TETRALOGY OF FALLOT SURGICAL REPAIR AND ASSOCIATED RIGHT VENTRICULAR REMODELING

Title page

TETRALOGY OF FALLOT SURGICAL REPAIR AND ASSOCIATED RIGHT VENTRICULAR REMODELING

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Descriptive note

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Abstract

Tetralogy of Fallot (TOF) is the most common cyanotic congenital cardiac defect with a global annual incidence of 40,000 cases. Advances in surgery and perioperative care led to improvements in perioperative mortality and, thus, a growing number of survivors. TOF survivors often suffer from complications related to a failing right ventricle. Follow-up studies evaluating TOF repair strategies suggest an association between the type of surgical repair strategy and late right ventricular health. However, surgical practices remain unchanged and led by institution-level biases. The body of evidence addressing outcomes based on TOF surgical repair strategy is weak and controversies persists on the management of these patients.

This thesis comprises 6 chapters that form the foundation of a multi-centre research program on outcomes after TOF surgical repair. The program uses various methodologies to generate evidence with a vision to change surgical practices.

Chapter 1 is an introduction providing background on TOF and contemporary areas of controversy.

Chapter 2 presents the results of a retrospective analysis evaluating the use of early echocardiogram parameters in predicting late cardiac magnetic resonance imaging evaluation of the right ventricle.

Chapter 3 presents the results of a retrospective cohort exploring the association between TOF repair strategy and development of right bundle branch block.

Chapter 4 presents the results of a multinational survey aiming to explore contemporary biases in TOF surgical repair strategy selection.

Chapter 5 presents the background, rationale, design and baseline cohort characteristics of the Tetralogy of Fallot for Life (TOF LIFE) study. The study is a multi-centre inception cohort study with a follow-up period of 2 years.

Finally, Chapter 6 discusses the conclusion, limitations, and future implications of this research program.

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God Bless

Contributions by Others

At the end of each chapter is a full account of authors' contributions.

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List of Abbreviations

ACCF: American College of Cardiology Foundation

AHA: American Heart Association

AP: Annulus preservation

CHD: Congenital Heart Disease

EACTS: European Association for Cardiothoracic Surgery

ECG: electrocardiogram

GCP: Good Clinical Practice

HRS: Heart Rhythm Society

ICH: International Conference on Harmonization

ICU: Intensive Care Unit

IEC: Independent Ethics Committee

IQR: interquartile Range

IRB: Institutional Review Board

LV: Left Ventricle

MCID: Minimal Clinically Important Difference

MRI: Magnetic Resonance Imaging

OR: Odds Ratio

PHRI: Population Health Research Institute

RBBB: Right Bundle Branch Block

REDCap: Research Electronic Data Capture

RV: Right Ventricle

RVEDDz: Right Ventricular End Diastolic Dimension z-score

RVEDVi: Right Ventricular End Diastolic Volume indexed

RVOT: Right Ventricular Outflow Tract

STS: Society of Thoracic Surgeons

TAP: Trans-annular patch repair

TEE: Trans-Esophageal Echocardiogram

TOF: Tetralogy of Fallot

TOF LIFE: Tetralogy of Fallot for Life

VSD: Ventricular Septal Defect

Chapter 1: Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic heart defect accounting for 7-10% of all CHD (1). Anterocephalad deviation of the infundibular septum in utero is responsible for the classic anatomical presentation of tetralogy of Fallot: right ventricular outflow tract stenosis, right ventricular hypertrophy, sub-aortic peri-memberanous ventricular septal defect, and over-riding of the aorta (figure 1). It has an estimated global incidence rate of nearly 40,000 patients annually. Untreated, one-year survival is 75% and falls dramatically to 30% at 10 years (2). In comparison, both early and late survival significantly improve following surgical repair, where >94% are alive at 20 years (3). In addition, these surgical repair operations are associated with a low early post-operative mortality 0.9%-1.3% inclusive of both staged and primary repair (4, 5). Given the significant improvements in early post-natal care and surgical management, there are growing numbers of survivors with congenital heart disease (CHD). However, these TOF survivors suffer from life-long complications that seem to be the consequence of right ventricular dilation that is related to the surgical repair strategy employed. These complications often impact on daily function and require multiple re-interventions, thus, carrying a burden on the child, their family and the health care system. This thesis aims to address a substantial knowledge gap that exists regarding the optimal surgical management strategy to reduce early and late clinical complications (figure 2).

1.1 Current evidence to suggest that surgical strategy is associated with right ventricular remodeling

The principle of surgical repair is to relieve the RVOT (Right Ventricular Outflow Tract) stenosis and close the VSD (Ventricular Septal Defect). The first TOF repair was conducted by Lillhei in 1955 using cross-circulation (6). This original repair strategy involved the use of a large trans-ventricular incision extending beyond the pulmonary annulus to allow for closure of the VSD and patch augmentation of the RVOT stenosis (figure 3). The aim was to completely relieve the RVOT stenosis and accept free pulmonary insufficiency. This repair is usually referred to as a standard trans-annular patch (TAP) repair with trans-ventricular approach to VSD closure. Historically, the surgical repair was viewed as “curative” and the residual pulmonary insufficiency was seen as “benign.” Patients from that surgical era have significantly better survival of 84-87% at 30 years after the repair in comparison to <5% if untreated (7, 8). These early studies also demonstrated a survival advantage for patients with higher RV/LV pressure (represents the degree of residual RVOT stenosis at the end of repair, 0.7-0.8 is usually accepted) (8-10).

Investigators later demonstrated that pulmonary insufficiency leads to various degrees of RV remodeling as early as 1 year after surgical repair (11). Compensatory mechanisms during childhood explain the lack of clinical presentation. Eventually, these compensatory mechanisms fail and repair survivors usually present with heart failure, arrhythmia, poor exercise tolerance, and even sudden cardiac death in early adulthood (12, 13). In attempt to halt this

cycle of pulmonary insufficiency and RV remodeling, repair survivors require pulmonary valve replacements years after the initial repair.

Recognizing the early and late outcomes following a standard TAP repair, several modifications to the original repair technique emerged in attempt to preserve the pulmonary valve. Zavanaella reported the use of a monocusp leaflet augmentation to the usual trans-annular patch in 1978. This technique limits early pulmonary insufficiency post-repair and led to early extubation and shorter ICU stay ($p<0.001$) in comparison to the traditional trans-annular patch(14). However, these monocusp extensions have limited durability and progressive moderate-severe pulmonary insufficiency is evident as early as 7-10 months after repair(14). Follow-up studies show that nearly 50% of patients have at least moderate pulmonary insufficiency and almost 20% required a pulmonary valve replacement at 10 years(14-16).

There is a growing interest in accepting a certain degree of residual RVOT stenosis and its protective role in RV remodeling. Attempts were made to conservatively repair the RVOT stenosis by using a minimal trans-annular patch that extends just below the annulus but does not cross the os infundibulum (the boundary between the conus/infundibulum and sinus of the RV). A trans-atrial/pulmonary approach is used to close the VSD (figure 4). Early reports by Karl and Mee demonstrate operative mortality of 0.5% and 95% freedom from re-operations at 5 years. The group in Melbourne has recently published long-term outcome data with 97% survival and 85% freedom from re-intervention at 25 years follow up (17).

A further modification to the repair was made in the 1990's with an aim to preserve the pulmonary annulus. The modern annulus preservation (AP) strategy involves a trans-atrial/trans-pulmonary approach to VSD closure and RVOT muscle resection. A valvotomy and commissurotomy is performed on the valve along with use of Hegar dilation. Patch augmentation of the infundibulum and main pulmonary artery are inserted based on intra-operative functional assessment of direct ventricular pressure and trans-esophageal echocardiography (figure 5).

The AP strategy results in limited RV remodeling and may reduce the need for re-interventions. A propensity matched retrospective analysis by Yun et al demonstrated that patients who received AP repair (n=57) had a higher freedom from pulmonary valve replacements at 15 years after surgical repair compared those with TAP repair (n=57) (74 and 100 % respectively, p = 0.015). This was hypothesized to be related to a reduction in pulmonary regurgitation by preserving the pulmonary valve(18). Frigiola et al. studied the physiologic and phenotypic characteristics of late survivors of TOF repair who do not require a pulmonary valve replacement by analyzing their cardiac MRI studies, echocardiograms and exercise test findings. Overall, patients free of a pulmonary valve replacement were found to have less regurgitation, some pulmonary valve obstruction, and unobstructed pulmonary artery branches (19). Overall data demonstrate that late adverse ventricular remodeling can be prevented by preserving pulmonary valve competency at the time of surgical repair. More

research is needed to understand the relationship between early remodeling and late outcomes.

The majority of available data on the impact of surgical strategy on remodeling and clinical outcomes are limited by confounding bias. One of the major causes of this bias is the lack of adjustment for pre-operative cardiac anatomy. A retrospective propensity-matched study including 185 patients who underwent surgery at SickKids Hospital between 1996-2002 addressed this issue. Patients were matched on indexed pulmonary annulus size, main pulmonary artery diameter, and left pulmonary artery diameter. These parameters were previously found to be important co-variates in predicting the choice of surgical strategy in regression analyses. This study demonstrated that the AP strategy required shorter bypass time than TAP repair in the overall cohort and in the anatomically matched subset (112±33 minutes and 150±52 minutes respectively, $P<0.0001$). In addition, this study demonstrates that TOF patients with equivalent pre-operative anatomy, those with AP repair had smaller RV volumes 15 years after repair when compared to patients who underwent a TAP repair (123 cc/m^2 ±26.8 for the AP group vs 180 cc/ m^2 ±36.1 for the TAP group. Echocardiographic measures of RV size (Right Ventricular End Diastolic Dimension, RVEDD z-score) were smaller in the AP group (RVEDDz =1.78±1.71) compared with the TAP group (RVEDDz =3.44±1.46), $p<0.0001$. Interestingly, similar echocardiographic findings were also noted at 16 months after repair, suggesting that early remodeling was predictive of late RV size. Patients after AP repair also required fewer catheter based re-interventions such as balloon or

stent procedures in comparison to patients with TAP repair, 8% vs 20% (p=0.050) respectively. Freedom from pulmonary valve replacement was also significantly higher in AP group (p=0.014) (20). The findings from this study suggest that the initial repair technique results in different degrees of RV remodeling and is associated with different incidence of cardiac complications and need for re-interventions.

1.2 Measuring RV remodeling: relying on surrogate data

It has been shown that RVEDD disproportionately increases during the first year after repair, reaching an inflection plateau 5-7 years following surgery (11). As time progresses and RVEDD increases, clinical complications such as arrhythmia and heart failure become evident, usually in the 3rd decade post repair (21). Therefore, RVEDD represents a surrogate marker for late (>10 years) patient-important clinical outcomes.

Cardiac MRI studies are considered gold standard for assessing ventricular volumes. However, conducting cardiac MRI in infants and young children will require the use of anesthesia/sedation to ensure good quality images. Since these studies are not part of clinical routine practice, ethical issues will arise when implementing such protocols. In addition, there will be added feasibility challenges with regards to the added MRI expenses as these studies will be conducted solely for research purposes.

In Chapter 2 of this thesis, we investigate the prognostic value of using early RVEDD measurements from echocardiography studies at 1-5 years after repair to predict RVEDVi (RV End Diastolic Volume indexed) on late cardiac MRI studies.

1.3 Choice of surgical repair strategy associated with late outcomes

Long-term follow up studies demonstrate good survival following TOF repair; >90% survival is reported at 20 years (3). The cohort studies have highlighted that repair is far from curative due to residual hemodynamic and electrophysiological lesions. Due to the progressive nature of these lesions, repaired patients have a constant hazard of death: Hickey et al estimated the risk of death at 0.5 $\pm$0.07% per year with an increase of 0.1% per decade and risk for re-operations ~1% per year(3). The majority of deaths are cardiovascular: 17-36% are sudden cardiac deaths and 14-24% are related to heart failure. Pulmonary valve regurgitation is the most common residual lesion and evident in about 50% of survivors, while 30% have RVOT stenosis (8, 22, 23). These lesions are progressive such that half of repaired survivors suffer from cardiorespiratory symptoms (including arrhythmia) and 1 in 10 will need a re-intervention (24). The most common type of re-intervention is a pulmonary valve replacement that is performed to relieve the symptoms and reduce the risk of sudden cardiac death (25).

Hemodynamic residual lesions and mechanical damage after repair are associated with higher prevalence of arrhythmia in TOF patients in comparison to the general population. Atrial arrhythmias occur in 1-11% of patients while ventricular tachyarrhythmia are evident in up to 22-33% of repaired TOF patients(26-28). The occurrence of these arrhythmias has a mutli-factorial etiology and include older age at repair which exposes the ventricle to longer periods of suboptimal oxygen saturations, and use of TAP repair which leads to pulmonary regurgitation and electromechanical complications (29). Retrospective cohort studies (specifically Gatzoulis et al) demonstrated that a QRS duration>180ms is predictive of death and clinical arrhythmias (30). Further work revealed that prolonged QRS duration in combination with LV dysfunction is a better predictor of such events.

In Chapter 3 of this thesis, we conduct a retrospective analysis of a combined cohort from two large pediatric surgery centres to determine the association of surgical repair strategy and incidence of right bundle branch block during follow up.

1.4 Multiple surgical strategies are implemented

Despite the emerging evidence demonstrating superior outcomes with the more conservative repair techniques, TAP repair with trans-ventricular VSD closure continues to be the predominant technique employed globally according to STS (52-66%) and EACTS (57.5%) databases (4, 5). Decisions on surgical strategy are “clear-cut” when the pulmonary annulus z-score size is too big or too

small. However, controversy arises when patients present with anatomical features that fall into the “gray zone.” There are many reasons to explain the discrepancies between evidence and surgical practices.

In Chapter 4 of this thesis, we conduct a survey of 18 international pediatric surgery centres to determine current surgical practices, the reasons behind biases in practice and research infrastructure. This survey was used as an initial step towards designing the TOF LIFE cohort study.

1.5 Limitations of current evidence

Existing literature in this field consists of international registries and multiple small single -centre retrospective reports. The largest published international registries are from the European Association of Cardiothoracic Surgeons (n=6654) and the Society of Thoracic Surgeons (n=3059). These registries were limited to reporting in-hospital and 30-day outcomes. The registries do not include morphologic data and thus preclude extensive understanding of the impact of varying operative strategies. For example, by not including the patients’ pre-operative clinical condition and their echocardiogram findings, the findings are significantly confounded and interpretability is limited. Intra-operatively, these registries lack granularity and use a simplified categorization for the type of repair (e.g. ventriculotomy/no ventriculotomy) and did not include detailed variables such as the size of ventriculotomy incision and how the infundibular chamber was managed. Furthermore, the absence of data around the post-operative recovery prevents the exploration of association

between the repair strategy and early post-operative complications (e.g. restrictive physiology). Most importantly, both of these registries are limited to hospitalization and 30-day data and thus do not provide insight into the late impact of repair strategy. Recognizing their limitations, both of these publications recommend initiation of a prospective multicenter collaboration to investigate these long-term complications (4, 5).

Most data on the impact of surgical strategy come from retrospective single centre experiences that are based on small sample sizes with unbalanced prognostic factors at baseline. TOF present over a spectrum of anatomical severity and many of the published reports draw conclusions without adjusting for these confounders through design or statistical analysis strategies. In addition, existing reports that investigate long-term clinical outcomes of repaired TOF patients are based on historic cohorts when perioperative care may not be comparable to modern day practices.

Chapter 5, outlines the design and rationale along with baseline cohort characteristics of the tetralogy of Fallot for Life (TOF LIFE) study. This large multi-centre cohort study aims to overcome these common limitations encountered with clinical studies in congenital heart disease to generate much needed evidence in this field.

1.6 Conclusion

Chapter 6 summarizes the key findings of this thesis, outlines the limitations of this work and highlights the future direction of this research program.

