA) and mitral incompetence. Journal of the Saudi Heart Association. 2013;25(2):135. Available from: https://doi.org/10.1016/j.jsha.2013.03.084

16. Naimo, P. S., Fricke, T. A., Udekem, Y., Cochrane, A.D., Bullock, A., et al. Surgical Intervention for Anomalous Origin of Left Coronary Artery From the Pulmonary Artery. *Ann Thorac Surg, 2016;* 101(5): 1842–8. http://dx.doi.org/10.1016/j.athoracsur.2015.11.020

17. Zhang C, Zhang H, Yan J, Hua Z, Song Y, Sun H, et al. Mid-Term Outcome for Anomalous Origin of the Left Coronary Artery From the Pulmonary Artery. *Heart, Lung and Circulation*, 2020 May;29(5):766–71. http://dx.doi.org/10.1016/j.hlc.2019.04.018

18. Rossouw, B., Zuhlke, L. & Lawrenson, J. Anomalous left coronary artery to pulmonary artery (ALCAPA) in Red Cross War Memorial Children's Hospital (RCWMCH), HREC/Ref: 340/2014, ANNUAL RESEARCH DAYS 2014 Department of Paediatrics & Child , UNIVERSITY OF CAPE TOWN

19. Leye, M. The Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery (ALCAPA) in Senegal. *International Journal of Cardiovascular and Thoracic Surgery*, 2017;3(2):9-13. http://dx.doi.org/10.11648/j.ijcts.20170302.12. Senegal.

20. Aliku, T. O., Lubega, S. & Lwabi, P. A case of Anomalous origin of the left coronary artery presenting with acute myocardial infarction and cardiovascular collapse. *African Health Sciences*, 2014; 14(1): 223-227. doi: 10.4314/ahs.v14i1.35

21. Alkhalifa, M. S. & Omar, A. M. Coronary anomalies in Sudanese patients: angiographic study and brief review. *Sudan Journal of Medical Sciences*, 2006;1(1): 43-47.

22. Tedla, M. G. & Worku, D. K. Anomalous Left Coronary Artery from the Pulmonary Artery: Mini-Review. *ARC Journal of Cardiology*, 2017; 3(1): 13-16. http://dx.doi.org/10.20431/2455-5991.0301003

23. Dilawar, M. & Ahmad, Z. Anomalous left coronary artery from pulmonary artery: Case series and brief review. *Open Journal of Pediatrics*, 2012; 2(1): 77-81. http://dx.doi.org/10.4236/ojped.2012.21013

24. Lardhi, A. A. Anomalous origin of left coronary artery from pulmonary artery: A rare cause of myocardial infarction in children. *Journal of Family and Community Medicine*, 2020; 17(3): 113-116. doi: 10.4103/1319-1683.74319

25. Pepeta, L. Aetiology, diagnosis, and management of heart failure in infants and children. *SA Heart*, 2017;14(1). http://dx.doi.org/10.24170/14-1-1862

3. APPENDICES

A. Letter of Approval from Research Ethics Committee

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

02-Dec-2019

Dear **Dr Ntombikayise Makhoba**

Ethics Clearance: **Clinical presentation and outcomes of Anomalous left coronary artery from the pulmonary artery : A retrospective study from January 1998- August 2019 at the Department of Paediatric Cardiology,Universitas Hospital.**

Principal Investigator: **Dr Ntombikayise Makhoba**

Department: **Paediatrics and Child Health Department (Bloemfontein Campus)**

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-HSD2019/1841/2801**

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; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council 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

Dr. SM Le Grange
Chair : 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**
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Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

B. Permission from FS DOH

health
Department of Health
FREE STATE PROVINCE

19 November 2019

Dr N Makhoba
Dept. of Paediatrics and Child Health
UFS

Dear Dr N Makhoba

Subject: Clinical presentation and outcomes of Anomalous left coronary artery from the pulmonary artery : A retrospective study from January 1998- August 2019 at the Department of Paediatric Cardiology, Universitas Hospital.

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za / makenamr@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day**

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 22/11/19

Head : Health
PO Box 227, Bloemfotein, 9300
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Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

C. Permission from Evaluation Committee

UNIVERSITY OF THE FREE STATE
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HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

MASTER OF MEDICINE

This is to certify that the Departmental Research Meeting approved of the following MMed research protocol:

DATE OF MEETING	1 March 2019

DEPARTMENT	Paediatrics and Child Health
STUDENT NUMBER	2016441103
INITIALS AND SURNAME OF CANDIDATE	N. G MAKHOBA
NAME OF DEGREE	MMed Paed
SUPERVISOR	DR A FERRIS
CO-SUPERVISOR	PROFFESSOR BROWN

TITLE OF THE RESEARCH PROJECT
CLINICAL PRESENTATION AND OUTCOMES OF
ANOMALOUS LEFT CORONARY ARTERY FROM
THE PULMONARY ARTERY

Bouwer — **RESEARCH CHAMPION** — 09 Sep 2019 — **DATE**

SUPERVISOR(S) — 04/09/2019 — **DATE**

HEAD OF THE DEPARTMENT — Prof SC Brown, B.MeD FCPaed DCH, Consultant Paediatric Cardiologist, MP0270954 Tel: 051 405 3241 — 04/09/2019 — **DATE**

D. Permission from HOD

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

[redacted]

The Chair: Health Sciences Research Ethics Committee
Dr SM Le Grange
For Attention: Mrs M Marais
Block D, Room 104,
Francois Retief Building
Po Box 339 (G40)
Nelson Mandela Drive
Faculty of Health Sciences
University of the Free State
Bloemfontein
9300

05 September 2019

Dear Dr SM Le Grange

Dr. NG Makhoba (Student number: **2016441103**)

Clinical Presentation and outcomes of anomalous left coronary artery from the pulmonary artery, a retrospective study from January 1998 to August 2019, at the Department of Paediatric Cardiology, Universitas Hospital.

