Dobutamine stress magnetic resonance imaging in tetralogy of fallot

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Title: Dobutamine stress magnetic resonance imaging in tetralogy of fallot

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DOBUTAMINE STRESS MAGNETIC RESONANCE IMAGING IN TETRALOGY OF FALLOT

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B Med Sci, BM BS

Thesis submitted in part fulfilment of the requirements for the degree of Medical Doctorate

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October 2013

ABSTRACT

This thesis evaluates the role of cardiac magnetic resonance (CMR) imaging in the assessment of patients with surgically repaired tetralogy of Fallot (TOF). CMR has become a powerful tool in the serial assessment of this group of patients and provides important information on cardiac structure and function long after surgical repair. Although there are a number of long-term effects of TOF repair, chronic severe pulmonary regurgitation (PR) continues to be considered one of the most important as this has detrimental effects on cardiac function with a risk of sudden cardiac death. The optimal timing of pulmonary valve replacement remains controversial and although CMR has provided valuable information on the volumetric changes associated with chronic PR little is know about the effects of stress with pharmacological agents such as dobutamine on ventricular function and whether this can be correlated with the need for pulmonary valve intervention. Therefore, the main aim of this thesis was to determine whether dobutamine stress CMR (DS-MR) has clinical utility in TOF patients with significant PR. Through this, it has been possible to evaluate the hemodynamic and volumetric changes during DS-MR in TOF patients and how these relate to baseline characteristics. The association between great artery flow analysis and volumetric analysis in TOF patients during DS-MR has also been assessed. For comparison the DS-MR protocol was also completed in a group of healthy volunteers and this has allowed documentation of a normal volumetric and contractile reserve response to dobutamine as measured by CMR. The thesis concludes that DS-MR is safe and feasible in TOF patients and that it has potential to demonstrate early systolic ventricular impairment in these patients. Through application of DS-MR in a larger population of TOF patients it may be possible to accurately determine which patients are best suited for early pulmonary valve intervention.

ACKNOWLEDGMENTS

There are a number of colleagues who have assisted me in the organization and completion of this research and thesis. Firstly I am grateful to Professor Reza Razavi and Dr Cathy Head for giving me the opportunity to take on this research and guiding me through the process. I have gained considerable knowledge in adult congenital heart disease and cardiac MRI, which would not otherwise have been possible.

Many thanks also to Professor Tobias Schaeffter for his support especially from a technical perspective, and also for my inclusion in some smaller physics based projects, which have significantly improved my understanding of CMR.

Dr Philipp Beerbaum oversaw the main aspects of the clinical research protocol; and without his involvement recruitment and completion of the protocol would have been extremely difficult. He was also instrumental in the production of the manuscripts related to this thesis.

Many thanks also go to the St Thomas' ACHD team particularly Professor Shakeel Qureshi, Dr Eric Rosenthal, Dr Chris Kiesewetter, Dr Gerald Greil and Dr Aaron Bell who helped with patient recruitment, management and clinical scanning.

Lastly, thanks go to Stephen Sinclair, senior MR radiographer who completed the majority of clinical scans, and all of the team in imaging sciences. This research would not have been possible without their input, organization and guidance.

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GLOSSARY

AO	Aorta
AO-FF	Aotic forward flow
AV	Atrio-ventricular
AVSD	Atrio-ventricular septal defect
BSA	Body Surface Area
CI	Cardiac Index
CMR	Cardiac Magnetic Resonance Imaging
CNR/SNR	Contrast to noise /signal to noise ratio
CO	Cardiac Output
Dob	Dobutamine
DS-MR	Dobutamine Stress Magnetic Resonance Imaging
EDV	End-diastolic Volume
Ees	End-systolic elastance
EF	Ejection Fraction
ESV	End-systolic Volume
Gd-DTPA	Gadolinium diethylenetriamine penta-acetic acid
GRE	Gradient echo
IVA	Isovolumic acceleration
LAD	Left anterior descending artery
LV	Left Ventricle
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NSF	Nephrogenic systemic Fibrosis
PA	Pulmonary artery
PA-BF	Total pulmonary artery regurgitant flow or back flow
PA-FF	Pulmonary artery forward flow
PA-RF	Pulmonary artery regurgitant fraction
PC-Flow	Phase contrast flow
PR	Pulmonary regurgitation
PVR	Pulmonary valve replacement
PW/CW	Pulse/Continuous wave Doppler
RCA	Right coronary artery
RV	Right Ventricle
RVOT	Right ventricular outflow tract
SA	Short axis (in relation to ventricular axis)
SAR	Specific Absorption Rate
SSFP	Steady state free precession
SV	Stroke Volume
TAPSE	Tricuspid annular plane systolic excursion
TDI	Tissue Doppler imaging
TFE	Turbo-field echo
TOF	Tetralogy of Fallot
TR	Repetition time
VCG	Vector cardiography
VSD	Ventricular septal defect
VT	Ventricular tachycardia

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Summary of Chapters

Chapter 1: This chapter provides a comprehensive review of the aetiology, pathophysiology and long-term complications of surgically repaired tetralogy of Fallot. This is followed by an introduction to the common imaging modalities used in TOF patients and then a review of stress imaging in congenital heart disease with a focus on TOF. Finally there will be a summary of MR hazards and safety recommendations especially applied to stress imaging. The chapter concludes with the aims of the research thesis.

Chapter 2: This describes the methodology of the patient based research protocols used. The CMR sequences used at rest and during dobutamine stress imaging will be reviewed and there will be an explanation of how the volumetric and arterial flow measurements were utilized to assess cardiac function. An explanation of the methods used in the development of new faster imaging techniques, which may be applied to stress imaging in the future is also described

Chapter 3: This chapter explores the utility of volumetric assessment using MRI. It will look at the standard approach of multi-slice SSFP imaging and compare this to the use of faster volumetric scanning which allows full cardiac volume assessment in a single breath hold.

Chapter 4: This second results chapter focuses on the flow measurements collated during the DS-MR study in TOF patients and healthy volunteers. Initially the focus is on general trends in flow in the great arteries from rest to peak dobutamine stress. Following this the flow measurements are correlated with

volumetric parameters and the agreement or discrepancies are described in detail.

Chapter 5: This chapter will focus on the accuracy of ventricular measurements at rest and during dobutamine stress imaging. The importance of this is to understand whether DS-MR is an accurate method of assessing ventricular function and therefore rationalize its potential clinical utility.

Chapter 6: The largest component of the ventricular data acquired from both patients and healthy volunteers is described in detail in this final results chapter. The importance of change in end-diastolic and end-systolic volumes of both ventricles during stress imaging and how this relates to ventricular contractile reserve is examined.

Chapter 7: The discussion chapter pulls together the result described in the previous chapters and explores the possibility of finding new parameters of ventricular dysfunction through stress imaging. The relevance of CMR stress imaging in congenital patients and its clinical utility is revisited. This chapter concludes with an overview of future perspectives relative to stress imaging in TOF.

Contribution to this work

The ethics and funding for this research project were in place when I started my research period but patient recruitment had not started. I was involved in devising the protocol with advice from Professor Razavi and Dr Head. I scanned all of the TOF patients recruited to this study with the assistance of a radiographer. I processed all the images and carried out all of the data analysis. Dr Israel Valverde completed inter-observer analysis. I am named as first author on two publications directly related to this research protocol and joint first authorship of one of the publications with Dr I Valverde. Volunteer data was acquired through collaboration with Dr Shelby Kutty, Assistant Professor of Paediatric Cardiology, University of Nebraska.

CHAPTER 1: TETRALOGY OF FALLOT

1.1 Introduction to Tetralogy of Fallot

Tetralogy of Fallot is the most common of the cyanotic congenital heart conditions and accounts for approximately 5-10% of all congenital heart disease, occurring in 3 per 10000 live births [1-4].

First described by Louis Arthur Etienne Fallot in 1888 as "La maladie Bleue" the final name tetralogy of Fallot is attributed to Canadian Maude Abbott in 1924 and reflects the classical tetrad of common features (i) ventricular septal defect, (ii) overriding of the aorta in association with the VSD, (iii) pulmonary stenosis and (iv), right ventricular hypertrophy [1] (Figure 1).

In embryonic life the defect is created by a combination of anterior mal-alignment and anterior deviation of the conal septum with infunbidular hypoplasia resulting in sub-pulmonary obstruction. This may be worsened further by hypertrophy of the septal and parietal muscle bundles resulting in severe right ventricular outflow tract obstruction. The pulmonary valve is often abnormal and there may be associated stenoses of the branch pulmonary arteries [1]. Additional features can include; anomalous coronary arteries, right sided aortic arch, aortic root dilatation, aortic regurgitation and aorto-pulmonary collaterals. All these may vary in their prevalence and severity [1-4].

The condition is associated with chromosomal abnormalities with as many as 1 in 8 patient having an abnormality such as trisomy 21, 18 or 13. More recently a strong link with a micro-deletion on chromosome 22 has been described allowing genetic screening to be offered to families and pre-natally. It is thought

that approximately 15% of all TOF patients have an abnormality of chromosome 22 [1].

Diagnosis can be made pre-natally with detailed fetal echocardiography and this allows for strategic surgical planning in early infancy. However the majority of children present with the condition after birth and symptoms vary depending on the degree of right ventricular obstruction and subsequent right to left shunt. In infancy classical symptoms are cyanotic “spells”, characterized by sudden and striking decrease in oxygen saturation due to acute complete or near complete pulmonary obstruction, which occur during feeding and on exertion [1-4].

Prior to the option of surgical repair, prognosis and survival for Fallot patients were poor. With progressive improvement in surgical technique those born with all variants of the disease can now expect to survive into adult life. Many of the current adult patients will have had a palliative aorto-pulmonary shunt in childhood prior to complete repair and this approach is still offered by some surgical centers (Figure 2). The disadvantage of a staged approach is the potential for long-standing pressure overload of the right ventricle with persistent cyanosis [1-3].

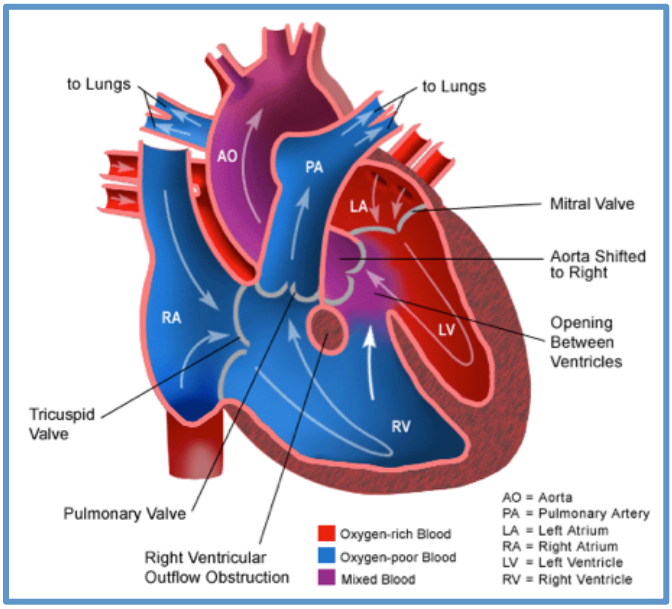


Figure 1: Anatomical Arrangement in Uncorrected Tetralogy of Fallot at Birth

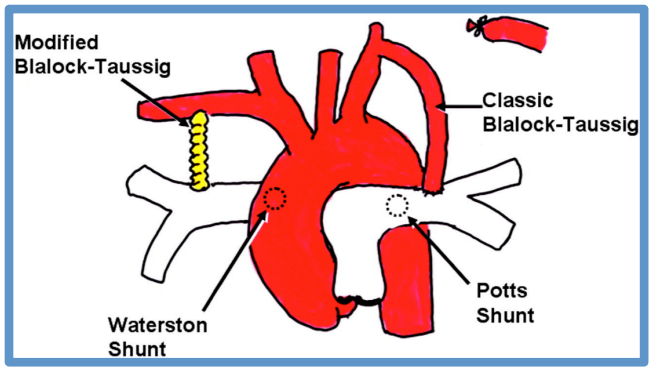


Figure 2: Palliative Surgical Shunts in TOF

Corrective surgical repair is now recommended in the first year of life and consists of a single staged reconstructive procedure. The goals for definitive repair consist of closing the VSD and relieving the RV outflow tract (RVOT) obstruction. Both trans-atrial/trans-pulmonary and trans-ventricular approaches to repair are described. The earlier technique for repair of TOF used a trans-ventricular approach, however currently the transatrial/transpulmonary approach is favored and has the advantage of avoiding a right ventricular incision emphasizing preservation of right ventricular structure and function and reducing the risk of scar related ventricular tachycardia (VT) [2]. If there is significant hypoplasia of the central pulmonary arteries staged reconstruction may be required.

The treatment of TOF has become one of the success stories in the management of congenital conditions and advances in surgical repair have been shown to improve life expectancy. Outcomes are generally excellent with early mortality less than 2% and nearly 90% alive 20 years after surgery [3].

Despite these advances there are a number of key post repair issues, which affect this patient group and require additional surgical intervention in later life. Many of these relate to the state of the right ventricle and its interaction with the pulmonary arterial tree and left ventricle [1, 2, 7, 8].

These are summarized below:

- Residual ventricular septal defect (VSD): can be encountered from either partial patch dehiscence or failure of complete closure at the time of surgery

- Aortic root dilatation and aortic regurgitation: during VSD closure the aortic valve can be damaged resulting in regurgitation. Patients may also have an intrinsic abnormality of the aortic root predisposing them to root dilatation and consequent regurgitation. This tends to be more common in TOF patients with pulmonary atresia and systemic to pulmonary artery collaterals [4, 5].
- Residual aorto-pulmonary collaterals: resulting in increased pulmonary perfusion and therefore potential left ventricular volume overload.
- RVOT obstruction, branch pulmonary artery stenosis or hypoplasia
- Left ventricular dysfunction: this is multi-factorial and has been associated with inadequate myocardial protection during repair, chronic LV overload due to long standing palliative arterial shunts and/or residual VSD. Both ventricles share a common pericardial space and are in continuity with each other via the septum and additional muscular structures. Interaction of the two ventricles results in alterations in systolic and diastolic function. The left ventricle is compromised when there is progressive right sided dilatation and this is likely to contribute to the risk of sudden cardiac death[6, 7].
- Atrial arrhythmia: atrial flutter and fibrillation are relatively common and contribute to significant late morbidity [8].
- Ventricular tachycardia (VT): the risk of VT increases with increasing right ventricular size and QRS duration. The arrhythmia focus is usually in the RVOT in the area of previous infundibulectomy or VSD closure. A QRS

duration exceeding 180ms is a highly sensitive marker for sustained VT and sudden cardiac death in adult patients [8].

- Pulmonary regurgitation (PR): this is associated with progressive right ventricular dilatation leading to RV failure. This is a common long-term outcome of repaired TOF and the importance and impact of this will be reviewed in more detail in the next section.

