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Structure-Function Studies in Adults with Repaired Tetralogy of Fallot

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Shamus O’Meagher
ABSTRACT

Presently, there are more adults than children with congenital heart disease. Although this represents an outstanding achievement of medical management, mostly through improved surgical techniques, numerous clinical problems plague these adult survivors. This thesis investigates some of the more important issues faced by one of the commonest groups of CHD survivors, adults with repaired tetralogy of Fallot.

Persistent issues of importance include; optimising timing of pulmonary valve replacement late after tetralogy repair; elucidating the determinants of exercise capacity; and outlining structure-function correlates using newly available technologies. Taken together, these questions are important to provide a greater understanding of clinical issues and to aid in generating solutions to these problems.

A significant amount of uncertainty surrounds the indicators for pulmonary valve replacement in adult patients with repaired tetralogy of Fallot. Regional bodies such as the American Heart Association, the American College of Cardiology and the European Society of Cardiology have produced guidelines as to when the pulmonary valve should be implanted. However, the indicators provided in these documents are somewhat non-specific and lack consensus. In any case, monitoring of ventricular structure and function in pre-pulmonary valve replacement patients remains important. Chapter 5 reports that a significant degree of right ventricular dilatation occurs over a relatively short period of time. We found that right ventricular volume
increased from slightly below to marginally above a commonly used indicator for pulmonary valve replacement over just 2 years. Importantly, Chapter 7 found that pre-surgical right ventricular outflow tract volume correlated negatively with post-surgical right ventricular function and exercise capacity. Furthermore, higher right ventricular muscular corpus volume before surgery was associated with lower improvement in global right ventricular volume after surgery. Global right ventricular volume is commonly weighted heavily as an indicator for pulmonary valve replacement. However, based on the results of Chapter 7, assessing regional right ventricular volumes may provide additional insights in the decision of when to surgically intervene. In light of the above mentioned results, regular monitoring of right ventricular volume via cardiac MRI with delineation of the right ventricular outflow tract and muscular corpus may be warranted.

Although previous reports suggest decreased exercise capacity in adults with repaired tetralogy of Fallot, we found exercise capacity to be near-normal in our cohort. Chapters 3 and 4 describe a normal metabolic response to exercise, and even though peak exercise reached a marginally lower level than predicted in a normal healthy population, our cohort exhibited significantly higher exercise capacity than previous research. Exercise capacity was, in part, maintained by increased right ventricular mass measured at rest and decreased pulmonary regurgitant fraction during exercise; Chapter 6 reports increased biventricular outputs and ejection fractions and decreased pulmonary regurgitant fraction as exercise intensity increased. Right ventricular mass and right ventricular mass to volume ratio were found to be positively correlated with peak exercise capacity in Chapter 3. We found
that with each 10 grams of increased right ventricular mass, peak work was 8 Watts higher. It seems, an adequate level of musculature and appropriate compliance of the right ventricle may be important in providing sufficient forward flow of blood into the pulmonary circuit and, in turn, maintaining exercise capacity.

Long-term survival in adult repaired tetralogy of Fallot has improved appreciably over time. However, the significant risk of sudden cardiac death remains of concern. To the best of our knowledge, Chapter 8 provides the first description of the causes of death in this cohort. We found that presumed arrhythmia leads to sudden cardiac death in two-thirds of cases. This is an important finding and may suggest that this patient cohort requires closer scrutiny in regards to arrhythmia detection and monitoring in both the clinical and research settings. This is clearly an important area for further detailed investigation.

In total, the studies within this thesis provides insight into some of the persistent issues faced by adults with repaired tetralogy of Fallot and may prove valuable in clinical decision making in this patient group.
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Original Papers


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O’Meagher S, Munoz P, Alison J, Young I, Celermajer DS, Puranik R. Structure-function correlates in adults with repaired tetralogy of Fallot. Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2010
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ABBREVIATIONS

BSA  body surface area
BT shunt Blalock-Taussig shunt
CO  cardiac output
CPET cardiopulmonary exercise test
ECG  electrocardiogram
EF  ejection fraction
LV  left ventricle
LVEDVi indexed left ventricular end-diastolic volume
LVESVi indexed left ventricular end-systolic volume
MRA  magnetic resonance angiography
MRI  magnetic resonance imaging
PA VSD pulmonary atresia with ventricular septal defect
PFTE polytetrafluoroethylene
PR  pulmonary regurgitation
PRF  pulmonary regurgitant fraction
PVR  pulmonary valve replacement
RV  right ventricle
RVEDVi indexed right ventricular end-diastolic volume
RVESVi indexed right ventricular end-systolic volume
RVMC  right ventricular muscular corpus
RVOT right ventricular outflow tract
SV  stroke volume
TAP transannular patch repair
TOF  tetralogy of Fallot
VE/VC02 ratio of minute ventilation to carbon dioxide production
VO2peak peak oxygen consumption
VSD  ventricular septal defect
CHAPTER ONE

INTRODUCTION
1.1 MORPHOLOGY

1.1.1 UNREPAIRED TETRALOGY OF FALLOT

Niels Stensen, a Danish anatomist and naturalist, provided the first case report of tetralogy of Fallot (TOF) in 1671. However, a more complete anatomical description was not presented until 1784 by William Hunter who eloquently wrote: “...the passage from the right ventricle into the pulmonary artery, which should have admitted a finger, was not so wide as a goose quill; and there was a hole in the partition of the two ventricles, large enough to pass the thumb from one to the other. The greatest part of the blood in the right ventricle was driven with that of the left ventricle into the aorta, or great artery, and so lost all the advantage which it ought to have had from breathing”. Numerous case studies followed but it was not until Etienne-Louis Fallot’s 1888 paper *L’anatomie pathologique de la maladie bleu* when it was recognised that TOF is one malformation of the subpulmonary infundibulum and pulmonary valve not a random occurrence of four unrelated anomalies. Fallot himself did not coin the phrase ‘tetralogy of Fallot’, rather, in the interests of brevity, it was popularised by Maude Abbott in 1924.

Four anatomical features are always present in TOF; a ventricular septal defect (VSD), an overriding aorta resulting from a rightward deviation of the aortic valve with biventricular origin of its leaflets, subpulmonary infundibular stenosis, and subsequent right ventricular hypertrophy. However, a spectrum of morphology exists in terms of the borders of the VSD, the extent of aortic override and variations in subpulmonary infundibular anatomy. At one end of the spectrum, severe pulmonary
obstruction can result in the most common TOF variant; pulmonary atresia with VSD (see 1.1.2). On the other hand, TOF can be hard to distinguish from VSD with overriding aorta and minimal pulmonary stenosis. Despite the variability in cardiac anatomy, anterocephalad deviation of the outlet septum and hypertrophy of the septoparietal trabeculations forming a narrowed path to the pulmonary valve represent the defining anatomical features of this condition. Essentially, TOF is one abnormality arising from a malformed infundibulum. In the most common form of TOF, to which the studies of this thesis are mostly dedicated, the outflow tract from the right ventricle is patent at birth, the heart has normal segmental anatomical structure and major internal cardiac abnormalities, other than the aforementioned tetrad of defects, are not present.

Figure 1.1. The anatomy of unrepaired tetralogy of Fallot. (Reproduced with permission from Thomas et al. Circulation 2007; 115: 1933-1947)
Ventricular septal defect

The VSD is normally large and non-restrictive which facilitates bidirectional shunting. The interventricular communication can be described as perimembranous in around 80 percent of Caucasian patients due to a fibrous continuity between the tricuspid and aortic valve leaflets, which form the postero-inferior border, and incorporates the interventricular part of the membranous septum. Twenty percent of Caucasian TOF patients have a VSD where the postero-inferior margin of the defect is muscular. In this case the septomarginal trabeculation is continuous with the ventriculo-infundibular fold and forms the muscular region.5

Overriding aorta

The anterocephalad deviation of the outlet septum leads to a doubly committed aortic valve. The degree of aortic override varies considerably and could be diagnosed as double outlet right ventricle when severe. In the presence of substantial subpulmonary outflow tract obstruction, right to left shunting predominates and results in deoxygenated blood being passed through the malformed aortic valve into the systemic circulation. The associated chronic volume overload has been linked to aortic root dilatation in adult repaired TOF.6, 7

Infundibular stenosis

The subpulmonary outflow tract obstruction is a result of hypertrophied septoparietal trabeculations in addition to anterocephalad deviation of the outlet septum. The muscular nature of this region facilitates a mutable entity subject to influence by
factors such as catecholamines which can result in increased obstruction and hypercyanotic spells.  

Areas of stenosis may continue more distally in the right ventricular outflow tract, and further still, into the pulmonary arteries. The pulmonary valve can be hypoplastic with dysfunctional bi-leaflets. Furthermore, the pulmonary trunk and pulmonary arteries can be underdeveloped with areas of focal stenosis.

1.1.2 TETRALOGY OF FALLOT VARIANTS

Although TOF variants are not the focus of this thesis, it is worth briefly detailing their anatomy to enable a more complete understanding of the morphological and related pathophysiological dissimilarities between these conditions and the rationale behind excluding these patients from some of our studies. Although some variants may seem similar anatomically and haemodynamically in a surgically repaired adult patient, we believe differences in such factors in utero and during pre-repair infancy will result in heterogeneous pathophysiology and justifies exclusion.

**Pulmonary atresia with ventricular septal defect**

Pulmonary atresia with VSD results from an advanced level of anterocephalad deviation of the outlet septum. However, in rare cases the pulmonary valve is imperforate as opposed to severely stenosed. Pulmonary blood flow is maintained through confluent left and right pulmonary arteries via a patent ductus arteriosus in around half of all cases. In the remainder of patients, where the pulmonary arteries are confluent, multiple aorto-pulmonary collateral arteries supply blood to the
pulmonary circuit. When the pulmonary arteries are discontinuous or absent, pulmonary blood supply is preserved via multiple collateral arteries in isolation or in combination with an arterial duct.

Management of pulmonary atresia with VSD is complicated by the fact that collateral arteries have a tendency to stenose over time and pulmonary hypertension may develop due to unrestricted flow.

**Tetralogy of Fallot with absent pulmonary valve**

Rudimentary circular leaflets at the ventriculo-pulmonary junction in addition to a malformed outlet septum results in an absent pulmonary valve and is observed in around 5 percent of TOF cases. The resultant free pulmonary regurgitation in foetal life causes right ventricular and pulmonary artery volume overload and subsequent dilation. Compression of the airways by dilated pulmonary arteries can cause inspiratory and expiratory stridor in extreme cases. Focal narrowing of the ventriculo-pulmonary junction and compression/obstruction of the airways leads often to hypoxaemia in these patients.

**Double outlet right ventricle – “tetralogy type”**

One variant of double outlet right ventricle is characterised by a marked aortic override resulting in an aorta which is more committed to the right ventricle than to the left. Although physiologically similar to TOF, surgical management must be altered to allow for the fact that left ventricular outflow tract obstruction may result
from traditional VSD repair. A longer patch may be necessary to avoid such a situation.¹¹

1.1.3 ASSOCIATED ANATOMIC ANOMALIES

Anatomic anomalies associated with TOF frequently occur and are not considered variants. The most common anatomic anomalies are: variation in origin and/or course of coronary arteries; hypoplasia or stenoses of the pulmonary arteries; patent oval fossa; major aortopulmonary collateral arteries; aortic arch anomalies; secondary muscular inlet VSD; right-sided aortic arch. Approximately 2 percent of patients with TOF also have an atrioventricular septal defect.⁹ Pre surgery pathophysiology and management are similar, however, surgical management is altered to suit the more complex anatomy.
Chapter 1 Introduction

1.2 EPIDEMIOLOGY AND GENETICS

TOF occurs in one in every 3600 live births and represents approximately 10% of all congenital heart disease, making it the most common cyanotic congenital malformation.\textsuperscript{12} Marginally more males than females are born with TOF.\textsuperscript{13} Australian data presents a similar situation with 3.2 TOF cases per 10,000 births, with males being slightly over represented in the group.\textsuperscript{14} Importantly, due to significant improvements in treatment, there are now more adults than children with congenital heart disease.\textsuperscript{15}

The precise cause of TOF is unknown and although its occurrence is difficult to predict, recurrence in a family is around 3%.\textsuperscript{16} However, microdeletion of the q11 region of chromosome 22 has been shown to be present in up to 25% of patients suggesting a strong genetic substrate to the formation of TOF.\textsuperscript{17} Di George syndrome and velocardiofacial syndrome, which have 22q11 deletions, are often associated and diagnosed with TOF.\textsuperscript{18,19} When patients with these syndromes are omitted, the prevalence of 22q11 microdeletions has been estimated to be approximately 6%.\textsuperscript{20} Importantly, late-onset neuropsychiatric disorders are also associated with 22q11 deletion with schizophrenia occurring in around 25% in such patients, necessitating appropriate monitoring.\textsuperscript{21} Other chromosomal abnormalities, including trisomy 13, 18 and 21, can also occur in as many as 13% of TOF patients. Because of the potential presence of the aforementioned chromosomal deletions, fluorescent in-situ hybridisation may be warranted in all patients diagnosed with TOF.
A number of risk factors for the development of TOF during pregnancy have been identified, including uncontrolled diabetes, phenylketonuria and first trimester retinoic acid ingestion.\textsuperscript{22}
1.3 DIAGNOSIS OF TETRALOGY OF FALLOT

1.3.1 ANTENATAL DIAGNOSIS

Antenatal diagnosis of TOF is possible via a foetal echocardiogram in those patients with suspicion of a positive diagnosis; known chromosomal abnormalities or extracardiac malformations. Primarily because the presence of poor prognostic indicators warrants referral for echocardiography, prenatal diagnosis results in poorer long-term outcomes than postnatal diagnosis. In any case, only around half of TOF cases are detected during foetal echocardiography. When foetal diagnosis is possible it permits greater avoidance of dangerous cyanosis via maintenance of ductal patency through early prostaglandin administration.

1.3.2 POSTNATAL DIAGNOSIS

Clinical presentation

The most prominent sign is cyanosis, which appears some time after birth. The degree and initial appearance of cyanosis depends upon the degree of pulmonary stenosis. Mild pulmonary stenosis results in no cyanosis and is described as acyanotic TOF. Cyanosis appears several months after birth when moderate pulmonary stenosis is present. In the case of severe pulmonary stenosis, cyanosis is also severe and occurs early in infancy. Cyanosis is evident on the lips and nail beds but is not associated with clubbing in modern times due to early surgical repair.
Hypercyanotic spells, brought on by crying, defecating, feeding or dehydration, which agitates the dynamic infundibular outflow tract causing obstruction, are common amongst TOF patients with the onset being at around 3-6 months of age. These spells are characterised by an abrupt and severe decrease in oxygen saturation, hyperpnoea, dyspnoea and lethargy. Episodes are usually transient and resolve within 30 minutes. However, in severe spells greater levels of cyanosis can occur resulting in syncope, convulsions, even myocardial and/or cerebral ischaemia or death.\textsuperscript{12}

A single and loud second heart sound may be present in patients with TOF. Furthermore, a systolic murmur associated with the degree of RV outflow tract obstruction will also be audible. A less prominent murmur will be present in patients with severe obstruction and only a small amount of regurgitant flow but is associated with a greater degree of cyanosis. Blood flow across the VSD is generally not audible due to non-turbulent blood flow across the communication.

**Diagnostic techniques**

Chest radiography, electrocardiography and echocardiography are the frontline diagnosis tools. If the clinical presentation suggests the lesion may be present, a chest radiograph and ECG should be performed. Echocardiography can subsequently confirm the diagnosis with a thorough assessment of intracardiac anatomy.
Typical radiographic appearance includes a normal sized heart with a boot shaped appearance due a lifted apex, caused by right ventricular enlargement, and concavity in the main pulmonary artery area. Upon ECG examination, right sided dominance will produce right axis deviation, tall R waves in V4 and V1 leads and a large S wave in lead V6 with a sinus origin of the rhythm. Even though this ECG appearance is not unusual for a newborn, in a normal child this will resolve, whereas in a TOF patient it will persist beyond infancy and even into adulthood.

Echocardiography can then be used to make a definitive diagnosis and assess the degree of severity of associated abnormalities; right ventricular outflow tract obstruction; pulmonary artery morphology; supplementary sources of pulmonary blood flow; ventricular septal defect and aortic override; and associated anatomic anomalies.

Cardiac magnetic resonance imaging (MRI) can be used when echocardiography provides inadequate imaging of stenotic or hypoplastic pulmonary arteries, major aortopulmonary collateral arteries or anomalies of the aorta and/or coronary arteries.
1.4 MANAGEMENT OF TETRALOGY OF FALLOT

The management of TOF has developed considerably over the years. Before the advent of surgical intervention, long-term prognosis was invariably poor. Presently, survival into adulthood is the norm, rather than a rare exception, due to the evolution of surgical techniques and a considerable body of research exists validating such approaches.

1.4.1 SURGICAL INTERVENTIONS IN CHILDHOOD

The age at which complete repair of TOF is performed has steadily declined over time. The current approach is generally either neonatal complete repair or neonatal palliation with a systemic to pulmonary shunt followed by a complete repair at the age of 4 to 6 months. Previously, a two-stage approach was almost uniformly used with complete repair being performed beyond infancy, which was the case for a number of the older participants of studies within this thesis. Performing a complete neonatal repair can provide immediate reduction in right ventricular pressure and volume overload, reduce the possibility of aortopulmonary shunt related stenoses in the branch pulmonary arteries, alleviate family anxiety, reduce the length of cyanosis and the risk of hypercyanotic spells, enhance overall growth and development, and decrease the likelihood of reintervention in the first year of life.\textsuperscript{16, 25} Conversely, there may be the risk of negative neurodevelopmental outcomes in neonates exposed to cardiopulmonary bypass\textsuperscript{26-28} and there is an association with larger transannular patching in neonatal complete repair.\textsuperscript{29, 30} Since both approaches have low peri-
operative mortality\textsuperscript{29, 30} and comparative long-term outcome data is lacking, institutional preference is usually the prime determinant in the approach used. Commonly used relative indications for primary shunt procedures include left anterior descending coronary artery arising from a right coronary artery that crosses the right ventricular outflow tract, associated non-cardiac anomalies, and severely hypoplastic pulmonary arteries.\textsuperscript{31} In any case, the palliative and reparative surgical procedures used in tetralogy of Fallot management are outlined below.

1.4.1.1 Palliative Procedures

Palliative procedures for the relief of cyanosis in TOF began in the early 1940s when Helen Taussig noted that patients with a patent ductus arteriosus did better than those with a closed duct, who almost universally died.\textsuperscript{32} In partnership with Alfred Blalock, the concept of keeping this duct open led first to animal experiments\textsuperscript{33} and later to the human implementation of an end-to-side anastomosis of the left subclavian artery to the left pulmonary artery (Blalock-Taussig shunt or BT shunt) in 1944.\textsuperscript{34} By 1951, 779 BT shunts had been performed by Blalock and his team. Ninety-nine of these patients died after surgery, however, 50 per cent were still alive after 20 years.\textsuperscript{35}

A number of variations to the BT shunt have been developed; the Potts shunt involves an anastomosis between the descending aorta and left pulmonary artery, however, these shunts have subsequently ceased to be utilised due to difficulty in closure during complete repair;\textsuperscript{36} the Waterston shunt implements an ascending aorta to pulmonary artery anastomosis and is technically easy to perform and
subsequently to close;\textsuperscript{37} a Cooley shunt utilises an ascending aorta to right pulmonary artery shunt.\textsuperscript{38}

**Figure 1.2.** Classic Blalock-Taussig, modified Blalock-Taussig, Waterston and Potts shunts (Reproduced with permission from Thomas *et al.* *Circulation* 2007; 115: 1933-1947)

A modified BT shunt was developed in 1962 to lower the risk of thrombosis associated with the peripheral nature of the original shunt design. The modified procedure involves the use of a prosthetic tube graft made of polytetrafluoroethylene (PTFE) between the subclavian artery and pulmonary artery.\textsuperscript{39} In current practice, either a modified BT shunt via a median sternotomy/posterolateral thoracotomy or an ascending aorta to main pulmonary artery shunt via a median sternotomy are mostly used.
Establishing a modified BT shunt improves pulmonary blood flow, increases growth of the pulmonary arteries, can reduce the use of transannular patching during complete repair\textsuperscript{40-42} and is associated with very low hospital mortality.\textsuperscript{43} However, shunt narrowing is common\textsuperscript{43} and there are small risks of excess pulmonary blood flow, pulmonary hypertension and heart failure; although these negative outcomes can be minimised by use of small diameter PFTE shunts.\textsuperscript{40}

1.4.1.2 Reparative Procedures

Complete repair of TOF began in several centres in the mid 1950s after the development of sound cardiopulmonary bypass circuit practices. These early procedures were performed via median sternotomy and longitudinal or transverse ventriculotomy. Where present, shunts were closed prior to cardiopulmonary bypass being established. Infundibular resection was then performed and ventricular septal defect was closure followed using a pericardial or prosthetic patch. A transannular patch was utilised when the pulmonary annulus required augmentation. Preservation of the pulmonary valve was considered desirable where achievable. Complications during this period included low post-operative cardiac output, inadequate system perfusion, pulmonary dysfunction, coronary air embolism, poor myocardial protection and coronary artery damage.\textsuperscript{44-53}

In the infancy of these complete repair procedures post-operative mortality was up to 60% but reduced to 7-14% by the mid 1960s as surgical techniques developed. Age less than 5 years at complete repair, transannular patch use, prior Potts shunt, severity of cyanosis, and in some centres, previous systemic to pulmonary artery
shunt, were found to be associated with higher mortality risk.\textsuperscript{44-53} Results from follow-up studies resulted in the widespread practice of performing shunts in children less than 5 years of age and aiming for complete repair in symptomatic patients between 8-12 years of age. Initial shunt placement was thought to develop the pulmonary bed, which would allow a more successful subsequent complete repair.\textsuperscript{54}

During the 1970s complete TOF repair began to be performed on increasingly younger patients. Follow-up studies during this period found that performing surgical repair as early as 1 month led to improved mortality and negligible heart block/neurological sequelae. Furthermore, the presence of a prior shunt may hamper right ventricular outflow tract growth. However, greater transannular patch use was required, which has negative late outcomes such as pulmonary regurgitation.\textsuperscript{55-58}
Figure 1.3. Complete repair of tetralogy of Fallot (Reproduced with permission from Thomas et al. Circulation 2007; 115: 1933-1947)
Long-term follow-up studies of complete repair patients from the 1950s and 1960s found that ventriculotomy and transannular patch placement was largely responsible for right ventricular dysfunction, decreased exercise tolerance, arrhythmia and sudden cardiac death.\textsuperscript{59-62} In an attempt to alleviate these negative outcomes, surgeons now commonly utilise a transatrial or transatrial-transpulmonary approach with sparing of the pulmonary valve. Complete neonatal primary repair results in early survival rates are presently 98-100\%.\textsuperscript{63-65} However, the majority of patients recruited to studies within this thesis were born in the late 1980s and early 1990s and almost solely underwent an early (<4 years of age) median sternotomy, shunt ligation (if present), right ventricular outflow tract incision, infundibular resection, ventricular septal defect closure with a Teflon patch and transannular patch augmentation of the outflow tract. This surgical approach is associated with higher levels of pulmonary regurgitation than transatrial or transatrial-transpulmonary techniques,\textsuperscript{29} however, long-term data is currently lacking comparing eras.