Figures

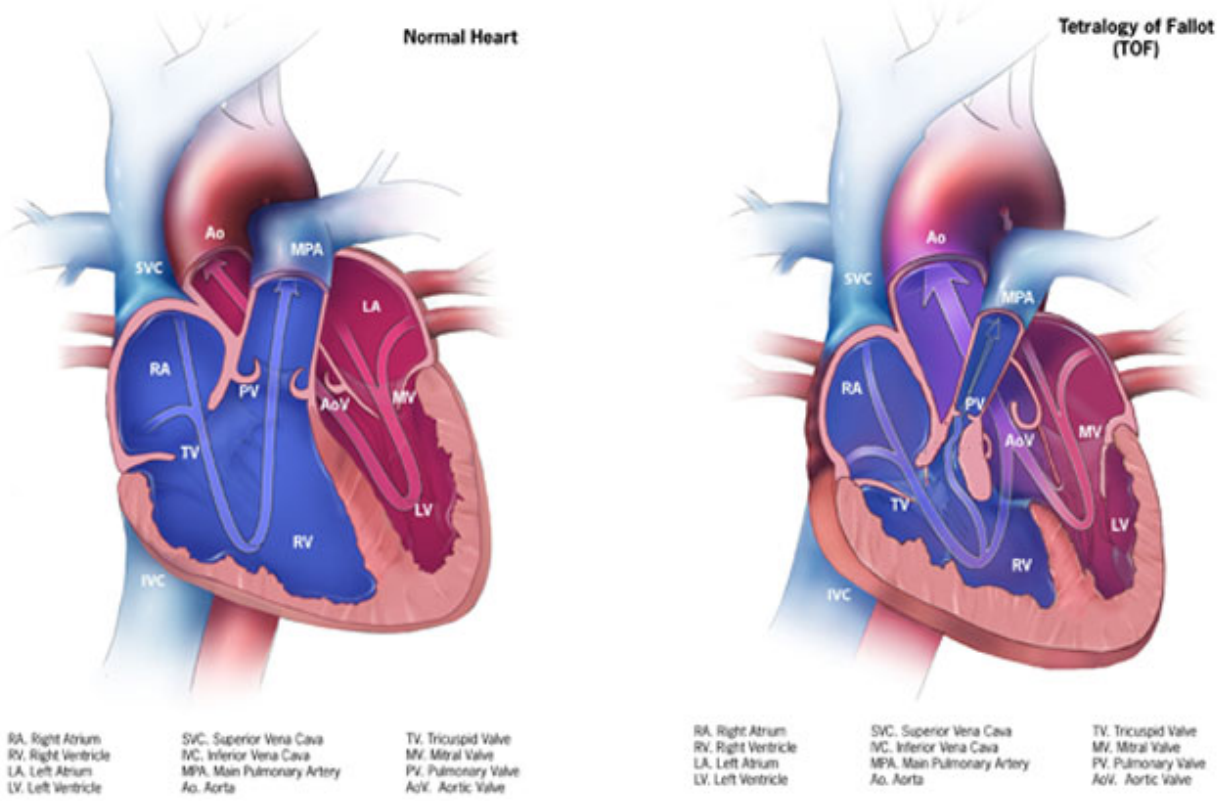

Figure 1: Anatomical features of tetralogy of Fallot (31)

This figure depicts the anatomical features of tetralogy of Fallot which results in mixing of the pulmonary and systemic circulation with cyanotic blood leaving the aorta to supply the systemic circulation.

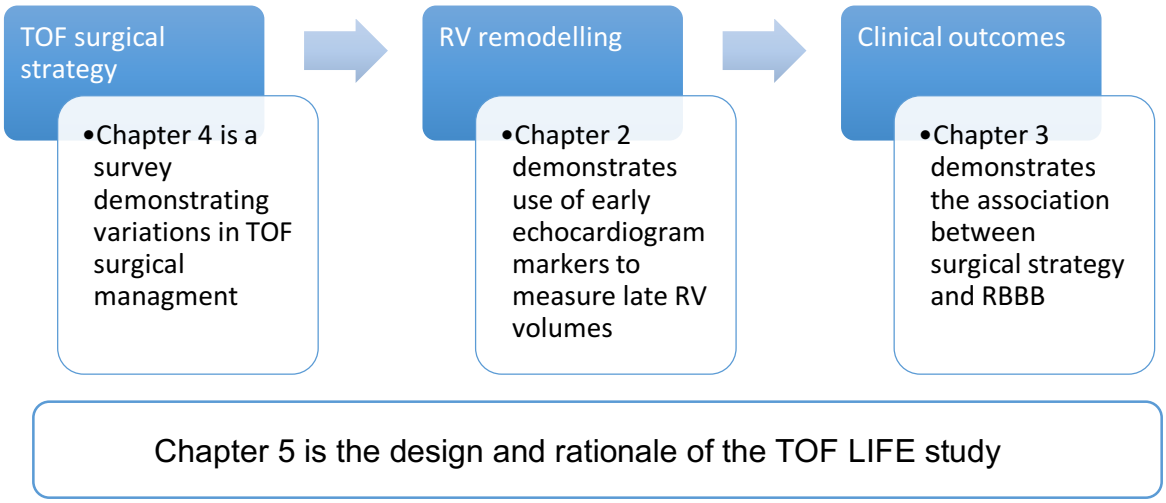

Figure 2: schematic representation of this thesis demonstrating the overall concept and how each chapter addresses each component of this theory

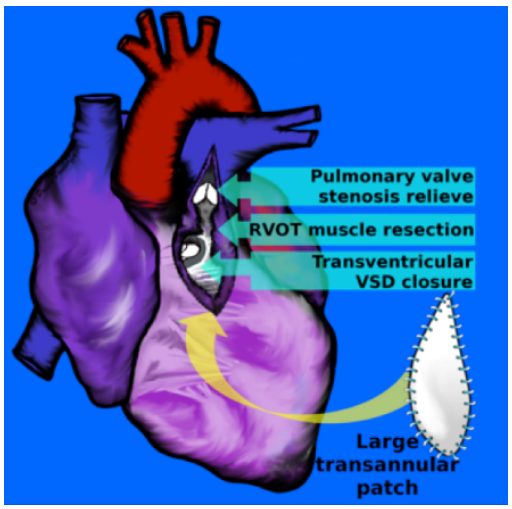

Figure 3: Transventricular VSD closure with or without a TAP

This is the technique described by Lillhei in 1955. A right ventricular incision is made that allows for VSD closure and resection/relief of muscle obstruction. The

incision is then closed with a patch that can span the annulus or remain below the pulmonary annulus.

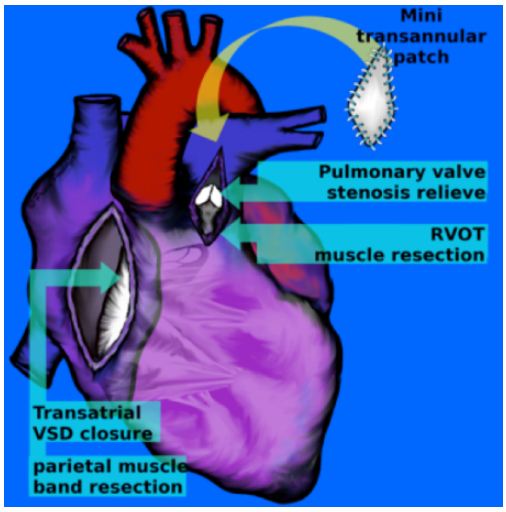

Figure 4: Transatrial/transpulmonary muscle resection with or without minimal TAP (minimal TAP)

The VSD is accessed through a right atriotomy. If needed a small vertical incision is made through the RVOT spanning the annulus but not extending beyond the OS infundibulum. This allows for relief of obstruction via muscle resection and patching.

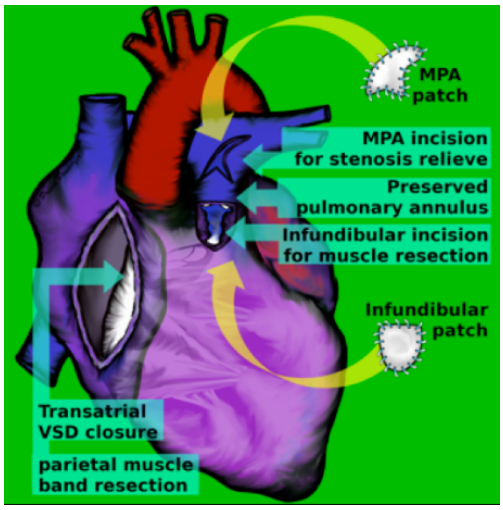

Figure 5: Transatrial/ transpulmonary repair with or without infundibular patch (AP technique). Transatrial VSD closure and muscle resection is achieved. Further muscle resection is performed in a transpulmonary approach. An infundibular patch is added for small infundibular chambers (not in a position or of a size sufficient to close the VSD). For an inadequate valve size, a limited TAP incision is made. Intraoperative balloon dilation of the pulmonary valve/annulus is also made as an attempt to decrease the need for a TAP

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Chapter 2: Early right ventricular dimension is a marker of late right ventricular volume after tetralogy of Fallot repair

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Abstract

Background: In repaired tetralogy of Fallot (TOF) patients, we sought to examine the relationship between early right ventricular end diastolic dimension (RVEDD) z-score obtained at 1-5 years after repair and late right ventricular end diastolic volume index (RVEDVi) obtained at 10-15 years. In addition, we investigated the impact of surgical repair strategy on the progression rate of right ventricular (RV) dilation.

Methods: A retrospective electronic chart review was performed of all patients with TOF pulmonary stenosis subtype who underwent surgical repair (excluding those with implanted valved conduits) at The Hospital for Sick Children between 1996-2002. All echocardiographic studies were analyzed in a core lab. RVEDVi values were obtained from cardiac MRI studies at 10-15 years after repair. A linear regression model was used to determine the relationship between early post-operative RVEDD z-score and late RVEDVi. Longitudinal analysis was performed on serial RVEDD z-score measurements to determine the rate of RV dilation. The effect of surgical strategy on RV remodeling was explored in both models; the analysis was repeated in a subgroup of “equivalent” pre-operative cardiac morphology based on pre-operative echocardiographic parameters.

Results: A total of 185 patients underwent TOF repair. Those repaired with a valved conduit were excluded (n=5). RVEDD z-score at 1-5 years post-repair was a predictor of late RVEDVi (n=57, R^2=0.47, p=0.002). Similar results were found in a subgroup analysis of anatomically equivalent patients at baseline (n=41,

R^2=0.53, p=0.008). Patients with a trans-annular patch repair (TAP) had faster progression of RVEDD z-score (0.37 higher every 5 years; p<0.0001) compared to those undergoing annulus preservation (AP) repair.

Conclusion: Echocardiographic RV dimensions measured 1-5 years after surgery are predictive of MRI RVEDVi at 10-15 years after TOF surgical repair. TAP repair is associated with more rapid progression of RV dilation.

Introduction

Surgical correction of tetralogy of Fallot often results in variable residual anatomic and hemodynamic lesions that are influenced by the surgical strategy performed (1). Repair of the right ventricular outflow tract (RVOT) obstruction results in variable degrees of pulmonary regurgitation, which is shown to be more severe in patients undergoing transannular patch (TAP) repair compared to patients undergoing pulmonary annulus preservation (AP) repair (2). Significant pulmonary regurgitation typically results in progressive right ventricular (RV) dilation.

Progression of RV dilation is typically monitored by echocardiography early after repair and by a combination of echocardiography and magnetic resonance imaging (MRI) once children reach an age where MRI can be performed without general anesthesia. Cardiac MRI is considered the reference technique for assessing right ventricular volumetrics (3). One of the commonly used measurements in echocardiography is RV end-diastolic dimension (RVEDD) as measured from short-axis or long-axis view. The prognostic value of early postoperative RVEDD measurements is unknown as is the influence of surgical strategy on the rate of RV dilation after surgery.

The main objective of this study was to determine the association between early echocardiographic RVEDD z-scores within 1-5 years after repair and indexed RV end diastolic volume (RVEDVi) as obtained from MRI at 10-15 years

after repair. The secondary objective was to determine the association between TOF surgical repair strategy and RVEDD z-score progression during follow-up.

Methodology

We undertook a single-center retrospective cohort study of patients diagnosed with tetralogy of Fallot with pulmonary stenosis who underwent surgical repair between 1996-2002. Patients were identified from the institution's electronic surgical and cardiology databases. Retrospective chart review was conducted. Patients who underwent repair with a valve conduit and were excluded from the study. All available echocardiographic studies were obtained and interpreted in a central lab to obtain standardized measures. Cardiac MRI study reports were reviewed to obtain the RVEDVi values from the most recent scan (prior to re-intervention when indicated).

Statistical Considerations

Continuous variables were described using means (± SD) or medians (IQR). Categorical variables were expressed as proportions (%). Linear regression using the least squares method was used to explore the association between early RVEDD z-score and late RVEDVi results, while adjusting for the surgical repair strategy. The independent variable in the analysis was the average of RVEDD z-scores obtained from echocardiographic studies conducted at 1-5 years after repair for each participant. The dependent variable is the RVEDVi. The linear regression model was then applied to a previously identified sub-group of propensity matched patients within this cohort. The propensity

matching was based on pulmonary valve annulus size, main pulmonary artery diameter, and left pulmonary artery diameter z-scores obtained from pre-repair echocardiograms. Previous analyses by our group demonstrated that these variables were significant factors in determining the repair strategy (4).

A longitudinal analysis with mixed effects model was performed on serial echocardiograph studies to demonstrate the effects of repair strategy (TAP or AP) on RVEDD z-score progression throughout follow-up.

All statistical analyses were performed using R statistical package. Complete case analysis strategy was followed when dealing with missing data. A complete case is defined as a patient with at least one echocardiogram study at 1-5 years post-operatively and a cardiac MRI prior to cardiac re-interventions. A p-value of 0.05 or less was considered to be significant.

Results

In total 185 TOF patients with TOF pulmonary stenosis underwent surgical repair between1996-2002. Five patients underwent repair with a valve conduit and were excluded from the study. The majority of participants in this cohort underwent primary repair (93%) with annulus preservation strategy (69%). Table 1 presents the baseline characteristics of this cohort. About 50% of the cohort underwent a cardiac MRI study at an mean of 13$\pm$ 2.2 years after the initial repair. Table 2 shows the baseline cohort characteristics of patients who had a cardiac MRI scan.

Early RVEDD z-score and relationship to late RVEDVi

Fifty-seven patients had both a cardiac MRI study and available early echo(s) (figure 1) and were included in the linear regression analysis. The analysis revealed that early RVEDD z-score at 1-5 years post-operatively was associated with RVEDVi measured at 10-15 years (R^2=0.47, p=0.002). This association maintained statistically significance when the model was applied to the sub-group of propensity matched patients (n=41, R^2=0.53, p=0.008).

Association of repair strategy with RVEDD z-score progression

A longitudinal analysis with a mixed effect model was performed on a total of 783 echocardiograph studies from 146 patients (figure 2). Those with TAP repair had a more rapid progression of RVEDD z-score over time in comparison with those who received AP repair. The rate of increase in right ventricular dimension was by 0.37 z-score for TAP patients in comparison to 0.25 z-score for AP patients every 5 years (p<0.0001). In addition, TAP repair was associated with a higher RVEDVi which was on average 34 ml/m^2 in comparison to patients with AP repair, 126 ml/m^2 vs 160 ml/m^2 (p=0.001). In addition, those with TAP repair had right ventricular dimensions that were 1.65 z-scores greater than those with AP repair throughout follow-up.

Discussion

Key findings

From this retrospective analysis of 185 repaired TOF patients, we demonstrated that late RVEDVi can be predicted by early RVEDD z-score from

echocardiographic studies. Surgical repair strategy can also influence the progression of RV dilation. These findings were reproducible in a sub-group of anatomically matched patients.

TOF surgical repair is not curative: repair survivors have a risk of ~1% per year for cardiac re-operations(1). Therefore, guidelines recommend at least annual follow-up with a trained cardiologist in congenital heart disease (class I recommendation, level of evidence C)(5). Monitoring of RV size and function is crucial for all patients, especially those with more severe pulmonary regurgitation. (2, 6). Assessment of RV volumes is challenging given the complex RV morphology and anterior position of the RV in the chest. Echocardiography is the first-line technique used to serially assess the RV in children with TOF; as it is non-invasive and does not require general anesthesia (7). Different echocardiographic measures for RV size and function have been proposed, but all have some limitations(3). In this study we looked at a simple measure of RV size for which z-scores were readily available for longitudinal imaging follow-up. RVEDD is limited to measuring the RV outflow component of the ventricle not including the inflow and trabecular parts. It is useful parameter for serial monitoring of RV remodeling. We wanted to study whether we could track early changes in cardiac remodeling and how it differs between two surgical techniques.

Despite the presumed accuracy of cardiac MRI, reliability in measurements is an ongoing challenge especially for right ventricular parameters(8). There is significant intra-and inter-observer variability that is

caused by variations in the quality of the images captured (e.g. coordination of breath holding), and challenges in analysis of these images(3, 9). For example, the manual contouring of the right ventricular endocardial borders is time consuming and highly operator dependent. Furthermore, physicians with a high level of expertise in cardiac MRI are required to interpret these studies especially the complex cases.