The vast majority of Fallot patients surviving into adult life have a degree of pulmonary regurgitation and over time this creates a significant burden in respect to symptoms and potential for further surgical intervention. The importance of this long-term complication of TOF repair creates many dilemmas for the clinician especially with regard to the timing of pulmonary valve replacement. Therefore the focus of the thesis will be on adult patients following surgical repair of tetralogy of Fallot who have chronic severe pulmonary regurgitation without other major complications from reconstructive surgery or complex TOF anatomy.

1.2 Pulmonary regurgitation: Why is it important?

Pulmonary regurgitation (PR) is one of the most common long-term outcomes of repaired TOF. Many patients require pulmonary valve replacement (PVR) in early adulthood and the timing of PVR is hotly debated and remains controversial. The following review will focus on the morbidity and mortality of this late complication and address the current literature relating to assessment and treatment of this condition:

1.2.1 Pathophysiology and haemodynamic effects

For many years free PR was considered an inevitable consequence of standard surgical repair. Much more emphasis was placed on correction of the severe RVOTO in infancy/childhood. The early surgical techniques to reconstruct the RV outflow tract using a trans-annular patch have subsequently resulted in significant PR. Although well tolerated for a number of years the long-term deleterious effects of chronic PR have become more apparent in recent studies [1, 9-11].

Physiologically PR is driven by diastolic difference between the pulmonary artery and right ventricle. In this low-pressure system forward flow can be maintained indirectly by work of the left heart and atrial contraction and additionally changes in airway or intra-thoracic pressure can alter the degree of regurgitation. The severity of PR is determined by the following factors: the degree of valvular incompetence or effective orifice for regurgitation, the balance between RV diastolic afterload and RV compliance and the duration of diastole.

The severity of regurgitation will worsen in situations which lead to raised pulmonary arterial pressures such as branch pulmonary artery stenosis, and these require intervention prior to definitive pulmonary valve surgery [1, 11-13]. Chronically the severity and haemodynamic impact of PR is dependant on the compliance of the RV. In a compliant ventricle there will be progressive dilatation and eventual dysfunction, whilst a restrictive RV may be relatively protective as this will raise the right ventricular diastolic pressure and decrease the gradient for PR. This type of physiology although related to a slower recovery after initial repair has been associated with superior exercise performance, less RV dilatation and fewer arrhythmias in later life [13, 14].

The continued increase in RV preload from chronic PR will eventually result in increased end-diastolic volume, followed by increased end-systolic volume and finally deterioration of myocardial function. The extent of RV dilatation and how this correlates with clinical symptoms and risk of premature cardiac death has been the focus of many research studies. Early observations reported that exercise dysfunction was related to cardiothoracic ratio (as a surrogate of RV dilatation) on chest radiography [1]. Subsequent work in animals and patients using a variety of imaging techniques has confirmed that RV dilation due to long standing PR has negative haemodynamic effects, reduces exercise capacity and predisposes patients to malignant cardiac arrhythmias [1, 11, 12].

The ongoing RV stretch affects the inter-ventricular conduction system and creates a mechano-electrical substrate for re-entry circuits predisposing to sustained ventricular tachycardia. QRS duration of 180ms or more has been associated with increase risk of sudden cardiac death [7, 8].

1.2.2 Pulmonary valve replacement: When Is the right time?

This leads to the much-debated topic of pulmonary valve replacement (PVR). This relatively low risk intervention is required in many TOF patients in early adulthood but timing remains controversial. PVR early in adult life may preserve RV function but at the cost of re-operation for a failing homograft in later life. The lifespan of pulmonary valve prostheses in adults ranges from 15 to 30 years and one series has reported that only 47% of patients were free from homograft dysfunction at 10 years [15]. This suggests that a significant proportion of patients will require re-intervention in later life. However when PVR is left too late there may be little or no improvement in RV size and function and resulting in the risks associated with this [16].

Current guidelines suggest intervention based on a combination of clinical factors including symptoms and rhythm disturbance, and quantitative and qualitative measures such as exercise test, echocardiography and cardiac magnetic resonance (CMR) findings [17, 18]. Most would agree that patients with overt heart failure symptoms or significant rhythm abnormality should be offered PVR, however there may be additional patients who do not fulfill the criteria but may be potential surgical candidates.

Imaging techniques will certainly help with this complex decision-making process and CMR has become a powerful tool to assess progressive right ventricular dilatation serially. Not only can it provide accurate volumetric measurements but it also allows complete anatomical assessment pre-operatively allowing visualization of additional late complications of TOF as described in section 1.1. Increasingly RV end diastolic (RV-EDV) and end systolic

volume (RV-ESV) measurements are being quoted as an indication for pulmonary valve replacement [19-21]. More recently reviews have suggested that there is no threshold above which RV volumes will not decrease after surgery. Although normalization of volumes is seen below RV-EDV 160ml/m^2 and RV-ESV 82ml/m^2 it suggests that these measures may not provide enough information to determine which patients will benefit most from surgery [22].

This leaves many unanswered questions. The impact of exercise testing and prediction of surgical outcome is still relatively unknown [23]. Additionally despite the advantages of CMR it appears that baseline volumetric and functional measurements do not give a complete picture of the RV and its potential response to surgery. The role of stress imaging in patients with significant PR and dilated RV may prove to be important and this will be explored further in this thesis.

1.3 Imaging in tetralogy of Fallot

It is clear that imaging plays a crucial role in the assessment and follow up of patients with TOF. At the bedside and in routine clinical practice echocardiography remains the first line investigation of choice. However over the past 10 years CMR has become the gold standard for assessment in congenital heart disease especially when focusing on the right ventricle [24]. The following summary will explore the use of echocardiography and CMR in general and its specific role in TOF.

1.3.1 Introduction to echocardiography

Echocardiography in most centers remains the first line imaging investigation of choice in adult patients with surgically repaired TOF. It is easily accessible, inexpensive and well tolerated by the patient. The following summary gives a brief overview of the basic principles applied to echo in this patient group.

Cardiac function:

This is assessed quantitatively and qualitatively. Visual estimation of bi-ventricular function is common especially for the right ventricle where geometrical assumptions do not allow easy quantification of diameters or volumes. In TOF a ratio to RV dimension compared to LV dimension measured just below the annular rings often gives an impression of whether the RV is significantly dilated. A RV/LV ratio of >0.65 suggests significant dilatation. The RV free wall is usually well seen in the apical 4ch view but assessment of the RVOT is very difficult due to its anterior position in the mediastinum [24]. Recent study has shown that there is a only a weak correlation between the 2D

measures of RV size as recommended by the American Society of Echocardiography and similar 2D dimensions as measured by CMR [25].

These limitations of 2D imaging have resulted in the development of surrogate markers of global RV function. A common parameter used is tricuspid annular plane systolic excursion (TAPSE), which documents longitudinal displacement of the annulus and is well validated as a marker of global function [26].

In general accurate echo assessment of RV dimensions and volumes continues to be challenging. This is especially true in congenital heart disease where the RV can be significantly dilated, resulting in under-estimation of ventricular dimensions. Figures 3 and 4 give an overview of RV echo parameters as recommended by the British Society of Echocardiography.

Flow assessment:

Doppler imaging remains the cornerstone of quantifiable arterial and valve flow in echo. Application of a pulsed Doppler signal in the RVOT and then a continuous wave Doppler in the main pulmonary artery allows quantification of the degree of pulmonary stenosis in the standard way using the continuity equation. Additionally by measuring the pressure half time of the pulmonary regurgitation CW Doppler signal it is possible to measure the severity of regurgitation and classify this from mild to severe. The classification of severity of PR is shown in Figure 4. Doppler indices are also used to determine the "Tei" or myocardial performance index. This is a ratio of RV inflow and outflow durations calculated from the PW Doppler profile [27]. It has been shown to be predictive of global RV function and although not used routinely may give useful

additional information especially when the RV free wall and outflow tract are difficult to image such as in TOF.

	Normal	Mild	Moderate	Severe
RV dimensions (apical 4 chamber)				
Basal RV diameter (RVD1) (cm)	2.0–2.8	2.9–3.3	3.4–3.8	≥3.9
Mid RV diameter (RVD2) (cm)	2.7–3.3	3.4–3.7	3.8–4.1	≥4.2
Base to apex length (RVD3) (cm)	7.1–7.9	8.0–8.5	8.6–9.1	≥9.2
RVOT diameters (parasternal SAX)				
RVOT at AV level (RVOT1) (cm)	2.5–2.9	3.0–3.2	3.3–3.5	≥3.6
RVOT at PV annulus (RVOT2) (cm)	1.7–2.3	2.4–2.7	2.8–3.1	≥3.2
PA diameter (parasternal SAX)				
Main PA (PA1) (cm)	1.5–2.1	2.2–2.5	2.6–2.9	≥3.0
RV area				
RV diastolic area (cm^2)	11–28	29–32	33–37	≥38
RV systolic area (cm^2)	7.5–16	17–19	20–22	≥23
RV function				
Fractional area change (%)	32–60	25–31	18–24	≤17
TAPSE	16–20	11–15	6–10	≤5

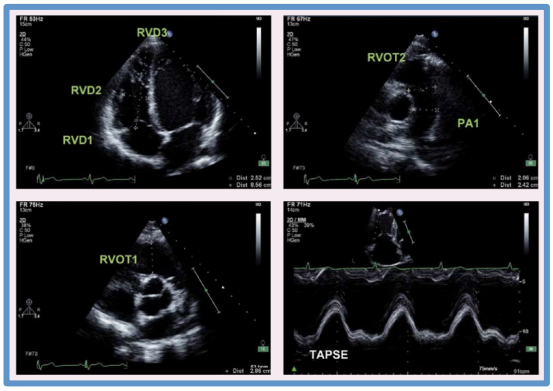


Figure 3: Standardized Echo Parameters For The Right Ventricle as published by The British Society of Echocardiography (BSE)

	Mild	Moderate	Severe
Jet size (CFM) (cm)	Narrow, <1.0	Intermediate	Wide, large
Regurgitant Fraction (%)	<40	40–60	>60
CW jet density/deceleration rate	Soft/slow	Dense/variable	Dense/steep
$RVOT_{VTI}$ / $LVOT_{VTI}$	↑	↑↑	↑↑↑

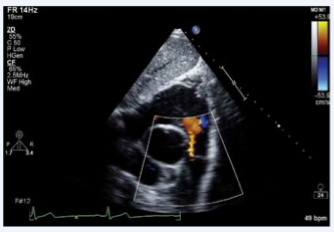


Figure 4: Echo Assessment of Pulmonary Regurgitation (BSE)

Tissue Doppler:

Over recent years tissue Doppler imaging (TDI) has become a popular way to examine regional myocardial displacement and how its correlation with diastolic and systolic function. It allows measurement of myocardial activation and therefore can also be used to determine inter and intra-ventricular dyssynchrony. Tissue velocity measurement of the tricuspid annulus gives

measures of peak systolic (Sa) as well as peak early diastolic (Ea) and late diastolic myocardial (Aa) velocities. In general a peak S wave less than 0.12m/s is thought to indicate an abnormality in function of the right ventricle [28, 29]. These indices have been shown to be decreased in TOF patients when compared to a normal cohort. It is also possible to assess these measures during stress echo, allowing better characterization of RV performance under stress conditions [30]. TDI measurements are a more accurate way to calculate the "Tei" index with the advantage over PW Doppler that the measures are taken in same cardiac cycle (depending on the software available).

Isovolumic acceleration (IVA) is an additional load independent measure of RV performance that has been used in the assessment of TOF patients, eliminating the problems of RV loading from severe PR [31, 32]. Tissue Doppler IVA is defined as the slope of the upstroke of the iso-volumic contraction wave on myocardial velocity tracings and has been shown to be a reproducible measure of RV systolic function in TOF patients. It may be useful in the long term monitoring of these patients as well as possibly predicting preclinical RV dysfunction [31, 32].

Three-dimensional imaging

This has been developed over the past 10 years and is now used routinely for assessment of left ventricular function and aortic and mitral valve function. 3D imaging of the right ventricle is theoretically possible and there are good post processing tools available to allow calculation of the end-diastolic and end-systolic volumes. However the usual geometrical limitation of RV imaging applies. Volumetric analysis may be hindered by the unique shape and orientation of the RV resulting in over or underestimation of volumes [28, 29]. This

is especially problematic in large right ventricles where there may be difficulty in imaging the whole area of interest, specifically a dilated RVOT, within the 3D sector width [33, 34]. This limits the accuracy of 3D volumetric assessment in patients with repaired TOF but with continued improvements in technology and software some of these technical problems may be overcome in the future.

Although this research originally intended to use echo in addition to CMR, due to technical difficulties and poor image quality the results have not been included in the main part of the thesis but are available for review in Appendix 2.

1.3.2 Introduction to cardiac magnetic resonance imaging

Cardiovascular Magnetic Resonance imaging has emerged over the past decade as an alternative, complementary and frequently superior imaging modality for the evaluation of patients with congenital heart disease. Major advances in MRI hardware and software, including coil design, faster gradients, newer pulse sequences and faster image reconstruction techniques, allow rapid, high resolution imaging of complex anatomy and accurate assessment of physiology and function. In addition CMR offers several advantages over other imaging modalities including a large field of view, unrestricted imaging windows, a capacity for true three-dimensional imaging, and a lack of ionizing radiation [24]. The basics of MRI originate from nuclear magnetic resonance imaging, an analytical technique, which has been available for over 50 years. The word nuclear was discarded in the 1980's due to the negative association with nuclear material. MRI is fundamentally a measurement of magnetism and in clinical practice the electromagnetic properties of the hydrogen are utilized to create images.

An MRI system is made up of three main components. Firstly the main magnet coils which generate a strong constant magnetic field. When a patient is positioned within a magnet bore the strength of this field is denoted by B_0 and this in turn defines the operating field strength of the magnet (Tesla). For cardiac MRI the most common field strength used is 1.5 or 3 Tesla. Other components of the MR system are the gradient coils, which create a gradient magnetic field and the radio frequency (RF) transmitter coil. The concept behind MRI is the spinning nuclear charge of the hydrogen nucleus, which produces a tiny

magnetic field called a magnetic moment. Hydrogen is one of number of elements whose nuclei exhibit magnetic resonance properties and due to its abundance in the human body makes it particularly favourable for imaging. In the normal environment the random orientation of millions of these spins results in no magnetic field. However these align themselves parallel with the large magnetic field generated by the superconducting magnet (B_o). The hydrogen nuclei also exhibit a rotation frequency known as precession, which is proportional to the strength of the field. When the RF coil delivers a radiofrequency pulse with a frequency identical to the precession frequency over a body region, the magnetic moment in that region will be flipped out at an angle to the magnetic field a process called excitation. The magnetic field now has 2 components one aligned with the external field, longitudinal magnetization and one perpendicular to the field known as transverse magnetization. When the RF pulse is stopped the protons relax back to their original state (relaxation) during which they release a signal in the form of RF energy. This is captured by an RF receiver coil and is used to create the final image. During relaxation the longitudinal magnetization increases with a speed defined by the T1 relaxation time and the transverse magnetization decreases with a speed defined by T2 relaxation time. The T1 and T2 relaxation times are tissue specific and therefore influence the signal emitted. Spatial information of the specified body part is created by Fourier transformation of the signal generated and in turn images are created [35, 36].