1.4.2 LATE PROCEDURES

1.4.2.1 Pulmonary Valve Replacement

In most cases, chronic pulmonary regurgitation develops after complete TOF repair, resulting from surgical disruption of the pulmonary valve and right ventricular outflow tract. Previous studies have suggested pulmonary regurgitation results in progressive right ventricular dilatation, exercise incapacity, arrhythmia and sudden cardiac death.\textsuperscript{60,66} Pulmonary valve replacement (PVR) is increasingly utilised in this patient cohort to reduce pulmonary insufficiency and remodel the right ventricle.
However, optimal timing of such valve implantation is an area of much uncertainty. The beneficial effects of PVR detailed below, need to be balanced with the risk of reoperation due to the limited lifespan of implanted valves of around 10 years.67

PVR techniques include utilising Gore-tex bivalves, homograft conduits and various other conduits (bovine jugular, Dacron porcine, stentless porcine). However the vast majority of patients within this thesis received a stented prosthesis, specifically, a Medtronic Mosaic porcine valve. This approach is favoured within our institution and elsewhere as it provides superior durability to homografts68-70 and allows future percutaneous pulmonary valve replacement.

The American College of Cardiology/American Heart Association Guidelines state that pulmonary valve replacement is reasonable in patients with severe pulmonary regurgitation and at least one of the following: symptoms; decreased exercise tolerance; moderate to severe right ventricular dysfunction; moderate to severe right ventricular enlargement; development of symptomatic or sustained atrial and/or ventricular arrhythmias; moderate to severe tricuspid regurgitation.71 The European Society of Cardiology Guidelines are in close agreement but add right ventricular outflow tract obstruction with right ventricular systolic pressure >80 mmHg (tricuspid regurgitation velocity on echocardiography >4.3 m/s) as a conjoint indicator for pulmonary valve replacement along with severe pulmonary regurgitation.72 In clinical practice, the degree of right ventricular dilatation is highly weighted in the decision of when to operate. Several studies have attempted to elucidate the degree to which the right ventricle may be allowed to dilate whilst still achieving normalisation of right
ventricular volumes after PVR. Indexed right ventricular end-diastolic volume (RVEDVi) cut points between 150 mL/m$^2$ and 170 mL/m$^2$ have been identified.$^{73-75}$ However, the validity of these findings may be called into question with some studies recruiting a low number of patients and/or utilising echocardiography rather than cardiac MRI in the assessment of ventricular volumes and function. Nevertheless, the lower end of this range is more commonly used by clinicians as an indication for PVR.

Geva (2013) recently proposed the indications for PVR in repaired TOF patients shown in Table 1.1.$^{76}$ These indications essentially summarise the need to monitor right ventricular size and function, pulmonary regurgitation and the burden of arrhythmia. Importantly, factors other than RVEDVi are given equal weighting as indications for PVR. Furthermore, the distinction made between symptomatic and asymptomatic patients is valuable since the threshold for intervention is lowered in those experiencing symptoms such as exercise intolerance, dyspnoea and syncope. Unfortunately for clinicians, there are no clear-cut answers on when to request PVR late after TOF repair and the key question remains whether or not to operate on an asymptomatic patient with a borderline size right ventricle.
Table 1.1. Proposed indications for PVR in patients with repaired TOF with moderate to severe pulmonary regurgitation (regurgitant fraction ≥25%)

1. **Asymptomatic patients with ≥2 of the following criteria:**
   a. RV end-diastolic volume index >150 mL/m² or z score >4. In patients whose body surface area falls outside published normal data: RV/LV end-diastolic volume ratio >2 71,76
   b. RV end-systolic volume index >80 mL/m² 74,79
   c. RV ejection fraction <47% 78-81
   d. LV ejection fraction <55% 79-81
   e. Large RVOT aneurysm 82,83
   f. QRS duration >160 ms 79
   g. Sustained tachyarrhythmia related to right-sided heart volume load 84
   h. Other haemodynamically significant abnormalities: 71
      - RVOT obstruction with RV systolic pressure ≥0.7 systemic
      - Severe branch pulmonary artery stenosis (<30% flow to affected lung) not amenable to transcathether therapy
      - Greater than or equal to moderate tricuspid regurgitation
      - Left-to-right shunt from residual atrial or ventricular septal defects with pulmonary-to-systemic flow ratio ≥1.5
      - Severe aortic regurgitation

2. **Symptomatic patients fulfilling ≥1 of the quantitative criteria detailed above. Examples of symptoms and signs include:**
   a. Exercise intolerance not explained by extracardiac causes (eg, lung disease, musculoskeletal anomalies, genetic anomalies, obesity), with documentation by exercise testing with metabolic cart (≤70% predicted peak VO₂ for age and sex not explained by chronotropic incompetence)
   b. Signs and symptoms of heart failure (eg, dyspnoea with mild effort or at rest not explained by extracardiac causes, peripheral oedema) 71
   c. Syncope attributable to arrhythmia

3. **Special considerations:**
   a. Because of higher risk of adverse clinical outcomes inpatients who underwent TOF repair at ≥3 years of age, PVR may be considered if they fulfil ≥1 of the quantitative criteria in section 1 81
   b. Women with severe pulmonary regurgitation and RV dilatation or dysfunction may be at risk for pregnancy related complication. Although no evidence is available to support benefit from pre pregnancy PVR, the procedure may be considered if fulfilling ≥1 of the quantitative criteria in section 1 85

Source: Geva (2013)76
Although the optimal timing of PVR remains difficult, there is more certainty that the procedure results in considerable short and medium-term benefit to TOF patients. A recent meta-analysis concluded from pool data of 48 included studies that postoperative mortality was low (30-day mortality 0.87%; 5-year mortality 2.2%), the 5-year PVR redo was 4.9%, RVEDVi decreased by 63 mL/m², pulmonary regurgitant fraction reduced by 39%, left ventricular ejection fraction marginally increased (1.8%), QRS duration slightly decreased (-2.9 ms), and NYHA class improved (-0.9). Right ventricular ejection fraction only improved by 1% when not corrected for change in right ventricular volume, however, corrected right ventricular ejection fraction improved by 21%. Although there has been universal agreement on improvements in right ventricular volumes, pulmonary regurgitant fraction and NYHA class, some variation has been noted in the change in right ventricular ejection fraction, left ventricular volumes, left ventricular ejection fraction and QRS duration. Furthermore, despite universal reporting reduced right ventricular volumes, the degree to which this reduction is due to outflow tract excision as opposed to muscular corpus remodelling has not been adequately investigated.

Few studies have documented the effects of PVR on exercise capacity. Poor baseline exercise capacity is ubiquitous in studies to date, however, only 2 studies have shown a significant improvement in exercise performance; Warner et al (2003) found that maximum workload and percentage of predicted peak oxygen consumption significantly improved in a subset of 6 patients, 36.7 months post PVR; Frigiola et al (2008) reported a significant decrease in ventilatory response to
carbon dioxide production (VE/VCO2) in 57 patients, 12 months after PVR. Other 
studies conducted to date have not found an improvement in maximal or submaximal 
exercise performance as a result of PVR.96, 99, 103 The lack of improvement in 
exercise performance after PVR raises the question of whether deteriorating 
exercise capacity is a valid indicator for such surgery. However, it may be possible 
that patients with deteriorating exercise capacity experience the greatest benefit from 
PVR. Such subgroup analyses are important to develop sound indicators for surgical 
intervention.

Despite recent efforts to study the effects of PVR, several questions remain 
unanswered and clinically important; little is known of the long-term effects of PVR, 
despite the importance of such information; the role of formal exercise testing in 
surgery timing decisions is not clear since there is a lack of correlation between 
symptoms, ventricular volume and exercise capacity; and the effects of PVR on 
cardiac function during exercise is poorly understood. Portions of this thesis attempt 
to answer some of these questions.

1.4.2.2 Percutaneous Pulmonary Valve Replacement

Although not discussed further in this thesis, it is worth noting that percutaneous 
approaches to placing a pulmonary valve have been developed in recent times with 
good early results.104, 105 Periprocedural mortality, late mortality and freedom from 
reoperation has been reported to be low.106 The main advantage of the procedure is 
the avoidance of serial sternotomies and the associated risks. However, the 
procedure is limited to those patients with a suitable conduit size and geometry; the
Medtronic Melody valve can be placed in conduits up to 22mm in diameter and the Edwards Sapien Valve up to 29mm in diameter. Therefore, patients with transannular patch repair are unsuitable for percutaneous pulmonary valve implantation as a first procedure to ameliorate late pulmonary regurgitation. Once a pulmonary valve of suitable diameter has been surgically implanted a percutaneous procedure may follow in the case of subsequent surgical valve failure. With current tendencies to perform valve sparing repairs and technological developments in percutaneous valves, future patients may be able to undergo this procedure without previous surgical valve implantation.

Rare but serious complications of percutaneous pulmonary valve implantation include coronary artery compression, stent fracture, stent embolisation, and valve failure, which can often be resolved by placement of a second valve.

1.4.3 MONITORING DISEASE PROGRESSION

1.4.3.1 Echocardiography

Echocardiography is a common tool in the diagnosis and follow up of TOF patients. This imaging modality is portable, cost-effective, and can be particularly useful in assessing measurements such as right ventricular or pulmonary artery systolic pressure. However, difficulty is encountered when attempting to acquire adequate images of right-sided structures and distal vasculature. Furthermore, echocardiography is very operator dependent. Therefore, echocardiography is a useful imaging modality for TOF patients in certain situations only. Cardiac MRI can
be more useful in assessing right ventricular volumes and function due to its superior ability to image the right heart.

1.4.3.2 Cardiac Magnetic Resonance Imaging

Cardiac MRI is currently the reference method for non-invasively assess pulmonary regurgitation, ventricular volume and ventricular function. Although pulmonary regurgitation can be evaluated via echocardiography and has good agreement with cardiac MRI, a full assessment pulmonary valvular flow, right ventricular morphology and function is far superior using the latter due to greater visualisation of the right heart and lack of geometrical assumptions. Evaluation of akinetic regions and/or areas of scarring in the right ventricular outflow tract are also possible, which is important in the assessment of arrhythmia risk. Furthermore, right ventricular outflow tract and pulmonary arterial tree anatomy can be thoroughly evaluated along with the relationship of the great vessels to the coronary circuit, which aids in determining whether patients are suitable for percutaneous pulmonary valve replacement.

Serial cardiac MRI evaluations allow clinicians to monitor progress and greatly aids in the decision of when to intervene with PVR in order to reduce pulmonary regurgitation and right ventricular volume. In those patients who have undergone PVR procedures, cardiac MRI allows a full assessment of post procedural valvular and ventricular function. Cardiac MRI follow-up is approximately 24 months in pre-PVR, clinically stable patients with only moderate pulmonary regurgitation and moderate right ventricular dilatation. Despite more than a decade of cardiac MRI collection across many centres internationally, little is known regarding the temporal
changes in ventricular volume and function in TOF patients. Elucidation of such data would allow recommendations on timing of clinical follow-up and permit greater planning of future interventions.

Section 2.1 contains a description of technical aspects of cardiac MRI as it applies to the assessment of TOF.

1.4.3.3 Measurements of Exercise Capacity

Exercise capacity has previously been shown to be impaired in adults with repaired TOF\textsuperscript{60, 61, 83, 111, 112} (detailed in section 1.6.2). The degree of exercise intolerance and temporal changes in peak and submaximal exercise capacity are commonly used as indicators of clinical status. The American College of Cardiology/American Heart Association Guidelines recommend periodic cardiopulmonary exercise testing (CPET) to monitor exercise capacity and assess the risk of exercise induced arrhythmias. These guidelines further state that PVR is reasonable in patients with decreasing exercise capacity. However, the interval required between CPETs and what constitutes “decreasing exercise capacity” are left to the clinician’s discretion. Nevertheless, maximal oxygen consumption, VE/VCO2 slope and NYHA functional class have been identified as independent predictors of death or hospitalisation,\textsuperscript{113} which indicates that monitoring peak and submaximal exercise capacity has at least some prognostic information and is a worthwhile procedure for monitoring progression of clinical status and risk stratification. However, specific rates of decline or cut off values have not been identified and, therefore, the CPET is currently a useful but imprecise tool. Knowledge of cardiac function during exercise may prove
to have more utility in assessing the clinical status of TOF patients. In this regard, the emerging technique of collecting cardiac magnetic resonance images of the exercising heart may provide valuable insights into cardiac function under stress and important prognostic information for this patient cohort.
1.5 PATHOPHYSIOLOGY OF TETRALOGY OF FALLOT

As detailed in sections 1.1.1 and 1.1.3, there is some heterogeneity within patients diagnosed with TOF. Specifically, there may be variation in the degree of aortic override, the size and nature of any ventricular septal defect, the degree of infundibular stenosis and the presence and severity of any associated anatomic anomalies. However, a generalised picture of the pathophysiology of TOF may be created.

1.5.1 PRE REPAIR

Before any palliative procedures are undertaken, cyanosis and hypoxaemia are commonly present. The VSD is usually large and non-restrictive, which creates a situation of equalised pressure between the left and right ventricles. The amount of pulmonary stenosis and right ventricular pressure establishes the level of pulmonary blood flow. Total systemic vascular resistance and venous return determine left ventricular systolic and aortic pressures. Infants may exhibit normal oxygen saturation and no cyanosis if they possess mild pulmonary stenosis and consequently the shunt through the VSD is left-to-right. This situation is commonly termed pink, acyanotic or precyanotic TOF. Generally, right-to-left shunting subsequently occurs as a result of increasing infundibular obstruction and cyanosis develops. Situations which increase venous return and decrease total peripheral resistance precipitate cyanosis; crying, cold temperatures or bathing. The amount of aortic override is not a determinant in the degree of cyanosis. Rather, cyanosis
worsens as pulmonary blood flow is further compromised by increased obstruction in the right ventricular outflow tract.\textsuperscript{12}

During cyanotic spells, a vicious cycle develops where an increased right-to-left shunt results in aortic oxygen desaturation, consequently systemic hypoxia and metabolic acidosis occur. Subsequent respiratory centre is stimulation causes hypernoea and catecholamine release, which increases infundibular stenosis and increases venous return with resultant deepening cyanosis. Furthermore, hypercapnia and respiratory acidosis occur as a result of decreased pulmonary blood flow and contribute to worsening hypoxaemia.

Squatting can help to relieve cyanotic spells and is a common position to find an infant with TOF. Systemic venous return and vascular resistance are increased in this position and result in decreased right ventricular outflow tract obstruction. Therefore, decreasing right-to-left shunting and increasing pulmonary blood flow.\textsuperscript{12}

Chronic cyanosis may result in polycythemia and/or multiple aorto-pulmonary collateral arteries. The former can result in increased risk of cerebrovascular accidents\textsuperscript{114} and the latter can cause late complications after total surgical repair.

1.5.2 POST COMPLETE REPAIR

As described in section 1.4.1.2, complete repair of TOF results in relief of pulmonary stenosis and elimination of the right-to-left shunt. As a result, pulmonary blood flow increases and cyanosis is relieved.\textsuperscript{115} The patient is commonly now left with free
pulmonary regurgitation, however, the pulmonary regurgitant fraction is rarely more than 40%. The degree of pulmonary regurgitation is limited since pulmonary forward flow occurs even without the contribution of the right ventricle, in a similar fashion to the Fontan circulation. This is due to the effects of inspiration on thoracic cavity pressure, ejection of blood from the left ventricle creating a negative pressure gradient across the pulmonary vascular circuit and right atrial contraction. Further, resistance in the pulmonary microvasculature is low and a short distance from the right ventricle. Consequently, right ventricular contraction propels blood through the low resistance pulmonary arterial circulation into the low-pressure pulmonary veins. Since there is no reversal of gradient, no impetus for back flow through the pulmonary circuit exists. However, pulmonary regurgitation can be exacerbated by such factors as branch pulmonary artery stenosis, annulus size of the pulmonary valve, pulmonary arterial compliance and pulmonary microvasculature function.

Although well tolerated for many years after complete surgical repair, the chronic volume overload created by pulmonary regurgitation leads to progressive right ventricular dilatation. The magnitude of the right ventricular response depends upon the quantity and period of pulmonary regurgitation and the nature of the right heart and pulmonary vascular circuit. Deterioration in right ventricular volumes and function is apparent in patients with at least moderate pulmonic regurgitation. However, temporal changes in pulmonary regurgitation, right ventricular size and function are poorly understood.
Bove et al. (1983)\textsuperscript{121} provided early insights into the effects of long-standing pulmonary insufficiency on right ventricular function. They assessed 20 patients, 9 years after total repair of TOF using echocardiography, radionuclide ventriculography and 24 hour holter monitoring. It was reported that patients with clinically significant pulmonary regurgitation had significantly higher right to left ventricular end-diastolic ratio and lower right and left ventricular ejection fractions. Further early studies confirmed the findings of Bove et al.\textsuperscript{122-124} Typical of the era though, age at repair was towards the end of the first decade of life, which restricts the relevance of these results to modern cohorts who typically undergo repair in infancy. More recent studies, however, have established the association between chronic pulmonary regurgitation and impaired right ventricular function.\textsuperscript{118, 120, 125-131} Koestenberger et al. (2011),\textsuperscript{131} for example, found that right ventricular ejection fraction was strongly correlated with severity of pulmonary regurgitation.

Chronic pulmonary regurgitation in the setting of right ventricular outflow tract aneurysm or akinesis has been suggested to be the main cause of right ventricular failure late after TOF repair.\textsuperscript{130} Transannular patch repairs are strongly associated with an aneurismal and akinetic right ventricular outflow tract have also been associated with higher pulmonary regurgitant fractions\textsuperscript{125} and sustained ventricular tachycardia.\textsuperscript{132, 133} Furthermore, fibrosis as a result of surgical intervention is common in the right ventricular outflow tract and has been found to be related to ventricular dysfunction, decreased exercise tolerance and increased levels of atrial natriuretic peptide.\textsuperscript{134, 135}
Regional wall motion abnormalities, including in the right ventricular outflow tract, have commonly been identified late after TOF repair. Vogel et al. (2001)\textsuperscript{136} reported right ventricular free wall reversed myocardial velocity in diastole in 48 of 74 patients studied. Of the 48 patients, 22 exhibited reversed systolic myocardial velocities in the right ventricular free wall and 19 patients had reverse diastolic myocardial velocity in the septum. QRS, QT and JT duration was found to be significantly longer in those patients with reversed myocardial velocity as compared to those with myocardial contractility. Weidemann et al. (2002)\textsuperscript{137} further confirmed the association between right ventricular deformation abnormalities and prolonged QRS duration. Enhanced quantification of regional function was developed by Menteer et al (2005)\textsuperscript{138}, which utilises MRI myocardial tissue tagging.

Subsequent studies have utilised similar techniques in combination with late gadolinium enhancement to identify the presence of ventricular fibrosis and its association with regional function abnormalities.\textsuperscript{83, 128, 134} Wald et al (2009)\textsuperscript{83} found that global right ventricular ejection fraction was positively correlated to right ventricular outflow tract ejection fraction and negatively correlated to right ventricular outflow tract dyskinesia and right ventricular outflow tract late gadolinium enhancement. Babu-Narayan et al. (2006)\textsuperscript{134} found greater levels of ventricular fibrosis in areas of previous myocardial insult and suggested patients who previously underwent extensive right ventricular outflow tract reconstruction with greater transannular patch use were more likely to exhibit late gadolinium enhancement in this region; 99% of the 92 patients included in this study exhibited indications of right ventricular outflow tract fibrosis. Miura et al. (1992)\textsuperscript{124} provided early evidence that
surgical approach to TOF repair can have significant long term implications, with transpulmonary-transatrial repaired patients exhibiting better global right ventricular function and less regional wall motion abnormalities as compared to patients who had undergone a transventricular repair. Overall, the right ventricular outflow tract is an important area to consider when for choosing surgical technique, assessing risk, monitoring clinical status and selection of patients for late surgical procedures.