RVEDVi is one of the easiest parameters used to accurately define the extent of RV dilation, thus, commonly used as a surrogate maker for RV health and related clinical outcomes(10, 11). In addition, threshold for timing of pulmonary valve replacement often refer to RVEDVi cut-offs to ensure the possibility of reverse remodeling after valve implantation(5, 12, 13). Cardiac MRI is the gold standard non-invasive imaging to measure RV volumes and geometry.

The predictive value of RVEDD z-score for late RVEDVi is a novel concept not previously published in literature. Published studies show poor correlation of various 2D echocardiograph parameters with **synchronous** cardiac MRI volumes(2, 14-16).

A common challenge in congenital heart disease research is the availability of longitudinal data given the risk of loss to follow-up (e.g. transitioning to adult care). In addition, retrospective analyses are limited by the precision of available data. The comprehensive clinical and imaging databases in our institution allowed for analysis of these long-term data. Despite the unique hypothesis, the model fit was modest at R^2=0.47. The right ventricle has a

complex 3D structure that is difficult to measure using 2D imaging. In addition, a better model fit may be achieved by incorporating more variables that influence RV remodeling such as timing of repair etc. However, we are limited in the number of predictors with the available small sample size. The high variability in determining RV volumes from cardiac MRI studies can also play a role in this model.

Larger cross sectional and longitudinal cohort studies are needed to robustly evaluate the correlation of various echocardiographic parameter (e.g. RVEDD, RV end diastolic area, RV mass and myocardial velocities) with synchronous and late RV geometry as measured by cardiac MRI. In addition, a larger sample size would allow for investigation of earlier echocardiographic measurements (i.e. within the early post-operative period) and their ability to predict late RVEDVi. These studies can be used to determine the role of 3D echocardiography in clinical practice to monitor RV health in an attempt to further limit the need for cardiac MRI in these patients.

Strengths and Limitations

This study looks at the relationship of early echocardiogram parameters and later cardiac MRI RV volumes from patients in the same surgical era. In the sub-analysis on the anatomically equivalent patients, we were able to control for important confounders (pre-operative morphology) in these models.

Despite the strengths of this analysis, it is important to mention our limitations. Given the retrospective nature of this work, we were limited by the clinically available data. For example, the size of trans-annular patches is not routinely measured during surgical repair and this may have improved model prediction and perhaps a gradient like effect on the rate of RV remodeling. In addition, we were restricted to follow-up cardiac studies only for patients who attended cardiology clinics at our institution. There is a possibility that by excluding children followed at other institutions we may have introduced a selection bias. There is an assumption that the more complex cases are followed by the heart centre in our institution.

The majority of work on congenital heart disease is limited by small sample sizes and/or event numbers, our work is no exception. In addition, the data reflect our surgical and cardiology practices in our institution. Management of congenital heart disease patients is highly influenced by institutional and health care provider expertise and potential biases. Therefore, caution should be exercised when generalizing conclusions regarding a type of repair and outcomes based on single-centre experiences.

Conclusion

This study suggests that clinicians can use RVEDD which is a relatively “simple” early echocardiographic parameter to predict future RV geometry. Clinicians can use our findings to identify high-risk patients for adverse

remodeling based on their early RVEDD and modify their plan for follow-up including the frequency of cardiac imaging to monitor the RV dilation.

Tables and Figures

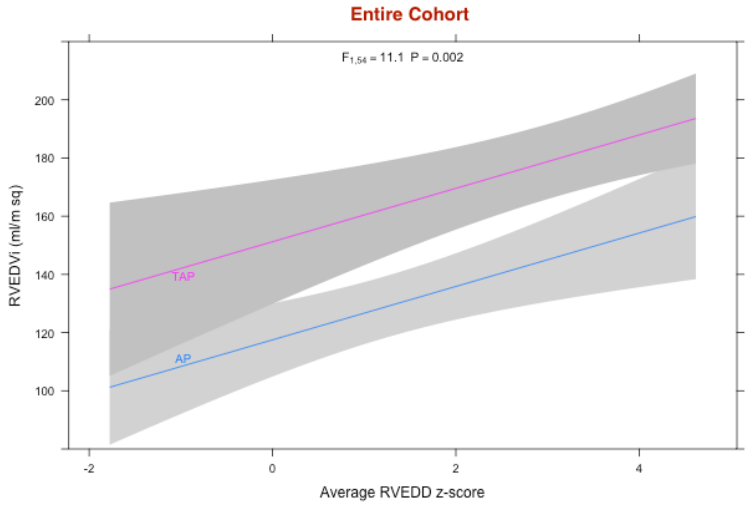
Variable	**N=180**	**AP (n=124, 69%)**	**TAP (n=56, 31%)**	**P-value**
Male, n (%)	89 (49)	61 (49)	28 (50)	0.92
Age at repair in years, median (IQR)	0.64 (0.39, 1.05)	0.6 (0.4, 0.9)	0.8 (0.3, 1.5)	0.16
Primary Repair, n(%)	168 (93)	118 (95)	50 (89)	0.14
Patients with CMR, n(%)	84 (47)	50 (40)	34 (61)	0.01
Age at CMR in years, means (±SD)	13.1 (±2.2)	12.3 (2.1)	14.2 (2.0)	0.67

Table 1: baseline characteristics for the overall cohort and for those undergoing annulus preservation and trans-annular patch repair. AP: annulus preservation, TAP:trans-annular patch repair, CMR: cardiac magnetic resonance

Variable	**MRI (n=84) 47%**	**No MRI (n= 96)**	**P-value**
Male, n (%)	40 (48)	49 (51)	0.66
Age at repair in years, median (IQR)	0.6 (0.33, 0.96)	0.67 (0.4, 1.2)	0.13
Primary Repair, n(%)	78 (93)	90 (94)	0.81
Annulus preserved (AP), n (%)	50 (60)	74 (77)	0.01
Trans-annular patch (TAP), n(%)	34 (40)	22 (23)	0.01

Table 2: Baseline cohort characteristics of patients who required a late cardiac MRI scan

A



B

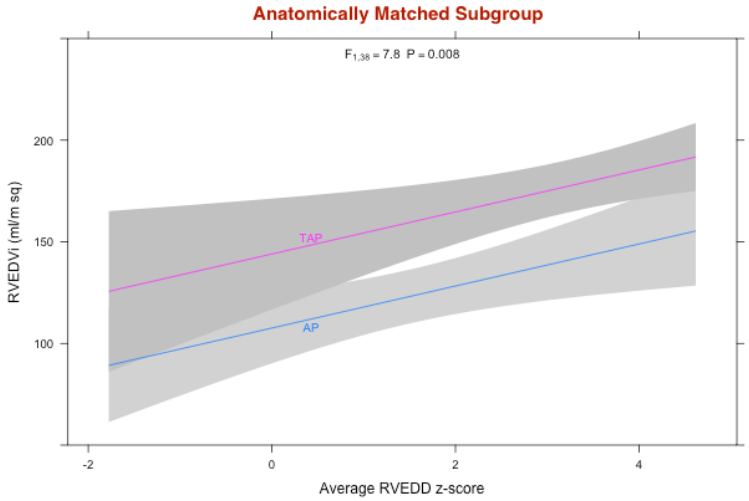


Figure 1: A) RVEDD z-score at 1-5 years post-repair is a predictor for late RVEDVi as obtained from MRI (n=57, R2=0.47, p=0.002). Pink line refers to the TAP patients and blue line refers to the AP patients. B) This correlation also holds true for anatomically matched patients (n=41, R2=0.53, p=0.008). AP: annulus preservation repair, TAP: trans-annular patch repair, RVEDDz: right ventricular end diastolic dimension z-score

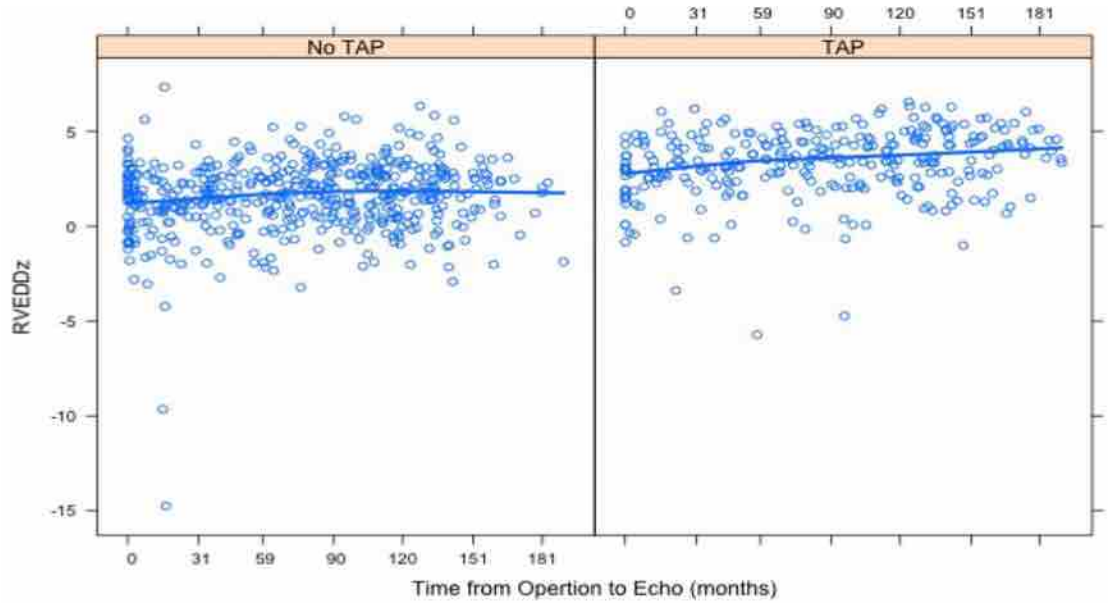


Figure 2: TAP patients had more rapid RVEDDz progression throughout follow-up (0.37 higher every 5 years; $p<0.0001$). Overall, TAP patients had RVEDDz that is 1.65 times higher than AP patients.

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Contributorship Statement

Sara Hussain contributed to the study design, statistical analysis, interpretation of data, writing the manuscript and provided critical revisions to the manuscript.

Ahmad Makhdoum contributed to the data collection and provided revisions to the manuscript.

Osman Al-Radi contributed significantly to the data analysis and interpretation of the results.

Lars Grosse-Wortmann contributed significantly to the design of the study, interpretation of the results and provided revisions to the manuscript.

Luc Mertens contributed significantly to the design of the study, interpretation of the results and provided revisions to the manuscript.

Emilie Belley-Cote contributed significantly to the revision of the manuscript.

Feng Xie provided critical revisions to the manuscript.

Andre Lamy provided critical revisions to the manuscript.

PJ Devereaux provided critical revisions to the manuscript.

Richard Whitlock contributed significantly to the interpretation of the results and provided critical revisions to the manuscript.

Glen Van Arsdell contributed significantly to the design of the study, interpretation of the results and provided critical revisions to the manuscript.

Chapter 3: Traditional tetralogy of Fallot surgical repair is associated with unfavourable right bundle branch block

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Abstract

Background: Right bundle branch block (RBBB), prevalent in survivors of congenital heart disease, is associated with ventricular dyssynchrony and decreasing left ventricular function. We sought to determine if tetralogy of Fallot (TOF) repair strategy influences the prevalence of RBBB.

Methods: We performed a retrospective chart review on consecutive TOF pulmonary stenosis repair cases conducted between 1996-2004 at 2 large pediatric centers. The presence of RBBB was determined from follow-up ECGs or Holter monitoring reports. The association of RBBB and TOF surgical repair strategy was investigated using multivariable logistic regression.

Results: A total of 402 TOF repair cases were performed at a mean age of 1.0 (±1.2) years. The majority were primary repair cases (84%) with a trans-atrial approach to ventricular septal defect (VSD) closure (94%) and minimal transannular patch to relief the right ventricular outflow tract stenosis (50%). RBBB was evident in 212 patients (53%) at a mean follow-up of 17.0 (±4.2) years. The odds of developing RBBB was 3.4 higher with a trans-ventricular approach to VSD closure compared to a trans-atrial approach (95% CI 1.1, 10.3; p=0.03). Use of a standard transannular patch (extending below the os infundibulum) increases the odds for developing RBBB by 4.6 times in comparison to an annulus preservation strategy (95% CI 1.0, 21.3; p=0.05).

Conclusions: A trans-ventricular approach to VSD closure and/or standard transannular patch repair were found to significantly increase the odds of

developing RBBB. Larger cohort studies are needed to confirm the impact of surgical repair on occurrence of arrhythmia and conduction disturbances.

Introduction

Surgical repair of tetralogy of Fallot (TOF) has been performed for over five decades. Advancement in surgical technique and perioperative medicine has led to a low contemporary perioperative mortality of less than 1% (1, 2). Despite modifications of the surgical techniques, many patients eventually develop reduced ventricular function on follow up (3, 4). Moreover, 43% of survivors suffer from clinically important atrial and ventricular arrhythmias that are often associated with incidences of sudden cardiac death(3). Right bundle branch block (RBBB) is the most common electrophysiological complication in TOF repair survivors with an estimated prevalence of 80% (5). Conduction delays play a role in ventricular synchrony and have implications on global ventricular function(6). Cardiac resynchronization therapy can be considered for repaired TOF patients to improve cardiac function and quality of life(7). The role of surgical repair strategy in causing conduction delays is not studied extensively in the available literature. We aim to determine the association between TOF repair strategies and the prevalence of late RBBB following repair.

Methods

All consecutive TOF pulmonary stenosis repair cases performed during the period of 1996-2004 were identified at Hospital for Sick Children (Toronto, Canada) and Royal Children's Hospital (Melbourne, Australia). Retrospective chart review was conducted to obtain pertinent operative details and clinical outcomes. Operative notes were used to determine the repair strategy based on the

classification used in figure 1. The presence of RBBB was determined through examination of available follow-up ECG's and Holter monitor reports. RBBB was diagnosed based on the criteria outlined in the "AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram"(8).

Statistical considerations

Continuous variables were described using means (+/- SD). Categorical variables were expressed as proportions (%). Logistic regression was performed to determine the association between surgical repair strategies and the occurrence of RBBB. Confounders such as age at the time of repair, sex, and preceding palliative procedures were adjusted for in the regression models. Significant multi-collinearity was found between "RVOT repair strategy" variable and "approach to VSD closure." Thus, two separate models were created. Models' discrimination and calibration were assessed using c-statistic and Hosmer-Lemeshow tests.

All statistical analyses were performed using SPSS statistical package (Version 23.0). Complete case analysis strategy was followed when dealing with missing data. A p-value of 0.05 or less was considered to be significant.

Results

A total of 402 TOF pulmonary stenosis repair cases were identified. Pulmonary valved conduits were implanted in 10 patients and these were excluded from the analysis. Another 10 patients were excluded due to missing outcome or predictor variables. Each institution contributed nearly an equal number of

participants. The mean follow-up time was 17 years (+/-4.2). The majority of participants in this cohort underwent a primary repair (84%). RBBB was found to be present in 212 (53%) participants. Table 1 summarizes the characteristics of this cohort.

Repair strategies performed

There were four repair strategies employed at the two institutions: 1) A standard trans-annular patch extending beyond the os infundibulum (standard TAP) and trans-ventricular VSD closure (n=15, 4%), 2) A patch is used to cover an incision made through the pulmonary annulus that did not cross the os infundibulum (minimal-TAP) and a trans-atrial VSD closure (n=202, 50%), 3) Annulus preservation with pulmonary valvotomy +/- infundibular chamber patch (AP +/- IP incision) and trans-atrial VSD closure (AP n=141, 35%, AP+IP n=44, 9%), 4) Annulus preservation with pulmonary valvotomy +/- infundibular chamber patch (AP + IP incision) and trans-ventricular VSD closure (n= 8, 2%).

Model 1: Approach to VSD closure and RBBB

A trans-atrial approach to VSD closure was performed in 94% of patients (378/402). RBBB was evident in 80% of those with a trans-ventricular approach in comparison to 54% of those with a trans-atrial approach; adjusted OR 3.4 (95% CI 1.1, 10.3; p=0.03) (see figure 2 and table 2).

Model 2: RVOT repair strategy and RBBB

The incidence of RBBB was significantly increased in those participants who received a standard TAP (86%) in comparison to the more conservative

strategies such as annulus preservation (56%), AP+ IP (68%) or minimal TAP (48%); adjusted OR 4.6, 95% CI 1.0, 21.3, p=0.05) (see figure 3 and table 2).