An in-depth knowledge of underlying MRI physics enhances the quality of interpretation of the imaging data and is necessary for understandings its pitfalls

and limitations. A more comprehensive review and discussion of the physics of CMR [37] are outside the scope of this thesis.

In TOF patients, CMR allows accurate quantification of right ventricular size and function in additional to anatomical assessment. The following summary reviews the technical considerations and sequences required for TOF assessment.

Motion compensation during Cardiac MRI: Cardiac and Respiratory Gating:

Cardiac and respiratory motion during MR image acquisition results in image blurring. To achieve good quality imaging, compensation for this motion needs to be considered. Image acquisition can be synchronized with the cardiac cycle using either prospective or retrospective electrocardiographic gating [38]. Accurate R wave peak detection on ECG monitoring is critical for good quality scans. Most MR systems currently use advanced triggering modules based on vectorcardiography (VCG) to improve R-wave detection in the MR environment. Movement of the thorax during scanning can also affect image quality and this can be avoided by acquiring images during an expiratory breath-hold. Patients with complex heart disease who are symptomatically breathless may struggle with lengthy breath-hold instructions. In these situations it is possible to obtain diagnostic quality cine images by averaging out respiratory motion artifact with the use of multiple signal averages during free breathing scans [38].

CMR Sequences: Spin Echo

Spin echo or "black blood" images of the heart and blood vessels, in which the blood-pool has no or little signal, are used to generate static anatomic images.

The blood appears black due to flowing spins moving out of the image plane between excitation and signal read-out. These are inversion recovery sequences and by using an inversion pulse, it is possible to achieve further suppression of signal from the blood pool and therefore better image quality. Predominantly used for static two-dimensional imaging, these images provide excellent anatomic detail of cardiac chambers, great vessels and pericardium. These sequences allow tissue characterization by altering the T1 and T2 weighting [38].

In TOF patients these sequences are commonly used to assess stented vessels especially the branch pulmonary arteries, as they are less prone to artefact seen with turbulent flow and metallic signal drop out. An example of black blood imaging in a Fallot patient and a patient with vasculitis and multiple pulmonary artery stenoses is shown in Figure 5.

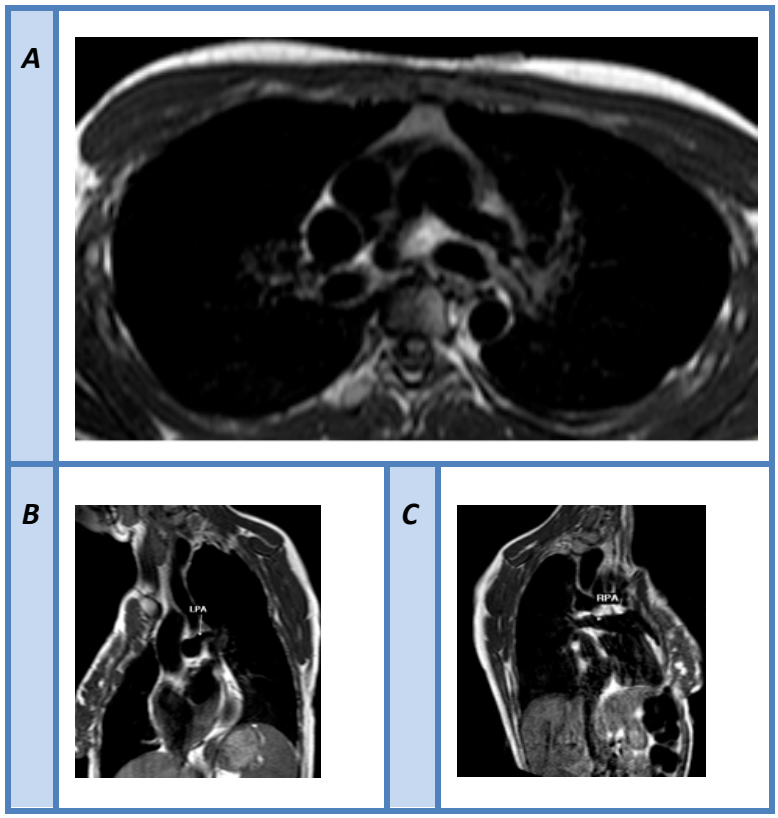


Figure 5: Black Blood Imaging
(A) Patient with multiple pulmonary artery stenoses, note the very narrow proximal left pulmonary artery
(B) Fallot patient with proximal left pulmonary artery stenosis
(C) Fallot patient with patent stent in the proximal right pulmonary artery

CMR Sequences: Gradient Echo

These sequences have become the mainstay for dynamic and structural imaging in all types of heart disease. They have fairly low soft-tissue contrast compared to spin echo and flowing blood appears bright as it has high signal intensity. Known as fast gradient echo (GRE) or cine turbo-field echo (TFE) imaging (or steady state free precession (SSFP) depending on scanner type) these sequences allow short acquisition times as they utilize segmental K-space filling. SSFP imaging allows more reliable endo-myocardial border recognition and faster acquisition times by use of shorter repetition times (TR) relative to the earlier techniques mentioned [39]. Parallel imaging can also be applied to further shorten imaging time and with application of multiple signal averages, images can be acquired during free breathing if clinically indicated [40]. In TOF patients this type of imaging provides valuable information regarding structure and function of the ventricle and ventricular outflow tracts.

Cardiac function:

The opportunity to create multi-slice and multi-phase (i.e. showing motion throughout the cardiac cycle) SSFP imaging provides a wealth of information on ventricular dimensions and function. Using this technique CMR has been shown to be highly accurate and reproducible making it the gold standard imaging technique [41]. In conditions such as TOF the ability to accurately measure ventricular size and function is essential for clinical decision making on potential surgical treatment such as PVR. The methodology and planning of these types of sequences and post processing to achieve measurements will be explored further in Chapter 2. Figure 6 shows an example of a short axis slice at the mid-

ventricle level in a patient with corrected TOF. This demonstrates the "bright blood" appearance and also the significant RV dilatation relative to the LV secondary to chronic pulmonary regurgitation.

Flow quantification:

Gradient echo imaging can also be phase encoded allowing non-invasive assessment of vascular blood flow. Velocity encoded or phase contrast flow imaging allows quantification of total blood flow and peak velocities and calculation of regurgitant volumes in great vessels. Most applications for measuring net flow have the velocity-encoding direction set to be through plane and perpendicular to the long access of the vessel of interest. In combination with volumetric assessment this creates specific information on the hemodynamic changes occurring in the heart and is essential for follow up of patients with significant valve insufficiency as in repaired TOF [40]. An example of a flow imaging velocity–time curve generated from post processing of the flow data is shown in Figure 7.

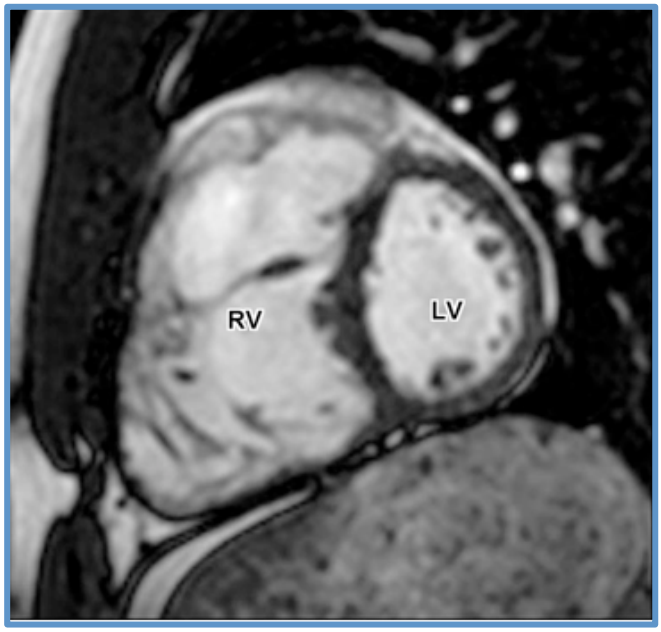


Figure 6: SSFP Imaging of the Ventricles
Short axis SSFP imaging at mid ventricular level of an adult patient with surgically corrected TOF. CMR assessment showed a significantly dilated right ventricle with preserved systolic function and severe pulmonary regurgitation

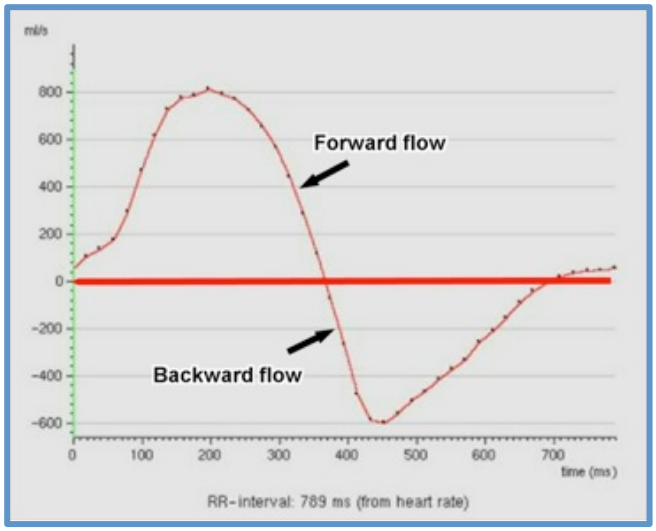


Figure 7: Flow Velocity-Time Curve in Tetralogy of Fallot
This graph shows the velocity-time curve for flow in the pulmonary artery in a patient with corrected TOF. There is significant backward flow, which correlates with severe pulmonary regurgitation in this patient.

Three-dimensional imaging:

Morphological assessment of the heart and thoracic vessels can be achieved without contrast injection using ECG-triggered 3D SSFP sequence with respiratory navigator gating. Initially developed for coronary artery imaging it is allows near isotropic imaging of the entire cardiac volume (Figure 8). This technique allows accurate multi-planar reformatting of any desired image plane during post-processing and is particularly useful in complex congenital heart disease [42]. In TOF patients this allows visualization of the coronary arteries clearly. In some TOF patients coronary artery morphology is abnormal and it is not uncommon for the right or left coronary artery to traverse the RVOT. When patients are being considered for pulmonary valve intervention this is extremely important as aberrant coronary anatomy may preclude certain therapeutic options such as trans-catheter pulmonary valve implantation. Additionally the option of reconstructing the whole heart volume in any plane enables the clinician to exclude abnormal pulmonary venous drainage or aorto-pulmonary collaterals, again important features that may be overlooked in functional 2D scanning. Figure 8 shows an example of an isotropic data set from a neonatal TOF patient showing an aberrant left coronary artery traversing the RVOT.

Angiography:

The administration of intra-venous CMR contrast agents based on gadolinium chelates allows the performance of 3D contrast enhanced CMR angiography providing high spatial and contrast resolution data of complex vascular structures. Post processing algorithms including surface volume rendering and curved multi-planar reformation of the raw data help to delineate vascular

anatomy. The sequence is a 3D acquisition of T1-weighted turbo field echo or fast gradient echo with flip angle of 40-45 degrees and very short echo times and repetition times. It can be performed in a time resolved or dynamic fashion with multiple short acquisitions that cover the entire volume of interest [40]. In TOF patients this type of imaging allows visualization of the right ventricular outflow tract, main and branch pulmonary arteries and helps to determine the presence of any aorto-pulmonary collaterals or associated aortopathy. Figure 9 shows an example of RVOT and pulmonary artery angiography in a patient with repaired TOF.

In summary CMR offers a huge amount of clinical data in congenital heart disease. In these patients, imaging should be undertaken by an experienced clinical team so that all aspects of abnormal anatomy can be considered throughout the scanning process. An example of a typical scanning protocol for a congenital patient is shown in Table 1.

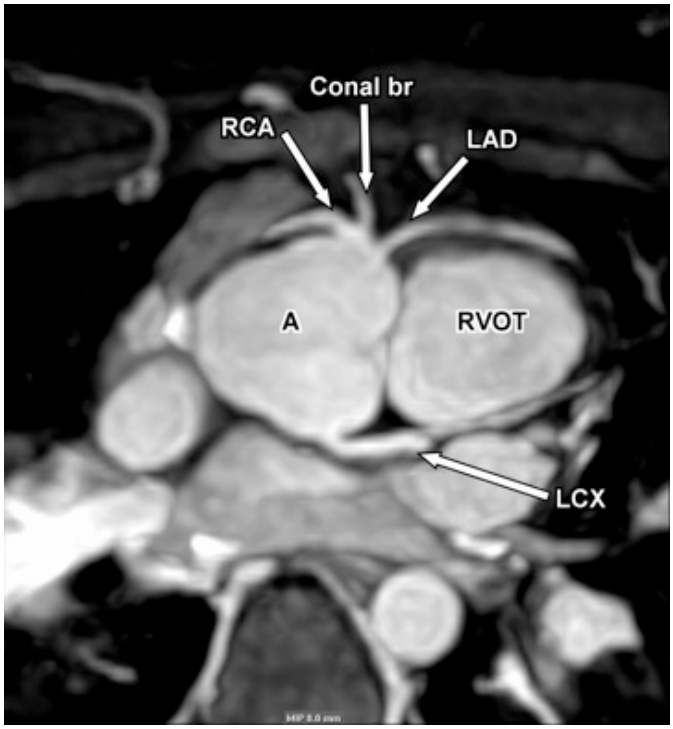


Figure 8: 3D SSFP Imaging of the Coronary Arteries
This data set was acquired in a neonatal patient with TOF. The left anterior descending artery (LAD) arises form the right coronary cusp and traverses the right ventricular outflow tract (RVOT).

