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CHARACTERISTICS OF TETRALOGY OF FALLOT IN CHILDREN SEEN AT CHRIS HANI BARAGWANATH HOSPITAL OVER LAST TWO DECADES.

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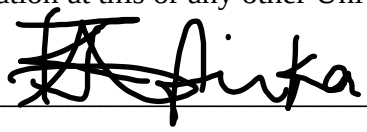
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A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Master of Medicine

Johannesburg 2022

DECLARATION

I, Jesmine Kamogelo Afrika, declare that this Dissertation Report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics, at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed: 

20th day of December 2022 in Klerksdorp

DEDICATION

To my husband James Afrika, our children, Matlhogonolo and Omaatla Jordan “OJ”Afrika, thank you for being the inspiration behind this work and your continued support and encouragement during this challenging and life changing period of my life.

PUBLICATION AND PRESENTATIONS ARISING FROM THE DISSERTATION

None

LIST OF ABBREVIATIONS

ASD	Atrial septal defect
AV	Aortic valve
AVSD	Atrioventricular septal defect
BVH	Biventricular hypertrophy
CA	Coronary artery
CAA	Coronary artery anomalies
CATCH	Cardiac anomalies, Abnormal facies, Thymic aplasia, Cleft palate, Hypocalcaemia
CDH	Congenital heart disease
CHARGE	Coloboma, Heart defects, Atresia of choanae, Retardation of growth, Genital abnormalities, Ear anomalies
CHBAH	Chris Hani Baragwanath Academic Hospital
CT	Computerized tomography
ECG	Electrocardiogram
ECHO	Echocardiogram
ECMO	Extracorporeal membrane oxygenation
FISH	Fluorescence in situ hybridization
IQR	Interquartile range
LAA	Left-sided aortic arch
LAD	Left anterior descending coronary artery
LBTS	Left “classical” Blalock-Taussig Shunt
LCA	Left coronary artery

LMBTS	Left modified Blalock-Taussig Shunt
LPA	Left pulmonary artery
MAPCAs	Major aorto-pulmonary collateral arteries
MRI	Magnetic Resonance Imaging
MRSA	*Methicillin Resistant Staphylococcus aureus*
PA	Pulmonary atresia
PLSVC	Persistent left superior vena cava
PO2	Partial pressure of oxygen
PV	Pulmonary valve
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale
PVR	Pulmonary valve regurgitation
PS	Pulmonary stenosis
QF-PCR	Quantitative fluorescent polymerase chain reaction
RAA	Right-sided aortic arch
RAD	Right axis deviation
RBBB	Right bundle brunch block
RBTS	Right “classical” Blalock-Taussig Shunt
RCA	Right coronary artery
RMBTS	Right modified Blalock-Taussig Shunt
RVH	Right ventricular hypertrophy
RVOT	Right ventricular outflow tract
RVOTO	Right ventricular outflow tract obstruction
TAP	Transannular patch

TOF	Tetralogy of Fallot
VSD	Ventricular septal defect
VACTERL	Vertebral anomalies, Anal atresia, Cardiovascular anomalies, Tracheoesophageal fistula, Oesophageal atresia, Renal and/or radial anomalies, Limb defects

ABSTRACT

Background: Tetralogy of Fallot (TOF) is one of the most common cyanotic congenital heart defects seen in children. There is limited data on the characteristics of TOF in African children.

Objective: To determine the clinical features, investigation findings, surgical interventions and outcomes of children with TOF in a South African tertiary care setting over a period of 20 years.

Methods: A retrospective, descriptive analysis was done on patients with TOF at the Chris Hani Baragwanath Academic Hospital (CHBAH), who had surgery between June 1998 and June 2018.

Results: One hundred, seventy-nine patients were included in the analysis. The median age of diagnosis was 13 months (IQR, 2.7 - 44.8 months). Hypercyanotic spells were documented in 90/179 (50.3%) patients. The most common associated genetic syndrome was 22q11 microdeletion (16/45; 8.9%). Associated cardiac anomalies included patent ductus arteriosus (4.5%), patent foramen ovale (11.2%), true atrial septal defect (5.6%) and atrioventricular septal defects (1.1%). Normal coronary artery variations were comprised of conus or infundibular arteries arising from the RCA which were mostly small (42/179; 23.4%), with fewer large vessels (6/179; 3.6%). Anomalous coronary arteries included a single coronary artery origin (7/179; 3.9%) and large LAD arising from the RCA and crossing the RVOT (2/179; 1.1%). A left-sided aortic arch (LAA) was diagnosed in 135/179 (75.4%) patients and a right-sided aortic arch (RAA) in 44/179 (24.6%) patients. Systemic-to-pulmonary shunts were performed in 19/179 (10.6%) patients, while 160/179 (89%) patients had corrective surgery. Severe pulmonary regurgitation was seen in 27/51 (52.9%) patients who had a transannular patch repair, with 18/27 (66.7%) subsequently having a pulmonary valve replacement.

Conclusion: This study shows that the characteristics of TOF in children in our centre are similar to those in other centres inside and outside of Africa.

ACKNOWLEDGEMENTS

I would like to extend my gratitude to my supervisors who have pushed me in the right direction from beginning to end with this research. Their constant support is highly appreciated and will forever be valued.