Discussion

Conduction delays are commonly seen after TOF surgical repair; RBBB is the most prevalent interventricular conduction abnormality (9). These conduction delays are associated with ventricular remodeling, fibrosis, and dyssynchrony, which have implications on cardiac morbidity. This two centre retrospective study demonstrated that trans-ventricular VSD closure with standard TAP repair significantly increase the odds of developing RBBB. This is an important finding given that approximately 60% of TOF repairs are performed using these techniques according to contemporary international registries (10, 11).

The Significance of Right Bundle Branch Block

RBBB following TOF repair was originally thought to be a “benign” condition (9). Prolonged QRS duration can be seen as a marker and a consequence of RV dyssnchrony which is most prominent in the infundibular region(12). Advanced cardiac imaging techniques reveal the importance of the infundibular region on global RV function. A study by Wald et al shows that infundibular dysfunction can impact exercise tolerance, susceptibility to ventricular arrhythmia and heart failure in repaired TOF patients(13). A large multi-centre retrospective analysis by Gatzoulis et al demonstrated that prolonged QRS interval, (especially when >180 msec) increases the relative risk for ventricular arrhythmia (41.9, 95% CI 14.7-119.4, p<0.0001) and sudden cardiac death (2.29, 95% CI 1.05-5.02, p 0.038) (3).

In addition, the presence of RBBB causes both intra-ventricular dyssynchrony in the RV free wall and inter-ventricular dyssynchrony that would lead to decreased LV function, which has further clinical implications(14).

Right Bundle Branch Block and Tetralogy Repair

The present study indicates that surgical approach is important; however, the etiology of RBBB following TOF surgical is likely multifactorial. Mechanical injury to the conduction system can occur during surgery especially during patch VSD closure and ventriculotomy incisions. Residual hemodynamic lesions can lead to further alterations at the cellular level of the myocardium that contribute to conduction abnormalities (3, 15). Reports that investigate the association between repair technique and occurrence of conduction delay were mostly published in the 1970-1980's (9, 16-18). There is heterogeneity regarding the impact of a trans-annular patch on the occurrence of post-operative RBBB. Hazan et al investigated 100 patients who underwent TOF repair 1977-1979 and the presence of trans-annular patch was not found to be significantly associated with RBBB(9). Gelband et al also conducted a retrospective analysis on 251 patients who underwent surgical repair of TOF, VSD or pulmonary stenosis in 1967-1970. They demonstrated that 100% of patients with a vertical ventriculotomy developed RBBB(19). These reports were limited by small sample sizes, were based on single-centre experiences, and are likely not generalizable to modern practices given changes in surgical strategies and age of repair.

Limitations

Although our analysis is based on contemporary surgical care of TOF patients, there are limitations worth considering. This was a retrospective analysis and is inherently associated with several well-known biases. Surgical strategy was determined from operative notes which may not be sufficient in distinguishing the actual extent of the RVOT incision especially differentiating between minimal TAP and standard TAP repairs. The availability of follow-up ECGs and Holter monitoring reports was different amongst the centres. In addition, limited data was available from pre-operative echocardiogram studies that precluded adjustment for pre-operative cardiac morphology. There was a relatively small number of patients receiving trans-ventricular VSD closure and/or standard trans-annular patch repair, which could be a marker of selection bias.

Conclusion

RBBB is commonly seen after TOF repair and can be used as quick, inexpensive and reproducible marker of RV dysfunction. Standard trans-annular patch and trans-ventricular VSD closure increase the odds of developing RBBB after TOF repair. A larger prospective study including institutions with a more traditional strategy of TOF repair would yield further insight and robustness to the findings.

Figures and Tables

Variable	N=402
SickKids, n(%)	180 (45)
Male, n (%)	236 (59)
Age at repair in years, median (IQR)	0.79 (0.50, 1.15)
Primary Repair, n (%)	339(84)
Trans-atrial VSD closure, n(%)	378 (94)
Annulus preservation (AP), n (%)	141 (35)
AP and infundibular incision (AP+ infund), n(%)	44 (11)
Minimal trans-annular patching (miniTAP), n(%)	202 (50)
Standard trans-annular patch (TAP), n (%)	15 (4)
RBBB, n(%)	212 (53)

Table 1: Summary characteristics of cohort

Model	Strategy	Odds	p-value	95% CI
Model 1 (VSD closure)	Trans-atrial	1.2	0.1	
	Trans-ventricular	**3.4**	**0.03**	**1.1, 10.3**
Model 2 (RVOT repair strategy)	miniTAP	0.8	0.2	0.5, 1.2
	AP	1.3	0.1	
	AP+Infund	2.0	0.1	0.9, 4.4
	Standard TAP	**4.6**	**0.05**	**1.0, 21.3**

Table 2: The increased odds of developing RBBB with a trans-ventricular VSD closure and a standard TAP according to logistic regression models. Mini-TAP:minimal trans-annular patch that does not extend across the os infundibulum, AP: annulus preservation, AP+infund: annulus preservation with an incision in the infundibulum, standard TAP: patch extends beyond os infundibulum.

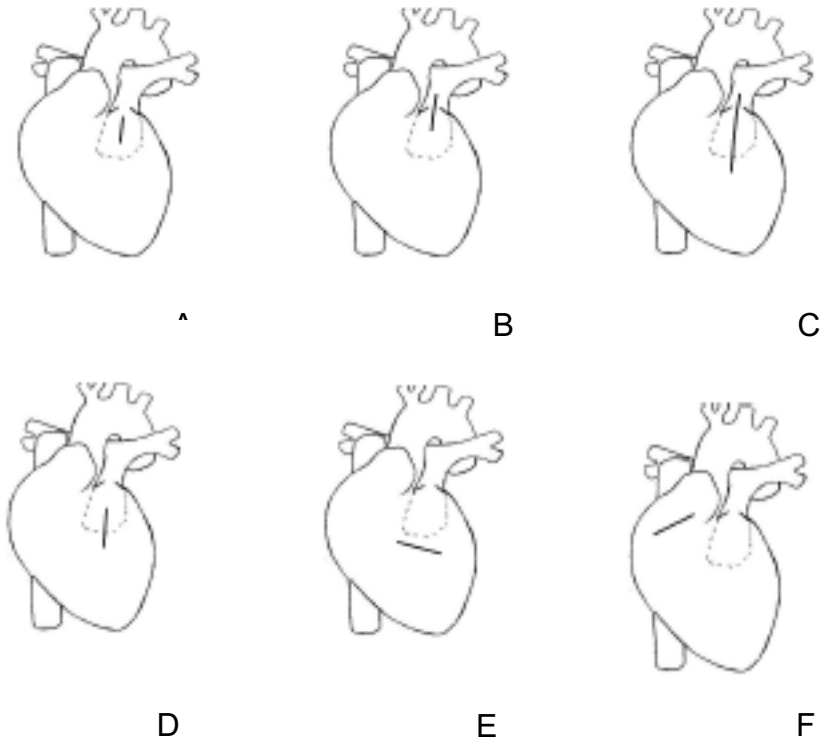

Figure 1: Classification of surgical repair strategy according to operative notes. A: annulus preservation approach with incisions that may be made above and below the annulus (AP and AP+Infund), B: an incision made across the pulmonary annulus and does not cross the os infundibulum (miniTAP), C: a large transannular incision that crosses the annulus and os infundibulum (standard TAP), D: a transventricular approach to VSD closure using a vertical incision, E: a transventricular approach to VSD closure using a horizontal incision, F: a transatrial approach to VSD closure.

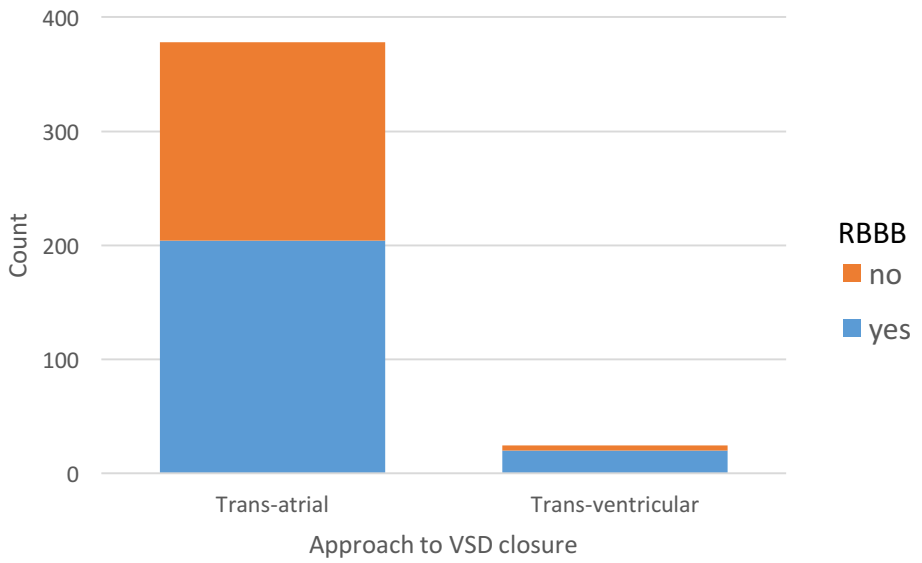

Figure 2: The prevalence of RBBB according to the approach used for VSD closure

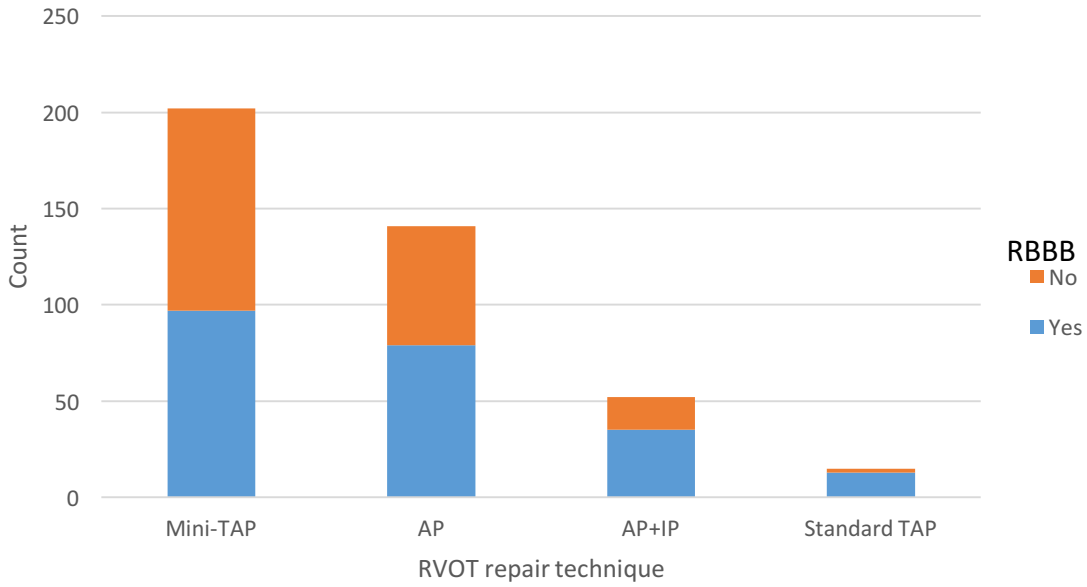

Figure 3: The prevalence of RBBB according to the RVOT repair strategy. Mini-TAP:minimal trans-annular patch that does not extend across the os

infundibulum, AP: annulus preservation, AP+infund: annulus preservation with an incision in the infundibulum, standard TAP: patch extends beyond os infundibulum.

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Contributorship Statement

Sara Hussain contributed to the study design, statistical analysis, interpretation of data, writing the manuscript and provided critical revisions to the manuscript.

Ahmad Makhdoum contributed to the data collection, interpretation of data, and provided revisions to the manuscript.

Charis Tan contributed to the data collection and provided revisions to the manuscript.

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Richard Whitlock contributed significantly to the study design, interpretation of data, and provided critical revisions to the manuscript.

Glen Van Arsdell contributed significantly to the study design, interpretation of data, and provided critical revisions to the manuscript.

Chapter 4: Survey of multinational surgical management practices in tetralogy of Fallot

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Abstract

Background: A wide variety of surgical strategies are employed in tetralogy of Fallot (TOF) repair. We sought to describe the international contemporary practice patterns for surgical management of TOF.

Methods: Surgeons from 18 international pediatric cardiac surgery centers (representing over 1800 TOF cases/year) completed a REDCap based survey. Participating countries include: China(4), India(2), Nepal(1), Korea(1), Indonesia(1), Saudi Arabia(3), Japan(1), Turkey(1), Australia(1), United States(2), and Canada(1). Summary measures were reported as means and counts (percentages). Responses were weighted based on case volume/center.

Results: Primary repair is the prevalent strategy (83%) with variation in age at elective repair (3 to >12 months of age). Nearly 47% of sites use patient age as a factor in determining the strategy, with age < 3 months being the common cut-off for staged repair. In addition, patient weight of < 3 kg is an indication for staged repair in 80% of participating institutions. Transatrial ventricular septal defect closure is the preferred approach at 62% of sites. Nearly 70% of responders reported using pulmonary valve z-score to guide right ventricular outflow tract management technique with the most prevalent cutoff for annulus preservation being a z-score of -3. Estimated incidence of annulus preservation is 53%. Minimal trans-annular incision is performed in >90% of all trans-annular repairs.

Conclusions: In this cohort representing 11 countries, there is variation in TOF surgical management. A large international prospective cohort study would allow

analysis of impact of underlying anatomy and repair strategy on early and late outcomes.

Introduction

Tetralogy of Fallot (TOF) is the fifth most prevalent congenital heart condition and has been studied extensively over the years. It has an incidence rate of 1 in 3500 live births so that approximately 38,000 patients are born with TOF annually around the world (1). Without treatment, 30% of patients survive to 10 years and 5% remain alive at 40 years(2). The first repair operation was performed by Lillehei in 1954 using cross-circulation and a trans-ventricular approach to the ventricular septal defect (VSD) closure and trans-annular patching (3). Since then, a spectrum of surgical alternatives to VSD closure and right ventricular outflow tract obstruction (RVOTO) relief have been developed and practiced worldwide.

Emerging data suggests that the repair technique has an impact on right ventricular (RV) physiology as early as 16 months after surgery and overall survival (4). Long-term follow-up studies have shown that the traditional trans-ventricular/transannular patching technique can result in severe pulmonary regurgitation that leads to RV dilation and dysfunction. The progressive RV failure in these patients significantly increases the risk for arrhythmia and sudden cardiac death (5). On the other hand, single-centre reports demonstrate that there is a survival advantage and higher freedom from re-operation for those with a mixed residual lesion (stenosis and regurgitation) at the level of the pulmonary annulus(4, 6). Despite these encouraging findings, studies have reported that 60 - 65% of cases are performed through the traditional trans-ventricular/trans-annular patching technique mainly due to surgeon preference (7, 8). The reluctance to adopt the annulus preservation (AP) approach may be explained by: 1) fear of leaving residual RVOT stenosis, 2) the current literature on

the impact of repair technique is of low quality consisting of small retrospective single-center reports and registries; none of the available data adjust or match participants on crucial confounders such as pre-operative cardiac morphology.

Therefore, a large international prospective cohort study is needed to establish strong evidentiary support in this field and to resolve the controversy around optimal repair technique. As background to designing such a study, we undertook a survey to determine the degree of heterogeneity in surgical practices before initiating larger clinical studies. The survey was also designed to determine the interest in conducting a large multi-center cohort study.

Material and Methods

A questionnaire was created with an aim of understanding the surgical practice patterns and research infrastructure at each site. The domains of the questionnaire were generated and reviewed by experts in the field before the distribution of the survey. The survey consisted of questions regarding characteristics of the center, TOF repair strategy and technique, post-operative care and follow-up practices, and available research resources. A convenience sample of pediatric cardiac surgeons from 18 international institutions was identified (one surgeon from each site). An invitation was sent to participants to complete the survey using REDCap (Research Electronic Data Capture). Participants were given a 2-week period to complete the survey; follow-up emails were then sent to participants with incomplete responses.

The information on the perceived repair strategies, post-operative care, and follow-up practices is presented by country. The overall summary measures for all countries, weighted by the total number of TOF repairs in each center, are also presented. The

summary measures reported are means for continuous data and counts (percentages) for categorical data. All analyses were performed using IBM SPSS Statistics 22.

Results

There was a 100% response rate to the survey with no missing data fields. These responses represent a total of 18 sites in 11 countries with an overall caseload of over 1800 tetralogy repairs annually. The participating sites represented USA, Canada, Australia, Japan, China, South Korea, Indonesia, India, Nepal, Saudi Arabia, and Turkey. Characteristics of participating sites are described in Table 1.