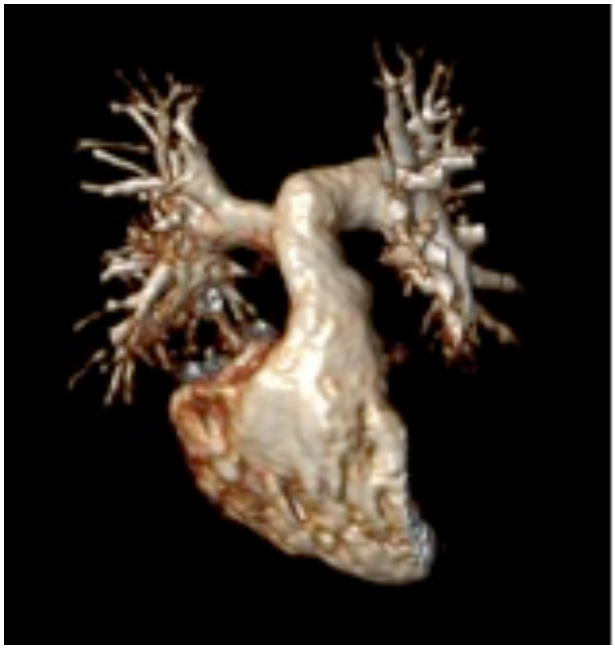


Figure 9: MR Angiogram of Pulmonary Arteries
Right ventricle, outflow tract, main and branch pulmonary arteries in an adult patient with repaired TOF. Large caliber branch pulmonary arteries are seen with no evidence of stenosis.

Table 1: A Typical CMR Protocol

SUGGESTED MRI PROTOCOL FOR CONGENITAL HEART DISEASE
1. ***Scouts and reference scans*** (parallel imaging)
2. ***Interactive imaging***
For acquisition of scan plane geometries including: Four-chamber, short-axis, RVOT, LVOT, pulmonary trunk through-plane, aorta through-plane, aortic arch, branch Pulmonary arteries 2 orthogonal in-plane views and through-plane
3. 2D multi-slice b-SSFP cine
Whole ventricle in short-axis or axial plane
4. 2D single-slice b-SSFP cine
Four-chamber view
RVOT (1-2 planes) and LVOT (1-2 planes)
Branch pulmonary arteries
Aortic arch
5. ***Phase-contrast velocity mapping***
Main PA through-plane
Ascending aorta through-plane
Vascular stenosis in-plane or through-plane
6. 2D multi-slice black-blood imaging- specifically to examine stenosis/stents
Branch pulmonary arteries
Aortic arch
Vascular stenosis
7. 3D contrast-enhanced MRA of the thoracic great vessels (1-3 dynamics)
8. Balanced-SSFP 3D ”whole-heart” volume

1.4 Stress Imaging

Stress imaging has been used for over 25 years and has become widely accepted as an important diagnostic tool in the assessment of coronary artery disease. Not only can wall motion abnormalities be appreciated in greater detail than at rest but information regarding perfusion can also be acquired [43, 44]. This type of imaging is now being applied to congenital patients, as in addition it is possible to demonstrate changes in contractile reserve and diastolic function [45]. The following review considers the role of stress imaging in patients with surgically corrected TOF.

Exercise capacity and achievement of maximal heart rate has been shown to be abnormal in TOF patients and there is a negative correlation with the severity of pulmonary regurgitation. Diller et al also showed that in a variety of patients with congenital heart disease abnormal heart rate response to exercise predicted survival [46, 47]. However more information is required about the functional cardiac changes and this has led to the development of combined imaging with physical stress. CMR imaging has proved to be the modality of choice. Study has shown that assessment of biventricular function and PR by CMR immediately following maximal exercise revealed an abnormal RV response (increase in RV-EDV with exercise) in a TOF patient group compared to controls [48]. Although physiological, exercise CMR is limited by patient motivation, difficulties with breathing techniques and lack of exercise during image acquisition, which may result in inaccuracies in volumetric and flow analysis [49] [45].

Pharmacological stress with agents such as dobutamine, which mimic the cardiovascular oxygen demands of exercise, have been widely used in the assessment of ischemic heart disease with good reproducibility and safety profiles [50]. Dobutamine is a positive inotrope and while it increases heart rate and blood pressure significantly, in healthy volunteers the volumetric changes are characterized by a decrease in ESV with stable EDV. This results in a marked increase in stroke volumes (SV) and ejection fraction (EF) [51-53].

Dobutamine effects in normal healthy volunteers have been extensively reported. Echo study has shown that in healthy volunteers being exposed to up to 10 μg/kg/min of dobutamine there is a gradual decrease in left ventricular end-systolic diameters with no significant change in end-diastolic diameters [53] . This explains the increase in LV stroke volume and ejection fraction and demonstrates normal contractile reserve [52-54]. However with dobutamine levels greater than 20μg/kg/min ESV continues to decrease and EDV also decreases resulting in minimal change in SV but continued increase in EF at each level [58]. Dobutamine stress magnetic resonance (DS-MR) studies have shown similar trends in normal individuals [59] although only data to a maximal dose of 15μg/kg/min are available. Tulevski et al reported that at this dose there is equivalent response to that seen with echo with minimal change in both right and left ventricular EDV but significant reduction in biventricular ESV [55, 56]. Study of patients with congenital heart disease has shown the potential of DS-MR in the assessment of diastolic and systolic function [57]. Tetralogy of Fallot patients with dilated right ventricles and significant PR have been shown to have preserved ventricular functional reserve with dobutamine concentrations of 7.5μg/kg/min

[58]. However there is also evidence of impaired ventricular relaxation in these patients [59]. How this impaired diastolic function correlates with need for PVR is yet to be determined. In TOF patients resting RV volumes are used in addition to clinical symptoms and exercise capacity to determine timing of PVR [18]. As yet there is limited data to determine whether these volumetric parameters during stress provide any additional information. Ubeing et al observed that RV-ESV may be the more valuable parameter, reflecting both RV volume load and RV myocardial contractility [60]. In a population of TOF patients undergoing dobutamine stress conductance catheter studies (10μg/kg/min dobutamine peak dose), larger RV-ESV was associated with reduced end-systolic elastance (Ees), a marker of load-independent myocardial contractility. RV-ESV correlated more closely with Ees than either RV-EDV or RV-EF. Hence, this showed that RV-ESV reflected not only RV volume loading but also intrinsic myocardial contractility and may be regarded as a non-invasive marker of contractility [60].

Therefore DS-MR imaging is likely to be valuable in the assessment of TOF patients with significant pulmonary regurgitation. Previous study has cautiously used low dose dobutamine protocols (up to 7.5μg/kg/min) [61] and this may miss important hemodynamic and volumetric changes, which become more evident at higher doses. Parameters such as RV-ESV may also provide more information about early RV systolic dysfunction especially in TOF patients and in combination with DS-MR this may prove to have clinical utility in the future.

The clinical utility of DS-MR, optimal protocol and volumetric and hemodynamic results in healthy volunteers and TOF patients will be fully described in Chapters 2 and 5. Safety considerations of CMR imaging and of DS-MR are explored in the next section of this chapter.

1.5 CMR Safety

CMR has many advantages over alternative imaging modalities; in particular it does not require ionizing radiation and allows imaging of the heart in any plane. However it is not completely risk free and there are many safety issues which still need to be addressed when considering a patient for CMR. A great deal of literature on MRI hazards and safety issues [66-70] is available and a comprehensive review and discussion of the subject is outside the scope of this thesis. However when considering any research protocol involving patients and volunteers it is essential to minimize hazards relating to MRI.

Magnetic Field

An MRI scanner such as the 1.5T scanner used in this study is superconducting and therefore continuously on field i.e. the magnetic field of the scanner is present at all times even when no scanning is taking place. This presents a significant potential hazard. Any ferromagnetic object such as an oxygen cylinder or dobutamine infusion pump will be attracted to the scanner and the force of attraction increases the closer you get to the magnet. Therefore a ferromagnetic object which may be easily controlled by a person at a distance from the scanner becomes impossible to control close to the magnet bore and consequently can be pulled uncontrollably into the magnet causing damage, injury or even death [43, 69, 70]. It is therefore essential that the all staff involved in MRI scanning are appropriately trained and that safety procedures are adhered to at all times. Patients and accompanying relatives must be carefully screened for metallic objects or metal devices before entering the MRI suite. Most implants used in patients with heart disease e.g. sternal wires; heart valves, stents, occluding devices and coils are not considered contraindications to MRI (although an

artefact local to the implant may be present). All patients complete a screening checklist prior to entering the MRI scanner to risk assess for contraindications to MRI and the strict exclusion criteria applied to our patients and volunteers are listed in section 2.2.1.

Pacemakers, and internal cardiac defibrillators (ICD), are considered strong relative contraindications to MRI although some reports of success do exist. In recent years CMR compatible pacemakers and ICD's have been developed and are now commercially available.

Thermal injury

The electro-magnetic RF fields used in magnetic resonance lie in the frequency range of radio waves. There is a potential risk of thermal injury to the patient and equipment due to the fact that the currents generated by the RF wave leads to tissue warming. Usually the increase in temperature is less than 1 degree Celsius. The specific absorption rate (SAR) is the RF output absorbed per time unit and kilogram. For safety reasons, the RF power emitted by the system into the body is monitored and the respective SAR values are limited accordingly. SAR limits are incorporated in the design of commercial MR pulse sequences to ensure that maximum changes in tissue temperature are kept below regulatory guidelines [69, 70]. The RF field may induce AC currents in metal implants or cables routed close to the patient (e.g., ECG cables), resulting in local warming.

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF) is a potentially fatal multisystem disorder primarily affecting the skin and has been associated with the use of gadolinium based contrast agents in patients with severe renal impairment (glomerular

filtration rate <30 mL/min/1.73m^2). The use of gadolinium based contrast agents for MRA must be avoided in these patients [62].

Dobutamine stress imaging

In addition to the hazards of MRI scanning there is the additional concern of using a pharmacological stress agent, dobutamine, with potential significant side effects. Patient safety in cardiac stress MRI is a major concern and requires a good understanding of contraindications, termination criteria, possible complications, and side effects. The MRI unit must be equipped with resuscitation equipment. The presence of a physician with experience in cardiac stress imaging, and advanced cardiac life support is required for such studies. Patient monitoring with continuous ECG and blood pressure is essential and use of pulse oximetry should be considered, especially in patients with congenital heart disease who may have shunts resulting in resting hypoxia. It must also be appreciated that dobutamine may predispose patients to arrhythmia most commonly ectopic beats, which may interfere with the R-R interval, and thus affect image acquisition with certain MRI sequences. Additionally although not a significant concern in the congenital patient group the presence of ischaemic changes on the ECG should be interpreted with care as ST segment abnormalities are often significantly affected by the magnetic field and therefore abnormalities may not be reliably detected [50 63] .

Recent studies have demonstrated high-dose dobutamine MRI to be safe and feasible in patients with suspected coronary artery disease (CAD) and with a low incidence of side effects [50, 64].

In congenital heart disease there has been a more cautious approach to the use of dobutamine and currently, a dobutamine dose of 7.5μg/kg/min has been considered to be the safest and most effective [65]. Previous echo study of TOF patients has used higher doses of dobutamine up to 40μg/kg/min and only reported one case of non-sustained ventricular tachycardia at a dose of 20μg/kg/min [66, 67].

1.6 Thesis Aims

The purpose of this research was to determine whether DS-MR has clinical utility in TOF patients with significant PR.

The following aims were defined:

1: To define the safety and feasibility of DS-MR up to a dose of 20μg/kg/min of dobutamine in TOF patients and a healthy volunteer group.

2: To determine the haemodynamic and/or volumetric changes during DS-MR in TOF patients and how these relate to baseline characteristics.

3: To determine whether the volumetric response during DS-MR seen in TOF patients is normal compared to a group of healthy volunteers.

4: To examine the association between great artery flow analysis and volumetric analysis in TOF patients during DS-MR.

5: To establish whether image analysis during DS-MR is accurate and reproducible.

6: To assess the utility of fast 3D volumetric assessment and its role in stress imaging.

CHAPTER 2: IMAGING PROTOCOLS AND METHODS

CMR continues to be the gold standard imaging modality in the assessment of patients with congenital heart disease. The previous chapter has discussed the merits of CMR in assessment of the right ventricle with particular reference to patients with surgically repaired TOF. Volumetric assessment in cardiac patients provides valuable information regarding volumes, regional wall motion abnormality and systolic function.

This chapter will document the protocols and methods used to assess patients with congenital heart disease especially those with surgically corrected TOF. The first part of the chapter will focus on bi-ventricular volumetric assessment in a variety of congenital patients and the comparison of standard approach of multi-slice 2D imaging to single breath hold 3D volume acquisition. Following this there will be a review of the CMR protocols used in the assessment of volumes and great arterial flows in TOF patients at rest and during DS-MR imaging. In addition the methods used in volumetric analysis and post-processing and the importance of observer variance are explored. The final sections of this chapter describe the Echo protocol performed in the TOF patients followed by a review of the statistical methods utilized in data analysis.

2.1 Volumetric Assessment 3D vs. 2D

Volumetric assessment of the cardiac ventricles has become an essential part of any CMR study [68-73]. Traditionally, cine images are acquired in the short axis (SA) orientation with multiple slices through the ventricles. Although well validated, this technique requires the acquisition multiple slices covering both ventricles requiring multiple breath holds.

3D imaging of the ventricles could circumvent these limitations and a number of techniques have been tried in recent years [74, 75 76]. One problem with these techniques especially using self-respiratory gating is long scanning times. For improved patient comfort and reduced scan time, assessment of cardiac function within one breath hold would be ideal. Functional studies of the heart under different patient conditions such as in stress MRI would also then be possible.

Therefore, we sought to evaluate a single breath-hold 3D cine b-SSFP protocol. To allow acquisition of a full ventricular volume in one breath-hold we used a 32-channel coil allowing for SENSE under sampling in both phase-encoding directions combined with further acceleration by partial Fourier encoding reconstruction. The protocol allowed assessment of the impact of injection of an extracellular contrast agent on contrast-to-noise ratio (CNR) between blood and myocardium, image quality with respect to endocardial blurring and accuracy of 3D cine b-SSFP as compared with cardiac volumes assessed by standard multi-slice cine SSFP used as a reference. The CMR sequences and study will now be discussed further.

3D Imaging Patient Population

Fifteen patients (mean age 35±13 years, 5 female, 10 male) attending for routine CMR were prospectively recruited. Twelve patients were referred for assessment of a cardiac congenital abnormality and three for assessment of suspected or known ischemic heart disease (Table 2). All patients gave written consent. Exclusion criteria were contraindications for CMR.

2.1.1 Data Acquisition

The patients were scanned using 1.5T MR-scanner (Achieva, Philips Healthcare, Best, The Netherlands) with a 32-element cardiac coil (16 anterior and 16 posterior elements with a 4x4 configuration, Philips Healthcare). Cardiac synchronization was performed with vector electrocardiography (VECG). After localization and a coil sensitivity reference scan, an interactive scan was performed in order to determine the geometry of the short axis (SA) view. This was used for planning the multiple slice 2D (M2D) and 3D ventricular volume scans. All patients underwent standard M2D cine b-SSFP sequence with multiple breath holds (2 slices per breath-hold, 12.3-17.2 seconds per breath hold, mean total scan duration 4.9mins) for volumetric and functional ventricular assessment. Additionally, in each patient a single breath hold 3D cine b-SSFP sequence pre and 1 minute post administration of Gd-DTPA (Gadolinium diethylenetriamine penta-acetic acid, 0.1mmol/kg) was performed (breath hold 18-26 seconds). The contrast agent was given as part of a first-pass MR angiogram, which was clinically indicated. Administration of gadolinium contrast agent at this timing interval allowed good mixing of the agent while maintain a high concentration in the blood pool. The 3D cine b-SSFP acquisition was

accelerated using a SENSE factor of 2 in both phase encoding directions (AP being the first phase encoding direction, and right-left (RL) being the second phase encoding direction) and partial Fourier reconstruction (factor of 0.625) in the first phase encoding direction, resulting in a net acceleration factor of 6.4. Comparative parameters for the M2D and 3D b-SSFP scans are shown in Table 3.