I, André Venter, hereby grant permission to conduct the above mentioned research project. The research will be completed in accordance with myself as Head of Department of Paediatrics and Child Health and Dr. Ferris as supervisor of this study.

Yours sincerely

Prof A Venter

Date

Department of Paediatrics and Child Health / Departement Pediatrie en Kindergesondheid
205 Nelson Mandela Drive/Rylaan, Park West/Parkwes, Bloemfontein 9301, South Africa/Suid-Afrika
P.O. Box/Posbus 339 (G69), Bloemfontein 9300, South Africa/Suid-Afrika, www.ufs.ac.za. F: +27(0)51 444 3230
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Prof SC Brown: T: +27 (0)51 405 3254, E: Gnpdscb@ufs.ac.za / Dr A van der Vyver: T: +27 (0)51 405 3184, E: Gnpdavdv@ufs.ac.za

E. Data collection form

Demographics

Record ID	_____
Enter the patient file number	_____
Date of birth	_____
Gender	◯ Male ◯ Female
Town	_____
Province	◯ Free State ◯ Eastern Cape ◯ Northern Cape ◯ North West ◯ Gauteng ◯ Kwazulu-Natal ◯ Limpopo ◯ Mpumalanga ◯ Western Cape

Confidential
t coronary artery from the pulmonary artery, a retrospective study from January 1998 to August 2019 at the department of Cardiology, Universitas Hospital
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Clinical Presentation

Record ID	_____
Date	_____
Weight	_____
Clinical symptoms	_____
Presenting diagnosis	_____
Ross Classification	_____

09-05-2019 08:12 projectredcap.org REDCap

Echocardiogram

Record ID	
Date	
LA (mm)	
z-score	
LVEDD	
z-score	
SF	
EF	
Mitral reg	
z-score	
Papillary Muscle Ischemia	
Comments	

Confidential
ft coronary artery from the pulmonary artery, a retrospective study from January 1998 to August 2019 at the department of Cardiology, Universitas Hospital
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Catheterization and Surgery

Record ID	
Date	
LVEDP	
MR class	
Collateral vessels	
Comments on Catheterization	
Surgery Date	
Nature of Surgery	

Post-Surgery First Echocardiogram

Record ID	
Date	
LA (mm)	
z-score	
LVEDD	
z-score	
SF	
EF	
Mitral reg	
z-score	
Papillary Muscle Ischemia	
Comments	

Confidential
ft coronary artery from the pulmonary artery, a retrospective study from January 1998 to August 2019 at the department of Cardiology, Universitas Hospital

Last Follow-Up

Record ID	
Date	
Echo	
Ross classification	
Outcome	◯ Alive ◯ Demised

F. Author guidelines

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2019 Volume 16 Number 4

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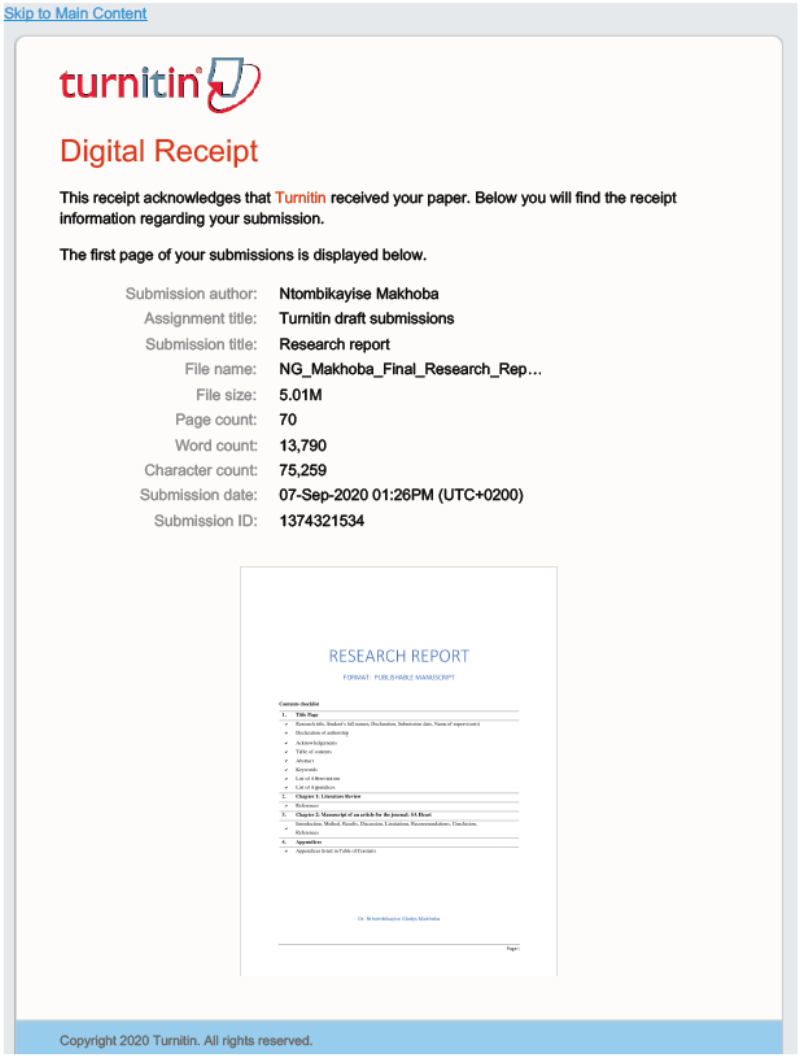