The survey included sites of various surgical volume capacities (15-450 repair cases per year). According to our survey the majority of sites (14/18) have a specialized cardiac pediatric intensive care unit (ICU) facility. Post-operative care was mostly commonly provided by pediatric ICU trained physicians (92%), pediatric cardiologist with interest in intensive care medicine (48%), and cardiovascular surgeons (42%). In addition, heterogeneity in the age of TOF diagnoses was noted amongst participating sites that may have an influence on the surgical management of their patient population (Figure 1).

Timing of Repair

The survey demonstrated that the majority of repairs were primary (83%). Most elective primary repair cases (60%) were performed at 6-9 months of age (figure 2). The decision to proceed with primary repair depended on patient's age and weight at time of repair. Patient's age was found to influence the repair strategy in 47% of participating sites. The most common cut-off for considering primary repair was 1-3 months of age. Patient's weight influences the timing of repair at 6 of 18 sites (14% weighted cases).

The majority of these sites (5/6) would consider primary repair for infants with a weight of 3kg and above.

Repair Technique

In 44% of sites, more than 1 general repair strategy was employed within the same institution. The choice of predominant repair strategy was influenced by institutional policy (54%), surgeon preference (40%), and level of evidence (10%) available to support the decision.

VSD closure: Approximately 38% of centres close the VSD through a ventriculotomy incision while 62% approach the VSD through a trans-atrial incision (figure 3).

RVOT management*:* Approximately half of surveyed centers operate with an aim to leave little or no obstruction at the level of the pulmonary valve. The estimated proportion of cases performed with AP, mini-TAP, and large TAP repairs is presented in figure 4. More than 70% of responders rely on the pulmonary valve z-scores to determine the management technique of the RVOT. A z-score of -3 (determined by pre-operative echocardiogram studies) is the most common cut-off to proceed with a trans-annular patch. For centers that attempt to preserve the pulmonary annulus (52%), the majority of valves (84%) were managed by a commissurotomy and a rigid bougie (Hegar) sizing during the repair procedure. At the completion of repair, the average acceptable peak trans-valvular gradient obtained by echocardiography is 38.6 mmHg (26-50 mmHg). Most centers aim for RV systolic pressure to be less than 0.8 of systemic blood pressure.

Follow-up practices

The majority (92%) of uncomplicated repaired patients attend clinical follow-up at least annually. Follow-up visits beyond the perioperative period are usually completed by the cardiovascular surgery service in 80% of cases. Otherwise, follow-up care is transferred to another service within the first month following a repair. Echocardiogram studies are the mainstay of follow-up; sedation is routinely used in 91% of studies performed in children 18-24 months of age. Cardiac MRI is routinely used in 17% of cases starting at a mean age of 10 years.

Discussion

TOF is one of the earliest studied congenital heart defects. There are a number of variations to the repair strategy employed world-wide. Emerging single center studies have demonstrated that repair technique may impact early and long-term morbidity and mortality (4, 6, 9). Therefore, a large mutli-centre clinical study is warranted to generate robust evidence in this field. We conducted a survey of 18 potential participating sites prior to commencing on a large cohort study to better understand surgical repair practices and interest in participation in this endeavor.

Timing of Repair

Our survey shows that approximately 83% of repairs were performed without preceding palliation, which is similar to the rate published from the STS database. The majority of primary elective repair cases in our survey (60%) were performed at 6-9 months of age. Data on North American practice shows repairs

being performed at 3-6months of age (7). Reasons for earlier elective repairs are not fully understood. Age of repair is usually influenced by the timing of presentation, presence of symptoms, practice preference, and greater resources for complex postoperative intensive care.

Repair strategy

This survey suggests that the majority of VSD repairs in TOF are performed through a trans-atrial approach (62%) and followed an annulus preservation strategy (53%) for managing the RVOT stenosis. A pulmonary valve annulus z-score of -3 was used as a cut-off to proceed with annulus preservation in most of these centers. The proportion of annulus preservation repair was significantly higher than reported by the EACTS and STS registries (1.5-20%) (7, 8). Measured data would be important to determine if perception and practice are fully correlated. It is also possible that practice has evolved to more transatrial repairs subsequent to the large EACTS and STS registry publications.

Variation in practice

This survey demonstrates regional variations in TOF management. The choice of surgical strategy for this population is highly influenced by surgeon preference and local policies. As such, a “standard” surgical strategy cannot be identified. We believe a rationale exists to conduct a large international multi-center inception cohort study to create strong evidentiary support for surgical management of tetralogy of Fallot patients.

Limitations

Although this survey presents a multinational picture of contemporary TOF surgical management, there are limitations that need to be taken into consideration. First and foremost, the results are a reflection of the surgeons' opinions that may suffer from recall bias. Also, there is a selection bias of participating centers and some regions were not included such as South America and Africa. Thus, it may be beneficial to increase the number of participating surgeons and centres. We attempted to achieve a balance between getting the necessary data on global practice and maintaining the simplicity and ease of completing the survey. Therefore, we elected to omit some operative details such as use of leaflet augmentation, prevalence of concomitant tricuspid valve repair, and approach to infundibular muscle resection. As our main aim of this manuscript was to convey surgical practices, we did not report on any morbidity or mortality outcomes.

In conclusion, this survey of 18 international pediatric cardiac surgery centers demonstrates variations in TOF surgical management and no accepted standard of practice. In addition, there are differences between these perceived practices and actual practices reported by large international registries. These discrepancies may be explained by the limitations of this survey or by evolving practice patterns. A multinational inception cohort study documenting the initial cardiac anatomy, surgical approaches, and intermediate and long-term outcomes is underway to more clearly inform these issues (NCT 2968264).

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none

Conflicts of Interest

Y. d'Udekem: Consultant/Advisory Board, Medical Specialties Distributors; G. S. Van Arsdell: Ownership Interest, Cell Aegis Devices; C. D. Fraser: Research Grant, Berlin Heart

Tables and Figures

Number of sites	18
Number of countries	11
Median TOF repair cases per year (min, max)	45 (15, 450)
Average number of surgeons per site (SD)	4 (± 2.46)
Median number of cases per surgeon (IQR)	16 (8, 40)
Most common age at diagnosis	1 month-<3months
Cardiac surgery patients in ICU are most commonly managed by	Pediatric ICU trained physicians, pediatric cardiologists with an interest in ICU medicine, and cardiovascular surgeons
Number of sites that use **both** intra-op TEE and direct pressure measurement to estimate RVOT pressure	12
Number of sites that use only intra-op TEE to measure RVOT pressure	3
Number of sites that only use direct pressure measurement of RVOT pressures	2

Table 1: Site Characteristics. Legend: ICU (intensive care unit), RVOT (right ventricular outflow tract), SD (standard deviation), TEE (trans-esophageal echocardiogram), TOF (tetralogy of Fallot)

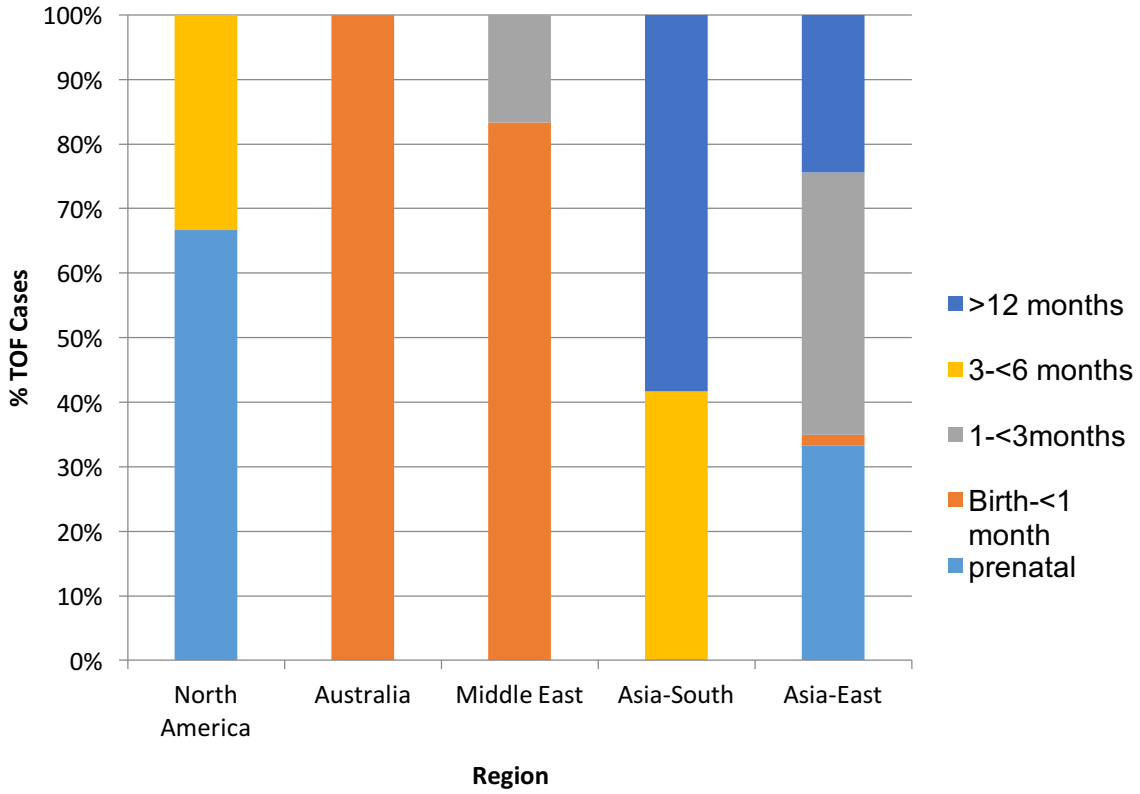

Figure 1: Variations in age of TOF diagnosis by region. Regions (number of sites): North America (3), Australia (1), Asia East (7), Asia South (3), and Middle East (4).

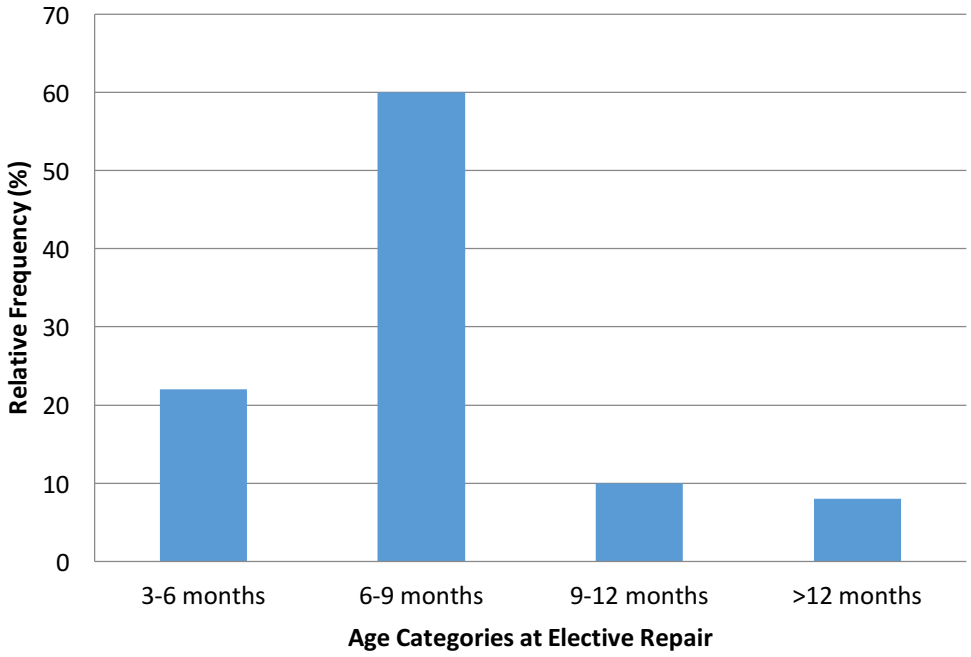

Figure 2: Age when elective repair would be considered

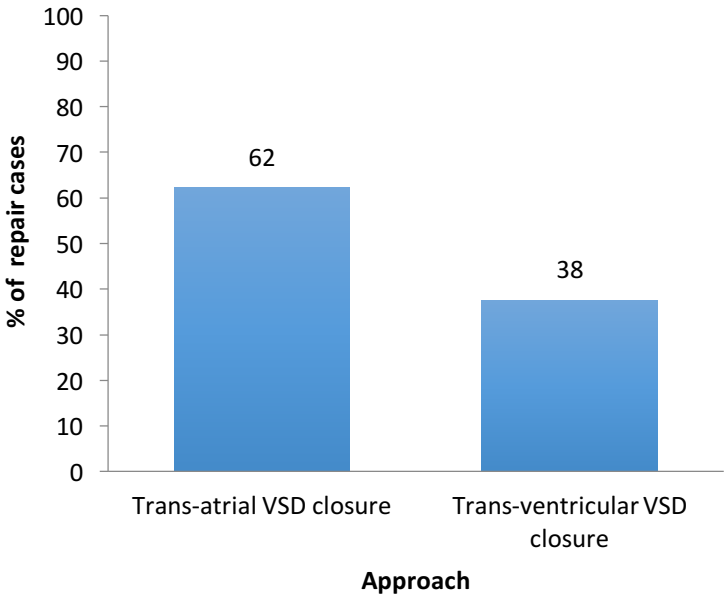

Figure 3: Proportion of VSDs closed by a trans-atrial and trans-ventricular approach

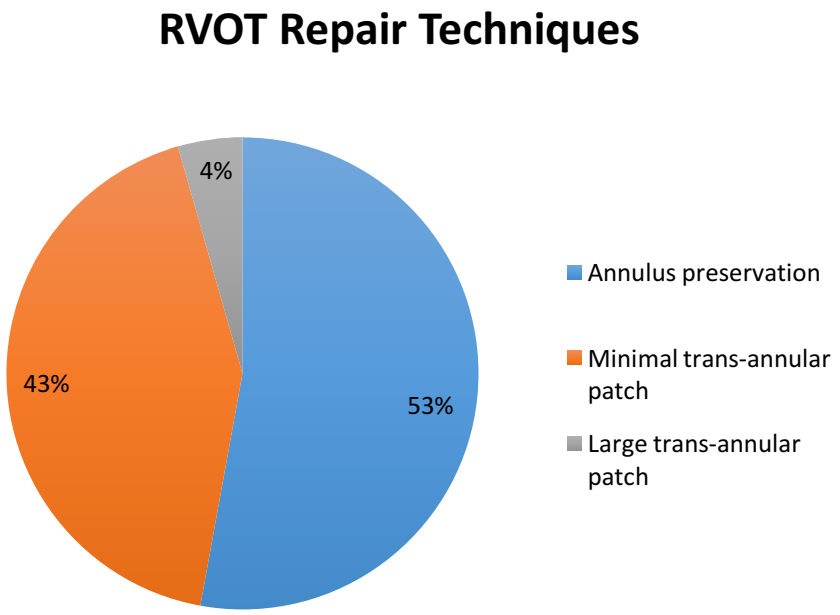

Figure 4: Common RVOT repair techniques performed

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Contributorship Statement

Sara Hussain contributed to the questionnaire design, conduct of the questionnaire, statistical analysis and interpretation of data, writing the manuscript and provided critical revisions to the manuscript.

Osman Al-Radi contributed significantly to the design of the survey and provided revisions to the manuscript.

Tae-Jin Yun contributed significantly to the design of the survey and provided revisions to the manuscript.

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Quazi Ibrahim contributed significantly to the desing of the survey, statistical analysis and interpretation of data.

Ingrid Copland contributed to design of the survey, conduct of the survey and provided revisions to the manuscript.

Richard Whitlock contributed significantly to the design of the survey, interpretation of data and provided critical revisions to the manuscript.

Glen Van Arsdell contributed significantly to the design of the survey, interpretation of data and provided critical revisions to the manuscript.

Chapter 5: Rationale, Design, and Preliminary Cohort Characteristics of the Tetralogy of Fallot for Life (TOF LIFE) Study

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Abstract

Background: Tetralogy of Fallot (TOF) surgical repair results in >95% survival into adulthood, but many survivors require cardiac re-intervention. There is no consensus on the optimal surgical strategy in TOF. Emerging evidence based on unadjusted small single centre reports show inconsistent results on the association between repair strategy and cardiac morbidity. The TOF LIFE study seeks to describe the contemporary surgical practice patterns in TOF and determine their association with RV remodelling and early clinical outcomes. We herein describe the rationale, design, and baseline cohort characteristics of the TOF LIFE study.