The existence of right ventricular diastolic dysfunction late after TOF repair is common.\textsuperscript{139-145} In restrictive right ventricular physiology, blood flow from right atrial contraction travels directly into the pulmonary circuit via the passive right heart as indicated by antegrade flow in the main pulmonary aretery late in diastole.\textsuperscript{140, 143, 144} The clinical implications of right ventricular diastolic function are unclear. Gatzoulis et al (1995)\textsuperscript{140} reported increased exercise capacity and less right ventricular dilatation in those patients with restrictive physiology when compared to those patients without restrictive physiology. Helbing et al (1996),\textsuperscript{141} however, found the opposite, with impaired exercise capacity associated with the presence of restrictive right ventricular physiology. Nevertheless, it is apparent that patients with right ventricular diastolic dysfunction have a lower chronic pulmonary regurgitant load.\textsuperscript{117}

Tricuspid regurgitation is a small but significant contributing factor towards right ventricular dysfunction, which occurs in around 32\% of repaired TOF cases and develops as a result of annular dilatation, secondary to right ventricular expansion, and/or valvular injury during complete repair.\textsuperscript{117} Tricuspid regurgitation can exacerbate right ventricular dilatation and cause right atrial enlargement.
Reports of left ventricular function in adult repaired TOF are variable. An early study conducted by Jarmankani et al. (1972)\textsuperscript{146} concluded that patients left ventricular ejection fraction remained suppressed at a mean of 2.5 years post corrective surgery. Age at repair was not reported but presumably complete repair was performed significantly later than infancy, as opposed to the current practice of early correction. However, Gatzoulis et al. (2000)\textsuperscript{129} reported normal left ventricular ejection fraction in 95 adult repaired TOF patients, 18 years after repair with a mean age at repair of 12.6 $\pm$ 10.5 years. It is clear, however, that the presence of left ventricular dysfunction is related to major adverse clinical events. Knauth et al. (2008)\textsuperscript{80} studied 88 adult repaired TOF patients utilising cardiac MRI and found that patients who suffered major adverse outcomes had significantly lower left ventricular ejection fraction. Ghai et al. (2002)\textsuperscript{147} also reported that left ventricular dysfunction is a risk factor for sudden cardiac death in TOF patients late after repair.

It seems reasonable, then, that abnormal interactions between the right and left ventricle are likely in the setting of the volume overloaded right heart. Oosterhof et al. (2006) compared 32 repaired TOF patients (age of repair: 6 years) with 10 pulmonary stenosis patients (age at repair: 4 years ; $p=\text{NS}$) at a mean of 24 years after repair and found that TOF patients had significantly lower left ventricular ejection fractions. This suggests that the volume loaded right ventricle has an important impact on the left ventricle. In fact, a correlation between right and left ventricular ejection fractions has been demonstrated on numerous occasions.\textsuperscript{81, 130, 148} Possible explanations include mutual myocardial fibres,\textsuperscript{149-151} electromechanical dyssynchrony,\textsuperscript{152} and geometrical interaction between chambers due to limited pericardial space.\textsuperscript{153}
Further late consequences of pulmonary regurgitation and subsequent right ventricular dilatation are discussed in section 1.6.
1.6 LATE OUTCOMES

1.6.2 EXERCISE CAPACITY

Exercise capacity has widely been reported to be suppressed late after the repair of tetralogy of Fallot. F60, 112, 134, 140, 141, 154-162 Fredriksen et al.159 found a peak oxygen consumption (VO$_{2\text{peak}}$) of 21 mL/kg/min and a peak heart rate of 149 beats per minute during cycle ergometry in 494 patients at a mean age of 32 years. Similarly, Samman et al.160 reported reduced VO$_{2\text{peak}}$ of 22 mL/kg/min (66% predicted) and peak heart rate of 146 beats per minute in ninety-nine 34 year old TOF patients. Babu-Narayan et al.134 reported marginally higher maximal oxygen uptake during cardiopulmonary exercise test of 27 mL/kg/min (80% predicted) in 92 adults with repaired tetralogy of Fallot. However, Babu-Narayan’s study utilised a treadmill protocol, thus increasing VO$_{2\text{peak}}$ by use of a larger muscle mass compared to bicycle ergometry. Maximal exercise capacity has also been shown to decrease over time. Kipps et al.161 described a reduction in VO$_{2\text{peak}}$ from 27 mL/kg/min (78% predicted) to 25 mL/kg/min (73% predicted) over a 2.8 year period in 179 repaired TOF patients with a mean age of 24 years at initial visit.

Pulmonary regurgitation has been associated with impaired exercise capacity. F60, 157 Carvalho et al.60 reported a significant negative correlation between pulmonary regurgitant fraction and both exercise duration and peak heart rate. Furthermore, patients with VO$_{2\text{peak}}$ less than 85% predicted had a significantly higher degree of
pulmonary insufficiency than those patients above 85% predicted VO$_{2\text{peak}}$. Norgard et al.$^{157}$ demonstrated significantly decreased VO$_{2\text{peak}}$ in patients with at least moderate pulmonary regurgitation as compared to patients with mild pulmonary regurgitation. However, when pulmonary regurgitation is alleviated via pulmonary valve replacement, either surgically or percutaneously, improved exercise capacity is not commonly observed.$^{73, 77, 89, 96, 102, 163-168}$

Reduced exercise capacity in adult repaired TOF could logically be thought to be associated with right ventricular dysfunction, however, evidence in this area is equivocal. Correlation studies have not consistently shown an association between right ventricular ejection fraction and peak or submaximal exercise capacity.$^{60, 169, 170}$ However, Geva et al.$^{81}$ retrospectively analysed cardiac MRI data and clinical status of 100 repaired TOF patients and reported that reduced right ventricular ejection fraction was associated with poorer clinical status, as assessed by New York Heart Association functional class. Furthermore, regional dysfunction has been shown to be associated with reduced exercise capacity. Wald et al.$^{83}$ used 3-dimensional models of the right ventricle, reconstructed from cardiac MRIs in 62 TOF patients, and found that right ventricular outflow tract ejection fraction was independently predictive of peak exercise capacity, whereas global right ventricular ejection fraction was not. Babu-Narayan et al.$^{134}$ added further evidence that regional rather than global right ventricular dysfunction is associated with exercise incapacity. Babu-Narayan restrospectively analysed late gadolinium enhancement score from cardiac MRIs in 92 repaired TOF patients. Overall, regional dysfunction was noted in areas of scar and patients with above mean late gadolinium enhancement score were
found to have lower peak exercise capacity. Scarring was particularly noted in regions of previous surgical insult such as the outflow tract (99%), interventricular septum (98%), inferior right ventricular insertion point (79%) and areas of trabeculated myocardium (24%).

Chrontropic incompetence has been widely reported to be present in repaired TOF. Diller et al. retrospectively analysed CPET results from 727 adult congenital heart disease patients between 1999 and 2005. Fifty-two per cent of repaired TOF patients exhibited chronotropic incompetence, defined as a chronotropic index (measured heart rate reserve/predicted heart rate reserve) less than 0.8. Wessel et al. reported reduced heart rates compared to controls at each stage and at maximal exercise during treadmill exercise using the Bruce protocol. However, resting heart rates were not different from controls. Interestingly, although reduced peak heart rate is likely to be related to reduced VO\textsubscript{2peak}, reduced submaximal heart rates have been shown to be unrelated to submaximal VO\textsubscript{2}. Vagal tone during exercise has been shown to be normal in repaired TOF, however, abnormalities in autonomic reflexes have been suggested as a possible mechanism of chronotropic incompetence. Ohuchi et al. concluded that blunted heart rate response to exercise is at least partly related to impaired cardiac autonomic activity. Davos et al. found globally impaired autonomic response to exercise with reduced baroreceptor sensitivity and heart rate variability. Both Ohuchi and Davos related impaired autonomic function to previous cardiac surgery, in particular, right ventricular outflow tract reconstruction.
Respiratory abnormalities in repaired TOF patients may also have a significant impact on exercise capacity. The presence of branch pulmonary artery stenoses has been suggested to have a negative impact on maximal oxygen consumption due to pulmonary blood flow maldistribution, ventilation-perfusion mismatch and inefficient gas exchange. Improved VO_{2peak} after balloon angioplasty of stenosed branch pulmonary arteries adds further weight to this assertion. Further possible respiratory influences on maximal exercise capacity are decreased respiratory vital capacity and increased ventilatory frequency.

Exercise incapacity in adult repaired TOF patients could to some extent be explained by physical inactivity. General advice to limit vigorous physical activity by medical practitioners may lead to patients approaching exercise with caution; viewing it as a potentially dangerous pursuit. Previous research has confirmed that physical activity levels are low and, importantly, that physical training results in improved exercise capacity in TOF patients.

As a predictive tool, cardiopulmonary exercise testing has proven to be very useful in the setting of adult repaired tetralogy of Fallot. Diller et al. found that peak heart rate is predictive of survival. Giardini et al. reported that VO_{2peak}, the slope of ventilation per unit of carbon dioxide production and New York Heart Association functional class are all independently predictive of death and hospitalization. Pre-surgical cardiopulmonary exercise test results are also predictive of outcome. Babu-Narayan et al. showed that pre pulmonary valve replacement VO_{2peak} is a strong predictor of early post-surgery mortality.
1.6.1 ARRHYTHMIA, SURVIVAL AND SUDDEN CARDIAC DEATH

As outlined in section 1.4.1.2, surgical repair techniques have significantly changed over the past several decades, which have resulted in improved survival rates.\textsuperscript{179} Transannular patch use has been associated with poor outcomes, as described above, however, conflicting results have been reported regarding the degree and type of patching on survival rates.\textsuperscript{66, 180} Regardless, survival has universally been described as excellent for many decades. Early studies by Katz et al. (1982)\textsuperscript{181}(an 8-year actuarial survival rate of 96\% in 414 patients repaired between 1967 and 1977), Rosenthal et al. (1984)\textsuperscript{182}(95\% cumulative survival 25 years postoperatively) and Nollert et al. (1997)\textsuperscript{183}(a 36-year acturarial survival rate of 96\% and normal life expectancy in 658 patients repaired between 1958 and 1977) reported encouraging results. More recently, Hickey et al. (2009)\textsuperscript{180} predicted a 40-year survival of 88\% for patients repaired in 1985, which matches the era of repair for most of the patients included in this thesis.

Despite encouraging survival rates, the burden of arrhythmia in adult repaired TOF patients is high. A recent multi-institutional study\textsuperscript{84} recruited 556 patients from 11 centres and found that 43\% had a sustained arrhythmia or an arrhythmia related intervention and 20\% had an atrial tachyarrhythmia. Right atrial enlargement, hypertension and number of cardiac surgeries were associated with intraatrial re-entrant tachycardia. Whereas, atrial fibrillation was associated with older age, decreased left ventricular ejection fraction, left atrial dilatation and number of cardiac surgeries. Ventricular arrhythmia was present in 15\% of patients and was associated
with QRS duration, left ventricular dysfunction and number of cardiac surgeries. It is apparent that the left side of the heart plays an important role in arrhythmogenesis.

The burden of arrhythmia in adult repaired TOF patients increases with age. The incidence of atrial and ventricular arrhythmias is low for the first 10 to 15 years after reparative surgery, followed by an increase thereafter.\textsuperscript{66, 84, 184} Although the overall burden of arrhythmia increases steadily with age, there are some differences in progression between subtypes. Atrial fibrillation is uncommon and less prevalent than intraatrial re-entrant tachycardia before 45 years of age. However, beyond this age the incidence of atrial fibrillation dramatically increases and becomes more common than intraatrial re-entrant tachycardia.\textsuperscript{84} The development of atrial fibrillation also tends to arise at an earlier age in TOF patients than in the normal population (>45 vs >65 years of age, respectively) and has a prevalence of 30% in patients over 55 years of age.\textsuperscript{84, 185} All atrial tachyarrhythmias are more common in patients who underwent palliation before corrective surgery.\textsuperscript{66}

Ventricular arrhythmias have a high prevalence of 15% in adult repaired TOF patients, with ventricular tachycardia representing the vast majority of these cases.\textsuperscript{62, 66, 84, 186} Pulmonary regurgitation leads to progressive right ventricular dilatation has been suggested as the main haemodynamic lesion resulting in sustained ventricular tachycardia and sudden cardiac death.\textsuperscript{66} QRS duration is lengthened by right ventricular dilatation and is strongly correlated with sustained ventricular tachycardia.\textsuperscript{59, 62, 66, 84, 187} Furthermore, QRS duration has been identified as an independent risk factor for malignant ventricular arrhythmias and sudden cardiac
Increased number of previous cardiac surgeries has also been suggested as a risk factor for ventricular arrhythmias, presumably via arrhythmogenic ventricular fibrosis at former incision sites.

Some studies have suggested pulmonary valve replacement results in decreased QRS duration and others have reported no change. One study suggested QRS duration decreases after such surgery but steadily increases thereafter. Meta-analyses have not provided clarification in this regard, with conflicting results as to whether pulmonary valve replacement decreases QRS duration in adult repaired TOF patients. More importantly, the long-term effects of pulmonary valve replacement on ventricular tachycardia and sudden cardiac death are also uncertain.

Little is known about the incidence and causes of sudden cardiac death. However, several studies have identified risk factors for ventricular tachycardia and sudden cardiac death (see Table 1.2). The highest risk patients have a clinical profile that includes having undergone multiple surgeries, an increased QRS duration, left ventricular systolic or diastolic dysfunction and age greater than 20 years.
## Table 1.2 Risk factors for ventricular tachycardia and sudden cardiac death (Source: Villifane 2013\textsuperscript{195})

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age at repair</td>
</tr>
<tr>
<td>Previous palliative shunts</td>
</tr>
<tr>
<td>Older age</td>
</tr>
<tr>
<td>Repeated syncope</td>
</tr>
<tr>
<td>Pulmonary regurgitation</td>
</tr>
<tr>
<td>Residual pulmonary stenosis</td>
</tr>
<tr>
<td>Severe right ventricular dilatation</td>
</tr>
<tr>
<td>Poor right ventricular function</td>
</tr>
<tr>
<td>Poor left ventricular function</td>
</tr>
<tr>
<td>Frequent ventricular ectopic beats on Holter monitoring or exercise test</td>
</tr>
<tr>
<td>QRS &gt;180ms</td>
</tr>
</tbody>
</table>


CHAPTER TWO

GENERAL METHODS
2.1 ETHICS APPROVALS

Ethics approval was granted for each of the studies within this thesis by the Sydney Local Health District Ethics Review Committee (RPAH Zone). Chapter 8 required additional approval from the Victorian Department of Justice Ethics Committee for access to the National Coronial Information System. Informed written consent was obtained from participants for each study other than Chapter 8, where access to coronial information was approved without individual consent.

2.2 CARDIAC MAGNETIC RESONANCE IMAGING

All magnetic resonance imaging was performed using a single 1.5T MR scanner (Philips Acheiva; Philips, Best, The Netherlands).

2.2.1 ASSESSMENT OF RESTING VENTRICULAR VOLUMES AND FUNCTION USING STANDARD CINE MAGNETIC RESONANCE IMAGING

Short axis, vertical long axis and 4-chamber views of both ventricles and outflow tracts were acquired over 9-12 slices utilising retrospectively gated steady-state free precession (b-FFE) cine MRI images. Imaging parameters acquired during a single breath hold were: TR=3.2 ms; TE=1.6 ms; flip angle=78°; slice thickness=8 mm; matrix=192x256; field of view-300-380 mm; and temporal resolution=40 ms. Assessment of ventricular volumes and function using short axis cine images were
manually traced along the endocardial border at end-diastole and end-systole using OSIRIX open source medical imaging software (32Bit v3.9.x). Simpson’s rule was used to calculate end-diastolic and end-systolic volumes for both ventricles; ejection fractions were calculated from these volumes.

Regional analysis of the RV volumes in systole and diastole was then performed, where the RV was divided in the fibrous RVOT and RVMC components. The delineation of these segments was based on the following criteria. The fibrous RVOT was contoured from the pulmonary valve leaflets superiorly, to the fibrous to muscular transition zone with in the RVOT anteriorly based on delayed enhancement studies. Posteriorly the fibrous RVOT was contoured to include volume until the superior aspect of the interventricular septum. An arbitrary line was contoured between the lower anterior and posterior landmarks to define the lower border zone of the fibrous RVOT. Fibrous RVOT measurements were independently analysed in all subjects by two observers with an intraclass correlation coefficient of 0.977 for end-systolic measurements and 0.923 for end diastolic measurements.

2.2.2 RESTING MAGNETIC RESONANCE FLOW CALCULATION

Pulmonary artery and aortic flow data were acquired during a breath-hold using a phase-sensitive (Venc set at 200 cm/sec and adjusted to avoid aliasing), gradient-echo sequence (TR, <5 ms; TE, <3 ms; flip angle, 15˚; slice thickness, 7 mm; field of view =300-380 mm matrix, 256x240, temporal resolution=30 ms). Imaging planes
were standardised as the main pulmonary artery midpoint and aortic sino-tubular junction. Through plane flow data was acquired utilising retrospective cardiac gating. Phase contrast images were used to obtain arterial blood flow via semiautomatic vessel edge-detection algorithm (View Forum, Phillips system) with manual operator correction. Pulmonary artery net forward flow (mL) and PR fraction (%) were calculated as total forward pulmonary flow minus retrograde pulmonary flow, and percent retrograde pulmonary flow over total pulmonary flow, respectively. Similar calculations were used to determine aortic and tricuspid forward flow and regurgitant fraction.

2.2.3 MAGNETIC RESONANCE ANGIOGRAPHY

Pulmonary artery morphology was assessed with a dedicated magnetic resonance angiography sequence (MRA). Administration of intravenous contrast (0.2 mmol/kg of gadolinium pentatate, Magnevist) was triggered visually and was acquired in a 15 second breath-hold. The 2-phased MRA was performed with a T1 weighted spoiled gradient echo sequence. The following imaging parameters were used: TR = 7 ms; TE = 3.5 ms; flip angle = 30°; matrix = 256 x 192; field of view = 480 mm; slice thickness = 3 mm, zip 2.

2.2.4 LATE GADOLINIUM ENHANCEMENT: SCAR/FIBROSIS IMAGING
Scar imaging within the myocardium was performed with segmented phase-sensitive inversion recovery sequences (image parameters: TR=2xRR interval; TE=3.4 ms; flip angle=25°; slice thickness=10mm; matrix=144x256; field of view=300-380 mm, acquired during a single breath-hold) 10 min post-administration of intravenous contrast (0.2 mmol/kg of gadolinium pentatate, Magnevist). Imaging included the entire short axis and long-axis planes of the left ventricle and right ventricle.

2.2.5 EXERCISE CARDIAC MAGNETIC RESONANCE IMAGING PROTOCOL

Cardiac function and flows were assessed using real-time free breathing magnetic resonance imaging at rest, 30% heart rate reserve (Level 1) and 60% heart rate reserve (Level 2). Target exercising heart rates were determined using the following calculation: target heart rate = resting heart rate + ([maximum heart rate − resting heart rate] x either 0.3 or 0.6). Maximal heart rate was obtained at peak exercise during the CPET described below.

Increase in heart rate was achieved using a custom built, MRI compatible step-style ergometer, which utilised fluid filled chambers to create resistance. Study participants were placed in the supine position with an approximately 45 degree bend at their knees to allow stepping exercise without contacting the MR tunnel. A 5 channel cardiac receive coil and vector-cardiogram leads were placed on the subject’s chest. During exercise, participants were verbally instructed to either increase or decrease their cadence to reach and then maintain the desired heart
rate. Once the heart rate had reached a plateau (typically after 1 to 2 minutes of exercise) at the target rate, imaging commenced.

Localiser and calibration scans were performed at the outset before the following real-time magnetic resonance images were captured at rest, Level 1 and Level 2: 4-chamber cine; short-axis cine stack (4 slices); aortic flow; and pulmonary artery flow. Real-time imaging parameters were: TR=4 ms; TE=1.4 ms; flip angle=60˚; slice thickness=8 mm; matrix=192x192; field of view 380 mm; and temporal resolution corresponding to 92ms. 100 temporal dynamics were obtained at each slice with corresponding velocity encoding (Venc 150-300 cm/s, adjusted to avoid aliasing). Imaging planes were selected and flow calculations were performed as described above. Ejection fractions at rest and during exercise were obtained from real-time 4-chamber cine images utilising OSIRIX software (32Bit v3.9.x) to trace the endocardial border during end-diastole and end-systole, as described above and previously validated. All real-time data was collected in less than 60 seconds from commencement of imaging protocol.