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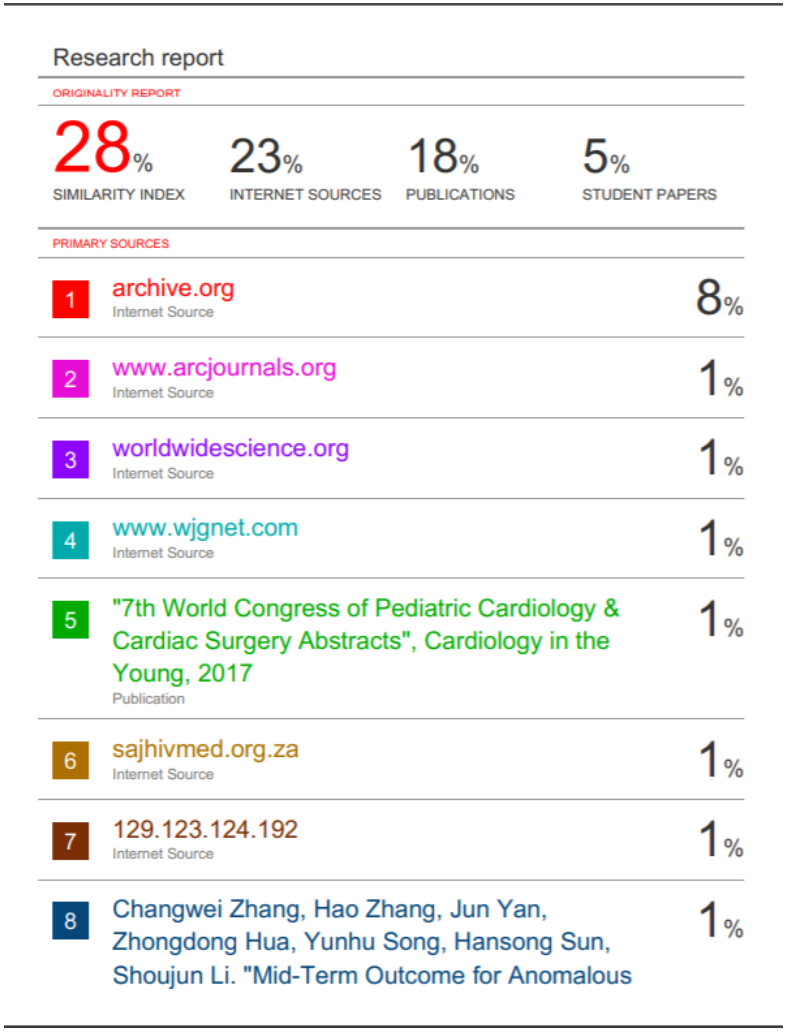

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Clinical presentation and outcomes of anomalous left coronary artery from the pulmonary artery: A retrospective study from January 1998 - August 2019 at the Department of Paediatric Cardiology, Universitas Hospital.

MMed Research Protocol

Department of Paediatrics and Child Health
University of the Free state

Dr N G Makhoba

11 September 2019

PROTOCOL TITLE

Clinical presentation and outcomes of Anomalous left coronary artery from the pulmonary artery: A retrospective study from January 1998 to August 2019 at the Department of Paediatric Cardiology, Universitas Hospital.

REGISTRAR NAME: Dr N.G Makhoba

STUDY LEADER: Dr A.R Ferris

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DEPARTMENT: Department of Paediatrics and Child Health

School of Medicine

Faculty of Health Sciences

University of the Free State, Bloemfontein

DATE OF SUBMISSION: **11 September 2019**

Table of Contents

1. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations

ALCAPA	Anomalous left coronary artery from the pulmonary artery
DOB	Date of birth
EF	Ejection fraction
FSDoH	Free State Department of Health
HSREC	Health Sciences Research Ethics Committee
LMS	Left main stem
LA	Left atrium
LAD	Left anterior descending artery
LCX	Left circumflex artery
LVEDD	Left ventricular end diastolic diameter
LVEDP	Left ventricular end diastolic pressure
MR	Mitral regurgitation
RCA	Right coronary artery
SF	Fractional shortening
ECHO	Echocardiogram
ECG	Electrocardiogram

Definitions

- Myocardium : is the muscular tissue of the heart.
- Congenital : born with it.
- Cardiac lesion : heart abnormality.
- Myocardial ischemia : decreased blood flow and decrease oxygen to the heart muscle.
- Myocardial infarction: no blood supply to heart muscle leading to tissue damage.
- Desaturated blood : low blood oxygen concentration.
- Cardiac output : the amount of blood the heart pumps out in a minute.

- Angina pectoris: severe chest pain, spreading to shoulders, arms and neck, all due to inadequate blood supply to the heart.
- Syncope : temporary loss of consciousness caused by a fall in blood pressure.
- Infant : a child older than one month but less than one year of age.

2. INTRODUCTION

Patients with anomalous left coronary artery from the pulmonary artery (ALCAPA) present with non-specific symptoms like irritability, feeding difficulties and signs and symptoms of cardiac failure. 90% of patients with ALCAPA die in the first year of life if not managed. It is therefore important to diagnose them in time and offer intervention, i.e surgery.

In this research project, a study will be done by the researcher with a view to look at clinical presentation and outcomes of patients that present with the diagnosis of ALCAPA to Universitas Academic Hospital.

The purpose of the study is:

- A self audit in the Department of Paediatric Cardiology and Cardiothoracic Department.
- To improve referral pathways from other hospitals in Free state,Northern Cape and Lesotho for management (e.g surgery) to be initiated sooner.
- To research and documucent data on ALCAPA in the Free state.