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BODY OF THE DISSERTATION

INTRODUCTION

Epidemiology of Tetralogy of Fallot

Tetralogy of Fallot (TOF) is one of the most common cyanotic congenital heart defects seen in children beyond the period of infancy, with an incidence of 0,34 in 1000 live births, affecting both males and females equally [1, 2, 3]. The defect comprises 8 to 10% of all cyanotic heart lesions [3, 4, 5, 6].

Clinical composition, aetiology and genetic associations

The description of TOF includes a combination of four cardiac malformations namely; i) right ventricular outflow tract obstruction (RVOTO), ii) large non-restrictive ventricular septal defect (VSD), iii) right ventricular hypertrophy (RVH) which is a result of the RVOTO, and iv) an overriding aorta [2, 3, 5, 7, 8, 9, 10, 11].

The aetiology of TOF is multifactorial and has been associated with environmental and genetic factors [3, 4, 11]. Other reported associations include untreated maternal diabetes, phenylketonuria and retinoic acid intake [1, 5, 11, 12]. The defect may occur in isolation or in association with other non-cardiac malformations and syndromes [3]. A common associated syndrome in 10 to 15% of TOF patients, is the 22q11 microdeletion or velocardiofacial syndrome [4, 5, 12, 13, 14]. TOF has also been diagnosed in patients with Trisomy 13, 18 and in 7% of patients with trisomy 21 [4, 5, 7, 11, 12, 15]. Other associations include Alagille syndrome and the VACTERL association [11, 16].

Clinical presentation and cardiac associations

The clinical presentation of TOF is largely dependent on the degree of the RVOTO [1, 17,18,19]. The RVOTO characteristically involves the subvalvar or infundibular area in all classical TOF cases [3, 5, 7, 9, 12]. Other levels of stenosis in combination with a VSD and aortic override includes the pulmonary valve (10%), a combination of the two; infundibular and valvar (30%), supravalvar and also the peripheral branch arteries [3, 5, 7, 9, 12]. RVH is a consequence of the RVOTO [9, 12, 20].

Patients with TOF with mild RVOTO, where there is little or no right to left shunting and are not clinically cyanosed are classified as "acyanotic TOFs" and those with more severe RVOTO, associated with cyanosis are classified as "classic TOFs" [5, 12, 20, 21, 22]. Patients with severe RVOTO usually present in the neonatal period or early in life, while those with mild RVOTO present much later [12, 20].

TOF can be associated with an ASD, which is called a pentalogy of Fallot [12]. Other cardiac associations include a PFO, a right-sided aortic arch (RAA) seen in 20-25% of the patients, persistent left superior vena cava (PLSVC), atrioventricular septal defect (AVSD) and major aorto-pulmonary collateral arteries (MAPCAs) [3, 5, 9, 12, 23, 24]. An anomalous origin and course of the coronary arteries may be seen in 4-6 % of TOF patients compared to < 1% in the general population [3, 5, 23, 24]. Only those anomalies in which a vessel crosses the RVOTO are clinically important. If damaged during surgery, this may result in myocardial infarction [3, 5, 12 23, 24]. Of concern is the presence of a large coronary vessel crossing the RVOT which would prevent a transannular patch augmentation of the RVOT. Other surgical techniques may be required to avoid the abnormal coronary vessel [3, 5, 23, 24].

The most important coronary anomaly is the left anterior descending (LAD) artery arising from the right coronary artery (RCA) or arising from the right sinus of Valsalva that crosses over the RVOT [3, 5]. Large conus or infundibular branches which provide blood supply to the RVOT are

also surgically relevant and can be the same size or bigger than the RCA [3, 5, 23]. The conus artery is the first anterior branch of the RCA, but may arise as a separate vessel or from the right sinus of Valsalva. A small conus artery which is regarded as a normal variation rather than a coronary artery anomaly, can be confused with an anomalous LAD artery [3, 5, 23, 24]. It can supply more than the RVOT and in some instances has been described to extend to the cardiac apex [25].

Hypercyanotic spells

A classical clinical feature of TOF is hypercyanotic spells which may be associated with worsening cyanosis and metabolic acidosis [5, 12, 20, 23, 26]. These episodes begin during infancy or in the toddler age group and are usually precipitated by dehydration or agitation [12]. The physiology of a hypercyanotic episode is caused by an imbalance in the pulmonary-to-systemic blood flow [12]. A drop in systemic vascular resistance (sepsis, fever) play important role in pathophysiology of hypercyanotic spells. A decrease in the arterial PO2 stimulates the respiratory centre and hyperventilation results. The resultant hyperpnea then increases the systemic venous return [12]. In the presence of a fixed right ventricular outflow tract obstruction (RVOTO), the increased systemic venous return results in increased right-to-left shunting and worsening cyanosis [9]. Patients instinctively alter their physiology by squatting [7, 20, 26]. This results in an increase in systemic vascular resistance with an increase in left to right shunting and subsequently an increase in pulmonary blood flow [5, 7, 26].

Medical measures to treat hypercyanotic spells include administration of oxygen, improved hydration, morphine, propranolol, sodium bicarbonate and phenylephrine which results in improvement of pulmonary blood flow and or an increase in the systemic vascular resistance [19, 20].