2.3 CARDIOPULMONARY EXERCISE TESTING

An electronically braked bicycle ergometer (Lode Corival; Lode BV, Groningen, The Netherlands) was used to perform progressive, maximal exercise tests. Ramped protocols were individually determined, as described by Jones et al (1985). A period of at least 2 minutes low resistance pedalling followed maximal exertion whilst
heart rate, blood pressure and ECG morphology was monitored. Breath by breath expiratory gas analysis (VMax229; SensorMedics; Yorba Linda, California) and ECG monitoring (Cardiosoft, version 6.51, GE Healthcare, Waukesha, Wisconsin) were performed. Blood pressure was periodically measured and oxygen saturation measurements (Radical, Massimo Corp, Irvine, USA) were also obtained continuously. Work rate, heart rate, blood pressure, oxygen consumption, carbon dioxide production, ventilation, oxygen saturation and ECG morphology continuously collected during the testing period.
CHAPTER THREE

STRUCTURE-FUNCTION CORRELATES IN ADULTS WITH
REPAIRED TETRALOGY OF FALLOT
3.1 INTRODUCTION

Exercise capacity has widely been reported to be impaired in adults with repaired tetralogy of Fallot (TOF).\(^6^0, 112, 134, 140, 142, 159, 162\) However, the relationship between exercise capacity and right ventricular (RV) structure and function has been only poorly characterised. Cardiac MRI parameters have exhibited weak relationships with peak exercise ability in previous research.\(^6^0, 83, 169, 170\) Exercise capacity must be, however, at least partially related to the capability of the RV to produce forward flow. The contractile performance of the RV is to some extent determined by RV mass, which is not currently used in clinical decision making, such as the timing of pulmonary valve replacement.

We aimed to determine whether RV mass is correlated with exercise capacity and could therefore provide a useful marker of clinical status and potentially future outcomes, in repaired tetralogy patients.
3.2 METHODS

3.2.1 STUDY POPULATION

Between September 2008 and February 2013, a total of 82 patients with TOF or tetralogy-type pulmonary atresia with ventricular septal defect (PAVSD) were prospectively recruited to undertake cardiopulmonary exercise testing and cardiac MRI, having been referred to our adult congenital heart service for assessment (table 1). Ethics approval was obtained from the Royal Prince Alfred Hospital Human Research Ethics Committee, Sydney, and all participants gave informed consent.

3.2.2 CARDIAC MRI PROTOCOL

Cardiac magnetic resonance imaging was performed as described in General Methods sections 2.2.1 – 2.2.3. In addition, end-diastolic traces of the right ventricular epicardial border, again using OSIRIX open source medical imaging software (32Bit v5.2), allowed calculation of RV mass. Reproducibility was assessed by repeating RV mass measurements by a second observer in 10 patients; the intraclass correlation coefficient was found to be 0.935.

3.2.3 CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing was performed as described in General Methods section 2.3.
3.2.4 STATISTICAL METHODS

Continuous variables are presented as mean ± SD. Pearson’s correlation and multivariable linear regression were used to assess associations between measures of cardiac structure by MRI and exercise capacity. Peak work was our primary outcome measure, and RV mass was our prespecified primary variable of interest. Multivariable models were adjusted for age and gender, with subsequent models additionally adjusting for other measures of cardiac structure and function as detailed in the results. Body surface area (BSA) was defined as $0.016667 \times \text{weight}^{0.5} \times \text{height}^{0.5}$ and the ratio of RV mass to BSA was also analysed. IBM SPSS Statistics (version 21.0; IBM Corp., Somers, NY) was used for statistical analyses. Statistical significance was inferred at two-sided $P$ value $<0.05$. 
3.3 RESULTS

3.3.1 PARTICIPANT CHARACTERISTICS

Table 1 shows patient characteristics. Eighty-two patients (age at evaluation 26 ± 10 years; mean age at repair 2.5 ± 2.8 years; 23.3 ± 7.9 years since repair; 53 males) were included in this study. The majority of patients had a primary diagnosis of TOF (n=73; 89%) with a fewer number having a primary diagnosis of PA VSD (n=9, 11%). Complete repair was performed using a transannular patch in 74 patients (90%), whereas a homograft was used in 3 patients (4%) and a valve sparing repair was performed in 2 patients (2%). Surgical data was not available for 3 patients due to the procedure being performed outside Australia and missing medical records.

3.3.2 CARDIAC MRI RESULTS

Table 2 shows cardiac MRI results. RV dilatation was observed (RVEDVi 153 ± 43.9 mL/m²; RVESVi 77.3 ± 31.2 mL/m²) and pulmonary regurgitation was moderate to severe (pulmonary regurgitant fraction [PRF]: 33 ± 14%). LVESVi was elevated (34.2 ± 11.3 mL/m²), however, LVEDVi was not abnormal (81.4 ± 14.7 mL/m²). Maintained LV and RV stroke volumes (LV SV 84.9 ± 19.8 mL; RV SV 135.4 ± 37.9 mL) and ejection fractions (LV EF 58.8 ± 7.7%; RV EF 50.5 ± 7.3%) were observed. Right ventricular outflow tract obstruction was assessed via the most recent echo using standardised AHA/ACC criteria⁷¹ and was noted in 12 patients (mild: 5 [6%]; mild-moderate: 4 [5%]; moderate: 1 [1%]; moderate-severe: 2 [2%]).
3.3.3 CARDIOPULMONARY EXERCISE TEST RESULTS

Table 3 shows cardiopulmonary exercise test results. Overall, exercise capacity was near-normal. Peak work was 88 ± 17% of predicted (172 ± 53 watts), VO2peak was 84 ± 17% predicted (32 ± 8 mL/kg/min) and peak heart rate was 90 ± 9% predicted (171 ± 16 bpm). Anaerobic threshold was above 60% of maximal exercise capacity when measured as a percentage of peak work (work at anaerobic threshold: 105 ± 35 watts; percentage of peak work: 62 ± 10) and peak oxygen uptake (VO2 at anaerobic threshold: 21.5 ± 5.6 mL/kg/min; percentage of peak: VO2 69 ± 12). The respiratory exchange ratio was 1.25 ± 0.12.

3.3.4 CORRELATIONS

In univariate analysis, RV mass (r=0.45, p<0.001), RV mass to RVEDV ratio (r=0.286, p=0.009) and RV mass to BSA ratio (r=0.28, p=0.01) were all positively correlated with peak work (see figures 1 and 2). The association of RV mass with peak work was such that for each 10 gram higher RV mass, peak work was 8 watts higher.

RV and LV cardiac output and stroke volumes also correlated with peak work (RV SV: r=0.396, p<0.001; RV CO: r=0.313, p=0.004; LV SV: r=0.642, p<0.001; LV CO: r=0.56, p<0.001). Significant positive correlations were observed between RV CO and LV CO (r=0.672, p<0.001), RV EF and LV EF (r=0.618, p<0.001), and RV SV and LV SV (r=0.547, p<0.001). The correlation between peak work and RVEDVi, RVESVi and PRF was not statistically significant (p>0.05 for each correlation).
Ve/VCO₂ positively correlated with RVEDVi, RVESVi, PRF and negatively correlated with RVEF at anaerobic threshold (RVEDVi: r=0.305, p=0.005; RVESVi: r=0.383, p<0.001; PRF: r=0.316, p=0.005; RVEF: r=-0.342, p=0.002) and at peak exercise (RVEDVi: r=0.349, p=0.001; RVESVi: r=0.448, p=<0.001; PRF: r=0.260, p=0.021; RVEF: r=-0.453, p<0.001).

In multivariable linear regression adjusted for age and sex, RV mass remained significantly correlated with peak work. This association was independent of all other tested cardiac MRI variables (see Figure 3). Similar results were found when these analyses were performed with RV mass to RVEDV ratio and RV mass to BSA ratio, rather than RV mass.

The above relationships were unaltered when the same analyses were performed excluding those 9 patients with underlying PA-VSD or the 8 patients with more than mild RV outflow tract obstruction.
### Table 3.1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n)</td>
<td>82</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26 ± 10</td>
</tr>
<tr>
<td>Males (n)</td>
<td>53 (65%)</td>
</tr>
<tr>
<td><strong>Primary diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>TOF</td>
<td>73</td>
</tr>
<tr>
<td>PAVSD</td>
<td>9</td>
</tr>
<tr>
<td><strong>Primary repair</strong></td>
<td></td>
</tr>
<tr>
<td>Transannular patch</td>
<td>74</td>
</tr>
<tr>
<td>Homograft</td>
<td>3</td>
</tr>
<tr>
<td>Valve sparing</td>
<td>2</td>
</tr>
<tr>
<td>Surgical data not available</td>
<td>3</td>
</tr>
<tr>
<td>Age at TOF repair</td>
<td>2.5 ± 2.8</td>
</tr>
<tr>
<td>Years since repair</td>
<td>23.3 ± 7.9</td>
</tr>
</tbody>
</table>

TOF, tetralogy of Fallot; PAVSD, pulmonary atresia with ventricular septal defect.

### Table 3.2. Cardiac MRI results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indexed left ventricular end-diastolic volume (mL/m2)</td>
<td>81.4 ± 14.7</td>
</tr>
<tr>
<td>Indexed left ventricular end-systolic volume (mL/m2)</td>
<td>34.2 ± 11.3</td>
</tr>
<tr>
<td>Left ventricular stroke volume (mL)</td>
<td>84.9 ± 19.8</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>58.8 ± 7.7</td>
</tr>
<tr>
<td>Left ventricular cardiac output (L/min)</td>
<td>6.1 ± 1.6</td>
</tr>
<tr>
<td>Indexed right ventricular end-diastolic volume (mL/m2)</td>
<td>153 ± 43.9</td>
</tr>
<tr>
<td>Indexed right ventricular end-systolic volume (mL/m2)</td>
<td>77.3 ± 31.2</td>
</tr>
<tr>
<td>Right ventricular stroke volume (mL)</td>
<td>135.4 ± 37.9</td>
</tr>
<tr>
<td>Right ventricular ejection fraction (%)</td>
<td>50.5 ± 7.3</td>
</tr>
<tr>
<td>Right ventricular cardiac output (L/min)</td>
<td>9.8 ± 3.3</td>
</tr>
<tr>
<td>Pulmonary regurgitant fraction (%)</td>
<td>33.0 ± 14.2</td>
</tr>
</tbody>
</table>
### Table 3.3. Cardiopulmonary exercise test results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak work (watts)</td>
<td>172 ± 53</td>
</tr>
<tr>
<td>% predicted peak work</td>
<td>88 ± 17</td>
</tr>
<tr>
<td>Work at anaerobic threshold (watts)</td>
<td>105 ± 35</td>
</tr>
<tr>
<td>% of peak work</td>
<td>62 ± 10</td>
</tr>
<tr>
<td>VO₂\text{peak} (ml/kg/min)</td>
<td>32 ± 8</td>
</tr>
<tr>
<td>% predicted VO₂\text{peak}</td>
<td>84 ± 17</td>
</tr>
<tr>
<td>Anaerobic threshold VO₂ as % of VO₂\text{peak}</td>
<td>69 ± 12</td>
</tr>
<tr>
<td>Peak heart rate (bpm)</td>
<td>171 ± 16</td>
</tr>
<tr>
<td>% predicted peak heart rate</td>
<td>90 ± 9</td>
</tr>
<tr>
<td>Peak respiratory exchange ratio</td>
<td>1.25 ± 0.12</td>
</tr>
<tr>
<td>Vₑ/VCO₂ at anaerobic threshold</td>
<td>25.3 ± 3.1</td>
</tr>
<tr>
<td>Vₑ/VCO₂ at peak</td>
<td>27.7 ± 4.1</td>
</tr>
</tbody>
</table>

VO₂\text{peak}, peak oxygen consumption; Vₑ/VCO₂, ratio of minute ventilation to carbon dioxide production.
Figure 3.1. Linear regression of peak work and RV mass

\[ r = 0.45 \]
\[ p < 0.0001 \]
\[ \text{slope} = 0.80 \pm 0.18 \]
Figure 3.2. Linear regression of peak work and RV mass: RVEDV

RV, right ventricle; RVEDV, right ventricular end-diastolic volume.
Figure 3.3. Association of RV mass with peak work, adjusted for RVEDVi, RVEF, PRF, LV CO and LV EF

Partial residual plot showing the association between RV mass and peak work, adjusted for indexed right ventricular end-diastolic volume (RVEDVi), right ventricular ejection fraction (RVEF), pulmonary regurgitant fraction (PRF), left ventricular cardiac output (LV CO) and left ventricular ejection fraction (LV EF). For each 10 gram higher RV mass, peak work was 7.5 watts (95% CI 3.3, 1.2) higher. Y axis recalibrated to the mean.
3.4 DISCUSSION

In this study, we have shown that RV mass, RV mass:RVEDV and RV mass:BSA positively correlated with peak exercise capacity, independent of traditional indicators of clinical status, in a group of adult repaired TOF patients with right ventricular dilatation, moderate to severe pulmonary regurgitation and near-normal exercise capacity. Furthermore, we have shown that PRF and RV dilatation result in altered respiratory dynamics during exercise as evidenced by positive correlations with $V_E/VCO_2$.

Previous research has not provided any certainty in the relationship between cardiac MRI variables and peak exercise capacity. Meadows et al.\textsuperscript{170} retrospectively studied cardiac MRI and CPET data from 37 adult patients with repaired TOF and found that RV EF was positively and independently correlated with $VO_2\text{peak}$, $VO_2$ at anaerobic threshold and oxygen pulse. Furthermore, Wald et al.\textsuperscript{83} performed regional analysis of RV function in 62 adult repaired TOF patients and reported that although global RV EF was positively correlated with $VO_2\text{peak}$, RV outflow tract EF was more strongly correlated on univariate analysis and independently correlated in multiple linear regression analysis with step-wise selection of variables. However, other previous studies have reported no correlation between RV EF and peak exercise capacity.\textsuperscript{60, 169} The lack of correlation between RV EF and peak exercise capacity in the current study may be explained by lack of statistical power generated from a comparatively high overall exercise capacity in our cohort. However, this possible lack of statistical power means the positive correlation between RV mass and peak work is even more striking.
The strong positive and independent correlation between peak work and RV mass indicates the importance of an effective level of musculature in the subpulmonary ventricle. Furthermore, a positive correlation between peak work and RV mass:RVEDV highlights the important contribution of RV compliance towards peak exercise capacity. These findings support the notion that RV volume alone may be less important than RV mass and its ratio to ventricular volume in the ability to produce forward flow of blood into the pulmonary circuit and overall exercise capacity. However, these patients with increased RV mass may also have increased LV mass, which may have a similar impact on exercise capacity. The lack of correlation between exercise capacity and traditional indicators of clinical status further underpins the importance of our findings. RV mass has previously been shown to be elevated in TOF patients as compared to controls\textsuperscript{130, 169} and represents a compensatory response to haemodynamic insults. RV hypertrophy is mostly thought to be a negative adaptive process and is likely in response to long-standing pulmonary regurgitation, however, from the evidence presented in our study, this adaptation may result in positive effects on exercise capacity. However, there is likely a point at which increased RV mass may decrease the ability to produce forward flow out of the right ventricle as a result of decreased cavity size and RV mass:RVEDV. Furthermore, RV hypertrophy may be viewed as maladaptive in patients with RV outflow tract obstruction, which was relatively uncommon in our series. Severe RVH could also potentially predispose to RV diastolic dysfunction, which was not formally assessed in the current study.
Not surprisingly, biventricular cardiac outputs and stroke volumes were positively correlated with peak work. Furthermore, substantial LV-RV interaction is evidenced by significant positive correlations between right and left ventricular systolic function. Clearly the right ventricle does not act in isolation and is heavily dependent on left ventricular function, and vice versa. This finding confirms previous research where significant ventricular-ventricular interaction has been reported.\(^8^1, 1^2^7, 1^3^0, 1^4^8\) It has been noted, however, that excessive RV hypertrophy can impinge on LV filling, which may have adverse effects on exercise capacity.\(^1^9^9\)

Although PRF has previously been reported to be correlated with peak exercise capacity,\(^6^0, 1^5^7\) when pulmonary regurgitation is alleviated via surgical insertion of a pulmonary valve, exercise capacity does not commonly improve.\(^7^3, 7^7, 8^9, 9^6, 1^0^2, 1^6^3-1^6^8\) RVEDVi also does not seem to be directly related to peak exercise capacity. However, both PRF and RVEDVi were negatively correlated with $V_E/VCO_2$ indicating altered respiratory dynamics during exercise. Altered pulmonary artery anatomy has previously been implicated in distorted pulmonary blood flow distribution, ventilation-perfusion mismatch and inadequate respiratory gas exchange,\(^6^1, 1^7^5\) and may therefore play a role in the development of exercise incapacity. However, it should be noted that $V_E/VCO_2$ is not a measure of either submaximal or maximal exercise capacity. Rather an elevated $V_E/VCO_2$ simply indicates an altered respiratory response to a given level of carbon dioxide production.

3.4.1 STUDY LIMITATIONS
The main limitation of the present study was that our cohort of adult repaired TOF patients demonstrated near normal exercise capacity, compared to previously reported groups. Caution therefore needs to be taken before generalising these results to the greater TOF population. Furthermore, it is possible that correlation between certain cardiac MRI and exercise variables were not present due to a lack of statistical power as a result, even though ours is a large study for this question. Analysis of RV mass is not commonly performed. However, with robust analysis protocols, we have performed these measurements with good reproducibility. Finally, this was a single centre study only.
3.5 CONCLUSIONS

In adult repaired TOF patients with moderate-severe pulmonary regurgitation and RV dilatation, RV mass is positively correlated with peak work output during CPET. This association is independent of other cardiac MRI variables. Importantly, traditional cardiac MRI indicators of clinical status are not significantly correlated with peak or submaximal exercise capacity. RV mass may provide a novel marker of clinical progress amongst this patient cohort.
CHAPTER FOUR

EXERCISE CAPACITY AND STROKE VOLUME ARE PRESERVED EVEN WITH SEVERELY DILATED RIGHT VENTRICLE, LATE AFTER TETRALOGY REPAIR
Chapter 4 Exercise Capacity and Stroke Volume are Preserved Even with Severely Dilated Right Ventricle, Late After Tetralogy Repair

4.1 INTRODUCTION

Pulmonary regurgitation (PR) is very common late after TOF repair in childhood due to the frequent need to open the right ventricular outflow tract across the pulmonary valve as part of the repair.117 Chronic exposure of the right ventricle (RV) to a regurgitant load may lead to progressive RV dilatation, and has been associated with adverse events such as increased symptoms, arrhythmia and death.66, 81, 115, 183, 200 Potential causes of RV dysfunction in adults with repaired TOF include abnormalities of the temporal pattern of RV mechanical activation.201 Although PVR is an effective way of reducing the volume load on the RV, there is no proof from prospective studies that it reduces the risk for adverse outcomes, such as sudden cardiac death, sustained ventricular arrhythmias or heart failure.73, 74, 77, 78, 97, 102 The timing of PVR, however, is an area of uncertainty. The European Society of Cardiology (ESC), the American College of Cardiology (ACC)/American Heart Association (AHA) and the Canadian Cardiovascular Society (CCS) have currently published guidelines for PVR in adults with repaired TOF.15, 71, 72 Severe PR, together with symptoms and/or moderate to severe RV enlargement, are suggested as indicators for PVR. However, there is some uncertainty regarding the definition of moderate to severe RV enlargement. Based on work conducted by Therrien et al.,73 the CCS guidelines suggest an RVEDVi of 170 ml/m² as an indicator for PVR, as dilatation beyond this is unlikely to result in normalisation of RV dimensions post-PVR. Alternatively, the ESC includes progressive RV dilatation in indications for intervention after repair of TOF, and refers to Oosterhof et al.74 when stating that RV size is unlikely to normalise after PVR when RVEDVi is allowed to dilate beyond 160 ml/m². The ACC/AHA guidelines, however, do not indicate what constitutes moderate to severe RV enlargement. In practice, an RVEDVi of 150 ml/m² is a commonly used RV volume for recommending
PVR in adults with repaired TOF. As PVR has limited durability, deferring this surgery for as long as possible may reduce the number of surgical procedures needed over a patient’s lifetime.

In this study, we sought to determine differences in cardiac structure, function and exercise capacity in such patients, above and below an RVEDVi of 150 ml/m².
4.2 METHODS

4.2.1 PATIENT POPULATION

Between April 2009 and February 2010, a total of 55 consecutive patients with previously diagnosed TOF or pulmonary atresia with ventricular septal defect (PAVSD) were prospectively recruited after being referred to our adult congenital heart service for a cardiac MRI and CPET (Table 4.1).

4.2.2 CARDIAC MRI PROTOCOL

Cardiac magnetic resonance imaging was performed as described in General Methods sections 2.2.1 – 2.2.3.

4.2.3 CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing was performed as described in General Methods section 2.3.

4.2.4 STATISTICAL METHODS

All data are presented as mean±SD or median and range. The patients were divided into two groups according to a prospectively defined cut-point for RVEDVi, at 150 ml/m². Secondary analyses were performed using RVEDVi cut-points of 160 ml/m² and 170 ml/m². Statistical comparison of parametric data was performed with a 2-tailed unpaired Student t test. Prespecified primary endpoints of interest were (1) for
MRI, the calculated LV cardiac output (as the best overall determinant of cardiac performance) and (2) for CPET, the maximum work achieved as a per cent of normal (control) values. All other non-primary comparisons were adjusted by the Hochberg modification of the Bonferroni correction. The relationship between dichotomous variables was tested with the $\chi^2$ test. A two-tailed $p$ value <0.05 was considered statistically significant. Pearson’s correlation coefficient was used to assess relations between cardiac MRI and exercise parameters. Statistical analysis was performed with SPSS V.19 for Windows (SPSS).
4.3 RESULTS

4.3.1 PATIENT POPULATION (n=55)

Fifty-five patients (mean age at repair 2.3±1.9 years; age at evaluation 26.2±8.8 years; range 15-49 years; 33 males) were included in this study. Demographic and surgical details are shown in Table 4.1. The primary diagnosis in the cohort was most frequently TOF (n=50; 91%) with a lesser number of PA-VSD (n=5; 9%). A transannular patch (TAP) repair was performed in 46 (84%) patients, while a homograft, valvectomy or valve-sparing repair was conducted in 2 (3.5%), 2 (3.5%) and 2 (3.5%) patients, respectively. Detailed operative data was not available for three patients due to missing medical records. Overall, the patients were assessed 23.6±7.2 years after surgical repair.