2.1.2 Image Quality Analysis

Accuracy of volumetric assessment tends to be dictated by the clarity of the endocardial border definition. If there is motion artefact due to breathing or arrhythmia this may significantly affect endocardial border by eye or by computer generated semi-automated software. McConnell et al devised a scoring system to evaluate image quality and this was used to determine whether the data collected by both the conventional multi-slice 2D imaging and the fast 3D volume were of adequate quality to allow volumetric analysis.

To do this the images were scored by independent observers. Using a mid ventricular reference image window and level settings were chosen to optimize contrast between blood pool and myocardium and these settings were applied to all images [77]. 10 patient data sets containing an example diastolic image from each of the 3 imaging types were randomly ordered and imaged scored by 4 experience independent observers. Image quality of 2D and 3D images was graded on a 4 point scale based on the visibility of the endocardial border (modified from McConnell et al [78]) . Score (1) Poor: endocardial border poorly visible or not visible (non-diagnostic), (2) moderate blurring of endocardial border, (3) good endocardial border visibility, (4) excellent image quality. This

method of scoring was also used for the volume assessments in the TOF CMR protocol described in the next section of this chapter.

Table 2: Fast 3D Imaging – Demographics

Patient	Age	Diagnosis
1	22	Aortic coarctation
2	52	AVSD repair
3	35	Aortic coarctation
4	60	Ischaemic heart disease
5	28	Tetralogy of Fallot
6	56	Ischaemic heart disease
7	71	Ischaemic heart disease
8	19	Aortic coarctation
9	38	Aortic coarctation
10	31	Aortic regurgitation
11	34	Ebstein anomaly
12	40	Aortic stenosis
13	29	Tetralogy of Fallot
14	34	Aortic coarctation
15	36	Pulmonary regurgitation and VSD

Table 3: Comparison of M2D SSFP sequence with the Single Breath Hold 3D SSFP sequence

Parameter	M2D SSFP	3D SSFP
Field of view (mm)	360-410	310-363
Spatial Resolution (mm)	2.1 x 2.14 x 10	2.13 x 2.26 x 10
Number of slices	10-12	10-12
Number of breath holds	5-6	1
Breath hold duration (s)	12.3-17.2	18-26
SENSE Factor (phase encoding direction)	2 (AP)	4 (2 AP x 2 RL)
TFE factor	7-12	12-18
Temporal Resolution (ms)	21-38	44-65
Cardiac Phases	20-30	20
TR / TE (ms)	1.6 / 3.2	1.8 /3.6

Contrast to Noise Assessment

Visual image scoring allows qualitative assessment but it is also necessary to perform a quantitative measure of image quality and this can be done using the contrast to noise ratio. This helps to determine whether the presence of gadolinium contrast agent significantly affects image quality and also whether there is a significant difference between the two different non-contrast scans. Contrast to noise ratio (CNR) for M2D, 3D pre contrast (3DNC) and 3D post contrast (3DC) was evaluated by measuring the mean pixel value (signal intensity SI) within a region of interest (ROI) for blood and a separate ROI for the myocardium. The blood pool ROI was drawn in the centre of the left ventricle and myocardium ROI the mid septum. All measurements were made at end-diastole. Mean and standard deviation (SD) signal intensity was also collected in the background (estimation of noise) in a region close to the chest wall. The 2D and 3D scans were acquired using SENSE, and it is therefore difficult to obtain an absolute measure of noise. However, for the 3D scans all imaging parameters (including coil sensitivity maps) were identical and the same region of interest was used.

Contrast to noise was then calculated by:

(mean SI blood- mean SI myocardium) / SD background noise

The results of the CNR measurements for the 3 different sequences and how this related to visual scoring and accuracy of volume assessment will be explored further in chapter 3.

Volumetric Analysis

The final comparative measure in this patient group was volumetric assessment of left and right ventricles. Volumetric analysis was performed in all patients for the M2D multi-slice stack and the pre and post contrast 3D volume. Endocardial borders were manually drawn for the three data sets allowing segmentation of both ventricle in systole and diastole using commercially available software (Philips, Viewforum). Papillary muscles were excluded for the left and right ventricles. End-diastolic (EDV) and end-systolic (ESV) volumes were calculated for the left (LV) and right ventricle (RV), from which the stroke volume (SV) and ejection fraction (EF) were derived. A detailed review of methods used to quantify ventricular volumes is available in section 2.2.

To further validate the methods, two experienced independent observers analyzed ten of the data sets to assess inter-observer variability.

The volumes measured by the 3 methods were compared using Bland Altman analysis to determine whether the fast 3D imaging is as accurate as conventional multi-slice 2D imaging. The results of this analysis will be described in full in Chapter 3.

This small study highlights the complexity of components involved in volumetric assessment. Although post-processing software used to measure cardiac volumes is semi-automated, accurate volume assessment requires experience to ensure that important factors that may affect image quality are taken into consideration. The following section will focus on volumetric assessment in TOF patients and healthy volunteers and introduce the methods used in stress CMR imaging.

2.2 CMR assessment in tetralogy of Fallot

CMR imaging in TOF patients incorporates assessment of anatomy, systolic function and arterial flow patterns in order to give a comprehensive review of the post surgical repair status. From previous studies we have seen that resting right ventricular volumes in TOF patients with severe PR do not easily predict which patients require PVR most urgently and have limited clinical application in terms of predicting improvement in RV function post PVR. Stress imaging with CMR and Echo has been limited to date partly due to concern about side effects with higher dose pharmacological agents such as dobutamine. In addition image quality tends to be compromised when using pharmacological or physical stress with either imaging modality.

The main focus of this thesis was to evaluate the volumetric response to stress using dobutamine as a surrogate for exercise. This was achieved using a staged CMR dobutamine protocol with the assessment of bi-ventricular volumes and great arterial flows at each stage. The following section details the CMR sequences and the dobutamine protocols used in TOF patients and in a group of healthy volunteers.

2.2.1 DS-MR Study Demographics

Between March 2007 and October 2009, 28 adult patients with surgically repaired TOF referred for CMR as part of their standard clinical care were recruited prospectively. Patients were selected based on echocardiographic findings of moderate to severe pulmonary regurgitation and dilated right ventricle. For comparison, we collaborated with a second centre (S.K., Nebraska, USA) and recruited ten healthy volunteers in 2010 for CMR assessment of

ventricular function at rest and dobutamine stress. This collaboration allowed utility of the same type of 1.5T Philips scanner, 32 channel coil and therefore identical sequences. The stress protocols were also identical.

2.2.2 Inclusion and exclusion criteria.

The exclusion criteria were:

- Patients and volunteers with contraindications for CMR including incompatible metallic implants or claustrophobia.
- Patients with contraindications to dobutamine administration (history of ventricular tachycardia, documented ischemic heart disease, poor left ventricular systolic function, severe aortic valve disease or significant pulmonary stenosis).
- Patients with more than trivial aortic and tricuspid regurgitation or any residual left-to-right shunt.
- Patient currently taking beta-blocker treatment.
- Volunteers with any cardiac history or history of any chronic illness

Medical records were reviewed for patient characteristics and anatomic and operative details and these together with volunteer characteristics are summarized in Table 4.

The local research ethics committees in each centre approved the study and informed consent was obtained from all. Details of the patient information leaflet, ethics approval and consent forms are available in Appendix 1.

Table 4: Study Population

Demographics	Fallot Patients	Healthy Volunteers
Study population	n=28	n=10
Gender	Male=14 (50%)	Male=5 (50%)
Age at CMR (y)	32.1 (16.2-60.1)	40.6 (23.9-51.8)
Age at TOF repair (y)	4.9 (1.0-31.1)	
Interval since TOF repair (y)	25.1 (14.1-47.3)	
Palliations prior to TOF repair	7/28	
TOF repair type		
• Trans-annular repair	13/28	
• Non-trans annular repair	3/28	
• Unknown	12/28	
NYHA classification	1.8 ± 0.6	
QRS duration (ms)	151 ± 7.7	
Baseline RV-EDV (ml/m^2)	134.5±31.4	76.6±14.3
Baseline RV-ESV(ml/m^2)	64.4±22.1	32.1±8.6

2.2.3 Cardiac magnetic resonance study

Patients and volunteers were scanned using 1.5T MR-scanner (Achieva, Philips Healthcare, Best, The Netherlands) with a 32 channel cardiac coil (Philips Healthcare). Cardiac synchronization was performed with vector electrocardiography (VECG). A full clinical protocol was performed on each patient (see chapter 1, table 1 for details). This commenced with a survey and reference scan. Anatomical planes were created using a real time "Interactive" sequence which allowed pre-scan planning of specific geometries such as right ventricular outflow tract view (RVOT), through plane ascending aorta (Ao) and pulmonary artery (PA) and branch pulmonary artery cross sections (required for flow quantification). This was followed by sequences required to assess ventricular function and flow and these will be explained in more detail below.

The final component of the clinical scan was an MR angiogram of the RVOT and pulmonary arteries and an isotropic 3D cardiac volume for anatomical review.

Volumetric Assessment

As discussed above cardiac volume assessment is a major component of CMR assessment. Good quality imaging is required to ensure accurate volume quantification. In TOF patients with severe PR there is often dilatation of the RV and RVOT. Conventionally volumes are measured using the short axis (SA) orientation, as this is optimal for the shape of the left ventricle. SA assessment of volumes in TOF patients has been validated and used routinely in clinical practice although it has been shown that assessment using axial slices is superior in terms of accuracy and observer variance [79]. This axial orientation allows better appreciation of the right-sided valve planes and right ventricular outflow tract dilatation. Therefore for the TOF patients the volume assessment was performed using the axial orientation rather than SA. In contrast in healthy volunteers we chose to assess ventricular function in the conventional way using SA slices. The impact of this change in orientation between the groups will be further explained in chapter 5.

In this research study the conventional multi-slice SSFP sequence was used to assess cardiac volumes. This multi-phase, multi-slice volumetric data set was acquired using a fast 2-dimensional balanced steady state free precession sequence (b-SSFP). Continuous slices (12-14, i.e. 6-7 breath-holds) were acquired in an axial orientation (transverse) for the TOF patients and in short axis orientation for the volunteers to cover the ventricles in accordance with standardized imaging protocols [79].

Imaging parameters were as follows: TR/TE=3.0ms/1.5ms, flip angle 60°, 30 cardiac phases per average heart beat, field of view 360x480 mm, matrix size 196x172, slice thickness 8-10 mm, no intersection gap, sensitivity encoding (SENSE) for spatial under sampling (factor 2).

Flow

In addition to volumetric assessment all patients and volunteers had pulmonary artery and aortic flow (PC-flow) quantified at rest and during DS-MR. All TOF patients studied had a degree of pulmonary regurgitation and the inclusion of flow assessment in the protocol was to determine how flow dynamics change during DS-MR and whether derived volumetric and flow parameters can be used interchangeably in the assessment of ventricular function in TOF patients. Both modalities are likely to suffer from some reduced image quality during DS-MR. Flow imaging in particular may also suffer from inaccuracy due to increased flow turbulences at higher blood flow rates [80] and be sensitive to errors from cardiac arrhythmia such as ventricular ectopics [81]. Hence, the focus was to examine the flow dynamics during DS-MR, how these effect the amount of pulmonary regurgitation and whether this has any bearing on the volumetric changes observed. Phase contrast (PC) flow-derived measures of right and left ventricular (LV) stroke volumes, absolute pulmonary artery backward flow volumes (PA-BF) and pulmonary artery regurgitant fraction (PA-RF) should agree with analogous volumetric-derived parameters at rest. However little is known about how this relationship changes with stress and this has been further evaluated in chapter 4.

Pulmonary artery (PA) and aortic (AO) flows were performed perpendicular to the vessel flow using a retrospective 2D phase contrast sequence during free breathing. Image planes were located for pulmonary artery flow at the midpoint of the main PA and just above the level of the sinus of the aorta and for the aorta within the ascending aorta at the level of pulmonary artery bifurcation.

Imaging parameters were as follows: TR/TE=4.4ms/2.4ms, flip angle 10°, velocity encoded value (VENC) set to 200-350 m/s, 40 cardiac phases per average heart beat, field of view 350x300, matrix size 256x256, slice thickness 8mm, duration (depending on heart rate) usually between 1.0 and 2.5 minutes.

PC-flow rates were calculated as area (semi-automated tracing the cross sectional area of the vessel of interest in the magnitude images) multiplied by the mean velocity (derived from the phase images)[82]. Flow parameters (forward flow, backward flow, stroke volume, regurgitant fraction, cardiac output) in the pulmonary artery and ascending aorta were normalized to the body surface area.

2.2.4 Dobutamine Stress Imaging

Safety considerations

Prior to commencement of the dobutamine stress MR imaging important safety precautions must be adhered to. Table 5 shows the safety checklist, which should be completed prior to scanning. Presence of resuscitation equipment and appropriately trained staff are imperative.

Table 5: DS-MR Safety Checklist

Checklist
1. Resuscitation equipment 2. Blood pressure, O2 saturation and ECG monitoring 3. MR compatible syringe driver for dobutamine administration 4. 12 lead ECG machine 5. Access to emergency drugs especially atropine 6. Clinician with Advanced Life Support training

Stress Protocol

A full anatomical and functional assessment including great artery flows and ventricular volumes was completed for each of the TOF patients at rest as previously described. On completion of the clinical scan, dobutamine hydrochloride (Hameln pharmaceuticals ltd, Gloucester, UK) was administered by continuous infusion into a large antecubital vein. An initial infusion of 10μg/kg/min (stage 1 DS-MR) of dobutamine was allowed to reach steady state over 3-5 minutes, with monitoring of the heart rate and blood pressure. At steady state, phase contrast flow imaging of aortic and pulmonary artery flow was completed followed by a b-SSFP axial multi-slice stack to assess ventricular function. Providing the patient remained asymptomatic, the dobutamine infusion was increased to 20μg/kg/min for a further 3-5 minutes (stage 2 DS-MR) and the CMR stress protocol repeated. Dobutamine was then discontinued and patients removed from the MR scanner to allow for a period of recovery.