The researcher will conduct a retrospective review of patient files and medical records in order to get the necessary information for the study. The study will gather information about outcomes of patients with ALCAPA, i.e when do they present, what is their referral diagnosis, how soon is surgery offered to these patients and their clinical status at follow up.

The study will involve the researcher, supervisor and co-supervisor, who will apply for ethics approval from the Health Science Research Ethics Committee (HSREC) as well as the Free State Department of Health (FSDoH). Permission to access clinical files will be obtained from the Head of Department of Paediatrics. The Biostatistics Department from the University of Free State will analyse the data.

3. BACKGROUND ON ALCAPA

Normal Anatomy of coronary arteries:

The entire blood supply to the myocardium comes from two main coronary arteries which arise from the right and left aortic sinuses of Valsalva.(1) The two main coronary arteries then descend towards the cardiac apex. The left main stem comes from the left sinus of Valsalva, it then crosses between the main pulmonary artery and the left atrial appendage. LMS on average has a length of 2-40mm and normally divides into left anterior descending artery and left circumflex artery. The right coronary artery comes from the right sinus of Valsalva. The LAD extend towards the apex of the heart in the epicardial fat across the anterior interventricular sulcus. Its length ranges from 10-13mm, it then divides to diagonal and septal branches. It provides blood supply to the anterior wall, apex and large portion of the interventricular septum. The left circumflex artery measures 5-8mm and crosses the coronary sulcus on the diaphragmatic cardiac surface. The LCX divides to obtuse marginal branches and provides large blood supply to the lateral wall of the left ventricle.

The RCA descends to the right between the pulmonary artery and the right auricle, then travels down across the right atrioventricular sulcus and extends posteriorly after the acute margin of the heart. It measures 12-14mm in length. During its descent it may divide into many branches, like the conus branch, sinoatrial branch, right ventricular branch, atrioventricular nodal branch, posterior descending branch and posterolateral branch. It provides major blood supply to the right side of the heart.(2)

Within the myocardium there are small arteries that divide repeatedly until they get to the endocardium. There is normally connections between coronary arterial branches measuring 25-200mm in diameter, they are called collaterals. They may be found superficial or subendocardial and they are able to enlarge if pressure gradient develops between branches.(1)

Normal variations of coronary arteries without structural heart disease:

The right and left coronary arteries come from the right and left aortic sinuses of Valsalva. They usually originate from the middle of the sinuses but they can sometimes come from sinotubular junction or even above it. The position of the ostium does not affect the blood flow through it. The shape of the ostium may be round, oval or elliptical. The arteries are often in a perpendicular position to the aorta wall, in other words they are radially organized in relation to the centre of the aorta.

A different origin of the conus branch of the right coronary artery occurs more often. About 1% of patients with bicuspid aortic valve present with left side anomalies (i.e LAD and LCX arteries). Not any of these anomalies show clinical complications.(1)

Anomalous origion of left coronary arterial branches from the right sinus valsalva:

The most common abnormality, accounting for about one third of all major coronary arterial anomalies, is the origin of left circumflex coronary artery from the right main coronary artery. The LCX artery tracks through behind the aorta to connect with its normal territory of supply. This anomality has no general clinical importance.

Far less commonly seen is origin of left main coronary artery from the right sinus of Valsalva, accounting for 1%-3% of major coronary arterial anomalies. This has great clinical significance.

The connection may take place in four ways: 1. posterior to the aorta; 2. anterior to the right ventricular outflow tract; 3. within the ventricular septum beneath the right ventricular infundibulum (this is the most common variant and 4. between the aorta and the right ventricular outflow tract. The first three connections have not been associated with sudden death or early myocardial ischemia. The connection that passes through the two big arteries has been associated with sudden death in children during or just after strenuous exercise. A number of these patients had had episodes of syncope or chest pain during previous exercise. In many of these patients, the ostium of the left main

coronary artery was slit like, with an intramural connection within the aortic root and adherent to it for about 1.5cm.

Sometimes the left anterior descending coronary artery stems from the right sinus of Valsalva or from the right main coronary artery. This abnormality is not usually seen in the absence of congenital heart disease, but is common in tetralogy of Fallot.(1)

Anomalous left coronary artery from the pulmonary artery

This is an unusual form of abnormality where babies are born with abnormal left coronary artery. There are two types of ALCAPA syndrome : one seen in young children less than a year and the adult type, each one of these present differently and have different outcomes. The young children present with myocardial infarction and symptoms of heart failure and about 90% of them die within the first year of life. It is unsual for ALCAPA syndrome to present in adults; if it happens they usually present with sudden cardiac death.(3)

If ALCAPA present in an adult a wide range of differential diagnosis should be intertained, examples myocarditis, dilated cardiomyopathy and coronary artery disease.(4)

In this abnormality the left coronary artery comes from the pulmonary artery, it usually makes a connection from the posterior facing sinus. This abnormality was first noticed by pathologists in 1866, and by the year 1962 Fontana and Edwards had already collected 58 cases of autopsy with this abnormality; a lot of these patients had died before 13 months of age. The first case of a death was reported by Bland et al, this was proven clinically and on autopsy in a 3 month old boy. This abnormality was then called Bland-White-Garland syndrome.(1)

ALCAPA affects 1 out of every 300 000 babies born alive. It accounts for 0.5% of all babies born with heart defects.(5) It is usually seen as an isolated defect, but in 5% of cases it may be associated with other heart abnormalities such as atrial septal defect, ventricular septal defect and aortic coarctation.

ALCAPA syndrome cause complications like myocardial infarction, left ventricular dysfunction and mitral regurgitation. Or silent myocardial ischemia, which can result to sudden death in patients who survive to adulthood.