Subjects with RVEDVi of >150 ml/m² (n=35) were later after initial repair (25.4±7.8 vs 20.7±5.8 years; p=0.009) and were older at the time of evaluation (28.4±9.7 vs 22.5±5.5 years; p=0.006). However, there was not a significant difference in primary diagnosis (>150 ml/m²; TOF n=33, PA VSD n=2 vs <150 ml/m²; TOF n=17, PA VSD n=3; p=0.249), age at complete repair (2.5±2.1 years vs 2.0±1.5 years, p=0.344), type of primary repair (TAP n=31, homograft n=0, valvectomy n=1, valve sparing repair n=1 vs TAP n=15, homograft n=2, valvectomy n=1, valve sparing repair n=1; p=0.36), gender (p=0.09).
# Table 1 Demographic and surgical data for all patients and by RVEDVi group

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>RVEDVi &lt;150 ml/m²</th>
<th>RVEDVi ≥150 ml/m²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>55</td>
<td>20</td>
<td>35</td>
<td>—</td>
</tr>
<tr>
<td>Age at evaluation (yrs)</td>
<td>26.2±8.8</td>
<td>22.5±5.5</td>
<td>28.4±9.7</td>
<td>0.006</td>
</tr>
<tr>
<td>Males</td>
<td>33</td>
<td>9</td>
<td>24</td>
<td>0.086</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
<td></td>
<td></td>
<td>0.249</td>
</tr>
<tr>
<td>TOF</td>
<td>50</td>
<td>17</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>PA VSD</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Primary repair</td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Transannular patch</td>
<td>46</td>
<td>15</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Homograft</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Valvectomy</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Valve-sparing repair</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Surgical data not available</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Age at primary repair (yrs)</td>
<td>2.3±1.9</td>
<td>2.0±1.5</td>
<td>2.5±2.1</td>
<td>0.344</td>
</tr>
<tr>
<td>Years since primary repair (yrs)</td>
<td>23.6±7.2</td>
<td>20.7±5.0</td>
<td>25.4±7.8</td>
<td>0.009</td>
</tr>
<tr>
<td>QRS duration (msec)</td>
<td>143±29</td>
<td>130±29</td>
<td>151±26</td>
<td>0.01</td>
</tr>
<tr>
<td>RVOT fibrosis</td>
<td>38</td>
<td>11</td>
<td>27</td>
<td>0.087</td>
</tr>
</tbody>
</table>

TOF, tetralogy of Fallot; PA VSD, pulmonary atresia with ventral septal defect; RVOT, right ventricular outflow tract.
4.3.2 MRI RESULTS (n=55)

For all subjects considered together, RV dilatation (RVEDVi 163±44 ml/m²; RVESVi 84±37 ml/m²) and moderate to severe PR (PR fraction 38±10%; PR volume 53±23 ml/beat) were observed (Table 4.2). Indexed LVEDVi was within the normal range (83±15 ml/m²), however, indexed LVESVi was elevated (36±11 ml/m²). Consistent with the RV dilatation, QRS duration was prolonged (143±29 ms) (Table 4.1), although the effect of LV parameters cannot be excluded. Biventricular indexed stroke volumes (SV) and EFs were maintained (RVSVi 79±17 ml/m²; LVSVi 47±8 ml/m²; RVEF 50±7%; LVEF 58±7%). Fibrosis was rarely detected in the RV body (n=1), and more frequently in the RV outflow (n=38).

4.3.3 CARDIOPULMONARY EXERCISE TEST RESULTS (n=55)

Table 4.3 shows cardiopulmonary exercise test results. Peak work rate reached 176±51 Watts, which represented 89±15% of that predicted. Peak oxygen consumption reached 85±15% of that predicted at 31±8 ml/kg/min. Peak heart rate achieved was 173±16 beats/min which was 92±8% of that predicted. Oxygen consumption at anaerobic threshold was 21±6 ml/kg/min which represents 68±12% of peak oxygen uptake. Ventilatory response to carbon dioxide (VE/VCO₂) was 25±3 at anaerobic threshold and 28±4 at peak exercise. Percentage of predicted peak work achieved significantly correlated with LVEDVi (p=0.048). There were no other significant correlations between the variables shown in Table 4.4.
### Table 2  MRI data for all patients and by RVEDVi group

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>RVEDVi &lt;150 ml/m²</th>
<th>RVEDVi ≥150 ml/m²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDVi (ml/m²)</td>
<td>163±44</td>
<td>121±20</td>
<td>187±36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVESVi (ml/m²)</td>
<td>84±37</td>
<td>57±14</td>
<td>100±30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVSVi (ml/m²)</td>
<td>79±17</td>
<td>64±10</td>
<td>87±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVCOi (l/min/m²)</td>
<td>5.7±1.5</td>
<td>4.5±0.9</td>
<td>6.4±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>50±7</td>
<td>54±6</td>
<td>47±7</td>
<td>0.007</td>
</tr>
<tr>
<td>PRF (%)</td>
<td>38±10</td>
<td>31±8</td>
<td>41±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRV (ml/beat)</td>
<td>53±23</td>
<td>34±12</td>
<td>62±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDVi (ml/m²)</td>
<td>83±15</td>
<td>76±11</td>
<td>87±15</td>
<td>0.117</td>
</tr>
<tr>
<td>LVESVi (ml/m²)</td>
<td>36±11</td>
<td>33±7</td>
<td>37±12</td>
<td>1</td>
</tr>
<tr>
<td>LVSVi (ml/m²)</td>
<td>47±8</td>
<td>44±7</td>
<td>49±7</td>
<td>0.064</td>
</tr>
<tr>
<td>LVCOi (l/min/ m²)</td>
<td>3.4±0.6</td>
<td>3.1±0.7</td>
<td>3.3±0.6</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58±7</td>
<td>58±6</td>
<td>58±8</td>
<td>1</td>
</tr>
</tbody>
</table>

RVEDVi, indexed right ventricular end-diastolic volume; RVESVi, indexed right ventricular end-systolic volume; RVSVi, indexed right ventricular stroke volume; RVCOi, indexed right ventricular cardiac output; RVEF, right ventricular ejection fraction; PRF, pulmonary regurgitant fraction; PRV, pulmonary regurgitant volume; LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic volume; LVSVi, indexed left ventricular stroke volume; LVCOi, indexed left ventricular cardiac output; LVEF, left ventricular ejection fraction.
Table 3  Cardiopulmonary exercise test data for all patients and by RVEDVi group

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>RVEDVi &lt;150 ml/m²</th>
<th>RVEDVi ≥150 ml/m²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak work (Watts)</td>
<td>176±51</td>
<td>176±54</td>
<td>177±51</td>
<td>0.935</td>
</tr>
<tr>
<td>% Predicted peak work</td>
<td>89±15</td>
<td>87±11</td>
<td>90±17</td>
<td>1</td>
</tr>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>31±8</td>
<td>31±5</td>
<td>31±10</td>
<td>1</td>
</tr>
<tr>
<td>% Predicted peak VO₂</td>
<td>85±15</td>
<td>87±12</td>
<td>84±17</td>
<td>1</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>173±16</td>
<td>176±15</td>
<td>171±16</td>
<td>1</td>
</tr>
<tr>
<td>% Predicted peak HR</td>
<td>92±8</td>
<td>93±7</td>
<td>91±9</td>
<td>1</td>
</tr>
<tr>
<td>VO₂ at AT (ml/kg/min)</td>
<td>21±6</td>
<td>21±4</td>
<td>21±7</td>
<td>1</td>
</tr>
<tr>
<td>% peak VO₂</td>
<td>68±12</td>
<td>68±9</td>
<td>68±14</td>
<td>1</td>
</tr>
<tr>
<td>Work at AT (Watts)</td>
<td>106±35</td>
<td>111±35</td>
<td>104±36</td>
<td>1</td>
</tr>
<tr>
<td>% Peak work</td>
<td>60±11</td>
<td>63±7</td>
<td>59±12</td>
<td>0.150</td>
</tr>
<tr>
<td>HR at AT</td>
<td>130±20</td>
<td>137±18</td>
<td>126±20</td>
<td>0.040</td>
</tr>
<tr>
<td>RER</td>
<td>1.27±0.12</td>
<td>1.26±0.12</td>
<td>1.28±0.12</td>
<td>1</td>
</tr>
<tr>
<td>V̇E/V̇CO₂ at AT</td>
<td>25±3</td>
<td>25±3</td>
<td>26±3</td>
<td>0.558</td>
</tr>
<tr>
<td>V̇E/V̇CO₂ at peak</td>
<td>28±4</td>
<td>27±4</td>
<td>29±4</td>
<td>0.752</td>
</tr>
</tbody>
</table>

VO₂, volume of oxygen consumption; VCO₂, volume of carbon dioxide production; HR, heart rate; AT, anaerobic threshold; RER, respiratory exchange ratio; V̇E, ventilation.
### Table 4  Cardiac MRI predictors of exercise capacity; univariate analyses

<table>
<thead>
<tr>
<th></th>
<th>% Predicted peak VO₂</th>
<th>% Predicted peak Work</th>
<th>AT as % of peak VO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p Value</td>
<td>r</td>
</tr>
<tr>
<td>RVEDVi (ml/m²)</td>
<td>−0.078</td>
<td>NS</td>
<td>0.2</td>
</tr>
<tr>
<td>RVESVi (ml/m²)</td>
<td>−0.103</td>
<td>NS</td>
<td>0.156</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>0.185</td>
<td>NS</td>
<td>−0.026</td>
</tr>
<tr>
<td>RVCOI (l/min/m²)</td>
<td>−0.133</td>
<td>NS</td>
<td>0.125</td>
</tr>
<tr>
<td>LVEDVi (ml/m²)</td>
<td>0.167</td>
<td>NS</td>
<td>0.271</td>
</tr>
<tr>
<td>LVESVi (ml/m²)</td>
<td>0.159</td>
<td>NS</td>
<td>0.156</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>−0.013</td>
<td>NS</td>
<td>0.058</td>
</tr>
<tr>
<td>LVCOI (l/min/m²)</td>
<td>−0.041</td>
<td>NS</td>
<td>0.218</td>
</tr>
</tbody>
</table>

RVEDVi, indexed right ventricular end-diastolic volume; RVESVi, indexed right ventricular end-systolic volume; RVCOI, indexed right ventricular cardiac output; RVEF, right ventricular ejection fraction; LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic volume; LVCOI, indexed left ventricular cardiac output; LVEF, left ventricular ejection fraction; NS, non-significant.
4.3.4 RVEDVi OF 160 ml/m² AND 170 ml/m² AS CUT-POINTS

Secondary analyses were performed using RVEDVi cut-points of 160 ml/m² and 170 ml/m². Comparing patients above and below an RVEDVi of 160 ml/m², LVEDVi (p=0.003) and LVSVi (p=0.008) became significantly higher in the more dilated group. All LV parameters became insignificant between groups when an RVEDVi of 170 ml/m² was used as a cut-point. There were no significances between group differences in any exercise parameter, when either of these secondary cut-points was used.
4.4 DISCUSSION

In this study, we have shown relatively normal submaximal and peak exercise parameters in a group of adult patients with repaired TOF, prospectively recruited from a single centre, with pulmonary regurgitation and right ventricular dilatation. When the group was divided into those above and below an RVEDVi of 150ml/m², there was no significant difference in measured values of maximal exercise capacity. In fact, exercise capacity was at near-normal levels, even in the more dilated group, despite greater PR, RV dilatation and lower normal RVEF. This leaves the crucial decision of PVR timing less certain, in adult patients with repaired TOF.

Over the entire cohort, measures of peak exercise capacity were higher than previously reported in similar groups of adult repaired TOF patients (VO2peak: 21.1-27.6 ml/kg/min; per cent achieved of predicted VO2 peak: 51-78%; peak work: 109-143 Watts; peak heart rate: 146-163 beats/min). Measures of ventricular function, age at evaluation, or age at TOF repair surgery do not explain the disparity in exercise capacity, as our results do not meaningfully differ from those of past research with respect to these parameters. Relatively preserved heart rate responses, and/or an era effect may contribute to these favourable results.

Chronotropic incompetence contributes to exercise intolerance and is related to long-term outcomes in repaired TOF. Our cohort exhibited a substantially increased heart rate at peak exercise compared with previous similar studies.
and offers in part an explanation for the preserved exercise capacity we observed. It should be noted that none of the patients in our study had evidence of resting or exercise-induced arrhythmia. There is also the possibility of an era effect, with our data being collected on a young group of patients in a later time period (2008-2011), compared with previous studies. In this regard, surgical technique, postoperative care and clinical management of patients may have differed from the previously published groups of patients.

Since adults with repaired TOF patients have previously been shown to respond positively to a structured program of physical activity, higher levels of physical activity in our patient group may also be a plausible contributor to the high exercise capacity we observed. Previous studies have shown physical activity levels to be low in adult repaired TOF patients, where this data was generated from the northern hemisphere. It is possible that our patients (in Australia) were encouraged to participate in physical activity from a young age, and this may have had an impact in preserving and optimising their exercise capacity, however, such data were not routinely collected. More investigation into the opportunities provided, and the impact of shifting attitudes regarding physical activity in this group of patients certainly deserves additional detailed study.

Our study demonstrates a lack of correlation between baseline RV volumes and peak exercise capacity in PR. This result is in keeping with previous studies which have similarly failed to show a relationship between RV dilatation and exercise capacity. Moreover, in the context of a dilated but not concentrically hypertrophied RV as a result of PR, LV systolic function is not impaired by ventricular interaction, as
may be the case of RV hypertrophy resulting from pulmonary stenosis. Since oxygen saturations and LV function are not compromised as the RV dilates, oxygen delivery to working muscles and exercise capacity would not be expected to decrease (unless the RV stroke volume fails). Our findings thus question the presumption that RV dilatation inevitably impairs exercise performance and forms an important piece of evidence as to why repaired TOF patients may not improve their exercise capacity after PVR. Although limited conclusions can be drawn from cross-sectional data, it is worth noting that the more dilated group was significantly older than the less dilated group. There is currently no satisfactory data regarding the temporal patterns of RV dilatation. Our findings suggest that long-term monitoring of RV structure is warranted which would be best addressed by a large prospective study.

Late after TOF repair, PR is known to be associated with RV dilatation and systolic dysfunction, which can result in heart failure, exercise intolerance, arrhythmia and death. The optimal timing of PVR in TOF patients is a point of contention, particularly in asymptomatic patients. The ESC, ACC/AHA and CCS have published guidelines for PVR late after TOF repair. There is general agreement that the decision for PVR involves consideration of the presence or absence of symptoms, the degree of PR, RV function, exercise capacity, arrhythmia and the degree of RV enlargement. There is, however, some disagreement about the volume to which the RV can be allowed to dilate prior to PVR, whilst still achieving beneficial remodelling post surgery. Threshold RVEDVi measurements of between 150 ml/m² and 170 ml/m² have been suggested as points above which normalisation of RV dimension becomes unlikely. In order to minimise the number of lifetime procedures in these subjects with PR, developing more specific markers for
detecting adverse adaptive mechanisms to PR would be useful in assisting decision making concerning the timing of surgery.

4.4.1 STUDY LIMITATIONS

The observed similarities in RV systolic function between the two groups in this study may be explained to some extent, by resting cardiac MRI measurements being compared with exercise variables measured at a point of maximal exertion. Future studies may need to focus on assessment of cardiac function during exercise to elucidate parameters more relevant to the maximally functioning heart. Furthermore, longitudinal data relevant to the chronically dilating RV may be important in understanding the RV-adaptive mechanisms of PR. Also, we have not directly examined two other factors that might influence the timing of PVR for dilated RV; propensity to arrhythmia or ability of the RV to diminish in size postoperatively. These other factors require consideration in clinical decision making.
4.5 CONCLUSIONS

We found peak exercise capacity to be higher than previously reported, and near-normal in our cohort of adults with dilated RVs late after TOF repair. Contributors may include appropriate peak heart rate, good physical activity levels or an era effect. Furthermore, our patients exhibited near-normal exercise capacity and maintained biventricular systolic function, even in those with RVs dilated well beyond 150 ml/m². These results question the validity of using this marker of RV dilatation as the major basis for replacing the pulmonary valve in this setting.
CHAPTER FIVE

PROGRESS OF RIGHT VENTRICULAR DILATATION IN ADULTS
WITH REPAIRED TETRALOGY OF FALLOT AND FREE PULMONARY
REGURGITATION
Chapter 5 Progress of Right Ventricular Dilatation in Adults with Repaired Tetralogy of Fallot and Free Pulmonary Regurgitation

5.1 INTRODUCTION

Long standing PR is a common occurrence after the repair of TOF due to pulmonary valve excision and/or the frequent use of transannular patch during initial repair of the right ventricular outflow tract. Exposure of the RV to a chronic regurgitant load leads to RV dilatation and has been associated with negative consequences such as exercise intolerance, arrhythmia and sudden cardiac death.\(^{60, 61, 66, 170, 204-206}\)

RV dilatation in the moderate to severe range is frequently observed in young adult life in repaired TOF patients, at which point replacement of the pulmonary valve is considered. PVR has been shown to be safe and effective in reducing PR, RV dilatation and QRS duration.\(^{69, 73, 74, 77, 102, 164, 165, 189}\) However, controversy surrounds the degree to which the RV should be “allowed to dilate” before the need for surgical intervention. Many centres advocate a conservative approach of performing surgery when RVEDVi reaches 150 mL/m\(^2\). However, there is some evidence that the RV can be allowed to dilate to as large as 170 mL/m\(^2\)\(^{73, 74}\) whilst still achieving normalisation of RV volume after PVR (RVEDVi ≤ 108 mL/m\(^2\))\(^{207}\). PVR timing is based on these RV volumetric cut-points, yet the progression of RV dilatation towards these milestones is poorly understood. Furthermore, the contributions of RV muscular corpus (RVMC) and RV outflow tract (RVOT) volumes in the temporal changes of global RV dilatation have yet to be investigated. Two recent reports have suggested only slow if any progression of RV volumes in this clinical context.\(^{89, 208}\) We therefore sought to characterize temporal changes in global RV, RVOT and RVMC volumes in TOF patients, in our adult congenital heart disease cohort.
Chapter 5 Progress of Right Ventricular Dilatation in Adults with Repaired Tetralogy of Fallot and Free Pulmonary Regurgitation

5.2 METHODS

5.2.1 PATIENT POPULATION

140 adult repaired TOF patients had undergone cardiac MRI in our imaging facility; 69 subsequently underwent PVR or percutaneous pulmonary valve implantation. Of the remaining 71 patients who had not undergone surgical or percutaneous procedure to implant a pulmonary valve, 14 had 1 or more follow up cardiac MRIs. Data was used in these 14 patients referred for 2 clinically indicated cardiac MRIs, and if more than 2 scans had been undertaken, the greatest inter-MRI period was chosen. Overall, the inter-cardiac MRI period was $2.1 \pm 1.0$ years.

5.2.2 CARDIAC MAGNETIC RESONANCE IMAGING PROTOCOL

Cardiac magnetic resonance imaging was performed as described in General Methods sections 2.2.1 – 2.2.3.

5.2.3 STATISTICAL METHODS

All data are presented as mean ± SD. Statistical comparison of initial and follow up MRI data was performed with a 2-tailed paired Student t tests. The pre-specified primary study endpoint was change in RVEDVi. As other endpoints were inter-related and the study was exploratory in nature, p-values were not adjusted for multiple comparisons. Pearson’s correlation coefficient was used to assess relations...
between change in RVEDVi and other MRI variables. Inter-observer variability in RVOT volume analysis was assessed via interclass correlation. Statistical significance was inferred at a two-tailed p-value <0.05. Statistical analyses were performed with SPSS V.21 for Windows (SPSS).
5.3 RESULTS

5.3.1 PATIENT POPULATION (N=14)

Cardiac MRI data was included from 14 patients (age at evaluation 26 ± 11 years; mean age at repair 3.2 ± 2.9 years; 7 males). Patient demographics and surgical details are outlined in Table 5.1. TOF was the primary diagnosis and a trans-annular patch repair had been performed in all 14 patients.

5.3.2 MRI RESULTS (N=14)

MRI results are displayed in Table 5.2. Initially, the cohort had moderate RV dilatation (RVEDVi; 142 ± 19 mL/m², RVESVi; 68 ± 17 mL/m²), moderate to severe PR (PR fraction; 33 ± 11%) and normal RV ejection fraction (RVEF; 53 ± 8%). Indexed LV end-diastolic volume (LVEDVi; 76 ± 10 mL/m²) and LV ejection fraction (LVEF; 61 ± 5%) were within normal ranges, however, LV end-systolic volume was mildly elevated (LVESVi; 30 ± 7 mL/m²). LV and RV stroke volumes were maintained (LVSV; 82 ± 15 mL, RVSV; 132 ± 21 mL). RVOT volume was 8.6 ± 4.6% of RV volume (indexed RVOT end-diastolic volume [RVOT EDVi]; 12 ± 7 mL/m²).