Each volunteer had a quantitative volume, aortic and pulmonary flow assessment at rest and during dobutamine stress using the same stress protocol as detailed above. However volumetric assessment was performed using the standard short axis orientation. This allowed the opportunity for further analysis

of circumferential motion of a normal left ventricle under stress conditions and further information regarding this can be found in the appendix.

Dobutamine infusion was discontinued if systolic blood pressure reached>180mmHg, heart rate >75% predicted (220 - age), or if patients experienced other significant side effects, such as dyssrhythmia or hypotension.

2.2.5 Volumetric and Flow Analysis - Post-processing

Volumetric Analysis

Both ventricles were segmented in systole and diastole using semi-automated commercially available software (ViewForum, Philips Medical Systems, Best, The Netherlands) with endocardial borders drawn manually by two independent observers. Papillary muscles were excluded for the left and right ventricles. End-diastolic (EDV) and end-systolic (ESV) volumes were calculated for the RV and (LV), from which the stroke volume (SV) and ejection fraction (EF) and cardiac output (CO) were derived. All volume measurements were indexed for body surface area and expressed as ml/m^2. Contractile reserve was defined as the percentage change in ventricular EF at each stage of dobutamine infusion compared with resting EF [91]. Volumetric assessment was completed for all patients at each stage of the dobutamine stress protocol. These results of this analysis will be fully explained in chapter 6 which will focus on the changes in ventricular volumes that occur under stress and how this relates to resting cardiac function in TOF patients and healthy volunteers.

Flow Analysis

Flow measurements were calculated by use of semi-automated vessel edge detection algorithm (Extended MR work space version 2.5.3.1, Philips Medical Systems, Best, The Netherlands.). Flows were documented in the following way:

1. Total aortic forward flow Ao-FF $^{(total)}$
2. Total pulmonary forward flow PA-FF $^{(total)}$
3. Total pulmonary regurgitant volume of backward flow PA-BF
4. Pulmonary stroke volume or effective forward flow PA-SV$^{(eff\ FF)}$ calculated by: (PA-FF) – (PA-BF)
5. Pulmonary artery regurgitant fraction PA-RF: expressed as a percentage of (PA-BF/ PA-FF $^{(total)}$) x 100

All flow measurements were indexed for body surface area and expressed as ml/beat/m^2.

LV and RV stroke volumes comparison with flow

The LV and RV SV were calculated from the volumetric analysis as *SV=EDV-ESV* [83]. In the absence of atrioventricular valve incompetence or intracardiac shunts, the ventricular SV should match the forward flow in its connected great artery [83].

Therefore the systemic antegrade output or LV stroke volume can be compared to the forward blood flow entering the aorta (Ao-FF) after each ventricular contraction.

Likewise the pulmonary antegrade output or RV-SV was compared with the total pulmonary artery forward flow (PA-FF).

Further comparisons between flow and derived volumetric parameters can therefore be made using the SV difference method as detailed below.

Pulmonary Backward Flow

The pulmonary artery backward flow (PA-BF) was defined as the absolute regurgitant volume (ml/m^2) across the pulmonary valve. In the absence of aortic valve incompetence or intra-cardiac shunts, the volumetric derived PA-BF can be calculated by the SV difference method [83] as:

$$\boldsymbol{PA\text{-}BF = RVSV - LVSV}$$

We compared this volumetric derived parameter with the PA-BF as assessed by PC-flow.

Pulmonary Regurgitant Fraction

Pulmonary artery regurgitant fraction (PA-RF) is commonly defined as the proportion of the regurgitant pulmonary flow per total forward flow/stroke volume.

The PA-RF can be calculated from the PC-flow [83] analysis as:

$$\boldsymbol{PA\text{-}RF\,[\%] = (PA\text{-}BF \,/\, PA\text{-}FF) \times 100}$$

By use of the SV-difference method as described above, the PA-RF can be calculated from the volumetric analysis as [83]:

$$\boldsymbol{PA\text{-}RF\,[\%] = (RVSV\text{-}LVSV \,/\, RVSV) \times 100}$$

We compared the PA-RF assessed by PC-flow analysis with the volumetric derived parameter.

The above parameters were compared at rest and during stress for all TOF patients and further details of the results are available in chapter 4.

2.3 Observer Variance

As we have already seen in the early aspects of this chapter volumetric assessment of cardiac ventricle is complex and requires experience both to acquire good quality images and in the post processing analysis to ensure accuracy. Volumetric assessment by CMR has been shown to be highly accurate and reproducible especially for the left ventricle and in healthy volunteers. When applying new techniques to groups of patients or analyzing volumes or flows in different physiological conditions it is important to establish whether these methods are robust. It is apparent that for RV assessment the axial imaging plane tends to give more accurate and reproducible volumes and this certainly influenced our protocol. The accuracy of volume assessment during DS-MR is less well described. Dobutamine stress magnetic cardiac resonance imaging (DS-MR) is widely used in the assessment of adult patients with ischemic heart disease [84] with good reproducibility and safety data [50]. However there is limited volume data in his group as the focus of these studies tend to be on regional wall motion abnormalities relating to underlying ischaemia. In congenital heart disease there is limited data related to volume assessment (see Chapter 1.4) but tends to be at a lower dose than the protocol we used [65]. Currently a maximal dose of 7.5mcg/kg/min dobutamine is considered safe and reproducible [61].

Section 2.1 describes the elements taken into consideration when evaluating a technique for accuracy. In order to determine the reproducibility and accuracy of the data collected during DS-MR similar analysis was completed at each level of stress testing in TOF patients and volunteers. The results of this will be available in chapter 4. The methods used are described below:

Volumetric Observer Variance

For inter-observer variability two observers (VP and IV) with over three years of CMR experience analyzed all TOF and volunteer data sets as described above at rest and both levels of dobutamine. Both observers also analyzed flow quantification for the PA and AO. Additionally, ten data sets for the TOF patients and all of the volunteer data sets were re-analyzed by a single observer (VP) to document intra-observer variability for volume and flow assessment.

Image Quality Assessment

Image qualitative analysis was performed, (as in Section 2.1) by two pediatric cardiologists with over five years experience in CMR. From 10 randomly chosen TOF patient data sets, and 10 volunteer DS-MR data sets a mid-ventricular slice was chosen in end-systole and end-diastole. Reference image window and level settings were used to standardize contrast between blood pool and myocardium in all images. Observers were blinded to the stage of DS-MR. Image quality was scored based on the visibility of the endocardial border, as reported by McConnell et al [85].

All measures of variability between observers or methods were compared either using the coefficient of variation or Bland Altman analysis.

The accuracy and reproducibility of these techniques will be discussed at length in Chapter 4.

2.4 Echocardiography Protocol in Tetralogy of Fallot

One of the initial aims of this thesis was to evaluate the utility of echocardiography in addition to CMR in the assessment of the cohort of TOF patients with PR at rest and during dobutamine stress. A baseline echo protocol was performed prior to each study and this included all of the standardized parameters of left and right ventricular function, valve assessment as well as tissue Doppler imaging and 3D volumetric assessment of the right ventricle. On completion of the baseline echo the patients completed the CMR and DS-MR protocols described above.

The echo assessment was performed within the MR scanner room. It was possible to use an XMR facility, which combines an X-ray table and MRI scanner (Figure 10). The patient was initially positioned on the X-ray part of the XMR system to allow the echo machine to be used within the scanning room (outside of the specified Gauss safety line). This allowed echo assessment to be performed on exactly the same day and within the same environment as the CMR assessment. Once complete the patient was moved along the XMR system and positioned within the MR scanner.

Prior to discontinuation of the dobutamine the patient was mobilized to the X-ray portion of the XMR table as described above and a limited stress echo was performed which included TDI assessment and 3D volume of the RV. A description of the echo protocol and specifics are detailed below.

Figure 10: XMR Facility
A combined X-ray and MRI scanner within interlocking table to enable imaging of the patient on the X-ray table initially then positioning of the patient within the MRI scanner

Resting Echo Assessment

Echocardiographic examination performed by a single sonographer (VP) in all study patients using IE33 machine (Philips Healthcare). For standardized 2D and TDI imaging a S5-1 sector array transducer with 5 to 1 MHz extended operating frequency range was used. The resting echo examination included assessment of the ventricles and cardiac valves according BSE standards.

Tissue Doppler

Tissue Doppler PW Doppler was recorded for the RV free wall (just inferior to the tricuspid annulus), septum and LV lateral wall in the apical four-chamber view. This allowed quantification of the peak systolic (S), early diastolic (E) and

late diastolic (A) wave velocity was measured for the basal segment of each wall. Measurements were taken by one investigator and obtained by averaging 3 consecutive beats.

3D assessment of the right ventricle

3DE was performed using the IE 33 (Philips, Andover, MA, USA) ultrasound machine with X3–1 matrix-array transducers (Philips). Image acquisition was performed from an apical window with the RV as the region of interest. To encompass the complete RV into the 3D dataset, a full volume scan was acquired in harmonic mode from four R-wave triggered sub-volumes. This scan was carried out during an end-expiratory breath-hold lasting 5 seconds when possible. The 3D dataset was stored in a DICOM format on a CD-ROM and transferred to separate workstations for off-line data analysis. Automated border detection and volume computation algorithm analysis of original raw was performed using dedicated RV analysis software (TomTEC, Munich, Germany). The 3D dataset could be manipulated offline to allow the best visualization of the RV inflow and outflow tracts. End-diastolic and end-systolic phases were defined and contours were manually drawn in end-diastolic and end-systolic images. These were propagated throughout the data set and in order to generate volumetric measures and ejection fraction.

Stress Echo Imaging

This aspect of the study was performed immediately after the completion of CMR stress protocol. The dobutamine infusion was continued at 20 μg/kg/min and limited echo parameters were collected. The intention was to assess TDI PW Doppler and a 3D RV volume, as per the protocol documented above. However this aspect of the protocol proved to be challenging due to significant motion

artefacts secondarily to tachycardia at this dose of dobutamine, which affected the 3D image acquisition and later analysis on the post processing software (see appendix 2).

2.4 Statistics

Statistical analysis was performed using Statistical Analysis Software (SASW) version 18. All data with a normal distribution are described as mean +/- one standard deviation. Comparison of volumes and flows from one level of stress to the next was evaluated using the 3 way ANOVA followed by paired student t test, as were the differences between sub-groups (defined by response in RV-ESV) with $p<0.05$, level of significance. Regression analysis was used to correlate the percentage change in volumes against EF. Inter and intra-observer variance was assessed using the coefficient of variance for the volumetric measurements at each level of DS-MR. The Bland-Altman analysis was used for comparison of volumetric versus PC-flow-derived analogous cardiovascular functional parameters and also to compare the volumetric assessment measured in M2D scan versus 3D volumes (pre and post contrast) [61] [86]. Image quality comparison was evaluated with Friedman ranks analysis.

CHAPTER 3: FAST 3D VOLUMETRIC IMAGING

3.1 Overview

The previous chapter discussed the protocols and techniques used for the evaluation of cardiac volumes in patients with congenital heart disease in particular repaired TOF and also in healthy volunteers. In this chapter the use of faster volumetric scanning is explored and data relating to a single breath hold volumetric assessment is discussed.

There is a move to produce faster MR sequences, which will allow rapid full volume assessment in a single breath-hold or during free breathing scanning. This would be preferable in sick patients who find the repetitive breath holds challenging. One approach to circumvent these limitations would be the acquisition of a 3D cine data covering both ventricles. Single breath-hold 3D cine techniques have been proposed by using either highly parallel imaging [87] or by exploiting the spatial-temporal correlations with *kt*-techniques [88, 89]. Unfortunately a major disadvantage of 3D cine acquisitions is reduced blood-myocardial contrast, which hampers clear delineation of endocardial borders. This has been demonstrated to be mainly due to the lack of blood inflow in large 3D volumes [90]. Application of a contrast agent was shown to improve the image contrast for 3D volumetric assessment using a *kt*-technique. However, this approach suffers from endocardial blurring related to the reconstruction algorithm, leading to an underestimation of end-diastolic volumes due to partial volume effects [88, 91]. Furthermore, as kt-techniques usually require a training

period either with an additional breath-hold, with the diaphragm in the same position or a longer breath-hold this requires considerable patient cooperation.
Recently, self-respiratory navigated techniques [74, 75] and highly under sampled reconstruction techniques have been proposed to acquire whole heart cine data sets [76]. One problem using self-respiratory gating techniques is long scanning times. Therefore, for improved patient comfort and reduced scan time assessment of cardiac function within one breath hold would be ideal. Such a technique could then be used during stress imaging which would limit the duration of stress and possible side effects that patients have to experience.

In order to determine whether such a novel technique could be applied to stress imaging it was necessary to first apply the sequence in patients at rest and compare the accuracy of cardiac volume evaluation.
The methodology of 3D imaging of the ventricles and the patient cohort used has been fully explained in the previous chapter. How this approach performs compared to the standard multi-slice acquisition will now be discussed.

3.2 Results of 3D compared with 2D imaging

The patient population and demographics have been described in chapter 2.1. Data were successfully acquired in all patients. The patients were predominantly adult congenital patients who had had corrective surgery of a structural abnormality in childhood. Volume data was acquired in the short axis orientation and three sets of volume data generated for each patient. The first data set corresponds to the conventional multi-slice 2D (M2D). The 3D SSFP full heart volume was performed immediately prior to and post contrast injection (see methods chapter 2) and these data sets were therefore classified as 3D non-contrast (3DNC) or 3D contrast (3DC). Images for the multi-slice 2D (M2D) images and the pre and post contrast images are shown in figure 11.

3.2.1 Scan duration

One of the most important features of the 3D approach is the reduction of total scan time. The mean breath hold (BH) duration for the acquisition of 2 slices for the M2D approach was 14.9s (12.3-17.2 for 2 slices), resulting in approximately 4 to 5 minutes for the complete ventricular volume data acquisition. In comparison 3D scans required a mean single BH of 20s (Table 3 Chapter 2).

3.2.2 Image Quality

M2D images provided the best visualization of the endocardial border with a mean score of 3.9. The 3D images pre contrast (3DNC) only achieved a mean visual score of 2.2 due to reduced contrast between blood pool and the endocardial border in the majority of images. The administration of contrast agent resulted in improvement in image quality with a mean score of 3.2. Friedman's ranks analysis showed the difference in image quality for the three scan types to be significant $p<0.01$ (Mean rank M2D 2.8, 3DC 2.02, 3DNC 1.18).