Methods: TOF LIFE is an international multi-centre inception cohort study with an aim to recruit 2000 TOF patients with an intention to repair and prior to any cardiac intervention. Clinical data including operative details is collected prospectively. Clinical echocardiogram studies are collected pre-operatively, at discharge, and at 2 years; studies are interpreted in a core lab. Patients are contacted by telephone at 30 days, and every 6 months, until the 2-year mark to inquire about the occurrence of clinical outcomes. At 2 years, the responsible follow-up physician is contacted to obtain the most recent clinic letter and echocardiogram study. Descriptive statistics are presented as means (SD), medians (IQR), and proportions (%) according to data type.

Results: Over 1100 participants have been recruited across 19 sites in 11 countries since June 2015. The majority of participants are male (62%) and

underwent a repair at a median age of 0.8 years (IQR 0.5, 2.3) and median weight of 8.0kg (IQR 6.7, 10.5). Over 94% of cases were primary repairs and conducted on an elective basis. The annulus preservation strategy was most prevalent (58%), followed by minimal trans-annular patching (24%) and standard trans-annular patching (18%). The repair cases had an average pump-time of 115±47.2 minutes and cross-clamp time of 75.7±35.7 minutes; multiple pump runs were required in under 10% of cases. Repair cases had a median hospital length of stay of 9 (6, 12) days. Survival exceeds 98% with 8% being re-hospitalized within a median time of 229 days (IQR 64.5, 456) from their initial repair.

Conclusions: The TOF LIFE study is the first large multicentre international prospective cohort study in this field. The conclusions from the study will lead to improved surgical decision making with regards to TOF repair strategy, resulting in the right repair strategy for the right patient.

Background

Advancements in surgical and perioperative care led to significant improvements in early survival (exceeds 98%) and clinical outcomes (1, 2). Long term follow-up studies demonstrate that TOF is a life long illness with survivors often developing RV (right ventricular) failure. Residual lesions at the time of surgical repair, mainly pulmonary insufficiency, have been shown to contribute to RV dysfunction that results in poor exercise tolerance and emergence of fatal arrhythmias in survivors(3, 4). In attempt to disrupt this cycle, many repaired survivors require cardiac re-interventions such as pulmonary valve replacements(5). Current evidence demonstrates that there is an association between clinical outcomes secondary to RV failure and the initial surgical repair strategy. Controversies exists when it comes to defining the optimal surgical repair strategy (degree of residual RVOT stenosis and regurgitation).

Generating evidence to address these controversies is not easy. Challenges in congenital cardiac studies include low overall prevalence of these conditions, large phenotypic variability at baseline, and variations in management across centres. While different inception cohort studies have been initiated by organizations like the Congenital Heart Surgeon's Society and the Pediatric Heart Network, the TOF LIFE study is the first multinational multicenter prospective observational cohort study addressing a specific surgical question. The aim of the TOF LIFE study is to define an optimal surgical repair strategy that is associated with improved post-operative right ventricular (RV) physiology in infancy that is associated with better longer-term patient important clinical outcomes. Moreover,

the study will provide a valuable source of high-quality prospective data to answer other numerous lingering questions in this field.

Evidence supporting an association between surgical strategy and RV remodeling

Liberal relief of RVOT stenosis results in significant pulmonary regurgitation immediately after repair. Compensatory mechanisms fail and progressive RV dilation along with tricuspid regurgitation result in significant atrial and ventricular arrhythmias. Repaired survivors from previous surgical eras have an ongoing risk of late sudden cardiac death of 0.5%/year with a long-term risk reaching 9% at 30 years (3, 4, 6). In fact, Gatzoulis et al reported that having a trans-annular patch poses a significant risk for developing sudden cardiac death (OR 11·7, 95% CI 1·33–103·1, P=0.027) (3, 7).

Recognition that the RV adapts to stress signals has led to the idea that leaving mixed residual stenosis and regurgitation may yield an adaptive change that limits RV dilation while still allowing for adequate cardiac output. Early attempts to limit pulmonary insufficiency and RV damage involve trans-atrial/trans-pulmonary repair with minimal trans-annular patching (mini-TAP) or complete annulus preservation (AP). Twenty-five year follow-up data from d'Udekem et al. demonstrated that these patients have a late survival of 96.9% and 85% freedom from pulmonary valve replacements (8). In contrast, long-term data on standard TAP strategies show a lower survival of around 85-90% (4). Recently, Frigiola et al. examined the physiologic and phenotypic characteristics

of a random sample of 50 late survivors of TOF repair who do not require a pulmonary valve replacement by analyzing their cardiac MRI studies, echocardiograms and exercise test findings. Out of the 14 patients who had normal exercise testing, only 3 were shown to have a trans-annular patch in their repair (21%). Overall, patients free of a pulmonary valve re-implantation were found to have mild residual pulmonary valve obstruction and unobstructed pulmonary artery branches (9); however, this data has significant limitations described below.

Preliminary data from our group

Our own retrospective propensity-matched study conducted at SickKids (Toronto) on 185 repair cases conducted between 1996-2002 demonstrates that for TOF patients with equivalent anatomy, trans-atrial ventricular septal defect (VSD) closure with annular preservation repair yields smaller RV volumes at 15 years in comparison to patients with trans-ventricular VSD closure and a trans-annular patch(TAP), 120 cc/m2 vs 180 cc/m2 ($p=0.0001$), respectively. Moreover, follow-up echocardiograms at 10-15 years following repair revealed that patients who received annular preservation repair had smaller RV chamber (RVEDDz =1.78) in comparison with TAP (RVEDDz =3.44), $p<0.0001$. Similar echocardiographic findings were also noted at 16 months following repair. In addition, patients who received annular preservation repair required fewer catheter-based re-interventions such as balloon or stent procedures in comparison to patients with TAP repair, 8% vs 20% ($p=0.071$) respectively. Freedom from pulmonary valve replacement was also significantly higher in

annular preservation repair patients (p=0.014)(10). The findings from this study suggest that the initial repair technique (AP vs TAP) results in different degrees of RV remodeling that becomes evident at 10-15 years and is associated with different incidence of cardiac complications and need for re-interventions. However, these findings must be validated in a larger multicenter cohort.

Surrogate markers for RV dilation

Indexed RVEDV (Right ventricular End Diastolic Volume) as obtained by MRI is an accurate measure of RV size. However, MRI frequently requires sedation in young children and thus, echocardiography and serial RVEDD (Right Ventricular End Diastolic Dimension) measurements are the mainstay of monitoring RV size. We performed a retrospective analysis to determine the association of early RVEDD with late RVEDVi in preparation to utilize RVEDD z-score as our primary outcome in the TOF LIFE study. This analysis revealed that RVEDD z-score at 1-5 years post-repair was a predicator for late RVEDVi (p=0.0016). A change in RVEDDz from 0 to 3 predicted an increase in RVEDVi of 28 mL. In fact, TAP repair was an independent predictor of a larger RVEDVi (p=0.0011). TAP patients had larger late RV volumes for the same early RVEDDz as those with AP repair (figure 1). Same findings were demonstrated in a sub-analysis of propensity matched patients. TAP was associated with more RV dilation throughout follow-up.

Disconnect between current practice patterns and evidence

Despite the emerging evidence suggesting superior outcomes with the annulus preservation technique, trans-ventricular VSD closure along with TAP repair continues to be the predominant technique employed globally according to STS (52-66%) and EACTS (57.5%) databases (1, 2). According to our own survey of 18 international pediatric sites (representing 1800 cases per year), over 40% of repair cases were conducted using the standard TAP technique (presented at the 52nd STS annual meeting)(11). In fact, 90% of surveyed surgeons agreed that the technique they follow is determined by personal preference and is not evidence-based. There is an overall reluctance in the surgical community to leave residual RVOT obstruction at the time of the initial repair. In addition, the AP repair is technically more demanding, sometimes requiring multiple cardiopulmonary bypass runs to optimize the repair. This results in increased operative time and perhaps increased early morbidity and mortality. In this setting of competing risks between approaches, the lack of high-quality evidence to support annular preservation has limited its uptake.

Limitations of current evidence

The following limitations of the current evidence warrant the conduct of a large cohort study to generate robust evidence in this field.

1. Single centre reports

Most data on the impact of surgical strategy arise from single centre experiences, which are retrospective and based on small patient populations.

This limits the generalizability of the results given the varied spectrum of disease and varied surgical strategy.

2. Retrospective registry data

The largest published registries are from the EACTS (n=6654) which includes data from multinational centres, and STS (n=3059) where data is limited to North American centres. These registries used in-hospital mortality as an endpoint and concluded that the trans-ventricular and TAP was associated with increased mortality. The registries do not include morphologic data and thus preclude extensive understanding of the impact of varying operative strategies. For example, by not including the patients' pre-operative clinical condition and their echo findings, it is hard to conclude whether the repair strategy is based on surgeon preference or clinical necessity. Intra-operatively, these registries used a simplified categorization for the type of repair (e.g. ventriculotomy/no ventriculotomy) and did not include detailed variables such as the size of ventriculotomy incision and how the infundibular chamber is managed. Furthermore, by not collecting information around the post-operative recovery it would be impossible to make associations between the repair strategy and early post-operative complications (e.g. restrictive physiology). Most importantly, both these registries are limited to hospitalization/30-day data and thus do not provide insight into the late impact of repair strategy. Recognizing their limitations, both these publications recommend initiation of a prospective collaborative multi-center study to investigate these long-term complications (3,8).

3. Lack of anatomical matching/adjustment

All currently published findings are not obtained from anatomically matched pairs or are not adjusted based on pre-operative anatomy. It is important to match or adjust based on pre-operative echocardiographic findings to allow stratification based on severity of the condition. In conditions where a spectrum of presentations is possible, it is difficult to draw conclusions on the impact of the repair strategy without basing this on matched patients with the same severity. This would also help eliminate many confounders that can alter the relationship between the operative strategy and outcomes. Controlling for baseline prognostic risk factors is ideally achieved through randomization in a randomized control trial. In observational studies such as TOF LIFE, we can achieve a balance in baseline prognostic risk factors during the design phase or through statistics. The results of the TOF LIFE study will be used to inform the design of a randomized control trial such as the interventions, outcomes and their MCID, and a better understanding of the research infrastructure of participating sites. We have thus chosen to adjust for baseline prognostic differences though statistical models with an aim to simplify recruitment and increase sample size.

Study hypothesis

The aim of the TOF-LIFE study is to investigate the relationship between pre-operative cardiac morphology, the choice of surgical repair strategy and early RV remodeling.

We hypothesize that in patients with equivalent preoperative anatomy, those with higher post-operative right ventricular outflow (RVOT) gradients and smaller pulmonary insufficiency (PI) jet width at vena contracta will have smaller right ventricular end diastolic diameter (RVEDD) at 2 years following repair in comparison to patients with a lower RVOT gradients and wider PI vena contracta.

Throughout the proposal, we will consider the annulus preservation strategy as any technique that results in higher post-operative right ventricular gradient and smaller pulmonary insufficiency jet width at vena contracta. The use of progressive lengths of a trans-annular patching (minimal TAP and standard TAP) in the outflow tract reconstruction results in a spectrum of decreasing post-operative RVOT gradient and wider PI jet width at vena.

Study Objectives

Primary Objective is to determine the association between TOF surgical repair technique (post-operative RVOT gradient and PI jet width) and right ventricular (RV) morphology and physiology at 2 years following repair while adjusting for crucial baseline cardiac anatomical features (pulmonary annulus, MPA and LPA sizes).

Primary Endpoint:

Indexed RV end diastolic diameter as obtained from echocardiography studies at 2 years post repair

Secondary Endpoints:

RV/LV (right ventricular/left ventricular) diastolic diameter ratio

RV function and LV function

Residual RVOT (right ventricular outflow tract) gradient

Pulmonary insufficiency vena contracta

Secondary Objectives are to describe:

- The contemporary pattern of palliation procedures (Blalock–Taussig shunt, RVOT stent, or balloon dilation), surgical repair strategy (staged versus primary repair), and surgical repair technique (annulus preservation, minimal trans-annular patching, standard trans-annular patching) at participating centers.
- The 30-day and 2-year cardiovascular mortality rate for patients with equivalent preoperative cardiac anatomy after various surgical repair techniques for VSD closure and RVOT management
- The interval mortality rate following various palliation techniques but prior to surgical repair
- The possible effect of palliative procedures (BT shunts, balloon dilation, stent insertion) on cardiac morphology (growth of the infundibular chamber, the pulmonary annulus and pulmonary artery branches' diameter) and subsequent repair technique.
- The relationship between repair technique/strategy and prevalence of post-operative restrictive physiology as defined by the presence of antegrade flow in pulmonary artery during atrial contraction on echocardiogram.

- The relationship between TOF repair strategy/technique on the incidence and prevalence of cardiac re-interventions (e.g. pulmonary valve implantation, RVOT stent insertion or balloon dilatation).

Methods

TOF LIFE is an international prospective multi-centre observational inception cohort study. Our goal is to recruit 2,000 patients with TOF prior to any intervention but with an intent for surgical repair. We will follow these patients for 2 years after surgical repair. Table 1 outlines the eligibility criteria.

Timelines (Figure 2)

Phase I: In-hospital phase

TOF patients admitted with intention for repair are offered the opportunity to participate in the study. A trained member of the research team screens patients based on the eligibility criteria. Upon obtaining written informed consent, data are collected prospectively until the patient is discharged from hospital. Intra-operative details will be collected including a photograph of the repaired heart for adjudication of RVOT management and patch measurements. The photograph is taken with a calibration ruler besides the RVOT to help ascertain the size of the patch used. The completed data collections sheets and echocardiogram studies are entered into an electronic data capture database for review, validation and analysis.

Phase II: Follow-up phase

Telephone follow-up: A member of the research team contacts the family at 30-days and every 6 months post-operatively. These are 5-minute standardized telephone calls in the patient's own language. There is a general inquiry into the health status of the patient, medications, recent cardiac-related events and hospital admissions. The patient's contact details are verified and updated as necessary to minimize loss-to-follow-up.

Routine outpatient clinical appointment follow-up: Patients with TOF require life-long cardiac follow-up and may require re-hospitalization and re-interventions. During routine clinical follow-up, an ECG and echocardiogram are performed. An introduction letter along with signed consent forms will be sent to the responsible follow-up physician when the patient becomes registered in this study. The physician's office will be contacted by the local research team to request copies of the clinic letter, echocardiogram reports/studies, and ECG at 2 years post-repair.

Event Reporting: If the patient had a cardiac related hospital re-admission or procedure, the institution where the patient was admitted will be contacted by members of the research team to request source documents. Participants are consented for data release from other institutions. If the patient is deceased, the death certificate and source documents will be requested from the institution where the death took place or from the patient's family physician if the death occurred outside of hospital. This will allow us to collect information about the

cause of death. The cause of death will be adjudicated to ensure correct classification of cardiovascular and non-cardiovascular causes.

Statistical Considerations

Descriptive Data

Baseline demographic characteristics of the study population will be presented by repair strategy. For continuous variables, means (standard deviations) or medians (inter quartile ranges) will be reported. Categorical variables will be presented as counts (percentages). In addition, we will present the mean and SD for post-operative RVOT gradient and PI jet width per surgical technique (AP, mini-TAP, and standard TAP)

Analysis of the primary end-point (RVEDD z-score)

The association of TOF surgical repair technique with change in RVEDD z-score at 2 years post-repair will be studied using multi-level (country, center, and participant) linear regression models. We will initially examine the association of each variable of interest with the outcome using univariate regressions. Then, a multivariable model of the outcome will be fitted including: the test variables representing each surgical technique (i.e. post-operative RVOT gradient and PI jet width), variables that are clinically important, and variables that are found significant ($p < 0.20$) at the univariable analyses. The final multivariable model will include the test variables, variables that are clinically relevant or significant at $p < 0.05$ or important confounders.

Analysis of secondary endpoints

The 30-day and 2-year cardiovascular mortality rates for patients with equivalent preoperative cardiac anatomy will be compared between various RVOT gradients and PI vena contracta using Kaplan-Meier curves, log-rank tests. Regression analyses will be performed to compare the hazard rates between the various surgical techniques while adjusting for patient's anatomy and other potential confounders. Multilevel mixed effects parametric survival model will be used to account the nested structure (country, center, and participant) of the data.