After 2.1 ± 1.0 years, RVEDVi had increased significantly (to 151 ± 20 mL/m², p=0.005; change=8.4 ± 9.3 mL/m², range=-6 to 26 mL/m²; annual mL/m² increase=4.3 ± 4.6; annual percentage increase=3.1 ± 3.3%). RVESVi (77 ± 19
mL/m², \(p=0.009\)) and RVMC indexed end-diastolic volume (RVMC EDVi; 138 ± 20 mL/m², \(p=0.014\)) also increased, and RVEF decreased (49 ± 7%, \(p=0.039\)). RVEDVi increased from below to above an RVEDVi of 150 mL/m² in 3 patients (see Figure 5.1). No other RV or LV structural or functional measures significantly changed in the period between MRIs.

Change in RVEDVi was significantly correlated with initial LVEDVi (\(r=-0.582, p=0.029\)), initial RVEDVi:LVEDVi (\(r=0.6, p=0.023\)) and change in RVMC EDVi (\(r=0.919, p<0.001\)) but not change in RVOT EDVi (\(r=0.182, p=0.552\)) (see Figure 5.2).
Table 5.1. Cohort characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n)</td>
<td>14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26 ± 11</td>
</tr>
<tr>
<td>Males (n)</td>
<td>7</td>
</tr>
<tr>
<td>Age at TOF repair (years)</td>
<td>3.2 ± 2.9</td>
</tr>
<tr>
<td>Years between TOF repair and 1st MRI</td>
<td>23 ± 8</td>
</tr>
</tbody>
</table>

TOF indicates tetralogy of Fallot
### Table 5.2. Cardiac MRI values at initial and follow up MRI

<table>
<thead>
<tr>
<th></th>
<th>MRI 1</th>
<th>MRI 2</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RVEDVi (mL/m²)</strong></td>
<td>142 ± 19</td>
<td>151 ± 20*</td>
<td>8.4 ± 9.3</td>
</tr>
<tr>
<td><strong>RVESVi (mL/m²)</strong></td>
<td>68 ± 17</td>
<td>77 ± 19*</td>
<td>9.2 ± 11.3</td>
</tr>
<tr>
<td><strong>RVMC EDVi (mL/m²)</strong></td>
<td>130 ± 19</td>
<td>138 ± 20*</td>
<td>7.6 ± 9.5</td>
</tr>
<tr>
<td><strong>RVOT EDVi (mL/m²)</strong></td>
<td>12 ± 7</td>
<td>13 ± 6</td>
<td>0.4 ± 1.7</td>
</tr>
<tr>
<td><strong>RVSV (mL)</strong></td>
<td>132 ± 21</td>
<td>132 ± 23</td>
<td>0.1 ± 13.8</td>
</tr>
<tr>
<td><strong>RVEF (%)</strong></td>
<td>53 ± 8</td>
<td>49 ± 7*</td>
<td>-3.6 ± 5.8</td>
</tr>
<tr>
<td><strong>RVCO (L)</strong></td>
<td>9.0 ± 1.3</td>
<td>9.0 ± 1.6</td>
<td>0.0 ± 1.4</td>
</tr>
<tr>
<td><strong>PRF (%)</strong></td>
<td>33 ± 11</td>
<td>33 ± 12</td>
<td>0.3 ± 4.4</td>
</tr>
<tr>
<td><strong>RV:LV ratio</strong></td>
<td>1.9 ± 0.3</td>
<td>1.9 ± 0.3</td>
<td>0.0 ± 0.2</td>
</tr>
<tr>
<td><strong>LVEDVi (mL/m²)</strong></td>
<td>76 ± 10</td>
<td>79 ± 11</td>
<td>3.0 ± 7.2</td>
</tr>
<tr>
<td><strong>LVESVi (mL/m²)</strong></td>
<td>30 ± 7</td>
<td>31 ± 7</td>
<td>1.1 ± 5.7</td>
</tr>
<tr>
<td><strong>LVSV (mL)</strong></td>
<td>82 ± 15</td>
<td>85 ± 15</td>
<td>3.3 ± 11.2</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>61 ± 5</td>
<td>60 ± 5</td>
<td>-1.1 ± 4.4</td>
</tr>
<tr>
<td><strong>LVCO (L)</strong></td>
<td>5.6 ± 0.6</td>
<td>5.8 ± 1.1</td>
<td>0.2 ± 1.1</td>
</tr>
</tbody>
</table>

* indicates p<0.05; EDVi indicates indexed end-diastolic volume;

ESVi, end-systolic volume; RVMC, RV muscular corpus; RVOT, RV outflow tract; SV, stroke volume; EF, ejection fraction; CO, cardiac output; PRF, pulmonary regurgitant fraction.
Figure 5.1. Right ventricular volume at first and second MRI

RVEDVi indicates indexed right ventricular end-diastolic volume.
Figure 5.2. Correlation of change in RVEDVi with change in RVMC EDV

RVEDVi indicates indexed right ventricular end-diastolic volume.
5.4 DISCUSSION

In our cohort of adult repaired TOF patients with free PR, RV volumes significantly increased over 2 years, from 5% below the commonly used RVEDVi indicator for PVR of 150 mL/m² to marginally above this cut-point. The observed RV dilatation was related to RVMC volume enlargement but not change in RVOT size, initial RVEDVi or initial PR fraction. In addition to RV dilatation, RVEF significantly decreased during the inter-MRI period.

The natural history of RV dilatation in repaired TOF has not been thoroughly studied. Our results are in contrast to previous reports which did not show a significant increase in RV size or deterioration of RV function over a similar period of time.89, 208 There was some variation in the degree of change in RV size, with 3 patients experiencing approximately up to 25 mL/m² increase in RVEDVi and 3 patients exhibiting minimal change in serial RV volumes. The RV dilated moderately in the remaining 8 patients. This variation can, to some extent, be explained by the degree to which the RVMC dilated. We showed that those patients with greater RVMC dilatation experienced greater increase in global RV size.

Progression of RV size is important in this setting, as it has significant implications for the timing of PVR and imaging follow up periods. Specifically, rapid RV dilatation may warrant early surgical intervention and short follow up periods. Early PVR may
have the advantage of preventing the potentially damaging effects of an enlarged RV.\textsuperscript{77, 209} However, reintervention due to limited valve lifespan \textsuperscript{210, 211} requires consideration, particularly in asymptomatic patients.

5.4.1 STUDY LIMITATIONS

This study was limited by the small number of patients and the relatively short time frame over which they were followed. There is also the possibility of selection bias from patients with echocardiographic evidence of a dilating RV being referred for cardiac MRI. Larger, long-term prospective studies are required to better understand progression of RV dilatation and its determinants throughout the lifespan of TOF patients.

5.5 CONCLUSIONS

The RV continues to dilate in many patients with PR late after TOF repair, approximately 5-10\% over 2 years. These data might inform a reasonable interval for serial MRI scanning, especially given the inaccuracy of cardiac ultrasound for precise measurements of RV volumes.
CHAPTER SIX

MECHANISMS OF MAINTAINED EXERCISE CAPACITY IN ADULTS WITH REPAIRED TETRALOGY OF FALLOT
6.1 INTRODUCTION

We have recently demonstrated that patients with repaired TOF have near normal exercise capacity, even in the setting of severe RV dilatation and severe PR.\textsuperscript{212} However, the mechanisms whereby cardiac output is augmented with exercise in this setting are poorly understood.

Recently, real-time MRI techniques have been developed, to allow imaging of cardiac structures and blood flow during exercise.\textsuperscript{213, 214} A thorough appreciation of the biventricular response to exercise in adult repaired TOF may facilitate a more complete understanding of the onset and underlying causes of exercise-related symptoms. Furthermore, in patients who are asymptomatic and have normal or near-normal exercise capacity the addition of real-time MRI imaging of the exercising heart may provide greater sensitivity in observing altered cardiac function, when compared to resting MRI alone.

We thus studied ventricular function and cardiac flows during exercise in adults with repaired tetralogy of Fallot with moderate to severe pulmonary regurgitation and RV dilatation and correlate these measures with objective assessments of exercise capacity.
6.2 METHODS

6.2.1 STUDY POPULATION

Sixteen adult repaired tetralogy of Fallot patients were prospectively recruited to undergo clinically indicated resting cardiac MRI, cardiac MRI during exercise and a standard CPET. The exercise cardiac MRI and CPET were performed on the same day as the resting cardiac MRI in all but 2 cases, where they returned within a month. Patients were included in the study if they had TOF as a primary diagnosis (TOF variants were excluded), were older than 15 years, had an RVEDVi > 105 mL/m2 and had a PR fraction > 20%. Eight healthy age and gender matched controls were also recruited for comparison. The control group underwent exercise cardiac MRI and CPET on the same day. Controls were included if they undertook 2 or less structured exercise sessions per week.

6.2.2 RESTING CARDIAC MRI PROTOCOL

Cardiac magnetic resonance imaging was performed as described in General Methods sections 2.2.1 – 2.2.2.

6.2.3 EXERCISE CARDIAC MRI PROTOCOL

Cardiac magnetic resonance imaging was performed as described in General Methods section 2.2.4.
2.4 BICYCLE CARDIOPULMONARY EXERCISE TESTING PROTOCOL

Bicycle cardiopulmonary exercise testing was performed as described in General Methods section 2.3.

2.5 STATISTICAL METHODS

All data are presented as mean ± SD. Statistical comparisons were performed with 2-tailed paired Student t tests; paired samples t test for within group comparisons and independent samples t test for between group comparisons. Pearson’s correlation coefficient was used to assess relations between resting cardiac MRI, exercise cardiac MRI and CPET variables. A two-tailed p-value of <0.05 was used to infer statistical significance. Statistical analyses were performed with SPSS V.21 for Windows (SPSS).
6.3 RESULTS

6.3.1 PARTICIPANT CHARACTERISTICS

All TOF patients (n=16) had a transannular patch repair at a mean age of 2.2 ± 1.3. In TOF patients, height was 173 ± 9 cm, weight was 69 ± 15 kg and there were 10 (63%) males. In the controls, group height was 180 ± 6 cm, weight was 77 ± 13 kg and there were 5 (63%) males. There were no statistically significant differences between the TOF and control groups in the above mentioned patient characteristics.

6.3.2 RESTING CARDIAC MRI RESULTS

Resting cardiac MRI results are shown in Table 6.1. Overall, the group had severely dilated RVs, moderate-severe PR fraction and lower-normal RVEF.
Table 6.1. Resting cardiac MRI results in TOF patients.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indexed left ventricular end-diastolic volume (mL/m²)</td>
<td>78 ± 11</td>
</tr>
<tr>
<td>Indexed left ventricular end-systolic volume (mL/m²)</td>
<td>32 ± 9</td>
</tr>
<tr>
<td>Left ventricular stroke volume (mL/beat)</td>
<td>83 ± 13</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>59 ± 6</td>
</tr>
<tr>
<td>Left ventricular cardiac output (L/min)</td>
<td>6.2 ± 1.0</td>
</tr>
<tr>
<td>Indexed right ventricular end-diastolic volume (mL/m²)</td>
<td>149 ± 37</td>
</tr>
<tr>
<td>Indexed right ventricular end-systolic volume (mL/m²)</td>
<td>73 ± 25</td>
</tr>
<tr>
<td>Right ventricular stroke volume (mL/beat)</td>
<td>139 ± 40</td>
</tr>
<tr>
<td>Right ventricular ejection fraction (%)</td>
<td>52 ± 7</td>
</tr>
<tr>
<td>Right ventricular cardiac output (L/min)</td>
<td>10.4 ± 3.3</td>
</tr>
<tr>
<td>Pulmonary regurgitant fraction (%)</td>
<td>35 ± 12</td>
</tr>
<tr>
<td>Regurgitant volume (mL/beat)</td>
<td>46 ± 27</td>
</tr>
</tbody>
</table>
6.3.3 EXERCISE CARDIAC MRI RESULTS

6.3.3.1 TOF patients vs Controls

There were no significant differences in biventricular ejection fractions between TOF patients and controls, other than lower RVEF during Level 2 exercise in TOF patients (51 ± 10% vs 61 ± 9%, p=0.045). Aortic and pulmonary artery net forward flow as well as ventricular output were significantly lower in TOF patients than controls at rest (aortic net forward flow: 72 ± 14 vs 98 ± 12 mL/beat, p<0.001; pulmonary artery net forward flow: 72 ± 20 vs 93 ± 9 mL/beat, p=0.009; LV output: 5.6 ± 1.4 vs 6.9 ± 1.5 L/min, p=0.042) and both levels of exercise ([Level 1: aortic net forward flow: 76 ± 14 vs 100 ± 14 mL/beat, p=0.001; pulmonary artery net forward flow: 74 ± 20 vs 96 ± 15 mL/beat, p=0.014; LV output: 7.7 ± 1.7 vs 10.1 ± 1.5 L/min, p=0.003; RV output: 7.5 ± 2.2 vs 9.6 ± 1.7 L/min, p=0.028] [Level 2: aortic net forward flow: 75 ± 11 vs 102 ± 19 mL/beat, p<0.001; pulmonary artery net forward flow: 69 ± 12 vs 95 ± 21 mL/beat, p=0.01; LV output: 9.3 ± 1.9 vs 13.1 ± 1.9 L/min, p<0.001]), despite no difference in heart rate (Rest: 76 ± 10 vs 70 ± 10 beats per minute, p=0.22, Level 1: 100 ± 10 vs 100 ± 5, p=0.735, Level 2: 123 ± 17 vs 127 ± 12, p=0.50) (see Figures 6.1 and 6.2).

6.3.3.2 Within group changes from rest to Level 2 during exercise cardiac MRI

Biventricular cardiac output significantly increased during exercise in both TOF patients (RV output: 5.2 ± 1.6 to 8.5 ± 1.6 L/min, p<0.001; LV output: 5.3 ± 1.0 to 9.3 ± 1.9 L/min, p<0.001) and controls (RV output: 6.6 ± 1.4 to 11.9 ± 1.7 L/min, p<0.001; LV output: 6.9 ± 1.5 to 13.1 ± 1.9 L/min, p<0.001), despite no significant
increase in aortic (TOF: 70 ± 12 to 75 ± 11 mL/beat, p=0.152; control: 98 ± 12 to 102 ± 19 mL/beat, p=0.306) or pulmonary artery net forward flow (TOF: 70 ± 19 to 69 ± 12 mL/beat, p=0.854; control: 93 ± 9 to 95 ± 21 mL/beat, p=0.648). TOF patients augmented forward flow out of the RV by significantly decreasing PR fraction (37 ± 15 to 31 ± 15%, p=0.002) and increasing RVEF (44 ± 7 to 51 ± 10%, p=0.025) and heart rate (75 ± 10 to 123 ± 17 beats per minute, p<0.001). LVEF also significantly increased in TOF patients (47 ± 8 to 52 ± 11%, p=0.015). Controls increased biventricular output via a significant increase in biventricular ejection fractions (RVEF: 49 ± 7 to 61 ± 9%, p=0.003; LVEF: 51 ± 3 to 56 ± 5%, p=0.004) and heart rate (70 ± 11 vs 127 ± 12 beats per minute, p<0.001) (see Figures 6.1, 6.2 and 6.3).
Figure 6.1. Tetralogy of Fallot and Control exercise MRI results

AoNFF: aortic net forward flow; PA NFF: pulmonary artery net forward flow; PRF: pulmonary regurgitant fraction; RVEF: right ventricular ejection fraction; HR: heart rate; TOF: tetralogy of Fallot.
**Figure 6.2.** Tetralogy of Fallot and Control exercise MRI results

LVCO: left ventricular cardiac output; RVCO: right ventricular cardiac output; TOF: tetralogy of Fallot.
Figure 6.3. Right ventricular ejection fraction at rest, Level 1 and Level 2 in tetralogy of Fallot patients and Controls

TOF: tetralogy of Fallot.
6.3.4 CARDIOPULMONARY EXERCISE TEST RESULTS

Overall, TOF patients exhibited near-normal exercise capacity. $V_E/V_{CO2}$ (27 ± 3 vs 27 ± 3, p=0.921), percentage of peak work at anaerobic threshold (66 v 8 vs 72 ± 7%, p=0.108) and respiratory exchange ratio at peak exercise (1.22 ± 0.1 vs 1.26 ± 0.08, p=0.347) were not significantly different between TOF patients and controls. When compared to control data, however, TOF patients had significantly decreased submaximal and maximal exercise capacity (Peak work: 172 ± 47 Watts [83 ± 15% predicted] vs 295 ± 52 Watts [121 ± 15% predicted], p<0.001; VO$_{2peak}$: 30 ± 9 mL/kg/min [73 ± 15% predicted] vs 44 ± 9 mL/kg/min [100 ± 16% predicted], p=0.006).

3.5 CORRELATIONS

RVEF at Level 2 correlated positively with PR fraction at Level 2 (r=0.575, p=0.025) and anaerobic threshold as a percentage of peak oxygen consumption (r=0.564, p=0.029). Change in RVEF from rest to Level 2 also positively correlated with anaerobic threshold as a percentage of peak oxygen consumption (r=0.684, p=0.005).

Resting cardiac MRI RVEDVi positively correlated with PR fraction at Level 2 (r=0.523, p=0.046) but not RVEF during exercise. RV end-diastolic (rest: r=0.766, p=0.001; Level 1: r=0.820, p<0.001; Level 2: r=0.798, p<0.001) and end-systolic (rest: r=0.711, p=0.002; Level 1: r=0.694, p=0.003; Level 2: r=0.662, p=0.007) areas used to calculate real-time ejection fractions from four chamber images during
exercise cardiac MRI strongly correlated with resting cardiac MRI RVEDVi and indexed RV end-systolic volume, respectively.
6.4 DISCUSSION

In repaired TOF patients with severe RV dilatation and moderate-severe PR, increasing exercise intensity during MRI resulted in increased heart rate, increased RVEF, increased biventricular cardiac output, decreased PR fraction and no change in biventricular net forward flow per beat. Maximal and submaximal exercise capacity during CPET were near-normal in TOF patients, suggesting that our observed cardiac responses to exercise provide a sufficient mechanism to maintain near-normal exercise capacity in this patient cohort, despite the significant residual right heart abnormalities.

In the healthy population, LV output increases during exercise in proportion to work rate in order to maintain adequate supply of oxygenated blood to working muscles. An increase in heart rate, stroke volume and ejection fraction leads to this increase in cardiac output. Our results in TOF patients and controls support these previous findings. Augmentation in RV forward flow during exercise is particularly important because of its relationship to LV preload and subsequent ejection into the systemic circulation. “Forward” RV output at rest is potentially compromised in TOF patients by regurgitation across the pulmonary valve. However, our results showed that PR fraction decreased as exercise intensity increased, which augmented net forward RV output. A likely explanation of the observed decrease in PR fraction during exercise may be reduced diastolic filling time, as heart rate increases.
Correlations between resting cardiac MRI RV volumes and functional outcomes have not previously been reported. In the present study, there were no relationships between resting cardiac MRI RVEDVi and submaximal or maximal exercise capacity. It is worth noting, however, that one patient with an RVEDVi of 270 mL/m² failed to increase RVEF during exercise and exhibited the poorest exercise capacity on CPET, which may suggest negative functional consequences with extreme RV dilatation.

The overarching narrative in TOF research describes an enlarged RV as impaired. However, we have presently and previously found that in our patients with severely dilated RVs and moderate-severe PR, exercise capacity is maintained at near-normal levels. This was achieved via increased RV output as a result of increasing heart rate, increasing RVEF and decreasing PR fraction. Furthermore, biventricular net forward flow and exercise capacity were not correlated to RV dilatation. Although our research has suggested functional outcomes may not be related to RV size, the possibility of malignant arrhythmia and sudden cardiac death in patients with severely dilated RVs necessitates careful consideration as to the degree to which the RV is allowed to dilate in adult repaired TOF patients before the pulmonary valve is replaced. Further research may reveal cardiac exercise MRI measures to be useful criteria for the optimal timing of pulmonary valve replacement in TOF. In particular, serial assessment of RVEF during exercise may provide invaluable insights into RV performance as the RV dilates and may eventually form part of clinical decision making.
6.4.1 STUDY LIMITATIONS

Cardiac responses to exercise are somewhat altered in the supine position. Venous return is augmented when compared to the upright position and results in higher preload and subsequent stroke volume. In fact, since stroke volume plateaus during exercise and it is at a higher level at rest in the supine position, it is not necessarily surprising that our measures of stroke volume did not increase. Calculating biventricular ejection fractions on exercise from four chamber cine images has previously been seen as a limitation. However, the accuracy of our measurements is supported by previous validation of this technique and strong correlation of retrospectively gated clinical cardiac MRI RVEDVi and indexed RV end-systolic volume with real-time four chamber end-diastolic and end-systolic volumes. Another limitation was that movement of subjects during exercise MRI and possible muscular fatigue at higher levels of exercise meant that we were unable to capture some of the data at maximal exercise.
6.5 CONCLUSIONS

Exercise capacity was maintained at near-normal levels in TOF patients via increased RV output, which was facilitated by an increased heart rate, increased RVEF and no change in biventricular net forward flow per beat, as exercise intensity increased. PR fraction decreased secondary to decreased diastolic time with increased heart rate. It is apparent that adult repaired TOF patients with severely dilated RVs develop compensatory mechanisms to augment forward flow out of the enlarged ventricle, and therefore, maintain near-normal exercise capacity.
CHAPTER SEVEN

RIGHT VENTRICULAR OUTFLOW TRACT ENLARGEMENT PRIOR TO PULMONARY VALVE REPLACEMENT IS ASSOCIATED WITH POORER STRUCTURAL AND FUNCTIONAL OUTCOMES, IN ADULTS WITH REPAIRED TETRALOGY OF FALLOT
7.1 INTRODUCTION

Trans-annular Patch repair of TOF leaves patients with PR which, in the long term, leads to RV dilatation, which in turn has been associated with exercise intolerance, arrhythmia, RV dysfunction and sudden cardiac death. As such, PVR is a very common late procedure in young adults with repaired TOF and has been shown to be safe and effective in reducing pulmonary regurgitation, RV volume, QRS duration and improving exercise capacity. However, these beneficial results need to be balanced against the risk associated with repeat PVR due to a limited lifespan of the implanted valve and the lack of conclusive evidence for improved survival. Thus, the timing of PVR is of great importance and is a point of current conjecture.