Diagnosis of TOF

Various clinical and radiological modalities are used to make the diagnosis of TOF. Central cyanosis and digital clubbing associated with an ejection systolic murmur caused by the RVOTO may suggest the diagnosis [3, 4, 5, 11]. A classical 'boot-shaped heart" may be seen on chest radiograph, with the heart size being normal or smaller than normal, with reduced pulmonary vascular markings [9, 20, 23]. The Electrocardiogram (ECG) commonly shows a right axis deviation (RAD) (+120 to +150 degrees) in cyanotic TOFs. The QRS axis can be normal in patients with acyanotic TOF [9, 23, 27]. Features of RVH evidenced by tall R waves in the anterior precordial leads and deep S waves in the lateral leads are common features [9, 23, 27].

Echocardiography (Echo) is the mainstay of diagnosis in patients with TOF [4, 5, 7, 12, 18, 20, 23, 24]. Other imaging modalities such as Computerized tomography (CT) and magnetic resonance imaging (MRI) may also be utilised to confirm the diagnosis [4, 12, 24]. Cardiac catheterisation may be used to define anatomy in more complex cases, to outline coronary anatomy, to assess for collateral vessels and to obtain intra-cardiac pressure measurements [3, 12, 20, 28].

Surgical intervention

Surgical correction is essential for survival and if left untreated, TOF is associated with a mortality rate of 35% in the first year of life and 50% in the next 3 years of life [29]. The goal of the surgical treatment is total correction [9, 20, 30]. Complete or total correction may be either valve-sparing or non-valve sparing [9, 20, 30]. Valve sparing surgery is done if the pulmonary valve is of adequate size and involves patch closure of the ventricular septal defect and widening of the RVOT with a patch following division and/or resection of the infundibular tissue [9, 20, 30]. If the pulmonary valve is hypoplastic, transection of the valve is done and a transannular patch is placed [9, 20, 30, 31, 32].

Palliative surgery which is a temporary measure, involves the placement of a systemic-to-pulmonary artery shunt to provide additional blood supply to the pulmonary circulation [9, 30]. The design of aorto-pulmonary shunts has changed over time and some designs are no longer used [9, 12, 20]. The older Waterston shunt which is a connection from the ascending aorta to the left pulmonary artery and the Potts shunt which is a connection from the descending aorta to the right pulmonary artery, have lost favour due to their potential to distort the branch pulmonary arteries or cause overshunting [9, 12, 20]. The classical Blalock-Taussig Shunt (BTS) devised by Alfred Blalock, Helen Taussig and Vivian Thomas in the 1950s, in which the subclavian artery is harvested and sutured to a branch pulmonary artery is also no longer used [9, 12, 20]. The modified BTS, which entails the placement of a Gore-Tex interposition graft between the subclavian artery or the innominate artery and ipsilateral pulmonary artery (PA) is the preferred surgical palliative procedure in the modern era [9, 12, 19, 20, 21, 22, 33]. Other modifications include a central shunt, which entails the placement of a short conduit between the ascending aorta and the main pulmonary artery [12, 20]. A central shunt may be the preferred option in infants with hypoplastic pulmonary arteries to allow them to grow [12, 20]. A BTS may also be the surgery of choice in patients with an abnormal coronary crossing the right ventricular outflow tract that would preclude a right ventricular outflow incision [9, 12, 20].

Outcome

The long-term outcome of surgically corrected TOF is generally good, however the surgery is not without complications. Pulmonary valve regurgitation (PVR) is one of the most frequent complications after total surgical repair of TOF [4, 31, 34]. This complication is mainly seen in patients who have had a transannular patch for a hypoplastic main pulmonary artery [4, 10, 18, 19, 31, 32, 34, 35]. Most patients who have had a transannular patch resulting in pulmonary valve

regurgitation will require a pulmonary valve replacement at a later stage either surgically or percutaneously [12, 20].

Other long-term complications include right bundle branch block (RBBB), and rarely complete heart block or ventricular arrhythmias, which may result in sudden death [12, 20]. Ventricular arrhythmias may occur as a result of ventricular dilatation caused by pulmonary valve regurgitation and can resolve after pulmonary valve replacement [9, 20]. Recalcitrant arrhythmias may require ablation or an implantable defibrillator [12, 20].

If left uncorrected, the chronic hypoxia caused by the RVOTO may have an impact on the patient's quality of life, growth and neurodevelopment [9, 20]. Death in uncorrected patients may then be caused by cardiac failure, arrhythmia, respiratory infection, or thromboembolic disease [9, 20]. Late corrections in older children, adolescents and adult patients are often undertaken in low income countries because of late presentation or lack of access to medical care [9, 20].

Motivation for the study

The study was undertaken at the Chris Hani Baragwanath Academic Hospital (CHBAH) which is a large tertiary health care centre situated in Southern Africa close to SOWETO. It offers Paediatric Cardiac services to indigent children from a large catchment area which includes SOWETO, most of Southern and Eastern Gauteng, and North West Province. Currently there is a paucity of literature describing the characteristics of African children with TOF. The large number of patients presenting to the hospital provide a unique opportunity to study the characteristics of patients with TOF in Southern African children.