It's important to diagnose and treat these patients promptly, offering them surgical intervention with the aim of creating a two-coronary-artery circulation system, this provides excellent results and eventually leads to myocardial recovery.(3)

The most common cause of myocardial ischemia and infarction in children is ALCAPA syndrome. Prompt treatment is required otherwise 90% of these children die in the first year if left untreated.(6)

Pathophysiology

ALCAPA result in abnormal left ventricular perfusion, which is due to the left to right shunt, this is called a "coronary steal" phenomenon. The coronary steal causes profound myocardial ischemia, leading to left ventricular dysfunction and mitral regurgitation.(7) During fetal life this abnormality has no harmful effects because pressures and oxygen saturations are the same in the aorta and pulmonary artery. Myocardial perfusion is presumed to be normal and there is nothing stimulating collateral formation. After birth pressures drastically drop in the pulmonary artery, which is carrying desaturated blood, these pressures drop below systemic pressures. Hence the left ventricle which has a high demand for oxygen receives desaturated blood at low pressures. Initially collateral blood flow is low. The left ventricular myocardial vessels enlarge to decrease their resistance and increase blood flow, but soon coronary vascular reservoir becomes exhausted and myocardial ischemia occurs. Initially there is transient ischemia which occurs during exertion such as feeding or crying. But ongoing demand of myocardial oxygen lead to infarction of the anterolateral left ventricular free wall, which results in compromise of left ventricular function. This leads to heart failure which is usually made worse by mitral regurgitation following dilated mitral valve ring or infarction and non-functioning of the anterolateral papillary muscle.(1) When collateral vessels develop between the normal right coronary artery and the abnormal left coronary artery, then there is increased blood

flow and so does the right coronary artery increase in size and become torturous; supplying the left ventricle then blood is directed to the low pressure system in pulmonary artery.(6) But because the left coronary artery is connected to the low pressure pulmonary artery, the collateral flow tends to flow into the pulmonary artery instead of the high resistance myocardial blood vessels; this called the pulmonary-coronary steal, with a left to right shunt. The shunt is often quite small in terms of cardiac output but relatively huge in terms of coronary flow. 15% of these patients make it to adulthood because myocardial blood flow can keep with myocardial function at rest or during exercise.(1)

Pathology

ALCAPA has been seen together with other heart defects like patent ductus arteriosus, ventricular septal defect, tetralogy of fallot, or coarctation f aorta. But in most cases it is seen as as an isolated disease. Left ventricular perfusion may be adequate to prevent ischemia if there is pulmonary hypertension as often seen in patients with a large ventricular septal defect. Under this situation a ventricular septal defect with decreased pulmonary arterial pressure is not to be closed as that may have fatal effects.

Normally in infancy the heart is big, the left ventricle and atrium are dilated and have thick muscle. The anterolateral papillary muscle is scarred and atrophic, and its chordae is often shortened. The poster papillary muscles has been affected the same way, in some studies.

The anterior mitral leaflet is commonly thickened and you may find diffuse endocardial fibroelastosis of the left ventricle. Due to infarction you find thinning and scarring of the anterolateral left ventricular wall and apex. Mural thrombi are also often seen.(1)

Clinical features

In infancy:

Occurrence of symptoms determined by the degree of collateral development and the related left coronary artery in ALCAPA syndrome.(6) Infants who develop early signs of cardiac failure have insufficient intercoronary collaterals and hence poor blood supply for myocardial function.(8)

Nothing is usually noted in newborns until the 10th week of life, when the patient present with paroxysmal attacks of acute discomfort worsened by exertion of nursing. The infant may initially look distressed as evidenced by expiratory grunting, then followed by general appearance of severe shock, severe pallor and cold sweat. At times there may be transient loss of consciousness which comes with unusual severe attacks. Burping seemed to relieve the discomfort at times and would shorten the length of attacks which last 5-10 minutes. After this the infant might nurse without difficulty and remain without symptoms for several days. It is assumed that these paroxysmal attacks in these infants are signs of angina pectoris. Not all infants present in this way. Many of them present with signs and symptoms of cardiac failure.(1)

Irritability and feeding difficulties when approaching second month of life should raise the suspicion of ALCAPA.(4) Another common presentation in infancy is dilated cardiomyopathy and mitral regurgitation.(7)

Diagnosis of ALCAPA in severely ill infants can be difficult because ECHO findings are less visible when collateral circulation is less developed.(9)

Older children and adults:

This group may present with angina, dyspnea, syncope, myocardial infarction or arrhythmia. Malignant ventricular arrhythmia is the most common presentation leading to sudden cardiac death. The few patients who survive to adulthood without surgery have well developed coronary collaterals with adequate perfusion of the left ventricle.(6)

Major manifestations of ALCAPA are impaired left ventricular function and myocardial ischemia.(10)

On physical examination:

ALCAPA patients have poor growth and signs of cardiac failure.(7) In children less than one year the heart is often big, with the left ventricle being the main ventricle affected. If left ventricular failure has caused significant pulmonary hypertension, it may lead to right ventricular enlargement and loud pulmonary component of second heart sound. If there is mitral regurgitation, the first heart sound may be soft or absent. Commonly apical gallop rhythms are seen. Murmurs can be audible or no murmur auscultated, you may hear a soft continuous murmur at the upper left sternal border that is the same as the murmur of a small patent ductus arteriosus, this is due to the ongoing flow from the anomalous coronary artery into the pulmonary artery. A murmur of mitral regurgitation may sometimes be heard also.(1)

Unexplained ,mitral regurgitation is a clue to the diagnosis of ALCAPA.(7)

Investigations

Electrocardiography:

Typically the ECG shows abnormal Q waves in lead 1, aVL and precordial leads V4-V6, because there is classically an anterolateral infarct by the time the infant presents for diagnosis. There may also be abnormal R waves or R wave progression noted in the left precordial leads. If this is found a consideration of other causes of myocardial infarction or occasionally cardiomyopathies cause this, R-wave abnormalities is not pathologically specific for ALCAPA, proper evaluation by other means then deems important.