Sample size justification

Average changes in the outcomes at 2 years compared to the baseline will be studied using a random intercept model of the following form:

$$(\text{Observed change in RV diastolic dimension z-score})_{ij} = \alpha_0 + b_{0i} + \beta_1 * X1_{ij} + \beta_2 * X2_{ij} + e_{ij}, \quad (1)$$

where observation on j^{th} individual in i^{th} centre is represented by ij^{th} subscript; $X1_{ij}$ and $X2_{ij}$ are the two dummy variables corresponding to the three repair techniques: annular preservation, mini TAP and large TAP, respectively. Here, annular preservation is the reference category. The random effect (intercept) for the i^{th} centre, $b_{0i} \sim N(0, \tau^2)$ and the random error term, $e_{ij} \sim N(0, \sigma^2)$ where b_{0i} and e_{ij} are independent of each other. It is anticipated that on an average, annular preservation, mini TAP and large TAP would be performed on 50%, 45% and 5% of cases, respectively. A preliminary analysis using Toronto SickKids data

suggesting a change of 0.5 to 1 unit in RV diastolic dimension z-score could be clinically important. The study will be powered to detect a minimum difference of 0.5 unit in changes in z-scores between repair techniques. To detect anticipated differences in average changes in RV diastolic dimension z-scores between mini TAP and annular preservation; large TAP and annular preservation at the overall 0.05 level of significance (α), powers are calculated based on Wald tests (two-tailed) for $_i$ in the linear mixed model (1) as

Power = $\frac{i}{\sqrt{Var(\hat{\ }_i)}}$ $z_{1\ \frac{0.05}{2\cdot 2}}$

where is the cumulative standard normal distribution function. Assuming an intra-centre correlation, ICC (ρ) of 0.10 in observed changes and within-centre variability (standard deviation) of σ=2.75, between-individual variability (τ^2) is estimated from the relation $\rho=\tau^2/(\tau^2+\sigma^2)$. The calculated powers for a sample of 2000 participants at different detectable differences in change in RV diastolic dimension z-scores are given in table 2.

Study management

The study is centrally coordinated by PHRI (Population Health Research Institute, Hamilton, Ontario) a joint institute of McMaster University and Hamilton Health Sciences. The central team at PHRI is responsible for the organization of the study, development of study database, data internal consistency checks, data analysis, and coordination of the international centres. The team is able to communicate with sites in English or other local languages. National leads are

responsible for research ethics applications at each site within their country, organization of training and follow-up meetings, dealing with issues related to recruitment, data quality, and ensuring high rates of follow-up.

We have collaborated with SickKids Hospital to set up core labs for centralized data interpretation of echocardiograms, ECGs and operative photographs. Potential sites are screened based on responses to a feasibility survey to ensure that each site has sufficient infrastructural capabilities to participate in the study. Prior to initiating a site, the site research team (including echocardiographers) are trained through a series of webinars to outline the data collection process and the required echocardiography views.

The Steering Committee of the TOF LIFE study includes Principal Investigators and National leaders from each participating region. The Steering Committee is responsible for the design, execution, analysis, and reporting of the trial, and assigns appropriate responsibilities to the other trial committees. The Steering Committee will hold the primary responsibility for publication of the study results. This committee convenes regularly by telephone conference to address policy issues and to monitor study progress, execution and management.

Ethical considerations

This study will be conducted in compliance with the protocol, principles laid down in the Declaration of Helsinki, and Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), where applicable. This study will also comply with local regulations within each country where patients

are enrolled. Before study initiation, the Investigator must have written and dated approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the protocol, consent/assent forms, patient recruitment materials/process and, where applicable, approval by the participating countries Competent Authority in accordance with local laws and regulations. All patient information will be stored on a high security computer system and kept strictly confidential.

Results

Since June 2015, the TOF LIFE study expanded to include 19 sites across 11 countries (figure 3). As of September 2020, 1119 participants were recruited (table 3). TOF was diagnosed postnatally in 784 (74%) of cases. The majority of patients were male (691, 62%). Patients underwent surgical repair at a median age of 0.8 years (IQR 0.5, 2.3) and median weight of 8.0kg (IQR 6.7, 10.5). A primary repair strategy was implemented in 94% of cases. In the 56 cases that were palliated initially, 79% received a systemic-to-pulmonary shunt. Although most cases were performed on an elective basis (96%), 1 in 5 patients had a history of hypercyanotic spell and 1% required prostaglandin infusion.

The annulus preservation strategy was most prevalent (58%), followed by minimal transannular patching (24%), and standard trans-annular patching (18%) as seen in figure 4. Repair cases had an average cardiopulmonary bypass time of 115±47.2 minutes and aortic cross-clamp time of 75.7±35.7 minutes. Multiple bypass runs were required in nearly 8% of cases. The median ICU length of stay

was 3 days (IQR 2.0, 5.0) and median hospital length of stay was 9 days (IQR 6.0, 12.0). Survival exceeded 98% thus far in the follow up period. Deaths occurred at a median of 13 days following repair (IQR 7.0, 52.0). About 8% of patients were re-hospitalized at a median of 229 days (IQR 64.5, 456) from repair.

Discussion

With the advancement in perioperative management, there is an increasing number of TOF repair survivors. Patients often suffer from life-long cardiac morbidity and mortality, often requiring cardiac re-interventions on the RVOT in an attempt to halt the process of adverse cardiac remodeling. There is heterogeneity in surgical management of TOF patients due to the lack of robust evidence to support surgical decision making.

TOF LIFE is the first known international prospective cohort study that aims to define the cardiac morphological features critical to the success of the surgical strategy chosen, the impact of repair strategy on degree of RV remodelling and early clinical outcomes. The proposed protocol has several methodological strengths that are anticipated to yield much needed robust conclusions in this field. The study is prospective allowing for data collection of accurate baseline and operative details such as the extent of the transannular patch. Necessary echocardiograph measurements are obtained by a blinded core lab team to standardize these measurements and limit biases. Regression models will control for pre-operative anatomy; TOF can present in a large

spectrum and baseline morphology can skew results significantly. Efforts are in place to include a variation of repair practices to improve the external validity of our conclusions.

The TOF LIFE study represents one of the largest international research initiatives undertaken in CHD. We anticipate that this study's conclusions will impact future clinical and academic efforts in this field. We aim to establish evidence-based decision making for TOF surgical management. The optimal repair strategy identified from this study would be associated with improved RV size and function. Thus, there will be fewer medical complications and re-interventions, reducing the burden on the patient and health care resources.

Tables and Figures

Inclusion	Exclusion
• Patients of any age with an intention to undergo TOF surgical repair • Diagnosis of TOF with RVOT stenosis. TOF is defined as anterio-cephalad deviation of the ventricular outlet septum with no more than 50% aortic override and a single outflow VSD. • Patients with coronary artery anomalies, right aortic arch, and 22q11 deletion may be included	• TOF with absent pulmonary valve or pulmonary atresia • Other major cardiac anomalies such AVSD, multiple VSDs, right atrial isomerism • Presence of major aortopulmonary collaterals (MAPCA's), this does not include prominent bronchial collateral arteries. • Unbalanced ventricles precluding biventricular repair • Major genetic abnormalities/syndromes e.g. trisomy 13,18, and 21 • Major extra cardiac anomalies e.g. diaphragmatic hernia, omphalocele, • Infective endocarditis as an indication to intra-cardiac repair • Stroke in the last 30 days prior to palliation or intra-cardiac repair • Known diagnosis of HIV or hepatitis B

Table 1: TOF LIFE eligibility criteria. TOF: tetralogy of Fallot, RVOT: right ventricular outflow tract, VSD: ventricular septal defect, AVSD: atrioventricular septal defect, MAPCA: major aortopulmonary collateral arteries

Mean change in RVEDD z-score in AP	Detectable difference in the change in z-score between repairs		ICC (ρ)	Common SD of changes in the z-score (σ)	Overall level of significance (α %)	No of centres	No. of individuals per centre	Power (%)	
	Mini TAP - AP	Large TAP - AP						Mini- TAP - AP	Large TAP - AP
0.25	0.50	0.80	0.10	2.75	5	25	80	96	70
0.25	0.50	0.90	0.10	2.75	5	25	80	96	80
0.25	0.50	1.00	0.10	2.75	5	25	80	96	89

Table 2: Calculated power at different detectable differences in change in RV diastolic dimension z-scores. With an expected sample size of 2000 participants (80 participants per site with 25 sites expected), this table represents the power to detect the difference in the change of RVEDD z-score between the various techniques. The change in RVEDD z-score between baseline and 2 years for the AP strategy will be used as the baseline for comparison.

Variable	n=1119
Age at repair (yr), median (IQR)	0.8 (0.5, 2.3)
Male, n(%)	691 (62)
Weight at repair (kg), median (IQR)	8.0 (6.7, 10.5)
Number with primary repair (%)	1063 (94)
Number of elective repairs (%)	1058 (96)

Table 3: Summary of cohort demographics, baseline characteristics, and surgical strategy

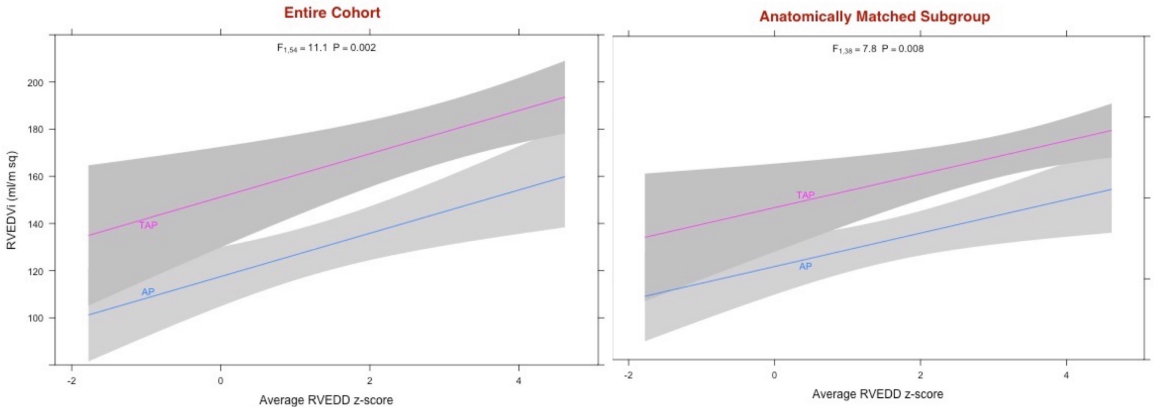
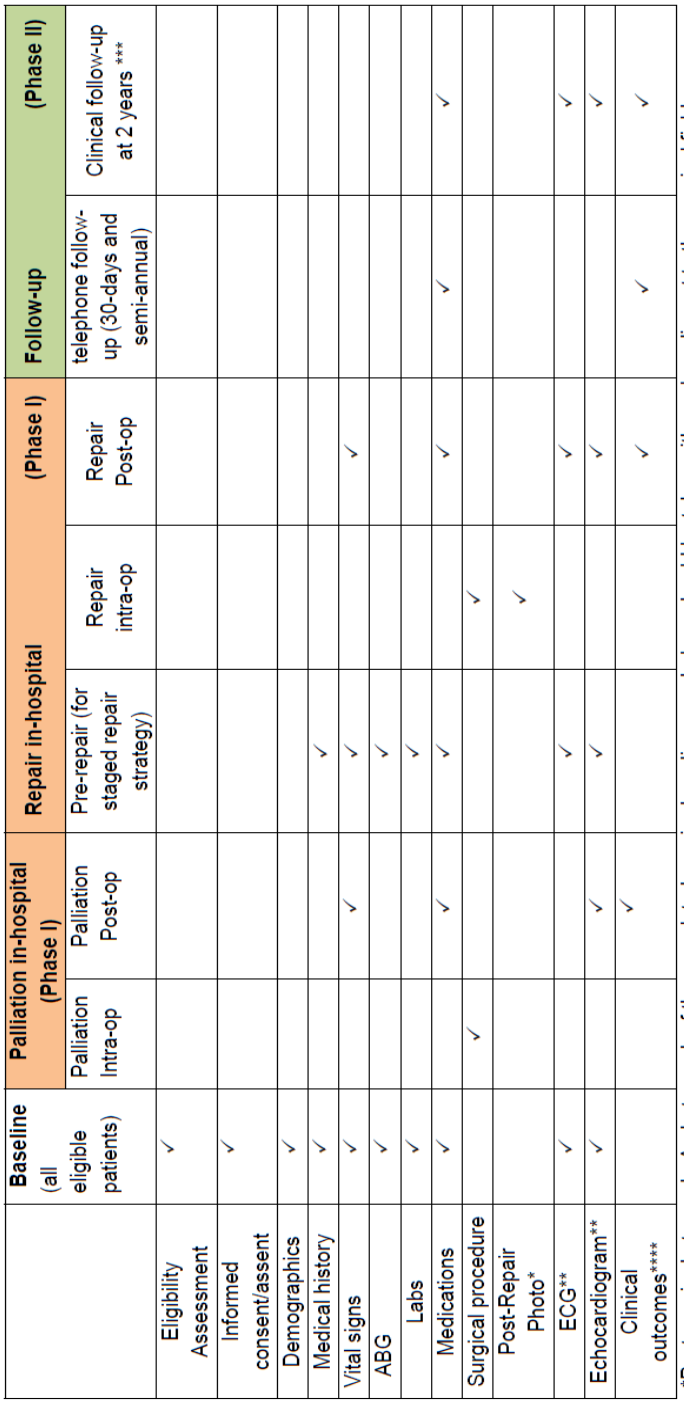


Figure 1: The correlation between early RVEDD z-score obtained by echo at 1-5 years post-repair and late RVEDVi measured by MRI. The analysis was conducted on the entire cohort and repeated for anatomically matched patients which yields similar finding



	Baseline (all eligible patients)	Palliation in-hospital (Phase I)		Repair in-hospital		(Phase I)	Follow-up	(Phase II)
		Palliation Intra-op	Palliation Post-op	Pre-repair (for staged repair strategy)	Repair intra-op	Repair Post-op	telephone follow-up (30-days and semi-annual)	Clinical follow-up at 2 years ***
Eligibility Assessment	✓							
Informed consent/assent	✓							
Demographics	✓							
Medical history	✓			✓				
Vital signs	✓		✓	✓		✓		
ABG	✓			✓				
Labs	✓			✓				
Medications	✓		✓	✓		✓	✓	✓
Surgical procedure		✓			✓			
Post-Repair Photo*					✓			
ECG**	✓			✓		✓		✓
Echocardiogram**	✓		✓	✓		✓		✓
Clinical outcomes****			✓			✓	✓	✓

*Post-repair photograph: A photograph of the completed repaired cardiac morphology should be taken with a ruler adjacent to the surgical field.
**Accept the most recent ECG or echocardiogram dated closest to the above pre-defined time periods. The echocardiogram and ECG will be transferred to PHRI for central reading.
*** Time window to accept cardiology visit information is 18 months-28 months post-operatively
***Clinical outcomes include heart failure, arrhythmia, re-hospitalization, cardiac re-interventions, and mortality
There will be no added interventions for the purpose of this research study. In addition, if an investigation is not performed or is of poor quality no repeats will be requested for this study

Figure 2: TOF LIFE study data collection summary

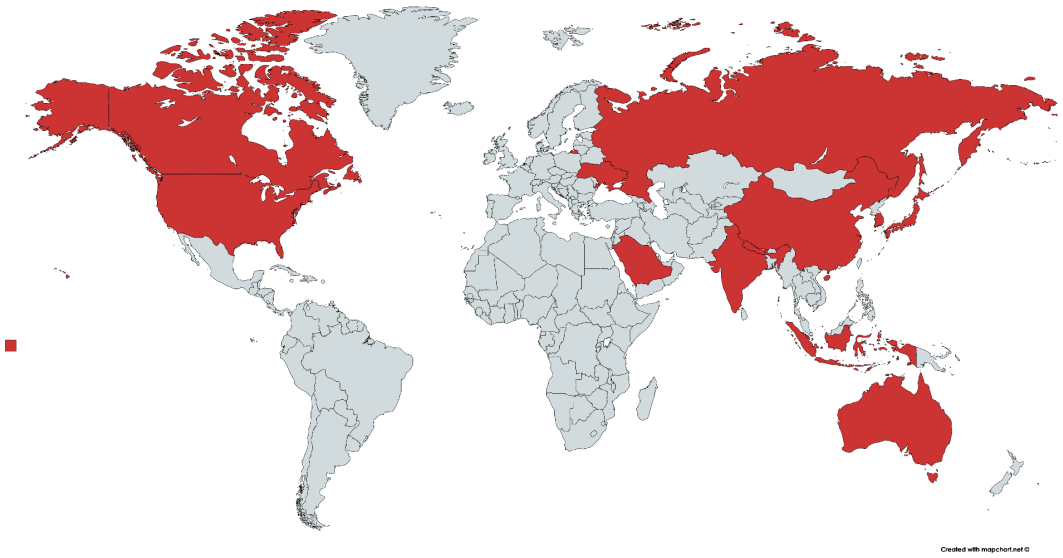


Figure 3: TOF LIFE is an international collaboration that includes sites across 11 countries

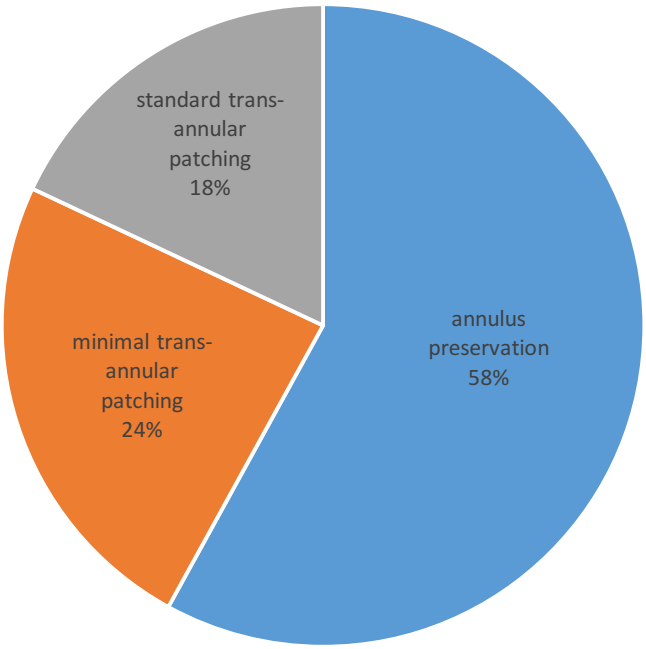


Figure 4: Overall breakdown of surgical strategy

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Contributorship Statement

Sara Hussain contributed significantly to the study design and daily operations of the study, interpreted the data and wrote the manuscript and provided critical reivisions to the manuscript.