The aim of the study is to determine the demographics, clinical presentation, electrocardiographic changes, anatomical characteristics, surgical interventions and outcomes in children with a diagnosis of TOF who underwent surgery in a Southern African Tertiary care

setting over a period of two decades and compare them to other centres, both in African and other countries.

MATERIALS AND METHODS

Study Design

A retrospective, descriptive study was done on all patients diagnosed with TOF, who had undergone surgery. The selection of patients to be included in the final analysis was done on patients who had undergone surgery, because they were expected to have complete records for analysis. Patients were identified using the electronic paediatric cardiology database. Data was sourced from the database as well as paper based clinical records.

Data collected included gender and age at the time of diagnosis and surgery, types of surgical interventions, documentation of hypercyanotic spells, associated genetic syndromes and post-surgical outcomes. Echocardiographic and cardiac catheterization reports were used to assess associated cardiac defects, the side of aortic arch and coronary artery anomalies.

Electrocardiography (ECG) definitions

Right axis deviation (RAD) was defined as the presence of a QRS axis greater than the lower limit for age, usually between +90 degrees and +180 degrees.

Right ventricular hypertrophy (RVH) was defined as: R wave in leads V1 and S waves which exceed the normal ranges for age, the presence of a Q wave in V1 and a T wave vector out of keeping for the patients age [9].

Electrocardiograms comprising 12 standard unipolar leads were individually analysed by the main study investigator using age specific criteria.

Statistical Analysis

All data was entered into an EXCEL spreadsheet and then imported into STATA version 14 for statistical analysis. Frequencies and percentages of characteristics such as gender, age of diagnosis, age at time of surgery, hypercyanotic spells and ECG changes were calculated and tabulated. Frequencies and percentages of anatomical variations were depicted using pie charts. Means and standard deviations were used for normally distributed data, and medians with IQRs were used for skewed data. The quantitative data including age at diagnosis, time of surgery and QRS axes were tabulated.

Ethical considerations

Ethical clearance was granted by the University of Witwatersrand Human Research Ethics Committee to conduct the study.

RESULTS/FINDINGS

Analysis was done on 179 patients with TOF who had surgery between June 1998 and June 2018, with complete data. Some ECGs were not available, and some were excluded because of poor quality. Consequently only 145 ECGs were included for analysis.

Demographic profile

There were more females (105/179; 58.7 %) than males (74/179; 41.3%), with a female to male ratio of 1.4:1. **(Table 1.1)**

Table 1.1 TOF and gender characteristics of patients

Sex	Frequency (n=179)	Percentage (%)
Female	105/179	58.7 %
Male	74/179	41.3%

Surgery

The median age of diagnosis was 13 months (IQR, 2.7 - 44.8 months). The mean age at the time of total corrective surgery was 50.2 +/- 44.5months. **(Table1.2)**

Table 1.2 Age at diagnosis and at surgery of TOF

	Age of diagnosis in months	Age of total corrective surgery in months
Mean	-	50.2
Standard deviation	-	44.5
Median age in months (IQR)	13.0 (2.7-44.8)	35.2 (18.3-67)

Hypercyanotic Spells

Hypercyanotic spells were documented in 90/179 (50.3%) patients. **(Table 2.1)**

Table 2.1 Hypercyanotic spell in patients with TOF

Hypercyanotic spells	Frequency (n=179)	Percent (%)
No	31/179	17.3%
Yes	90/179	50.3%
Not documented	58/179	32.4%

Genetic associations

The genetic analysis was incomplete as not all patients were tested. Of the 45 patients that were phenotypically microdeletion 22q11 syndrome (CATCH 22), 16/45 (35.6%) cases were confirmed using FISH (Fluorescence in situ hybridization) analysis. Trisomy 21 was confirmed in 9/179 (5.0%) patients on chromosomal analysis. One (1/179; 0.6%) patient had a 20p12 deletion. One patient (1/179; 0.6%) with Noonan's syndrome and one (1/179; 0.6%) with CHARGE syndrome were diagnosed clinically.

Seven patients with Trisomy 21 (7/9, 77.8%) had the classical form of tetralogy of Fallot comprising aortic override, PS, VSD and RVH. The remaining two (2/9, 22.2%) patients had an atrioventricular septal defect (AVSD) associated with infundibular stenosis.

Electrocardiographic characteristics in patients with TOF

A total of 145/179 (81.0%) ECGs were available for analysis. One hundred and thirty-two (132/179; 73.7%) ECGs were done pre-operatively and 13/179 (7.3%) were done post-operatively. RAD and RVH was present in 118/132 (89.3%) of pre-operative patients, a normal QRS axis with RVH was present in 12/145 (8.3%) and 2/145 (1.4%) patients had a left axis deviation (LAD) with RVH. The latter two patients had an associated AVSD. The mean QRS axis was rightward, 97.7 degrees (SD +/- 64.6 degrees, range, 150-180 degrees).