Previous reports have documented the effects of PVR in adults with impaired exercise capacity prior to PVR and have failed to consider regional aspects of RV structure in assessing the responses to PVR surgery. In particular, we were concerned that dilatation of the RVOT would not necessarily diminish after PVR (as opposed to likely diminution in size of the RVMC) and that residual enlargement of the RVOT would be associated with (i) failure to normalise RV volumes after PVR and (ii) failure of exercise capacity to improve. We therefore studied regional RV volumes and exercise capacity, in adults with PR after TOF repair, before and after clinically indicated PVR.
7.2 METHODS

7.2.1 PATIENT POPULATION

Between April 2009 and December 2012, a total of 18 repaired TOF patients referred to our adult congenital heart service for a cardiac MRI and CPET were prospectively recruited to undergo these assessments both before and approximately one year after surgical PVR (Table 7.1).

7.2.2 CARDIOVASCULAR MRI PROTOCOL

Cardiac magnetic resonance imaging was performed as described in General Methods sections 2.2.1 – 2.2.3.

7.2.3 CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing was performed as described in General Methods section 2.3.

7.2.3 STATISTICAL METHODS

All data are presented as mean ± SD. Statistical comparison of pre and post-PVR data was performed with a 2-tailed paired Student t tests. Pearson’s correlation coefficient was used to assess relations between pre-PVR RVEDVi and post-PVR
changes in MRI and CPET variables. Interclass correlation was used to assess inter-
observer variability in RVOT volume analysis. Statistical significance was inferred at
a two-tailed p-value <0.05. Statistical analyses were performed with SPSS V.21 for
Windows (SPSS).
7.3 RESULTS

7.3.1 PATIENT POPULATION (N=18)

Eighteen patients (mean age at repair 2.0 ± 1.1 years; age at evaluation 25 ± 8 years; 14 males) were studied. Demographic and surgical details are shown in Table 7.1. All included patients had a primary diagnosis of TOF and had a trans-annular patch repair. A Medtronic Mosaic porcine valve was implanted in 15 patients (83%), a pulmonary homograft in 2 patients (11%) and an aortic homograft in 1 patient (6%). Overall, PVR surgery was performed 23 ± 7 years after initial TOF repair and the post-PVR assessment was performed 14 ± 3 months after the procedure.
Table 7.1. Cohort characteristics

<table>
<thead>
<tr>
<th>Participants (n)</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25 ± 8</td>
</tr>
<tr>
<td>Males (n)</td>
<td>14</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 ± 8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 ± 14</td>
</tr>
<tr>
<td>Age at TOF repair (years)</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>PVR details</td>
<td></td>
</tr>
<tr>
<td>Bioprosthesis (n)</td>
<td>15</td>
</tr>
<tr>
<td>Pulmonary homograft (n)</td>
<td>2</td>
</tr>
<tr>
<td>Aortic homograft (n)</td>
<td>1</td>
</tr>
<tr>
<td>Cross clamp time (min)</td>
<td>47 ± 18</td>
</tr>
<tr>
<td>Pulmonary artery augmentation (n)</td>
<td>10</td>
</tr>
<tr>
<td>Transventricular incision (n)</td>
<td>18</td>
</tr>
<tr>
<td>Years between TOF repair and PVR</td>
<td>23 ± 7</td>
</tr>
</tbody>
</table>

PVR indicates pulmonary valve replacement; TOF, tetralogy of Fallot
7.3.2 MRI RESULTS (N=18)

MRI results are presented in Table 7.2. Pre-operatively, the group had severe RV dilatation (RVEDVi; 186.3 ± 32.3 mL/m², RVESVi; 98.3 ± 30 mL/m²) and moderate to severe PR (PR fraction; 39.7 ± 5.7 %). LVESVi was elevated (34.9 ± 12 mL/m²), however, LVEDVi was within the normal range (84.7 ± 14.7 mL/m²).

Changes observed after PVR are shown in Table 7.2. There were the expected significant reductions in RVEDVi (186.3 ± 32.3 vs 114.2 ± 19.7 mL/m²; p<0.001), RVESVi (98.3 ± 30 vs 61.9 ± 16.7 mL/m²; p<0.001), RV SV (p<0.001), RV CO (P<0.001), PR fraction (p<0.001), tricuspid regurgitant fraction (p=0.023) and RV to LV ratio (2.2 ± 0.4 vs 1.3 ± 0.2; p<0.001). There were no significant changes in LV structure or function as a result of PVR.

Figure 7.1 shows pre and post-operative RVEDVi for each patient. All patients showed a decrease in RVEDVi after PVR, however, “normalisation” (RVEDVi ≤ 108 mL/m²) was only achieved in 7 of the 18 patients. The mean pre-PVR RVEDVi in the group that did normalise was 165 ± 19 mL/m² and was 200 ± 33 mL/m² in those who did not. The largest RV to achieve normalisation had a pre RVEDVi of 190 mL/m².

Regional analysis of right ventricular outflow tract and right ventricular muscular corpus
Pre-PVR volumes and ejection fractions for the fibrous RVOT and RVMC are shown in Table 7.4. RVOT end-systolic volume (RVOT ESV; 36.7 ± 23.6 mL) was larger than RVOT end-diastolic volume (RVOT EDV; 30.6 ± 18.2 mL), indicating dyskinetic movement of this segment in systole. By contrast, the RVMC did contract, as expected (RVMC end-systolic volume [RVMC ESV]; 145.2 ± 48.4 mL, RVMC end-diastolic volume [RVMC EDV]; 314.1 ± 60.8 mL). Due to RVOT expansion during RV contraction, RVOT ejection fraction measured during systole was “negative” (-23.8 ± 37 %), whereas RVMC ejection fraction was positive (54.6 ± 7.7 %).
### Table 7.2. Magnetic resonance imaging results

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>P value</th>
<th>Change</th>
<th>Correlation of change with pre PVR</th>
<th>RVEDVi</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEDVi (mL/m^2)</strong></td>
<td>84.7 ± 14.7</td>
<td>88.6 ± 16.9</td>
<td>0.159</td>
<td>3.9 ± 11.2</td>
<td>0.235</td>
<td>0.348</td>
<td></td>
</tr>
<tr>
<td><strong>LVESVi (mL/m^2)</strong></td>
<td>34.9 ± 12</td>
<td>36.9 ± 9.6</td>
<td>0.361</td>
<td>2.1 ± 9.3</td>
<td>0.096</td>
<td>0.704</td>
<td></td>
</tr>
<tr>
<td><strong>LV SV (mL)</strong></td>
<td>92.3 ± 17.1</td>
<td>98.8 ± 20.5</td>
<td>0.071</td>
<td>6.5 ± 14.3</td>
<td>0.467</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td><strong>LV EF (%)</strong></td>
<td>59.7 ± 7.6</td>
<td>58.6 ± 5.6</td>
<td>0.559</td>
<td>-1.1 ± 7.5</td>
<td>0.266</td>
<td>0.286</td>
<td></td>
</tr>
<tr>
<td><strong>LV CO (L/min)</strong></td>
<td>6.7 ± 1.6</td>
<td>6.7 ± 1.8</td>
<td>0.981</td>
<td>0.01 ± 1.9</td>
<td>-0.293</td>
<td>0.238</td>
<td></td>
</tr>
<tr>
<td><strong>RVEDVi (mL/m^2)</strong></td>
<td>186.3 ± 32.3</td>
<td>114.2 ± 19.7</td>
<td>&lt;0.001*</td>
<td>-72.1 ± 20.4</td>
<td>-0.815*</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td><strong>RVESVi (mL/m^2)</strong></td>
<td>98.3 ± 30</td>
<td>61.9 ± 16.7</td>
<td>&lt;0.001*</td>
<td>-36.3 ± 19.2</td>
<td>0.395</td>
<td>0.361</td>
<td></td>
</tr>
<tr>
<td><strong>RV SV (mL)</strong></td>
<td>162.2 ± 23.4</td>
<td>99.9 ± 16.7</td>
<td>&lt;0.001*</td>
<td>-62.3 ± 14.2</td>
<td>0.099</td>
<td>0.696</td>
<td></td>
</tr>
<tr>
<td><strong>RV EF (%)</strong></td>
<td>48 ± 7.6</td>
<td>46.6 ± 7.2</td>
<td>0.272</td>
<td>-1.4 ± 5.2</td>
<td>0.420</td>
<td>0.232</td>
<td></td>
</tr>
<tr>
<td><strong>RV CO (L/min)</strong></td>
<td>11.8 ± 2.7</td>
<td>6.8 ± 1.5</td>
<td>&lt;0.001*</td>
<td>-5.0 ± 2.6</td>
<td>-0.179</td>
<td>0.266</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary regurgitant fraction (%)</strong></td>
<td>39.7 ± 5.7</td>
<td>4.8 ± 3.6</td>
<td>&lt;0.001*</td>
<td>-34.8 ± 6.5</td>
<td>-0.483*</td>
<td>0.05*</td>
<td></td>
</tr>
<tr>
<td><strong>Tricuspid regurgitant fraction (%)</strong></td>
<td>9.0 ± 8.6</td>
<td>4.8 ± 4.7</td>
<td>0.023*</td>
<td>-4.2 ± 6.5</td>
<td>-0.228</td>
<td>0.378</td>
<td></td>
</tr>
<tr>
<td><strong>RV:LV ratio</strong></td>
<td>2.2 ± 0.4</td>
<td>1.3 ± 0.2</td>
<td>&lt;0.001*</td>
<td>-0.93 ± 0.31</td>
<td>-0.104</td>
<td>0.505</td>
<td></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>74.1 ± 13.8</td>
<td>76.8 ± 15</td>
<td>0.009*</td>
<td>2.7 ± 3.8</td>
<td>0.147</td>
<td>0.561</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates p≤0.05; EDVi, indexed end-diastolic volume; ESVi, indexed end-systolic volume; SV, stroke volume; EF, ejection fraction; CO, cardiac output.
Figure 7.1. Indexed right ventricular end-diastolic volume before and after pulmonary valve replacement.
7.3.3 CARDIOPULMONARY EXERCISE TEST RESULTS (N=18)

Cardiopulmonary exercise test results are presented in Table 7.3. Pre-operatively, submaximal and peak exercise capacity was normal. Oxygen consumption ($\text{VO}_2$) at anaerobic threshold as a percentage of $\text{VO}_2^{\text{peak}}$ was 66.7 ± 13.7 %, $\text{VO}_2^{\text{peak}}$ was 34.6 ± 9.8 mL/kg/min$^{-1}$, percentage of predicted $\text{VO}_2^{\text{peak}}$ achieved was 85.3 ± 15.0 %, peak work was 200.6 ± 52.2 Watts and percentage of predicted peak work achieved was 93.1 ± 16.2 %. $\text{VE}/\text{VCO}_2$ was within normal range at anaerobic threshold (25.4 ± 3.8) and at peak exercise (28.5 ± 4.8). There was no evidence of chronotropic incompetence in the patient group (peak heart rate; 175.9 ± 18.5 beats per minute, percentage of predicted peak heart rate achieved; 92 ± 10 %).

Work at anaerobic threshold increased (118.9 ± 34.4 vs 132.9 ± 43.7 Watts, p=0.037) and respiratory exchange ratio at peak exercise (1.27 ± 0.11 vs 1.18 ± 0.12, p=0.008) decreased at the post PVR assessment. No other submaximal or maximal cardiopulmonary exercise test measures were significantly different between pre and post-PVR assessments
Table 7.3. Cardiopulmonary exercise test results

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>P value</th>
<th>Change</th>
<th>Correlation of change with pre PVR RVEDVi</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work at anaerobic threshold as percentage of peak work (%)</td>
<td>60.0 ± 9.8</td>
<td>65.9 ± 12.2</td>
<td>0.068</td>
<td>5.9 ± 12.9</td>
<td>-0.119</td>
<td>0.639</td>
</tr>
<tr>
<td>Work at anaerobic threshold (Watts)</td>
<td>118.9 ± 34.4</td>
<td>132.9 ± 43.7</td>
<td>0.037*</td>
<td>14 ± 26.2</td>
<td>-0.048</td>
<td>0.849</td>
</tr>
<tr>
<td>Peak work (Watts)</td>
<td>200.6 ± 52.2</td>
<td>199.7 ± 47.1</td>
<td>0.741</td>
<td>-0.9 ± 11.2</td>
<td>0.075</td>
<td>0.769</td>
</tr>
<tr>
<td>Percentage of predicted peak work achieved (%)</td>
<td>93.1 ± 16.2</td>
<td>91.2 ± 11.6</td>
<td>0.508</td>
<td>-1.9 ± 11.7</td>
<td>-0.454</td>
<td>0.058</td>
</tr>
<tr>
<td>VO₂ at anaerobic threshold as percentage of peak VO₂ (%)</td>
<td>66.7 ± 13.7</td>
<td>68.1 ± 11.7</td>
<td>0.656</td>
<td>1.4 ± 13.1</td>
<td>-0.306</td>
<td>0.217</td>
</tr>
<tr>
<td>VO₂ at anaerobic threshold (mL/kg/min⁻¹)</td>
<td>22.4 ± 6.11</td>
<td>23.7 ± 8.8</td>
<td>0.381</td>
<td>1.2 ± 5.9</td>
<td>-0.07</td>
<td>0.782</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min⁻¹)</td>
<td>34.6 ± 9.8</td>
<td>34.3 ± 8.5</td>
<td>0.86</td>
<td>-0.2 ± 5.1</td>
<td>0.264</td>
<td>0.291</td>
</tr>
<tr>
<td>Percentage of predicted peak VO₂ achieved (%)</td>
<td>85.3 ± 15.0</td>
<td>88.9 ± 14.4</td>
<td>0.287</td>
<td>3.6 ± 13.9</td>
<td>0.117</td>
<td>0.643</td>
</tr>
<tr>
<td>Respiratory exchange ratio at peak exercise</td>
<td>1.27 ± 0.11</td>
<td>1.18 ± 0.12</td>
<td>0.008*</td>
<td>-0.1 ± 0.1</td>
<td>0.126</td>
<td>0.619</td>
</tr>
<tr>
<td>Vₑ/VCO₂ at anaerobic threshold</td>
<td>25.4 ± 3.8</td>
<td>25.2 ± 2.3</td>
<td>0.66</td>
<td>-0.28 ± 2.6</td>
<td>-0.208</td>
<td>0.221</td>
</tr>
<tr>
<td>Vₑ/VCO₂ at peak VO₂</td>
<td>28.5 ± 4.8</td>
<td>29.4 ± 3.6</td>
<td>0.328</td>
<td>0.9 ± 4.0</td>
<td>-0.424</td>
<td>0.079</td>
</tr>
<tr>
<td>Peak heart rate (Beats per minute)</td>
<td>175.9 ± 18.5</td>
<td>170.4 ± 10.8</td>
<td>0.137</td>
<td>-5.5 ± 14.9</td>
<td>-0.486*</td>
<td>0.041*</td>
</tr>
<tr>
<td>Percentage of predicted peak heart rate achieved (%)</td>
<td>92 ± 10</td>
<td>89 ± 5</td>
<td>0.076</td>
<td>-3.5 ± 8.0</td>
<td>-0.377</td>
<td>0.123</td>
</tr>
</tbody>
</table>

* Indicates p≤0.05; VO₂, oxygen consumption; Vₑ, ventilation; VCO₂, carbon dioxide production
7.3.4 CORRELATIONS OF PRE-PVR RVEDVI WITH POST-PVR CHANGES

Pre-PVR RVEDVi was found to correlate with the post-operative change in RVEDVi (see Figure 7.2, change=-72.1 ± 20.4 mL/m², r=-0.815, p<0.001), change in PR fraction (change=-34.8 ± 6.5 %, r=-0.483, p=0.05) and change in peak heart rate (change=-5.5 ± 14.9 bpm, r=-0.486, p=0.041). Pre-PVR RVEDVi did not correlate with post-PVR change of any other MRI or CPET variable.

7.3.5 CORRELATIONS OF PRE-PVR RVOT AND RVMC VOLUMES WITH POST-PVR OUTCOMES

Correlations between pre-PVR RVOT volumes and post-PVR measures are shown in Table 7.3 and Figures 7.3 and 7.4. RVOT EDV and RVOT ESV negatively correlated with post-PVR RV EF (r=-0.53, p=0.024 and r=-0.557, p=0.016, respectively), delta RV CO (r=-0.619, p=0.006 and r=-0.730, p=0.001, respectively), post-PVR VO_{2peak} (r=-0.489, p=0.039 and r=-0.485, p=0.041, respectively) and delta VO_2 at anaerobic threshold (r=-0.541, p=0.02 and r=-0.480, p=0.044, respectively). RVMC EDV and RVMC ESV were negatively correlated with delta RVEDVi (r=-0.594, p=0.009 and r=-0.646, p=0.004, respectively) and delta RVESVi (r=-0.681, p=0.002 and r=-0.792 and p<0.001, respectively) but not with any functional parameters.
Table 7.4. Pre-PVR RVOT and RVMC volumes and correlations with post-PVR results

<table>
<thead>
<tr>
<th></th>
<th>Pre-PVR RVOT (mean ± SD)</th>
<th>Post-PVR VO2 at AT</th>
<th>Post-PVR Peak VO2</th>
<th>Delta RVEDVi</th>
<th>Delta RVESVi</th>
<th>Delta RV CO</th>
<th>Delta % Predicted Peak VO2</th>
<th>Delta VO2 at AT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVOT EDV (mL)</td>
<td>30.6 ± 18.2</td>
<td>-0.53</td>
<td>-0.487</td>
<td>-0.489</td>
<td>-0.619</td>
<td>-0.541</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVOT ESV (mL)</td>
<td>36.7 ± 23.6</td>
<td>-0.557</td>
<td>-0.485</td>
<td></td>
<td>-0.73</td>
<td>-0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVMC EDV (mL)</td>
<td>314.1 ± 60.8</td>
<td></td>
<td>-0.594</td>
<td>-0.681</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVMC ESV (mL)</td>
<td>145.2 ± 48.4</td>
<td></td>
<td>-0.646</td>
<td>-0.792</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVOT EF (%)</td>
<td>-23.8 ± 37.0</td>
<td></td>
<td></td>
<td>0.52</td>
<td>0.505</td>
<td>0.556</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVMC EF (%)</td>
<td>54.6 ± 7.7</td>
<td>0.563</td>
<td></td>
<td>0.494</td>
<td>0.69</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Only statistically significant (p<0.05) Pearson's correlation coefficients are displayed. RVOT indicates RV outflow tract; RVMC, RV muscular corpus; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.
Figure 7.2. Correlation of change in indexed right ventricular end-diastolic volume with pre-pulmonary valve replacement indexed right ventricular end-diastolic volume.

$r = -0.815$

$p < 0.001$
Figure 7.3. Correlation of post-pulmonary valve replacement right ventricular ejection fraction with right ventricular outflow tract end-diastolic volume.

\[ r = -0.53 \]
\[ p = 0.024 \]
Figure 7.4. Correlation of post-pulmonary valve replacement peak oxygen consumption with right ventricular outflow tract end-diastolic volume.
7.4 DISCUSSION

In repaired TOF patients with severely dilated RVs and severe PR, PVR resulted in smaller RVs and lower PR but did not significantly alter ejection fraction or exercise capacity. The largest pre-PVR RV to achieve “normalisation” (RVEDVi ≤ 108 mL/m^2) had a pre-operative RVEDVi of 190 mL/m^2, although some smaller RVs failed to normalise. There was a strong negative correlation between pre-PVR RVEDVi and post-PVR change in RVEDVi. Importantly, the volume of the RVOT pre-PVR correlated negatively with RV function and exercise capacity, after PVR.

Our results are in general agreement with past findings that PVR leads to decreased RV volumes but has little effect on overall ventricular function in adults with repaired TOF.\textsuperscript{69, 73, 74, 77, 102, 164, 165} To the best of our knowledge, all studies to date using cardiac MRI have observed a decrease in indexed RV volumes and PR fraction, in this situation.\textsuperscript{73, 74, 77, 102} One study showed an increase in RV ejection fraction,\textsuperscript{77} whereas others have either shown no change or an increase in effective RV ejection fraction.\textsuperscript{73, 74, 102} A meta-analysis conducted by Cheung \textit{et al.}\textsuperscript{164} confirmed that RVEDVi, RVESVi and PR fraction decrease as a result of PVR but RV ejection fraction does not change significantly.