Deteriorating ventricular function accompanied with signs of ischemia on ECG is suggestive of ALCAPA.(9)

Noninvasive imaging:

ALCAPA if often confused with cardiomyopathy because on **CXR** you get severe cardiomegaly, with predominance of the left atrium and left ventricle. You also get features suggestive of pulmonary edema.

Nuclear myocardial perfusion imaging is very sensitive showing decrease uptake in the anterolateral ischemic region. Of note, this is not a specific finding as it has also been seen in cardiomyopathies.

Standard method of diagnosis is with an **echocardiography with doppler color flow** mapping, this replaced cardiac catheterization.

Even if the attachment of the coronary artery to the great artery is uncertain by the two-dimensional imaging, the presence of diastolic flow in the pulmonary artery is informative. Increased echogenicity of the pupillary muscle and adjacent endocardium due to fibrosis and fibroelastosis may be seen.(1)

A study done at a children's hospital with a 25 year experience of treating patients with ALCAPA came up with an ECHO findings suggestive of ALCAPA, of note in 46% of ECHOs done, the anomalous coronary artery was not visualised. However the following seven ECHO findings were described:

- 91% being flow reversal within the left coronary artery.
- 85% identification of collateral coronary artery flow.
- 81% right coronary artery dilation.
- 79% abnormal flow signals within the pulmonary artery
- 74% mitral regurgitation
- 66% left ventricular systolic dysfunction
- 57% left ventricular endocardial fibroelastosis.

The very first ECHO had more than 5 of the above findings in the patients that were studied. Left ventricular dysfunction being the most common by 90% in infants compared to 37% in older children. Instead the older group had lots of collateral formation.(11)

Transesophageal echocardiogram is helpful in cases where transthoracic ECHO cannot help visualise the origin of left coronary artery from the pulmonary trunk.(4)

Shortening fraction, ejection fraction, left ventricular end diastolic dimension, and severity of mitral regurgitation were used to assess ventricular function. All patients had normal ejection fraction and shortening fraction at last follow up(12)

In older patients **Computed tomography scans** have shown high resolution in defining coronary artery anatomy and its origin. Rapid acquisition time is the main advantage of a CT scan. ECG gating of the scans requires a slow heart rate or for the heart rate to be slowed with medication, especially in a young child. There is a lot of radiation exposure with CT scans but it has excellent ability to define coronary artery abnormalities.(1)

Cardiac catheterization and Angiography

Currently the use of cardiac catheterization and angiography is only if the results of non-invasive imaging are uncertain. In the past cardiac catheterization and angiography were used for diagnosis of congenital coronary abnormalities. In symptomatic infants, diagnostic cardiac catheterization shows low cardiac output and high filling pressures and usually pulmonary hypertension to a certain degree. Slight increase in left ventricular end diastolic pressure is all you see in asymptomatic older patients, output and pressures are normal. There may be a left to right shunt at the pulmonary arterial level, but the shunt may be small so its absence does not rule out the diagnosis of ALCAPA. Ventriculography shows the presence and severity of mitral regurgitation, it also shows dilated left ventricle and atrium, with dysfunction of anterolateral left ventricular free wall.

Aortic root angiography shows dilated right coronary artery and if there are large collaterals, it also shows filling of the left coronary artery and passage of contrast from the left coronary artery to the main pulmonary artery. Even though the main pulmonary artery angiography may show reflux of contrast into the origin of the left coronary artery, not this, nor left ventriculography can exclude the diagnosis of ALCAPA reliably.(1)

Dilated, tortuous right coronary artery originating from the right sinus and supplying the left coronary system draining through left coronary artery into posterior part of main pulmonary artery, with a lot of collaterals between the right and left coronary system were seen on Computed tomography coronary angiography.(13)

Sasikumar et al, proved majority of infants (82%) had moderate to severe ventricular dysfunction at presentation, and none had ventricular dysfunction (defined as EF<50%) in the group older than one year. Children older than one year had significant (moderate to severe) mitral regurgitation compared to infants.(14)

Natural history of ALCAPA

Approximately 87% of patients born with this unusual anomaly presents during infancy. Out of these 65% to 85% die before the age of one year due to uncontrollable heart failure, this usually happens after 2 months of age. Few children get better spontaneously. Others might never have symptoms, this could be due to a lot of collaterals and a limiting small opening between the origin of the left coronary artery and the pulmonary trunk. Having said this, these people are still at high risk of sudden death, especially during exercise. Some presents as adults with angina induced by exercise or with heart failure secondary to mitral regurgitation.(1)

Treatment

To establish a dual coronary system with long term patency is the goal of modern surgical management of ALCAPA.(8) The first most effective form of surgical treatment was to prevent the steal phenomenon by ligating the left coronary artery from its origin from the pulmonary artery. A lot of older children benefit from this procedure, especially if they have severe coronary to pulmonary arterial shunting, but late sudden death may still occur. Tying of the origin of the left coronary artery and restoration of blood flow through with a subclavian arterial or saphenous venous graft has been a success, although graft thrombosis and stenosis has occurred before. Late blockage changes in saphenous vein grafts has been seen, which may complicate the patients course because around 3 years

after revascularization, there is a significant reduction in collaterals from the right coronary artery.

For longer survival its better to use grafts from the internal mammary artery , this may be desirable in older children.