Thirteen out of one hundred and forty-five (13/145; 9.0%) ECGs were obtained in the post-operative period and showed a right bundle branch block with normal QRS axis in all. **(Table 3.1)**

Table 3.1 Electrocardiographic abnormalities seen in the patients with TOF

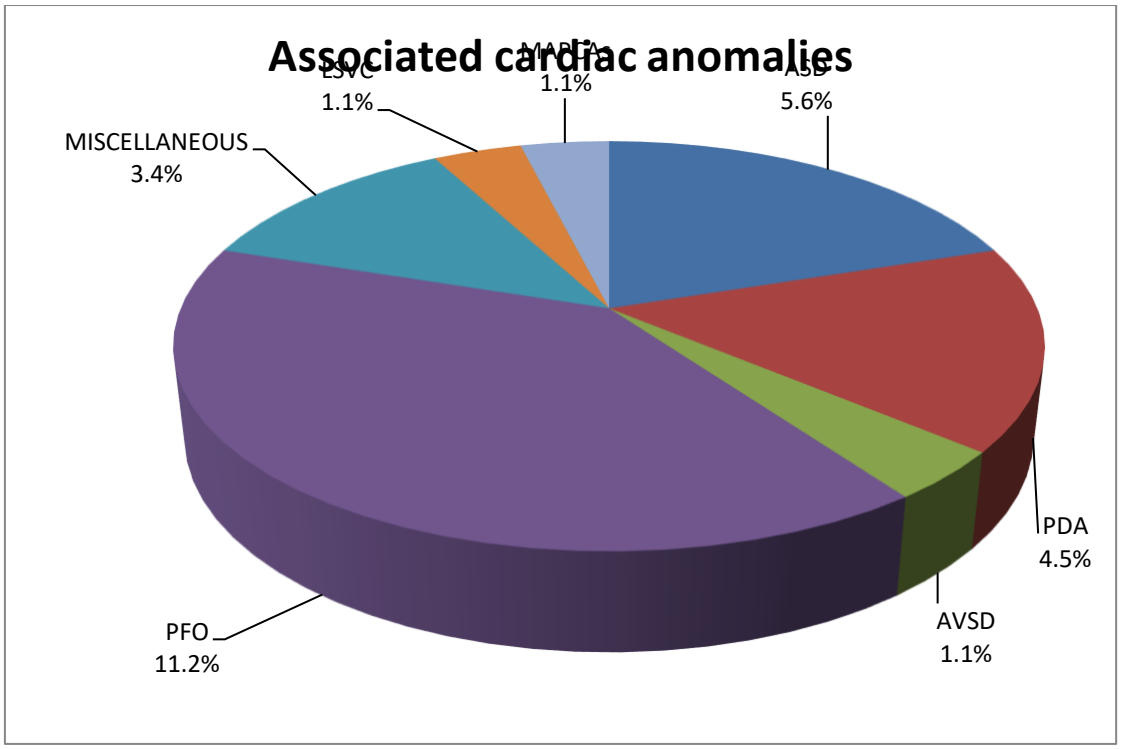
ECG changes	Frequency (n=145)	Percentage (%)
Normal axis/ RVH	12/145	8.3%
LAD/ RVH	2/145	1.4%
RAD/ RVH	118/145	81.3%
RBBB (post op ECGs)	13/13	100%

Abbreviations: ECG-electrocardiogram, RVH-right ventricular hypertrophy, RBBB-right bundle branch block, RAD-right axis deviation, LAD-left axis deviation

Aortic arch sidedness and associated cardiac anomalies

A left-sided aortic arch was more common (135/179, 75.4%) than a right-sided aortic arch (44/179, 24.6%). A PFO was present in 20/179 (11.2%) patients and was the most common cardiac association. True ASDs were found in 10/179 (5.6%) patients, PDAs in 8/179 (4.5%) patients, while AVSDs, a LSVC and MAPCAs in 2/179 (1.1%) patients each and miscellaneous (anomalous right subclavian artery, bicuspid aortic valve, bicuspid pulmonary valve, dysplastic pulmonary valve, retro-aortic innominate vein and tricuspid valve chordae prolapse) with 1 patient each (6/179; 3.4%). **(Figure 1.1)**

Figure 1.1 Tetralogy of Fallot and associated cardiac anomalies



Abbreviations: ASD-atrial septal defect, PDA-patent ductus arteriosus, AVSD-atrioventricular septal defect, PFO-patent foramen ovale, Miscellaneous (anomalous right subclavian artery, bicuspid aortic valve, bicuspid pulmonary valve, dysplastic pulmonary valve, retro-aortic innominate vein and tricuspid valve chordae prolapse), LSVC-left superior vena cava, MAPCAs-major aortopulmonary collateral arteries.

Coronary artery anomalies

Coronary artery variations were diagnosed angiographically in 57/179 (31.8%) patients. The most common coronary artery variant was a small conus branch arising from the RCA in 42/179 (23.4%) patients and a large conus branch arising from RCA in 6/179 (3.6%) patients, both of which are normal coronary artery variants found in TOF. Anomalous coronary arteries found included a single CA origin with no vessel crossing the RVOT in 7/179 (3.9%) patients and large LADs arising from RCA and crossing the RVOT in 2/179 (1.1%) patients. Surgical approach was only affected in the latter 2 patients. **(Table 4.1)**

Table 4.1 TOF and associated coronary abnormalities and variations

Coronary variations	Frequency (n=179)	Percent (%)
Small conus branch arising from RCA (normal variant)	42/179	23.4%
Large conus branch arising from RCA (normal variant)	6/179	3.4%
Single CA	7/179	3.9%
Large LADs arising from RCA and crossing RVOT	2/179	1.1%
Total	57/179	31.8%

Right ventricular outflow obstruction (RVOTO)

Angiographic reports were utilised to assess the levels of RVOTO in the study cohort. The most common and characteristic level of obstruction was at the infundibulum (subvalvar) occurring in 179/179 (100%) consistent with the original anatomical description of TOF. The majority of patients had multilevel RVOT stenosis 107/179 (59.8%), with a minority 72/179 (40.2%) having infundibular stenosis only.