Despite the general consensus on the beneficial effects of PVR, when to perform the procedure is a point of much contention. Besides increasing RV volume, a decrease in RV ejection fraction, worsening maximal exercise capacity, deteriorating symptomatic status, RV hypertension, tricuspid regurgitation, branch pulmonary
arterial stenosis, sustained tachyarrhythmia, RV outflow tract aneurysm and decreased RV longitudinal curvature have all been suggested as important in the PVR timing decision. However, the key in the ability to prognosticate is obtaining long-term outcome data, which is currently lacking.

In the present study 7 of 18 patients achieved normalisation of their RVEDVi. In those patients who did normalise, a pre-PVR RVEDVi of 165 ± 19 mL/m² was observed and in those who did not it was 200 ± 33 mL/m². Although four patients achieved normalisation with a pre-PVR RVEDVi above 165 mL/m², the group that failed to normalise had substantially larger RVs; only one patient was below a pre-PVR RVEDVi above 165 mL/m². There was also a strong correlation between pre-PVR RVEDVi and post-PVR change in RVEDVi. We conclude that normalisation of RVEDVi is less likely to occur above a pre-PVR RVEDVi of 165 mL/m². Therefore, the widely used RVEDVi cut-point for PVR of 150mL/m² likely provides an appropriately conservative indicator for PVR timing.

We have now shown that larger pre-PVR RVOT size is associated with poorer post-PVR RV function and exercise capacity. Furthermore, larger RVMC volumes are associated with less favourable improvement in RV volumes after PVR surgery. We believe delineation of RVMC and RVOT volumes adds value to pre operative cardiac MRI assessments and may aid in the selection of patients for PVR. Previously, Wald et al have highlighted the role of RVOT function in determining RV ejection fraction
and exercise capacity, in adults with repaired TOF (prior to PVR), consistent with our current observations.⁸³

Inadequate resection of the RVOT during PVR and may result sluggish RV systolic performance post-PVR. A large and dyskinetic RVOT does not actually contribute to effective RV forward flow. The RVOT may act as a reservoir, filling during systole and emptying back into the RV during diastole; as indicated by a negative RVOT ejection fraction. Alternatively, long-term exposure of the RV to a large and non-contractile RVOT may have deleterious effects on RV function and subsequently exercise capacity, even when the RVOT has been adequately resected during PVR. Overall, it seems possible that conservative transannular patch use during initial TOF repair in infancy and aggressive RVOT resection at the time of PVR may have long-term beneficial effects.²¹⁸

Warner et al.⁶⁹ reported a post-PVR increase in peak exercise capacity as indicated by improved peak work and percentage of predicted peak work achieved. These conclusions were drawn, however, from a subset of only 6 patients. Other studies have shown an improvement in submaximal, rather than peak, exercise capacity.⁷⁷.⁶⁵ Eyskens et al.⁶⁵ showed an increase in ventilatory anaerobic threshold and Frigiola et al.⁷⁷ reported a decrease in the VE/VCO₂ slope. Overall, PVR does not seem to have a substantive and reproducible effect on exercise capacity.
The observed lack of improvement in peak or submaximal exercise capacity in our TOF patients is not surprising, given the high overall exercise performance and lower-normal RV ejection fraction of the cohort before undergoing PVR. In the absence of a training stimulus, an improvement in exercise capacity would not be expected in the setting of preserved ventricular function. Past studies showing improvements in exercise capacity may have done so by enrolling patients with more marked pre-operative exercise abnormalities. Furthermore, it may be methodologically unsound to compare cardiac function derived from supine MRI with CPET variables measured in the upright position, during maximal exertion. Future studies may need to incorporate exercise studies performed in the supine position. Real time MR scanning of the exercising heart could provide invaluable insights into the relationships between PVR, the RV, cardiac function and exercise capacity.

7.4.1 STUDY LIMITATIONS

Analysis of RVOT volume is a relatively novel technique but in our hands and with rigorous definition, could be measured with good reproducibility. This required the identification of highly reproducible landmarks, which could be consistently and clearly identified. Future imaging techniques such as using higher magnetic field strength and 4D flow may allow even greater delineation of anatomical structures within the right ventricle. Another limitation is the relatively small number of participants enrolled in the study, however using each patient as their own control allowed sufficient statistical power to study relationships between cardiac structure and function, in this clinical setting.
7.5 CONCLUSIONS

After PVR in young adults with repaired TOF and severe PR with dilated RVs, RV volume reduction is greatest in those with the largest RVs preoperatively, and RV volume normalisation is rare with a pre-operative RV volume over 165 mL/m². Larger pre-surgical RVOT volume was associated with poorer RV function and lower exercise capacity after PVR surgery. This observation may inform pre-operative patient selection as well as surgical technique; further studies are required to examine these possibilities.
CHAPTER EIGHT

CAUSES OF DEATH IN TETRALOGY OF FALLOT IN ADULTS
Chapter 8 Causes of Death in Tetralogy of Fallot in Adults

8.1 INTRODUCTION

Late outcomes in repaired tetralogy of Fallot have dramatically improved over recent decades resulting in an increased number of adult survivors. A shift from ventriculotomy and trans-annular patch repairs towards a transatrial/transpulmonary approach has likely contributed significantly to this. However, these encouraging trends are accompanied by the rare but definite risk of malignant arrhythmia and sudden cardiac death.

Chronic pulmonary regurgitation and QRS duration have been associated with arrhythmia and sudden cardiac death in adult tetralogy of Fallot. Although pulmonary valve replacement results in decreased pulmonary regurgitation and right ventricular volumes, evidence of post procedural risk reduction is lacking. Risk stratification, particularly identifying high-risk individuals for sudden cardiac death, remains problematic and an area of importance. Due to the paucity of data in this area, we aimed to define the causes and circumstances of adult tetralogy of Fallot deaths from coronial findings in Australia, over the past two decades.
8.2 METHODS

8.2.1 DATA COLLECTION

Coroners’ reports from all Australian states (1990-2011) were obtained where tetralogy of Fallot was a recorded diagnosis, in subjects aged ≥16 years, excluding deaths associated with heart surgery. Direct access to autopsy and police report files was possible in the most populous state, New South Wales. Access to autopsy and police report information was via the web-based National Coronial Information Service in other Australian states. The circumstances of death were obtained from police reports; macroscopic and histological findings were analysed from autopsy reports.

8.2.1.1 Circumstances of Death

We classified circumstances of death as being death during exertion or death at rest. Place of death was classified as at home; in hospital or elsewhere.

8.2.1.2 Cause of Death

All cause mortality was classified as sudden cardiac death; (unexpected likely cardiac death which occurred less than 24 hours after symptoms commenced) and non-sudden cardiac death; death from all causes other than sudden cardiac death.

Right Ventricular Fibrosis was defined by the presence or absence of focal scarring (or collagenous deposits) seen on microscopy. Given that the microscopy specimens were focal sections of the myocardium and imaging was not performed, objective quantification of the overall fibrosis burden was unable to be determined.
8.2.2 DATA ANALYSIS

Significance was assessed between the sudden cardiac death and non-sudden cardiac death groups using an independent samples student’s t test for continuous variables and the Chi squared test for dichotomous variables. Normality was assessed using the Kolmogorov-Smirnov test. The level of significance was set at $2P \leq 0.05$. In cases where circumstances or causes of death were uncertain, the data was treated as missing. Statistical analysis was performed using SPSS version 19.0.0 (SPSS Inc., Chicago, IL, USA).
8.3 RESULTS

Characteristics of the cohort identified are detailed in Table 8.1. Of the 23 decedents identified (mean age at death 36 ± 14 years), 17 were identified as having sudden cardiac death as their cause of death, 4 were classified as non-sudden cardiac death and cause of death was not able to be accurately determined in 2 cases. Using New South Wales prevalence estimates, this represents a death rate of approximately 1-10 in 10000 cases (recognising the likely significant underestimation resulting from ascertaining coronial cases only).

Death occurred at rest in 14 and on exertion in 5 cases; death was at home in 11, in hospital in 6 and outdoors in 6. Circumstance of death was not able to be determined in 4 cases. 14 decedents had had surgical repair, 3 were unrepaired, 1 had had a palliative shunt and status of surgical repair was not available in 5 patients. Only 2 patients had a bioprosthetic pulmonary valve in place at autopsy. Suicide (n=1), pulmonary artery dissection (n=1), aortic root abscess secondary to staphylococcal endocarditis (n=1) and bleeding peptic ulcer (n=1) were the causes of death in the non-sudden cardiac death group. One decedent where cause of death was not able to be determined was a 25 year old female with prior craniotomy for cerebral abscess who exhibited a residual abscess on autopsy and was on anti-epileptic therapy. She presented with nausea, vomiting and hypotension, became syncopal and never regained consciousness despite haemodynamic improvement. The second patient was a 36 year old female who sustained a fall at home a week prior to death, developed progressive abdominal distension and did not seek treatment. She was found deceased by her mother. In the entire group, heart weight was
markedly above normal values (333 ± 166 grams above normal). Right ventricular fibrosis was documented in 17 of 23 cases (74%).
## Chapter 8 Causes of Death in Tetralogy of Fallot in Adults

### Table 8.1. Characteristics of decedents

<table>
<thead>
<tr>
<th></th>
<th>Sudden cardiac death ($n=17$)</th>
<th>Non-sudden cardiac death ($n=4$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± SD</td>
<td>n</td>
</tr>
<tr>
<td>Age at death (years)</td>
<td>38.7 ± 15.9*</td>
<td>17</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 ± 11</td>
<td>15</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.3 ± 20.3</td>
<td>15</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>640 ± 202</td>
<td>16</td>
</tr>
<tr>
<td>Heart weight compared to normal (g)</td>
<td>379 ± 170</td>
<td>15</td>
</tr>
<tr>
<td>Heart weight indexed to body surface area (g/m$^2$)</td>
<td>357 ± 91.9</td>
<td>15</td>
</tr>
<tr>
<td>Males (n)</td>
<td>13</td>
<td>76</td>
</tr>
<tr>
<td>RV fibrosis (n)</td>
<td>14</td>
<td>82</td>
</tr>
<tr>
<td>Surgical details</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaired (n)</td>
<td>10</td>
<td>59</td>
</tr>
<tr>
<td>Unrepaired (n)</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Palliative repair (n)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Pulmonary valve replacement (n)</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Circumstances of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death occurred during exertion (n)</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>Death occurred at rest (n)</td>
<td>10</td>
<td>59</td>
</tr>
<tr>
<td>Place of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home (n)</td>
<td>10†</td>
<td>59</td>
</tr>
<tr>
<td>Hospital (n)</td>
<td>1†</td>
<td>6</td>
</tr>
<tr>
<td>Outdoors (n)</td>
<td>6†</td>
<td>35</td>
</tr>
</tbody>
</table>

*p<0.05 on independent samples t test. †p<0.05 on Chi Squared analysis. Circumstances of death were unknown in 2 cases.
8.4 DISCUSSION

In this study, we have demonstrated that sudden cardiac death is the more frequent mode of death in adults with tetralogy of Fallot. Although only age at death and place of death were significantly different between the sudden cardiac death and non-sudden cardiac death groups, there were trends towards larger hearts and more deaths during exercise in the sudden cardiac death group. We do acknowledge, however, the small number of non-sudden cardiac death patients in this series.

The evolution of surgical technique in repair of tetralogy of Fallot over several decades has resulted in improved survival rates. However, late outcomes of more recently adopted techniques, such as early complete repair with pulmonary valve sparing, have yet to be evaluated. Despite increasingly favourable survival rates, sudden cardiac death remains a significant concern late after tetralogy of Fallot repair. In large, long-term follow up studies, the lifetime risk of sudden cardiac death has ranged from 2.0 to 8.3%. Gatzoulis et al. followed 793 repaired tetralogy of Fallot patients and reported an 8.3% risk of sudden cardiac death, 35 years from repair.

Although sudden cardiac death is the most common cause of death in adult repaired tetralogy of Fallot, the annual incidence of these events has been reported to be low at 0.15%. Identifying high-risk patients who may require preventative measures is an area of importance and continuing research. Nollert et al. followed 490 tetralogy of Fallot patients, repaired between 1958 and 1977, at a mean age of
8.6 ± 12.2 years. Higher pre-operative NYHA score, no previous palliation and increasing time from repair were found to be risk factors for sudden cardiac death. Gatzoulis et al.\textsuperscript{66} documented QRS duration, QRS rate of change, pulmonary regurgitation and age at repair as risk factors for sudden cardiac death in those with tetralogy of Fallot repair at age 8.2 ± 8 years.\textsuperscript{66} Although certain risk factors have been identified, it is possible that these results are less relevant to the current young adult cohort of repaired tetralogy of Fallot patients who have undergone modern surgical techniques.

Although the precise cause of sudden cardiac death is difficult to determine at autopsy, pre-existing ventricular and atrial arrhythmias as a result of tetralogy of Fallot repair and subsequent haemodynamic lesions are commonly implicated.\textsuperscript{66, 224} Preventative measures include a move from ventriculotomy and trans-annular patch repairs towards a transatrial/transpulmonary approach, pulmonary valve replacement in the presence of severe right ventricular dilatation and the placement of implantable cardioverter defibrillators. The timing of pulmonary valve replacement and use of implantable cardioverter defibrillators remains an area of contention; however, their effectiveness in reducing arrhythmic events when appropriately deployed has a reasonable level of consensus.\textsuperscript{73, 74, 164, 187, 226-228}

The high occurrence of sudden cardiac death in our study cohort further emphasises the established risk of these devastating events in tetralogy of Fallot patients. Risk stratification remains an area of uncertainty and is vitally important for judgements.
relating to preventative strategies. Further research is required to develop guidelines to allow greater clarity in clinical decision-making in this patient group.

8.4.2 STUDY LIMITATIONS

Our study was limited by obtaining coronial cases only, leading to a likely significant underestimation of tetralogy of Fallot deaths. Many cases may not have been referred to the coroner for investigation due to cause of death being presumed to be related to tetralogy of Fallot. A further limitation was the small numbers of non-sudden cardiac death, which limits comparisons within the cohort. Nevertheless this is, to our knowledge, the largest autopsy series of adults with tetralogy of Fallot yet reported.
8.5 CONCLUSIONS

Young adult death in tetralogy of Fallot patients has a wide variety of causes; presumed arrhythmia leading to sudden death accounts for approximately two-thirds of cases. Greater age at death and place of death were related to sudden cardiac death. There were also trends towards larger hearts and more deaths during exercise in the sudden cardiac death group. Given the high incidence of sudden cardiac death, evolving surgical techniques and uncertainty surrounding risk stratification and preventative strategies, continuing research in this area is required.
CHAPTER NINE

CONCLUSIONS AND FUTURE DIRECTIONS
Significant improvements in surgical treatment and long-term management of TOF patients have lead to increasing numbers surviving into adulthood. In fact, there are now more adult TOF patients than children.\textsuperscript{15, 229} Despite improving survival rates, persistent issues such as ventricular dysfunction, exercise incapacity, need for late surgical intervention, arrhythmia management and sudden cardiac death have been reported this patient cohort and are poorly characterised. The studies within this thesis endeavour to address several aspects of these issues to provide improved insights into clinical management of adult repaired TOF patients.

### 9.1 EXERCISE CAPACITY IN ADULTS WITH REPAIRED TETRALOGY OF FALLOT

Despite previous research suggesting reduced exercise capacity in adults with repaired TOF, the studies within this thesis report near-normal exercise capacity in our patient cohort. Several explanations may be offered to explain this finding. Firstly, the patients included in these studies were asymptomatic and exhibited good overall clinical status. Second, TOF patients have previously exhibited increased exercise capacity in response to physical training.\textsuperscript{177} Therefore, relatively higher physical activity compared to earlier reported cohorts may offer a further explanation (although we cannot make this conclusion since physical activity levels were not systematically recorded). Third, patients may have been more vigorously encouraged to reach peak effort during cardiopulmonary exercise testing. This assertion is supported by a relatively high mean peak respiratory exchange ratio of 1.27. Anecdotally, it was perceived that virtually all patients provided a maximal
effort, which may not be the case in previous reports and can be the difference between a normal and a marginally sub-normal result. Fourth, our patients may have received different surgical and clinical care. For example, a mean age at repair below 2.5 years is relatively young and these procedures may have been performed in such a way as to impart less myocardial injury and potentially improved long-term function. Finally, we showed normal or near-normal ventricular function during rest and exercise. Chapter 4 reported normal biventricular ejection fractions and cardiac outputs during rest and normal heart rate at peak exercise. Chapter 6 described normal ventricular response to exercise, albeit at a marginally lower level than controls.

Chapter 3 detailed the positive correlation between RV mass and peak exercise capacity, which highlights the importance of adequate musculature of the right ventricle in order for adequate blood to flow into the pulmonary circuit. Furthermore, the positive correlation between RV mass:RVEDV indicates that peak exercise capacity is heavily reliant on RV compliance. Importantly, traditional markers of clinical status exhibited no relationship with exercise capacity. RV mass may provide a novel marker of patient progress and may be worth considering in clinical decision making.

Overall, the studies within this thesis highlight that adults with repaired TOF may not necessarily experience exercise incapacity to the extent previously reported.
9.2 VENTRICULAR STRUCTURE AND FUNCTION IN ADULTS WITH REPAIRED TETRALOGY OF FALLOT

At rest, our cohort of TOF patients exhibited right ventricular dilatation, moderate to severe pulmonary regurgitation, normal left and right ventricular ejection fractions and normal left and right cardiac outputs. Although, the degree of right ventricular dilatation varied, mean levels had reached the clinical threshold where pulmonary valve replacement would be considered. Despite significant dilatation, the right ventricle was able to produce adequate forward flow into the pulmonary circuit.

Chapter 3 showed that interaction between the left and right ventricle plays an important role in forward flow both into the systemic and pulmonary circuits. Undoubtedly, the right ventricle does not act alone and requires consideration in the setting of a biventricular symbiosis.

Chapter 6 reported a normal ventricular response to exercise in adult repaired TOF patients. Interestingly, pulmonary regurgitant fraction reduced as exercise intensity increased, which augmented net right ventricular output. Presumably, reduced diastolic filling time and altered right ventricular compliance provides a likely explanation.

The degree to which the right ventricle dilates over time is an important and previously unanswered question for clinicians. Chapter 5 detailed a significant increase in right ventricular volume from slightly below to marginally above the level at which pulmonary valve replacement is commonly considered over a 2 year period.
This finding highlights the possibility of rapid increases in right ventricular volume and the need for regular monitoring with the aid of cardiac MRI.

9.3 PULMONARY VALVE REPLACEMENT IN ADULTS WITH REPAIRED TETRALOGY OF FALLOT

The results presented in chapter 7 broadly supported previous findings; pulmonary valve replacement resulted in reduced right ventricular volumes and pulmonary regurgitation but did not change right ventricular ejection fraction or exercise capacity. Importantly though, pre-surgical right ventricular outflow tract volume negatively correlated with post-surgical right ventricular function and exercise capacity. Furthermore, higher pre-surgical right ventricular muscular corpus volume was associated with less improvement in global right ventricular volume after pulmonary valve replacement. These findings highlight the importance of delineating between transannular patch and muscular corpus volumes in both clinical and research situations. Furthermore, our results support the current movement towards valve-sparing repairs in infants with TOF. In adult TOF patients who have undergone a transannular patch repair, monitoring right ventricular muscular corpus volume rather than global RV volume may be more important in terms of post-surgical outcomes.

The timing of pulmonary valve replacement remains a vexing problem. Our findings further support a conservative approach of using an indexed right ventricular end-diastolic volume of 150 mL/m² as an indicator for this procedure.
9.4 CAUSES OF DEATH IN ADULTS WITH REPAIRED TETRALOGY OF FALLOT

Despite significant improvements in long-term survival, sudden cardiac death remains an area of concern in adult repaired TOF. To the best of our knowledge, Chapter 8 provides the first description of the causes of death in this patient cohort. Presumed arrhythmia lead to sudden cardiac death in approximately two-thirds of cases. Arrhythmogenic causes of sudden cardiac death are poorly understood and are an area for further detailed research.

9.6 FUTURE DIRECTIONS

Large, long-term prospective studies detailing the progression of ventricular structure and function, symptomatic status, arrhythmia and exercise capacity would allow a better understanding of the pathophysiologic development of TOF over time. To date, little is known in this regard.

Long-term outcomes after pulmonary valve replacement would also be useful in the assessment of surgical timing and approaches. Randomised controlled trials would be particularly useful in determining optimal timing of pulmonary valve replacement, however, such studies would likely need to be multicentric to have sufficient and clinically relevant power. Nevertheless, the importance of such timing decision warrants closer scrutiny and coordinated efforts between adult congenital heart disease centres may prove especially useful in this area of research.
Important emerging imaging techniques may play an important role in determining relationships between cardiac structure and function. Cardiac MRI 4D flow is a significant development and provides the opportunity to better understand intracardiac and great vessel flow patterns. The development of faster and higher resolution cardiac MRI sequences along with MRI compatible breath-by-breath expiratory gas analysis and more advanced MRI compatible ergometers will allow greater examination ventricular dynamics and the contributors to reduced exercise capacity in adult repaired TOF. Furthermore, the relationships between exercise capacity and ventricular structure and function during peak exercise may soon be able to be examined using these techniques.

After consideration of the results contained within this thesis, one of the more important areas for future research may be to elucidate the causes, frequency and pathophysiology of arrhythmia in adult repaired TOF. Large, multi-centre studies would be useful in examining the complex interplay between ventricular volumes, myocyte function and neural activation.
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