The standard approach which has been proven successful in many centres is the direct re-implantation of the origin of the left coronary artery into the aorta (with a button of pulmonary artery around the origin). There is an alternative approach called takeuchi procedure, where an aortopulmonary window is created and then a tunnel fashioned that directs blood from the aorta to the left coronary artery ostium.

Early surgical intervention to establish a two coronary system has been shown to have important outcomes. Significant preoperative mitral insufficiency has been shown to be a risk factor for both mortality and need for late mitral valve surgery, this is because of papillary muscle infarction and dysfunction.(1)

It is not necessary to repair or replace the mitral valve at the time of ALCAPA repair, unless mitral regurgitation remains persistent and depending on the severity, management can be planned for later date.(12)

It’s important to encourage very early surgical correction of ALCAPA before ischemia occurs because this makes ICU management easier should a patient complicate and require ICU, It also helps prevent the complication of mitral regurgitation, But note it does not decrease perioperative risk associated with this major surgery.(11)

Early diagnosis and treatment of ALCAPA is important for faster myocardial recovery.(8)

Complications

- Patients may need respiratory support during surgery, (e,g with ECMO). They may also need ICU management post operation.
- Other complications may be moderate to severe mitral regurgitation with left ventricular dysfunction, this usually improved in the first year of follow up.
- A mitral valve replacement if valve severely damaged.
  In small babies with severe mitral regurgitation it might be better not to touch the mitral valve as repair is very difficult technically.(15)
- Supravalvular pulmonary stenosis, baffle obstruction, baffle leaks and aortic regurgitation may be experienced in patients who had Takeuchi surgery.(16)

Outcomes of ALCAPA

There is excellent short term and midterm outcomes of surgical treatment for ALCAPA patients. Within the first six months post-surgery normal left ventricular function is expected.(17) A close follow up is warranted in patients with persistent mitral regurgitation and a moderate rate of late mitral valve repair.(16) 92% of patients had normal left ventricular function at last follow up, moderate mitral regurgitation seen on 3% of patients and those that required re-intervention were about 17%.(15)

Due to papillary muscle ischemia survivors after infancy have improved left ventricular function but continue to have mitral regurgitation.(7)

In all patients the follow up ECHO showed improved left ventricular ejection fraction and degree of mitral regurgitation was less.(7) ECG is important in long term follow up to look for arrhythmias whilst ECHO looks at left ventricular function and mitral regurgitation.(7)

In majority of patients ALCAPA mitral regurgitation has been shown to improve without concomitant mitral valve repair.(14) After dual coronary repair the overall survival rate was 92%.(8).

4. AIMS AND OBJECTIVES

AIM

To describe the clinical presentation and outcomes of anomalous left coronary artery from the pulmonary artery in paediatric patients presenting at the Department of Paediatric Cardiology, Universitas Hospital from January 1998 to August 2019.

Primary Objectives:

1. Determine the clinical presentation and severity of symptoms using the Ross classification (Appendix 1).
2. Describe the clinical status of the patient at last follow up, including the clinical outcome (Ross classification) and survival.

Secondary Objectives:

3. Determine the age at which patients present with symptoms.
4. Determine the referral diagnosis of the patients.
5. Describe the type of interventions and when it occurred during the study period.

5. Methodology

5.1 Study Design

This will be a retrospective record review and a descriptive study of medical records of patients seen at the Department of Paediatric Cardiology between January 1998 and August 2019.

5.2 Setting

The research project will be conducted in the Department of Paediatric Cardiology at Universitas Academic Hospital in Bloemfontein, South Africa. Patient records from Free State, Northern Cape and Lesotho will be included.

5.3 Population and Sample

A sampling method will not be required in the study,since all medical records that meet the inclusion criteria will be included in the study, no sampling will be done. 30 medical records are expected over the study period.

5.3.1 Inclusion criteria

- Paediatric patient must have presented with diagnosis of ALCAPA between 1 January 1998 and 31 August 2019.
- Children of all ages will be included (18 years or less)

5.3.2 Exclusion Criteria:

- Patients presenting with other coronary anomalies.
- Patients with associated lesions which may influence clinical symptomatology

5.4 MEASUREMENT

5.4.1 DATA Collection

The researched will collect data from the Paediatric Cardiology database system. The first step will be to identify patients with ALCAPA in the database. The patient number of the identified patients will be used to retrieve medical records of the patients. Medical records are kept in the Department of Paediatric Cardiology and will be retrieved with the assistance of the Department's secretary.

A data form (Appendix 2) will be used to collect clinical data from the medical records. The data form will be designed in REDCap® and the REDCap® online database will be used to collect the information electronically. The online database

The researcher will enter the data in the database. The researcher and study leader will have full access to the study records at all times during the data collection period. Patient information will be kept confidential. Any information linking the patient e,g file number

will be removed before sending for data analysis.

5.4.2 Ross classification

It is a standardized tool used to grade the severity of cardiac failure symptoms in children. It encoporates feeding difficulties, growth problems, and symptoms of exercise intolerance into a numeric score. That score is then used to determine how severe heart failure is in a child.

5.5 PILOT STUDY

In order to determine the accuracy and effectiveness of the data collection form, a smaller version of the research study will be conducted. Possible problems and pitfalls in the proposed data collection technique will be identified and changes will be made accordingly. The first 5 medical records identified in the database will be used in the pilot study and if no changes are required, the data will be used in the main study.

5.5.1 Statistical Analysis

Descriptive statistics namely means and standard deviations or medians and percentiles will be calculated for continuous data. Frequencies and percentages will be calculated for categorical data. The statistical analysis will be done by the Department of Biostatistics at the University of free state.

6. IMPLEMENTATION OF THE FINDINGS

The results of the study will be made available to the Head of the Department of Pediatric Cardiology and Cardiothoracic Surgery.