The group of patients with multilevel RVOT stenosis had combinations of subvalvar and valvar stenosis in 66/107 (61.7%), subvalvar and supravalvar stenosis in 15/107 (14.0%) patients and subvalvar, valvar with supravalvar stenosis in 26/107 (24.3%) patients.

Surgical interventions and their outcomes

Palliative shunts were done in 19/179 (10.6%) patients (16 Blalock-Taussig shunts (BTS), 3 central shunts) and total corrective surgery in 160/179 (89.4%) patients as a first operation. Twelve of the nineteen (12/19; 63.2%) patients who initially had a BTS went on to have total corrective surgery at a later stage. These were designated as a two-staged surgical approach. One out of the nineteen 1/19 (5.3%) patients in the palliative group was subsequently deemed not to have suitable anatomy for corrective intracardiac repair (Trisomy 21 with AVSD and single atrioventricular valve).

Six out of nineteen (6/19; 31.6%) patients who had undergone palliative surgery were still awaiting corrective surgery by the time data analysis was done.

Surgeries done in the palliative group included 16/19 (84.2%) who had modified Blalock-Taussig shunts; 8/19 (41.2%) who had right-sided shunts to the right pulmonary artery and 8/19 (41.2%) had left-sided Blalock-Taussig shunts to the left pulmonary artery. Three out of the

nineteen (3/19; 15.8%) patients had central shunts from the aorta to main pulmonary artery for small pulmonary arteries measuring 2 mm.

One-staged total corrective surgery was undertaken in 160/179 (89.4%) patients. The majority of these operations, 117/160 (73.1%), were performed within the second decade of the study period. Approximately half (82/160, 51.3%) of the patients had valve sparing surgery, 5 of whom had pulmonary valvotomies, 76/160 (47.5%) patients had transannular patch interventions and 2/160 (1.3%) patients had a Rastelli procedure using a contegra graft as a primary operation because of coronary anomalies that prohibited a surgical incision in the RVOT.

Complications

The most common complication post corrective surgery was pulmonary valve regurgitation in 51/160 (31.9%) patients following transannular patch repairs. Severity grading of the pulmonary regurgitation was mild (10/51; 19.6%), moderate (14/51; 27.5%); severe (27/51; 52.9%) in this group of patients. Six patients (6/160; 3.8%) developed heart block post-surgery. One patient, with 3rd degree heart block immediately post-surgery required a permanent pacemaker. The other five patients presented with a variety of heart blocks more than 6 months post-surgery. Two patients developed 1st degree heart block, two progressed to 3rd degree heart block requiring permanent epicardial pacemakers, and one patient developed a bifascicular block 3 years after surgery that required a transvenous permanent pacemaker.

Seven patients (7/160; 4.4%) developed infective endocarditis with vegetations in the RVOT more than two months post-surgery. Two patients had positive blood cultures that yielded *Klebsiella pneumoniae* in one and *Staphylococcus aureus* in the other patient. The other 5/7 (71.4%) patients had negative blood cultures.

One patient developed cerebral palsy following a successful resuscitation during surgery.

Re-intervention post corrective surgery was undertaken in 20/160 (12.5%) patients, mainly in the form of pulmonary valve replacements. The mean age of pulmonary valve replacements done for severe pulmonary valve regurgitation in 18/160 (11.3%) patients was 161 months (13.4years) with a standard deviation of 29 months (2.4years). The other 9/27 (33.3%) patients with severe pulmonary valve regurgitation were awaiting pulmonary valve replacement by the time the study was conducted.

Other re-interventions included an aortic valve replacement for a dysfunctional stenotic bicuspid aortic valve one year after the original TOF surgery and placement of a left pulmonary artery stent 2 years after the original surgery to relieve a left pulmonary artery stenosis.

Mortality

Nine out of one hundred and seventy-nine (9/179; 5.0%) patients died post-surgery, 3/9 (33.3%) patients from the two-staged corrective surgery group and 6/9 (66.7%) following one stage corrective surgery. There was a case fatality rate of 5.0% **(Table 5.1)**

Peri-operative deaths occurred in 7/9 (77.8%) and 2/9 (22.2%) were post-operative deaths. The most common cause of peri-operative death was sepsis, which was seen in 3/9 (33.0%) patients. Other causes of death documented included a ventricular arrhythmia in one patient, and ECMO-related complications in another patient. The cause of death was not documented in four patients.

Table 5.1 Cumulative frequency and percentages of postoperative complications post palliative and total corrective surgery

Post op complications		Frequency (n=65)	Percent (%)
Mortality (n=9)	**Palliative surgery (two-staged surgery)**	3/9	33.3%
	Total corrective surgery	(1/3)	(33.3%)
		6/9	66.7%
Morbidity (n=65)	Pulmonary valve regurgitation	51/160	31.9%
	Vegetations (Infective Endocarditis: post-surgery)	7/160	4.4%
	Heart block	6/160	3.8%
	Cardiac arrest (intra-op)	1/160	0.6%
	Total	**65/160**	**40.7%**

DISCUSSION

In our cohort, TOF was associated with a female predominance, which is similar to a study that was done in the Middle East (Egypt and Saudi Arabia) by Alassal et al [15], but contrary to studies from Bangladesh, Iran and Nigeria and Philadelphia, where a male predominance was observed [1, 2, 14, 36].