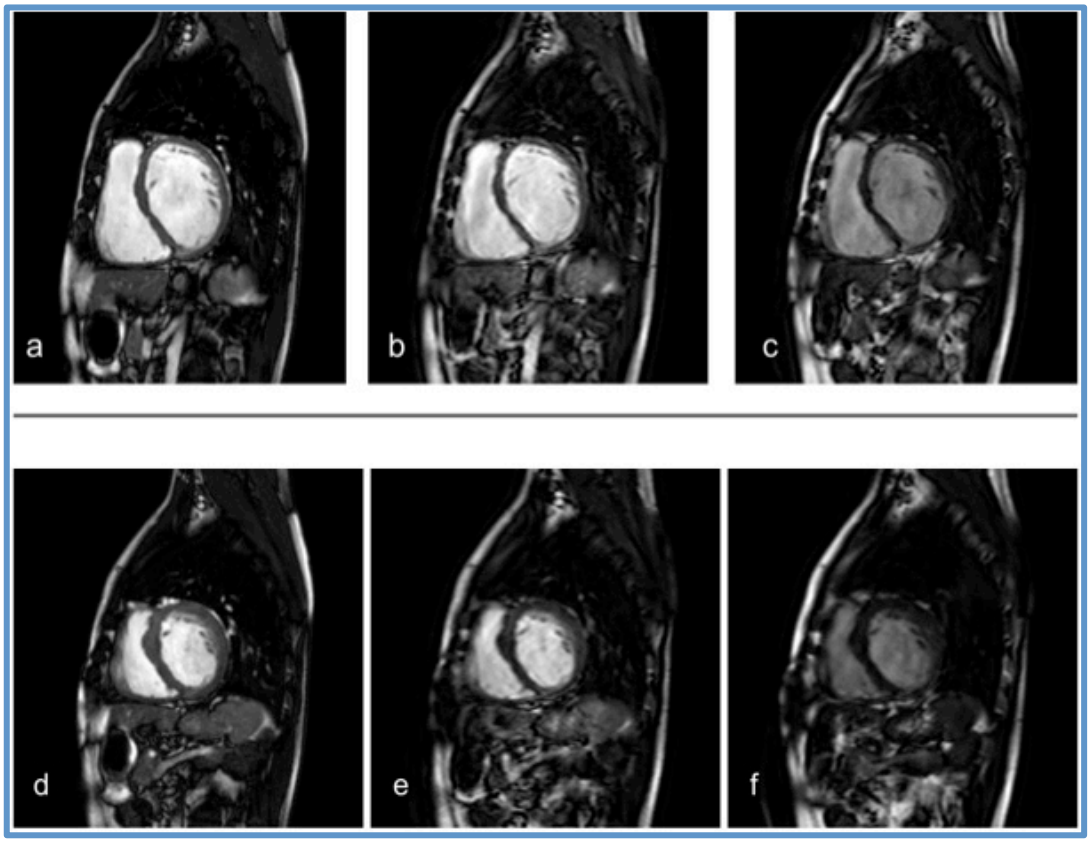


Figure 11: Mid-ventricular images for M2D and 3D Sequence
M2D images (a) diastolic phase (d) systolic phase
3D images post contrast (b) diastolic phase (e) systolic phase
3D images pre contrast (c) diastolic phase (f) systolic phase

Table 6: Contrast to Noise Assessment

Contrast to Noise Measurements	
Scan type	**CNR**
M2D	**234.17**
3DC	**203.70**
3DNC	**136.06**

3.2.3 Blood-Myocardial Contrast

Contrast to noise results for all three image types are shown in Table 6. The M2D and 3D images post gadolinium showed greater contrast between myocardium and blood pool than the 3D images pre contrast. These had the least contrast and therefore the worst delineation of the endocardial border as supported by the visual scoring results.

3.2.4 Ventricular volume analysis

Left and right ventricular parameters for all three scan groups are shown in table 7. Statistical analysis (t-test) showed no significant difference for measured LV and RV-EDV and ESV between the M2D and 3DC images. However, Bland Altman plots showed greater bias and standard deviation (Figs. 12 and 13) when comparing the M2D with 3DNC images.

Range and mean of intra and inter observer variability using the 3D and the M2D method are shown in Tables 8 and 9. For inter-observer variability no statistical differences were found comparing the mean values for the 3D data and for the M2D data for both ventricles. Additionally the coefficient of variance (COV) was calculated for all parameters to further assess inter-observer agreement. This confirmed good inter-observer agreement with COV of less than 10. The only exceptions to this was for RV-ESV 3DNC images where the COV was 13.2, suggesting less good agreement in the measurement of the volumes in this group.

For intra-observer variability, using the 3D method there was also no statistical difference, confirming good reproducibility for these techniques. Intra-observer was only completed for the LV measurements.

Table 7: Right and Left Ventricular Parameters

	CMR technique					
	M2D		3DNC		3DC	
Volume (ml)	**Mean±SD**	**Range**	**Mean±SD**	**Range**	**Mean±SD**	**Range**
LV-EDV	159.3±52.1	94-320	151.1±45.4	93-283	162.7±54.4	93-332
LV-ESV	66.8±45.6	27-187	64.6±46.4	23-189	70.2±49.5	28-208
LV-SV	92.5±21.4	62-133	86.5±20.8	48-127	92.5±22.5	55-130
RV-EDV	161.0±47.8	71-277	149.2±48.5	48-258	163.0±46.5	69-268
RV-ESV	70.7±33.3	14-146	67.0±30.9	14-140	74.7±33.8	17-147
RV-SV	90.3±18.9	57-131	82.2±20.9	34-118	88.3±18.6	52-121

Table 8: Inter-Observer Variability of M2D and 3D Imaging

Inter-observer variability								
	Range Difference %				**Mean difference %**			
	LV-EDV	**LV-ESV**	**RV-EDV**	**RV-ESV**	**LV-EDV**	**LV-ESV**	**RV-EDV**	**RV-ESV**
M2D	[-12.1 ; 8.3]	[-9.7 ; 17.6]	[-10.6 ; 10.2]	[-9.5 ; 8.0]	-2.1	0.86	1.12	-0.53
3DC	[-10.7 ; 14.1]	[-13.8 ; 16.5]	[-13.8 ; 3.6]	[-9.2 ; 9.5]	-2.75	1.05	-2.89	0.59
3DNC	[-28.3 ; 29.9]	[-2.7 ; 10.7]	[-6.1 ; 11.0]	[-8.4 ; 19.7]	-0.86	3.21	2.17	2.69

Table 9: Intra-Observer Variability for M2D and 3D Imaging

Intra-observer variability				
	Range Difference %		**Mean difference %**	
	LV-EDV	**LV-ESV**	**LV-EDV**	**LV-ESV**
M2D	[-1.1 ; 3.6]	[-2.0 ; 3.0]	0.34	0.52
3DC	[-2.1 ; 3.4]	[-1.3 ; 3.5]	-0.01	1.31
3DNC	[-3.0 ; 3.3]	[-3.1 ; 2.4]	-0.33	-0.22

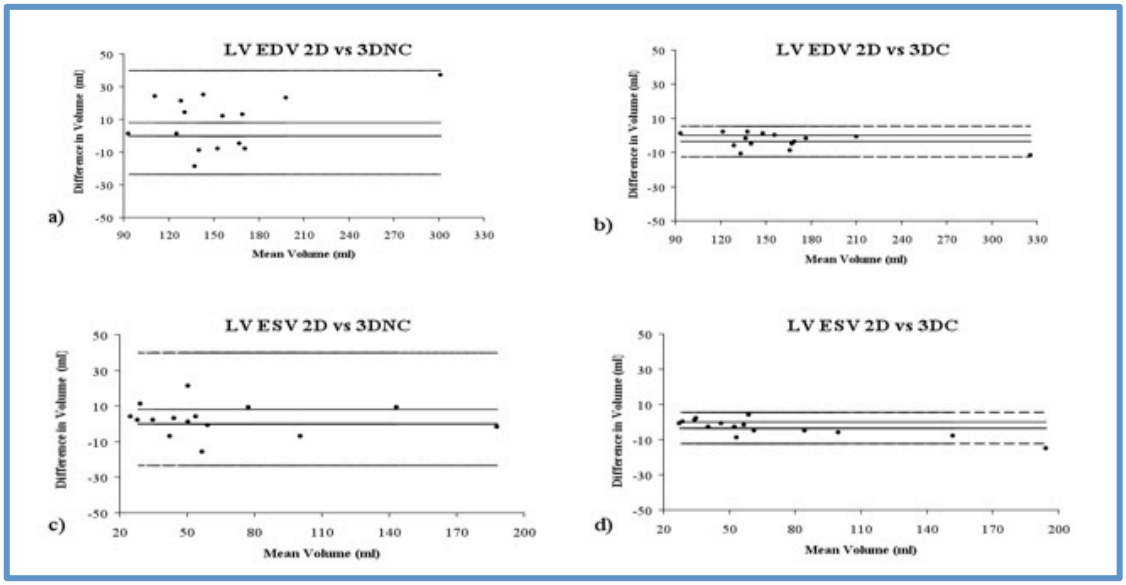


Figure 12: Bland Altman Plots for Left Ventricular Parameters

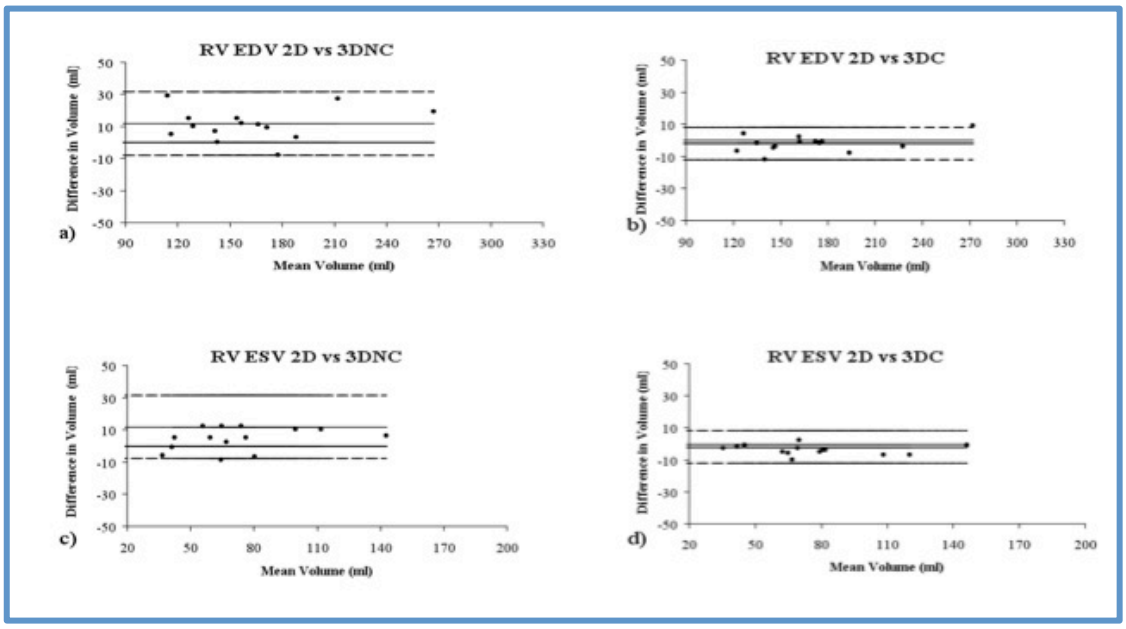


Figure 13: Bland Altman Plots for Right Ventricular Parameters

3.3 Summary

This small study illustrated that fast ventricular volume assessment is achievable in a variety of patients with structural heart disease. The comparative volumetric results showed that whilst multi-slice SSFP imaging of the ventricles has the best image quality it is possible to obtain good quality images with faster scanning but that the addition of contrast significantly improved endocardial definition and therefore accuracy of volumetric measurements.

CHAPTER 4: DISPARITY BETWEEN FLOW AND VOLUMETRIC ASSESSMENT

4.1 Overview

Flow assessment of the great arteries has also become an essential CMR tool especially in patients with structural heart disease where shunts and regurgitation fractions will guide intervention for specific abnormalities. In patients with repaired TOF pulmonary regurgitation is an important determinant of late outcome. The degree of regurgitation is either described as the pulmonary reverse/back flow or the back flow is expressed as a fraction of the forward flow, known as the regurgitant fraction (RF). This measurement may now contribute to the recommendations for pulmonary valve intervention [92]. PC flow assessment of valve function has been shown to be reproducible and accurate and there is also data which shows that at rest functional parameters such as ventricular stroke volume derived from MR volumes measurements correlate well with analogous parameters measured by PC flow [93, 94]. However there is relatively limited data on how flow measurements may change during stress imaging. Additionally the robustness and relative agreement of flow and volumetric parameters during stress imaging and under different levels of dobutamine stress is yet to be explored [104, 105].

The following chapter will review the accuracy of flow measurements compared to volumetric assessment in repaired TOF patients and in normal volunteers. Initially there is an explanation of the inclusion and exclusion criteria of patients during DS-MR. This is followed by review of the heart rate changes observed

during DS-MR and whether this may impact on comparative cardiac parameters. There will also be full explanation of the flow measurements collected during the study and how these are affected by stress. The final part of this chapter will focus on flow versus volumetric measurements and how closely they compare during DS-MR.

4.2 Results of Phase contrast flow during DS-MR

4.2.1 Study Population

Flow and volumetric measurements were completed in all TOF patients and in 10 volunteers. A total of 28 patients (chapter 2, table 4) with repaired TOF were included in the DS-MR part of the study. Of these only 18 patients completed both stages of the DS-MR protocol. Details of the exclusions are described below and schematically represented in figure 14.

Of the 28 patients recruited into the study, 24 completed stage 1 dobutamine (10μg/kg/min). Four patients were excluded, 2 due to claustrophobia later in the scan and 2 due to frequent ventricular ectopics which were not seen during baseline scanning. Twenty patients continued to stage 2 dobutamine (20μg/kg/min), four patients were excluded following stage one: Two patients due to minor side effects and intolerance of dobutamine (nausea, headache) and 2 due to attainment of >75% of maximal predicted heart rate during stage 1. Two further data sets were not included in the final analysis due to incomplete volumetric data at stress. For both of these patients the data set was acquired with the most basal slice starting too high within the ventricle, therefore a portion of the ventricle could not be included in the volumetric analysis. This is probably due to a change in diaphragm position due to increasing breathing

activtity during stress. It was not possible to repeat the volumetric stack during DS-MR as this would result in significantly prolonged exposure to dobutamine and the risks associated with this.

Comparative data analysis was performed on the 18 patients who completed both stages of DS-MR. Therefore the results presented from this point will describe trends and observations documented in the 18 patients who completed both levels of the DS-MR protocol. Population details relative to the 18 included are shown in Table 10.

All 10 volunteers completed the protocol without side effects or complications.