The study results may be used to do a self-audit in these departments, to determine if factors can be identified that will improve patient outcomes e.g. referral pathways (one aspect is the distance travelled by patients).

7. TIME SCHEDULE

Planning, Literature Review and Protocol	June – August 2019
Apply for ethics approval	11 September 2019
Apply for Free State Department of Health approval	Mid-October 2019
Final ethics approval	December 2019
Pilot study	January 2020
Data collection	January 2020
Data Analysis (Biostatistics)	February 2020
Complete final manuscript	March 2020

8. BUDGET

The budget for the study is R1000. Refer to Appendix 3, for the breakdown.The researcher will cover the costs.

9. ETHICS

The protocol will be submitted for ethics approval to the Health Science Research Ethics Committee (HSREC) at the University of the Free State, Health Sciences. This will be done electronically on the RIMS system.

Following conditional ethics approval, the protocol will be submitted to the Free State Department of Health. Once approved, final ethics approval will be obtained.

Permission to access clinical files will be requested from the Head of the Paediatric Cardiology Department.

Since the study will be retrospective using medical records only, no consent will be required. Data collection will commence only after all regulatory approvals have been received.

10. REFERENCES

1. Feltes HDADJDRESTF. Heart disease in infants, Children, and Adolescents [Internet]. seventh. Feltes HDADJDRESTF, editor. Wolters Kluwer/Lippincott Williams & Wilkins; 2008. 702-709 p. Available from: http://www.lww.com

2. Kastellanos S, Aznaouridis K, Vlachopoulos C, Tsiamis E, Tousoulis D. World Journal of Cardiology. 2018;10(10):127–40.

3. Exhibit E. ALCAPA Syndrome : Not Just a Pediatric. 2009;9.

4. Saedi S. The role of echocardiography in anomalous origin of coronary artery from pulmonary artery (ALCAPA): Simple tool for a complex diagnosis. 2019;(November 2018):177–81.

5. Zhang HL, Li SJ, Wang X, Yan J, Hua ZD. Preoperative Evaluation and Midterm Outcomes after the Surgical Correction of Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery in 50 Infants and Children. 2017;130(23).

6. Yolcu M, Bilal MS, Avsar MK, Yildirim O. Case Report A patient with anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA syndrome) and 13 live births. 2019;30(3):3–4.

7. Kamran M, Memon Y, Amanullah M, Ma MA. Anomalous Left Coronary Artery from Pulmonary Artery : An Important Cause of Ischemic Mitral Regurgitation in Children. 2019;11(4):2–8.

8. Birk E, Children S, Katz J, Vidne B. Anomalous origin of the left coronary artery from the pulmonary artery: Diagnosis and postoperative follow up. 2000;(March 2014).

9. Rodriguez- M, Abnormali- K. Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery : 2015;42(4):6–13.

10. Zhang C, Luo Q, Li Y. Predictors of Short-term Outcomes Following Repair of Anomalous Origin of the Left Coronary Artery From the Pulmonary Artery in Chinese Children : A Case-Control Study. 2018;32:2644–51.

11. Patel SG, Frommelt M, Frommelt P, Cramer J. Congenital Heart Disease. J Am Coll

Cardiol [Internet]. American College of Cardiology Foundation; 2016;67(13):969. Available from: http://dx.doi.org/10.1016/S0735-1097(16)30970-6

12. Cabrera AG, Chen DW, Pignatelli RH, Khan MS, Jeewa A, Mery CM, et al. Outcomes of Anomalous Left Coronary Artery From Pulmonary Artery Repair : Beyond Normal Function. Ann Thorac Surg [Internet]. Elsevier; 2015;99(4):1342–7. Available from: http://dx.doi.org/10.1016/j.athoracsur.2014.12.035

13. Miranda WR, Wejner-mik P, Lipiec P, Peruga JZ, Mozdzan M, Kasprzak JD. Transthoracic echocardiographic diagnosis of late-presentation Bland-White-Garland (ALCAPA) syndrome. 2018;2018.

14. Sasikumar D, Dharan BS, Arunakumar P, Gopalakrishnan A. The outcome of mitral regurgitation after the repair of anomalous left coronary artery from the pulmonary artery in infants and older children. 2018;27(March):238–42.

15. Alqathamy H, Elwy A, Ragheb A, Alfaraidi Y, Donato RM Di. Total anomalous pulmonary venous connection repair ; risk factors and outcome Long term results of surgical management of anomalous origin of the left coronary artery from pulmonary artery (ALCAPA) and mitral incompetence Howida Alqathamy , Adel Ragheb , Wael Hussain , Yahia Alfaraidi , Roberto Di Donato Impact of clinical factors on response to clopido- grel therapy in patients with acute coronary syndrome Ibrahim M . Hassan , Amr Hassan Mostafa , Naguib. J SAUDI Hear Assoc [Internet]. King Saud University; 2013;25(2):135. Available from: http://dx.doi.org/10.1016/j.jsha.2013.03.084

16. Follow-up CAL, Naimo PS, Fricke TA, Udekem Y, Cochrane AD, Bullock A, et al. Surgical Intervention for Anomalous Origin of Left Coronary Artery From the Pulmonary Artery in. Ann Thorac Surg [Internet]. The Society of Thoracic Surgeons; 2016;101(5):1842–8. Available from: http://dx.doi.org/10.1016/j.athoracsur.2015.11.020

17. Zhang C, Zhang H, Yan J. Mid-Term Outcome for Anomalous Origin of the Left Coronary Artery From the Pulmonary Artery. Hear Lung Circ [Internet]. Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) and the Cardiac Society of Australia and New Zealand (CSANZ); 2019;86:1–6. Available from: https://doi.org/10.1016/j.hlc.2019.04.018