The median age at diagnosis of TOF was 13 months (1.1years), with an IQR of 2.7months to 44.8 months (3.6years). A similar later age of presentation with a mean of 51.6 months (4.3 years) was documented by Animasahun et al. from Nigeria [36]. The late presentation in our study may reflect a lack of awareness of congenital heart disease and their signs by caregivers and medical professionals from our referral centres. Contrary to this, the mean age of presentation in the western world is much earlier because of available resources for early diagnosis such as foetal Echo [14,37].

Hypercyanotic spells where patients exhibit episodes of increased cyanosis was documented in half (50%) of the study cohort. This may not be a true reflection of the frequency but may be due to lack of recognition of hypercyanotic episodes by caregivers. In a study done by Kabir J et al in Bangladesh, 42% of their patients had hypercyanotic spells which is similar to our study [1].

Not all of the study patients were tested for genetic abnormalities which is a limiting factor in our ability to compare genetic abnormality prevalence with other centres. The 22q11 microdeletion (CATCH 22) syndrome, which is one of the most common genetic abnormalities associated with TOF, has been documented in 10-20% of patients with TOF [13, 14]. The 22q11 microdeletion syndrome was the most common genetic abnormality in our study cohort with 16/45 of the patients having confirmed positive FISH results. The second most common syndrome reported was Trisomy 21 confirmed in 5% (9/179) of the patients. In contrast, a study done in Algeria found Trisomy 21 present in 3.6% of the patients [38]. All patients in both our

study and the Algerian study were diagnosed clinically and confirmed on chromosome analysis [38].

A right-sided aortic arch commonly seen in TOF is a clinically insignificant anatomical variation where the aortic arch crosses over the right main bronchus instead of the left main bronchus, this was documented in 44/179 (25%) of the study patients. This was similar to a study done in Egypt where the majority of their patients 147/183 (80.3%) had a left-sided aortic arch. The remaining patients had a right-sided aortic arch [39].

Coronary artery anomalies (CAA) have been reported in 2% to 14% of cases in patients with TOF according to angiographic, surgical and autopsy series and their presence is vital in planning surgery in patients with TOF [6]. The identification of an abnormal coronary vessel crossing the RVOT is important as this will determine the kind of surgical approach used. An RVOT conduit as opposed to a transannular patch to avoid the abnormal vessel may be the preferred strategy. If this abnormal coronary vessel crossing the RVOT is injured it may result in myocardial ischaemia [6].

A conus or infundibular coronary vessel was the most common coronary artery (CA) variant seen in the study population in 42/179 (23.4%) patients. Although these vessels encroach on the RVOT, most were small and did not affect the surgical approach. The surgical repair was only affected in 2/179 (1.1%) patients in our study where the LAD arose from the RCA and crossed the RVOT. A Rastelli procedure, whereby a conduit was placed from the right ventricle to the pulmonary artery in the form of a bridge over the aberrant vessel was done in these two patients. Other coronary artery variants that were found in the study population but did not affect surgery were, a single CA origin crossing the RVOT and large conus branch arising from RCA. Neither of these 2 variants affected the surgical approach.

In contrast, a study from Bangladesh documented coronary anomalies that included a LAD originating from the RCA and crossing the RVOT in 2/52 (3.8%), a single ostium coronary

artery, in 2/52 (3.8 %) patients and an RCA arising from posterior sinus in 2/52 (3.8%) patients [1, 3].

In addition, a study conducted by Ajaja and colleagues in Morrocco found that 9/90 (10%) patients had coronary anomalies [6]. These included 3/9 (33%) patients with an anomalous origin of the LAD from RCA, 1/9 (11%) patient with an anomalous origin of RCA from the left coronary origin and a large infundibular branch crossing the pulmonary infundibulum in 5/9 (56%) patients. All patients had complete surgical repair and none of the coronary anomalies affected the type of surgery [6].

Most of the 19 study patients who had palliative surgery had modified BTS performed. The majority of the shunts (80.0%) were done during the first decade of the study period. Three patients had central shunts from the ascending aorta to the MPA done for small pulmonary arteries.

Of the 19 patients that had palliative shunts done before total corrective surgery, 12 were done before 6 months of age after the neonatal period and 2 done within the neonatal period. This finding is similar to a study done between 1995 and 2006 involving 208 patients by L. Mercer-Rosa and colleagues from Philadelphia where 22 (10.6%) patients underwent initial palliative shunts, of which 15 were done within the first 6 months of life and 7 during the neonatal period [14]. These findings are consistent with the choice of palliation of young symptomatic children with TOF in an era where surgical treatment was limited by the available technology at the time.