Emilie Belley-Cote contributed to the interpretation of data and provided critical revisions to the manuscript.

Ingrid Copland contributed to the daily operations of the study and provided revisions to the manuscript.

Quazi Ibrahim contributed to the statistical considerations and calculation of sample size and provided revisions to the manuscript.

Luc Mertens contributed significantly to the study design, daily operations of the echocardiogram core lab, and provided revisions to the manuscript.

An Qi contributed to the study design and conduct of the study.

Yves D'Udekem contributed to the study design and conduct of the study.

Sylvanus Fonguh contributed to the statistical analysis and provided revisions to the manuscript.

Feng Xie provided revisions to the manuscript.

PJ Devereaux contributed to the study design and provided revisions to the manuscript.

Andre Lamy contributed to the study design and provided revisions to the manuscript.

Glen Van Arsdell contributed significantly to the study design, conduct of the study, data interpretation and provided critical revisions to the manuscript.

Richard Whitlock contributed significantly to the study design, conduct of the study, data interpretation and provided critical revisions to the manuscript.

Chapter 6: Conclusions and Future Directions

Background

This doctoral thesis explored contemporary tetralogy of Fallot (TOF) surgical management strategies and their association with right ventricular (RV) remodeling. The literature review and original studies in this thesis explore the use of early echocardiographic surrogate markers for late adverse RV remodeling following repair, the association of repair strategy with late right bundle branch block, the variations in surgical management of TOF, and the design and rationale of a multicentre cohort study addressing the optimal TOF surgical repair strategy - an important question in this field.

Summary of findings

This thesis is based on a multi-pronged clinical research program exploring outcomes following TOF surgical repair.

In chapter 2, we report on a retrospective cohort of 185 TOF patients repaired at SickKids Hospital during 1996-2002. We used a linear regression model to determine the predictive value of early post-repair RV end diastolic dimension (RVEDD) measured on echocardiogram for later RV volumes, a commonly used measure of RV remodeling. This study concluded that early RVEDD can help predict late RV volumes on cardiac magnetic resonance imaging (MRI) scans, R^2=0.47. In summary, almost half of the variability (or changes in) late RVEDVi is explained by early RVEDD on echocardiograms. Using longitudinal analysis, we showed that trans-annular patch (TAP) repair

leads to more rapid RV dilation than annulus preservation (AP) repair. Studies on congenital heart disease face methodological challenges due to inherent natural history of these conditions including low prevalence and occurrences of late "hard" clinical outcomes. Therefore, clinical studies in congenital heart disease often focus on surrogate outcomes. Based on the results of this study, validating RVEDD's association with late outcomes, we elected to use RVEDD as a primary end point for the tetralogy of Fallot for Life (TOF LIFE) study which will be discussed later.

In Chapter 3, we report on a retrospective cohort study combining patients form SickKids Hospital in Toronto, Canada, and Royal Children's Hospital in Melbourne, Australia. Between the two centres, 402 TOF repairs were performed between 1996 and 2002. The majority of these repairs were primary and conducted with a trans-atrial approach to ventricular septal defect (VSD) closure along with a minimal trans-annular patch. At a mean follow-up of 17 years, over half the cohort had developed a right bundle branch block. QRS prolongation is a sign of RV remodelling; subsequently conduction delays adversely impact interventricular function(1). Using logistic regression, we found that a trans-ventricular incision along with standard transannular patch repair approach to the VSD in TOF repair was associated with an increased odds of conduction delays, suggesting an association between surgical repair strategy and late adverse clinical outcomes.

Since the first TOF repair in 1954, surgeons have developed different repair strategies (2). We were, therefore, interested in describing current surgical

practices among pediatric centres world-wide. In chapter 4, we report on a survey of 18 pediatric cardiac surgery centres in 11 countries aiming to evaluate variation in TOF repair practice and research infrastructure as initial steps to setting up the TOF LIFE study. In 44% of the institutions, surgeons used more than one repair strategy. The choice of the strategy was influenced by institutional policies, surgeon preference and evidence. Despite current evidence suggesting an association between repair strategy and adverse RV remodeling especially with more liberal relief of RVOT stenosis, our survey revealed over 60% of repairs were performed with a standard trans-annular patch with trans-ventricular VSD closure. These results illustrate that there is a wide variation in surgical practice (even within the same centre) and these practices are not necessarily evidence-based.

The results highlighted in the previous chapters helped in designing and implementing the TOF LIFE study. In chapter 5, we outline the design, rationale, and baseline cohort characteristics of the TOF LIFE study. The TOF LIFE study is a large multicentre cohort study that will recruit 2000 TOF participants prior to any cardiac interventions and with a follow-up period of 2 years after surgical repair. The primary objective of the study is to define the association between different surgical strategy with early RV remodeling endpoints from echocardiogram studies at 2-year follow-up. As of September, over 1100 participants were recruited from 19 sites spanning 11 countries. The majority of the cohort thus far underwent a primary elective repair with an annulus preservation strategy (58%), 24% a minimal trans-annular repair, and 18%

standard trans-annular repair. The TOF LIFE study design aimed to address the limitations of published clinical studies on TOF. At baseline, we will adjust for important confounders and effect modifiers as defined from previous work using regression models. Importantly, a baseline echocardiogram study measures phenotypical confounders because TOF presents a spectrum of severity. In addition, we plan to enroll 2000 participants from international sites which, overcoming limitations of small single centre cohorts. Finally, a prospective analysis will allow for more accurate and adjudicated data collection than retrospective analyses. Importantly, we will adjudicate operative technique using intra-operative photographs. Furthermore, we have established a core lab to standardize key echocardiogram measurements. TOF LIFE offers a unique opportunity of creating a cohort who can be followed long-term to answer many controversies in the field.

Limitations of work done

Despite the evidence generated by the studies conducted in this thesis, important limitations are worth mentioning.

In chapters 2 and 3, retrospective cohort designs addressed our research questions. Inherent limitations exist when using such retrospective designs and chart review. For example, we were limited in adjudicating the surgical strategy used. The os infundibulum is not an easily found surgical landmark. Therefore, the number of standard TAP repairs can be underestimated. In addition, using clinically available data limits how we can control for important confounders or

effect modifiers at baseline. For example, in chapter 3, it was hard to find pre-operative echocardiogram reports, which prevented us from adjusting for pre-operative morphology during our analysis.

There is also a question about the external validity of our results. The surgical practice patterns of the SickKids Hospital and the Royal Children's Hospital in Melbourne differ from that outlined in global registry data. For example, these centres have higher rates of AP and mini-TAP and very low rate of standard TAP repairs. This highlights the importance of multi-centre data to increase the generalizability of the evidence generated from research.

Inherent to clinical research on congenital heart disease, these methodologies are limited by the low prevalence and thus the small sample sizes. A good example is that in chapter 3, our analysis of malignant arrhythmias or cardiac re-interventions was limited by the low number of outcomes for a logistic regression analysis. Thus, we decided to explore the association of surgical repair strategy with conduction delays as the outcomes were more numerous.

Another important limitation of congenital heart disease is follow-up. For example, in chapter 2, our linear regression analysis was based on 57 patients for whom we had early postoperative echocardiogram studies and had a cardiac MRI (prior to re-intervention). This can create bias in that these patients maybe the ones with the most RV remodeling thus requiring a cardiac MRI before undergoing a pulmonary valve re-implantation. At the time when this study was conducted, there was no consensus as to when cardiac MRI scans should be

performed in follow up, and this was left to the discretion of the follow up physician. In an ideal world, this study should be conducted by having a follow-up cardiac MRI on the complete cohort, which would be limited by feasibility and funding.

In Chapter 4, we used a survey to understand the variations in surgical TOF management. We did encounter a number of challenges and limitations with this design. First, there was a selection bias in the surgeons we sampled. The survey was based on a convenience sample of pediatric cardiac surgeons who may have similar biases when it comes to TOF surgical repair to the investigators. This survey could be improved by random sampling of surgeons from a database. In addition, the responses may be altered by recall bias. For example, the proportion of each repair strategy can be under or overestimated. We also encountered some challenges when designing the survey questions to effectively capture the wide variations in practice. We collaborated with a number of experts in this field to review the survey prior to disseminating it to the participants to ensure its completeness and ease.

Chapter 5 describes the methodology of the TOF LIFE Study. Despite the strengths of this study including its large sample size, multi-centre participation, and adjustment for preoperative morphology, we encountered a number of challenges so far. In attempt to improve the generalizability of the results from the TOF LIFE study, we included institutions who may be inexperienced in participating in multi-centre studies. At the start of the study, some centres did not have designated research coordinator and relied on clinical staff for screening

and recruitment etc. This resulted in a slower than expected recruitment rate. Therefore, our research team helped to fund research staff where needed. In addition, some of these centres were not familiar with electronic data collection. In response, we created a series of webinars in English and Mandarin to provide all the necessary information to enter data in our electronic database system.

During a trip to the TOF LIFE Chinese sites in December 2018, the recruitment teams highlighted an important limitation which is a high attrition rate. This was especially true for the sites in China where patients from remote areas would come to the tertiary pediatric centres for their repair operation and would return to their homes thereafter. These patients may have little or no access to medical care and thus would limit the number of events reported or echocardiograms obtained at 2 years. In order to overcome a high attrition rate, we planned to contact patients periodically (every 6 months) to update their contact information and ensure a good rapport with the research team. In addition, we have created multiple portals for communication with patients including telephone, email, and social media (especially WeChat in China).

Another bias that may exist in a non-randomized comparison of techniques relates to expertise. Annulus preservation strategy is technically more difficult than the standard trans-annular patch technique, often requiring multiple bypass runs. Higher volume centres where surgeons are trained to perform the AP technique may have higher AP repair rates and are more equipped to manage complications of leaving a higher RVOT gradient. We will seek to adjust for these effect modifiers in our analysis of the TOF LIFE results by

including them as terms in our regression models or through sensitivity analysis by centre.

In addition to variation in clinical practices, our Core Lab has detected variations in the quality of the echocardiograms from participating sites that may preclude analysis of important echocardiogram parameters. The TOF LIFE echocardiogram team at SickKids review the echocardiograms from each participating site and provide periodic feedback to help improve the quality of these images. In addition, we will conduct interim analyses for quality control periodically throughout the remaining recruitment. To resolve any issues with regards to image requisition, we refer sonographers to a webinar for image requisition that was created based on the *ASE guidelines*. Moreover, we have set-up teleconferences and face-to-face meetings to resolve more outstanding issues.

Future direction

During my work on this thesis, several ideas have stemmed to further develop this TOF research program.

1) Extend the follow-up of TOF LIFE participants to 15 years following repair

Research in congenital heart disease often relies on the use of surrogate markers which have inherent limitations and dangers. Clinical presentation of RV failure usually become apparent 10-15 years after repair such as the need for pulmonary valve replacement(3). This follow up should ideally involve cardiac MRI scan and an exercise stress test. Despite the challenges that will be

encountered, such as costs and minimizing the attrition rate, such long-term prospective data will be valuable for future decades of research on RV remodeling as it includes both clinical and imaging data. It will be important to include more modern ways of patient follow up such as using social media and communication applications to facilitate research.

2) *Include a biobank component to the TOF LIFE study.*

During our collaboration with SickKids Hospital, there is an interest in setting up a biobank to collect blood samples and RVOT muscle tissues at the time of surgery. There is an interest in determining the stress signals at the cellular levels that are responsible for the RV response to volume or pressure stress signals. In the future, we for see a move towards “personalized surgery” that would take into account the individual’s genotype and their potential response to the particular surgical repair technique. A biobank would also allow for testing of novel drugs that may interfere with the RV remodelling cellular signals.

3) *A randomized control trial of surgical repair strategy*

The results of the TOF LIFE study will inform the design of a randomized control trial to determine the optimal surgical strategy that results in the best outcome profile for survivors. First, the TOF LIFE study will help us determine what the intervention and control group will consist of. Currently, standard TAP is suggested to have more late adverse outcomes in comparison to the more conservative approaches such as minimal TAP or AP. Therefore, including a standard TAP arm of an RCT may lack equipoise in the congenital community. However, controversies still exist on the RV remodeling following minimal TAP

and AP strategies. In addition, the minimal TAP strategy can overcome many technical challenges encountered with the AP strategy. Therefore, an RCT of AP vs minimal TAP may be reasonable to consider. Another methodology consideration is the unit of randomization: whether that would be the patient or their surgeon in a cluster design. Another issue to resolve is establishing appropriate eligibility criteria for such a trial. As mentioned in earlier chapters, surgical decisions on repair strategy are more difficult and controversial when the patient's morphology falls in the "gray zone." The TOF LIFE study results will help us define that gray zone in baseline morphology (e.g. size of pulmonary valve annulus) where management decisions are not clear cut. Finally, the TOF LIFE study results will help us to better define our objectives and endpoints. For example, we will have a large database to define the minimal clinical important difference in the change of RVEDD. The MCID in RVEDD will help guide clinical decision making when following repair survivors with serial echocardiogram studies and in powering research studies that use RV failure as an outcome.

Summary

The chapters in this thesis provide insight into the RV remodeling following TOF surgical repair. The TOF LIFE cohort study outlined in chapter 5 will provide evidence to address important knowledge gaps in surgical decision making. I believe that the TOF LIFE study along with future clinical research in this program will ultimately help generate evidence for a fast-growing number of congenital heart disease survivors. Even though repaired TOF patients require life- long

follow-up, our results can decrease the burden of adverse outcomes for TOF patients, their families, and our health care system.

Health Research Methodology skills utilized in each chapter

Chapter 1: Introduction

- Critical appraisal skills

Chapter 2: Early right ventricular dimension is a marker of late right ventricular volume after tetralogy of Fallot repair

- Descriptive statistics
- Linear regression
- Subgroup analysis
- Repeated measures

Chapter 3: Traditional tetralogy of Fallot surgical repair is associated with unfavourable right bundle branch block

- Descriptive statistics
- Logistic regression
- Multicollinearity
- Testing for model discrimination
- Missing Data

Chapter 4: Survey of multinational surgical management practices in tetralogy of Fallot

- Descriptive statistics

- Survey methods and implementation
- Conceptualization and measurement concepts related to surveys
- Missing Data

Chapter 5: Rationale, Design, and Preliminary Cohort Characteristics of the Tetralogy of Fallot for Life (TOF LIFE) Study

- Formulating a research question and study objectives
- Study protocol development
- Design of cohort study
- Data collection and adjudication
- Sampling and sample size
- Ethics of research

Chapter 6: Conclusions and Future Directions

- Research and critical appraisal skills
- Randomized control study design

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