Total corrective surgery is the target treatment for TOF and offers good long-term survival [14]. The mean age at corrective surgery in 160 of the study patients (160/179; 89.4%) was 50.2 months (4.2years). Those having valve-sparing surgery (82/160; 51.3%) had a mean age of 73 months (6.1 years), while those who had a transannular patch (76/160, 47.5%) were younger and had a mean age of 34 months (2.8years). The 2 patients who had a Rastelli procedure, were

7 and 9 years old. Most patients in a study from Philadelphia had a transannular patch done 73/120 (60.8%) at a far younger mean age of 5 months [14].

These findings suggest that younger patients and particularly those with a hypoplastic pulmonary valve, are more likely to have a transannular patch procedure. Corrective surgery at an early age is likely to be associated with a prolonged hospital stay and increased rate of re-intervention in the form of pulmonary valve replacement after a TAP (transannular patch) repair at a later stage.

Corrective surgery was mostly performed in the second decade of the study period (105/160, 65.6%), which is reflective of the advances in surgical techniques and post-operative care in the paediatric population over the last few decades. A similar trend was noted in a study by Animasahun BA et al in Nigeria [36].

Better post-surgical outcomes were seen in patients that had one-stage total corrective surgery in our cohort as compared to patients that had two-staged corrective surgical repair. Pulmonary valve regurgitation was the most common post-operative complication followed by heart block, infective endocarditis, cardiac arrest, sepsis and death. There were a total of 9 deaths with a case fatality rate of 5.0% in our cohort. In comparison, a study done in Bangladesh by Kabir et al showed that the most common post-surgical complications were RV failure, VSD patch leakage, pulmonary valve regurgitation (moderate to severe), septicaemia and death [1]. There were a total of 12 (21.1%) deaths in this study with a case fatality rate of 23%. Nine of the patients died shortly after their centre was opened. This suggests that a learning curve was in progress.

The main long-term complication of TOF repair following a transannular patch is pulmonary valve regurgitation with most patients needing a pulmonary valve replacement in the future [31, 40]. Fifty-one study patients (51/160, 31.9%) developed pulmonary regurgitation of which 27/51 (52.9%) were severe, following a transannular patch. Eighteen out of the 27 patients (66.7%)

with severe pulmonary regurgitation went on to have a surgical pulmonary valve replacement. The remaining patients were awaiting the pulmonary valve replacement at the time of the study analysis. In contrast, a study done by Kay Woon Ho et al from Singapore showed a much higher percentage (80%) of patients who had transannular patch developing pulmonary valve regurgitation [35].

Current evidence supports early corrective TOF repair which is associated with fewer long-term complications [26, 34]. Most patients in the study cohort had corrective surgery at a later age, between 2 and 6 years of age, mostly because they presented beyond the neonatal period. The age of full correction in the western world is much earlier at 3-6 months of age as shown by Agarwala et al. from Chicago [31]. The later surgical repair shown in this study and other studies from the African continent are due to various factors including the lack of fetal echocardiography to allow for prenatal diagnosis and the lack of awareness by both caregivers and healthcare workers resulting in later presentation [31]. Poor socioeconomic conditions are also a major contributor to patients not being able to access medical facilities particularly if they come from remote rural areas.

Cunningham et al [41] found that early primary repair can be safely performed without increased morbidity or an increase in hospital resource utilization in a study in Washington [41]. They also showed that elective repair in patients older than 2 months of age, irrespective of patient size can be safely performed without any increase in re-intervention rates e.g. in a form of pulmonary valve replacements [41].

CONCLUSION

Our study shows that the anatomic variations of TOF, clinical characteristics, type of surgical intervention and their long-term complications are similar to those in other centres both inside and outside of Africa, despite later presentation and later surgical intervention.

STUDY LIMITATIONS

The retrospective nature of the study resulted in the potential loss of information that may have benefited the final analysis. TOF is a disease where prognosis is largely dictated by right ventricle function and detailed indices of this function would have provided useful information. Another important limitation in this regard would be lack of multimodality imaging in the form of cardiac MRI to assess RV function, size and fibrosis

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APPENDIX A: TURNITIN REPORT

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	Elective Early Primary Repair of Tetralogy of Fallot: Analysis of Intermediate Term Outcomes", The Annals of Thoracic Surgery, 2017 Publication	
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UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr KG Afrika

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M1811102

NAME: (Principal Investigator)	Dr KG Afrika
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Paediatric Cardiology Division Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Characteristics of Tetralogy of Fallot in children who have had a surgical procedure at the Chris Hani Baragwanath Hospital over two decades
DATE CONSIDERED:	30/11/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor A Cilliers and Dr P Raphulu
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/12/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore reports and re-certification will be due early in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

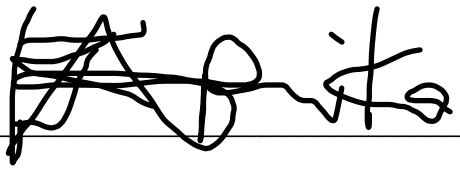
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PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C: PLAGIARISM DECLARATION

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS SENATE PLAGIARISM POLICY:

I Jesmine Kamogelo Afrika (Student number: 0502731E) am a student registered for the degree of Masters in Medicine (Paediatrics) in the academic year 2022. I hereby declare the following:-I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong. -I confirm that the work submitted for the assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise. -I have followed the required conventions in referencing the thoughts and ideas of others. -I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing. -I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

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