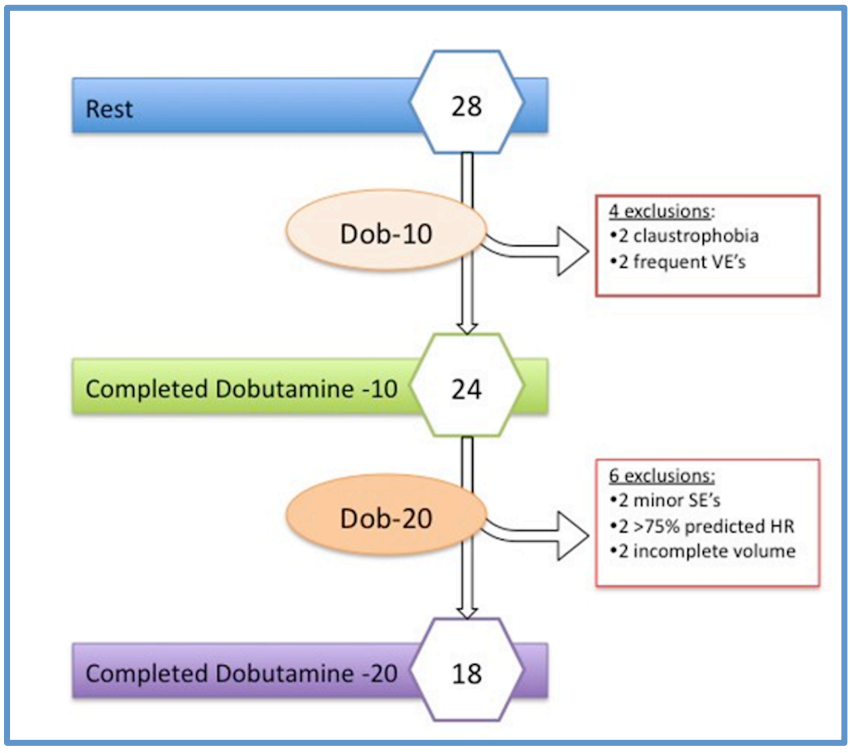


Figure 14: Exclusion criteria for Fallot patients during DS-MR
A total of 18 patients completed the full stress protocol with complete ventricular and flow data collated. There were no documented serious side effects of dobutamine. Minor side effects included headache, nausea and awareness of tachycardia.

Table 10: DS-MR Study Population

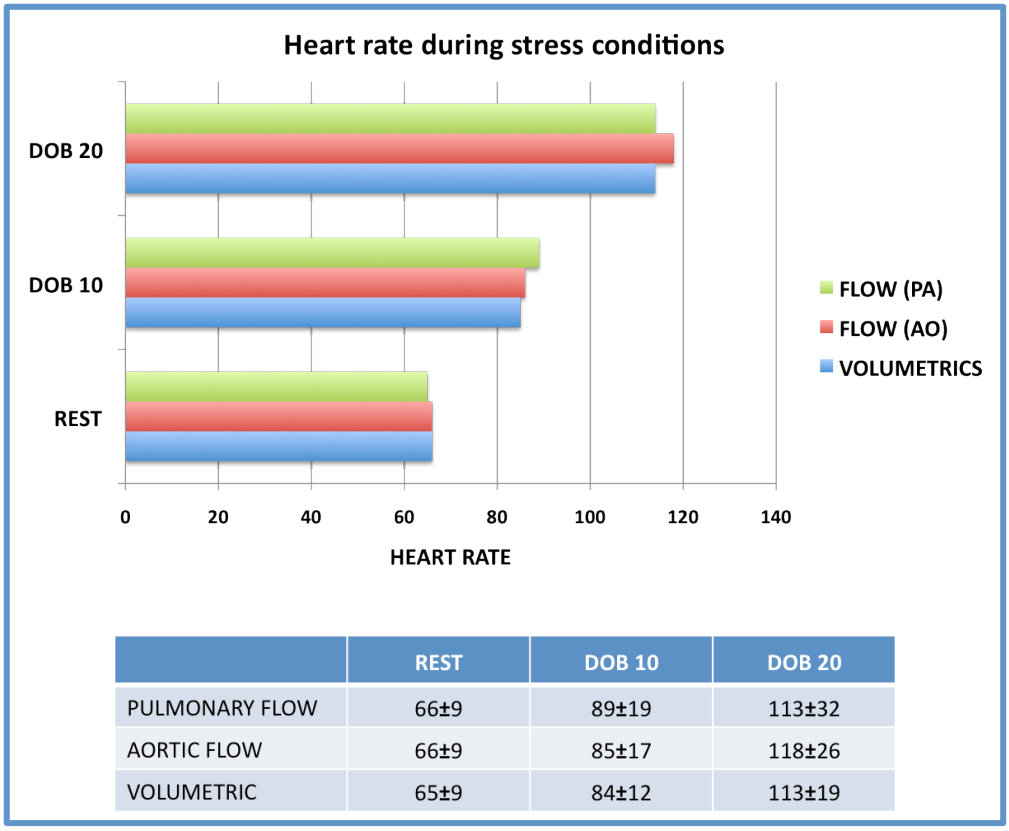
Demographics	Fallot Patients	Healthy Volunteers
Study population	n=18	n=10
Gender	Male=10 (56%)	Male=5 (50%)
Age at CMR (y)	31.9 (16.2-60.1)	40.6 (23.9-51.8)
Age at TOF repair(y)	4.6 (1.3-20.2)	
Palliations prior to TOF repair	7/18	
TOF repair type		
• Trans-annular repair	8/18	
• Non-transannular repair	3/28	
• Unknown	7/18	
NYHA classification	1.8 ± 0.6	
QRS duration (ms)	151 ± 7.7	
Baseline RV-EDV (ml/m^2)	126.4±27.2	76.6±14.3
Baseline RV-ESV(ml/m^2)	57.2±18.8	32.1±8.6
Baseline RV-EF (%)	55±7	59±4
Baseline LV-EDV (ml/m^2)	73.0±12.4	76.9±12.5
Baseline LV-ESV (ml/m^2)	31.1±8.2	33.4±7.5
Baseline LV-EF (%)	58±6	57±4
Pulmonary Regurgitant Fraction (%)	43±15	

4.2.2 Haemodynamic effects of dobutamine stress

There was a significant and sustained increase in heart rate for both the control and the TOF patients during dobutamine stress ($p<0.05$) and these results are explained in chapter 6. It is also important to ensure that heart rate changes are similar during flow and volume measurements as if vastly different this could lead to considerable error when comparing analogous volumetric and flow parameters. The PC-flow sequence used was free breathing and was performed prior to the volumetric SSFP multi-slice stack being completed for both patients and volunteers. Comparative heart rates in the Fallot group for each level of stress and sequence used are shown in Figure 15. This shows that there was little variability in heart rate during flow assessment in contrast to volume assessment and therefore it felt that this is unlikely to have caused bias in the comparison between volumetric and flow derived hemodynamic parameters.

4.2.3 Quantitative Analysis – Flow Measurements

Although the focus of this chapter is the comparison of volumetric and flow parameters it is important to understand some of the changes observed in flow measurements especially in the TOF patients during DS-MR. The following section will focus on the general flow findings in volunteers and TOF patients and this will be followed by the comparison between flow measurements and volumetrically derived analogous parameters.



	REST	DOB 10	DOB 20
PULMONARY FLOW	66±9	89±19	113±32
AORTIC FLOW	66±9	85±17	118±26
VOLUMETRIC	65±9	84±12	113±19

Figure 15: Heart Rate Changes during Stress Conditions
The above figure shows the heart rate in Fallot patients at rest and during dobutamine stress imaging. The coloured bars represent the different type of assessment made, either flow or volumetric and the associated heart rate during that assessment.

Table 11: Flow Parameters for Fallot Patients during DS-MR

Parameter (ml/beat/m²)	Stage of DS-MR			Significance (Paired t test) p value		
	Rest	10	20	Rest-10	Rest-20	10-20
AO-FF	39.5±5.5	44.1±8.7	38.2±8.1	<0.05	0.3	<0.05
PA-SV (eff FF)	39.0±9.8	42.3±7.4	35.6±10.3	0.2	0.3	<0.05
PA-FF (total)	69.7±15.1	74.7±17.3	62.2±16.5	0.05	<0.05	<0.05
PA-BF	30.7±14.2	32.3±16.3	26.6±13.5	0.31	<0.05	<0.05
PA-RF (%)	42.6±14.6	41.1±14.6	41.4±15.5	0.43	0.53	0.83
PA-CI (l/min/m²)	2.6±0.7	3.6±0.7	4.1±1.1	<0.05	<0.05	<0.05

Ao-FF: Aortic forward flow, PA-SV: pulmonary artery stroke volume or effective forward flow, PA-FF: total pulmonary forward flow, PA-BF: pulmonary back flow, PA-RF: pulmonary regurgitant fraction, PA-CI: pulmonary cardiac index

Table 12: Flow Parameters for Normal Volunteers during DS-MR

Parameter (ml/beat/m²)	Stage of DS-MR			Significance (Paired t test) p value		
	Rest	10	20	Rest-10	Rest-20	10-20
AO-FF	43.7±6.3	55.0±9.5	49.8±8.3	<0.05	<0.05	<0.05
PA-FF	43.4±6.1	54.6±11.4	48.9±9.2	<0.05	<0.05	<0.05

Ao-FF: Aortic forward flow, PA-FF: total pulmonary forward flow

Flow Parameters

Flow measurements were obtained as described in Chapter 2. Tables 11 and 12 shows flow measurements for aortic and main pulmonary artery flow at rest and during DS-MR in Fallot patients (the statistical analysis performed on this data comprised of a series of multiple t-tests; in retrospect it would have been more accurate to analyse the data using ANOVA for repeated measures with Bonferroni post hoc testing and this is considered as a limitation of the data presented).

For all flow parameters from rest to stage 1 of the DS-MR protocol there is a small increase in arterial forward flow. This is a statistically significant increase in the normal group and for the aortic forward flow in the TOF group. Following this there generally appears to be a reduction in stroke volumes at higher levels of DS-MR and this probably reflects the shorter cardiac cycle due to rapid heart rates at DS-MR stage 2. Overall as can be seen in the TOF group despite the reduction in pulmonary artery total forward flow there is a significant increase in derived pulmonary artery cardiac index as a result in the increase in heart

rate. Interestingly pulmonary artery backward flow initially increases in line with the other flow measurements but then decreases again at higher levels of DS-MR. Despite this there is no change in the calculated pulmonary artery regurgitant fraction and this highlights how this measure of pulmonary regurgitation may be limited, as it does not give a true reflection of volumetric change through the pulmonary valve.

4.3 Accuracy Of Flow Versus Volumetric Derived Parameters

A variety of studies have looked at the correlation of flow derived stroke volumes with volumetric derived parameters with good agreement between the different methods. This has results in flow and volume measurements being interchangeable and complimentary especially when evaluating patients with complex structural heart disease with shunts and regurgitant valves. Little is known about whether this accuracy is maintained during dobutamine stress. Whilst evaluating the volumes and flow it became clear that for the TOF patients at higher levels of stress there were inconsistencies in the comparative flow and volumetric stroke volumes. This is further explored in the next section.

Flow vs. Volumes

Aortic forward flow (antegrade systemic stroke volume) and pulmonary artery forward flow (antegrade pulmonary stroke volume) measured by PC-flow and derived from volumetric measurements were compared at rest and during DS-MR All TOF patients had a degree of pulmonary regurgitation. There was no evidence of pulmonary, aortic or atrio-ventricular (AV) valve regurgitation in any of the volunteers.

The Bland-Altman analysis and Pearson correlation coefficient were used for comparison of volumetric versus PC-flow-derived analogous cardiovascular functional parameters, as shown in Table 12 and 13 and Figures 16 and 17.

4.3.1 Systemic Antegrade Output

Volumetric LVSV vs. PC-Flow AO-FF

Volunteers

At rest there is good agreement for stroke volumes measured by flow and volumes for the systemic circulations. The correlation between flow and volume derived antegrade output continues to be good throughout stress with good limits of agreement and Pearson's correlation of 0.94, 0.78 and 0.93 for rest, dobutamine 10 and dobutamine 20 respectively. This is confirmed in the Bland Altman plots (Figure 16).

TOF Patients

Within the TOF group, two patients were excluded from this analysis as aliasing was found in the flow analysis of the aorta. Aliasing occurred in a number of patients and this is due the velocity PC-flow sequence being set lower than the peak velocity achieved during stress. In the remaining 16 patients an excellent agreement was found at rest (mean ± limits of agreement, -0.8 ±5.7 ml/beat/m^2). During stress imaging, however, the agreement deteriorated at Dobutamine-10 (-3.1±17.9 ml/beat/m^2) and even further at Dobutamine-20 (5.2±30.6 ml/beat/m^2) as shown in Table 13 and Figure 17. The correlation between volumetric and PC-flow was excellent at rest (Pearson=0.88) but deteriorated progressively at dobutamine-10 (Pearson=0.41) and dobutamine-20 (Pearson=0.32).

4.3.2 Pulmonary Antegrade Output

Volumetric RVSV vs. PC-Flow PA-FF

Volunteers

In this group there was good correlation between volumetric and flow derived parameters at rest and during stress. There is little scatter in the Bland Altman analysis and Pearson correlation was above 0.90 for all 3 stages of the DS-MR protocol.

TOF Patients:

For this parameter of total RV output per heartbeat, there was excellent agreement at rest (mean ± limits of agreement, -0.1 ± 7.6 ml/beat/m^2) although still not as good as the agreement of LVSV and AO-FF (see Figure 17). During stress imaging however, the agreement and correlation was again reduced with large scatter during Dobutamine-10, but this did not further deteriorate at dobutamine-20 (see Table 13 and Figure 17). The correlation was excellent at rest (Pearson=0.96) and kept moderately strong even during Dobutamine-10 (Pearson=0.75) and Dobutamine-20 (Pearson=0.83)

4.3.3 Pulmonary Regurgitant Volume

Volumetric RVSV-LVSV vs. PC-Flow PA-BF

Three patients had mild aortic regurgitation (>10%) and were excluded from this particular analysis for consistency. A reasonably good agreement was found at rest (mean ± limits of agreement, -3.6 ± 15.1 ml/beat/m^2). During stress imaging, the agreement deteriorated at Dobutamine-10 (-1.7 ± 23.9 ml/beat/m^2) and remained on this level at Dobutamine-20 (5.4 ± 24 ml/beat/m^2) as shown in Table 13 and Figure 18. The correlation was excellent at rest (Pearson=0.85) and

kept moderately strong even during Dobutamine-10 (Pearson=0.81) and Dobutamine-20 (Pearson=0.78).

4.3.4 Pulmonary Regurgitant Fraction

Volumetric RVSV-LVSV/ RVSV vs. PC-Flow PA-BF /PA-FF

Three patients had mild aortic regurgitation (>10%, see above) and were excluded also in this particular comparative analysis for consistency. As shown in the Bland-Altman plots (Figure 18), there was only limited agreement at rest with some bias and wide scatter (-5.6 ± 22.8%), resulting in an increased bias and wider limits of agreement compared to the pulmonary regurgitant volume (see above). The agreement did not further deteriorate during Dobutamine-10 (-3.8 ± 19.2%) and Dobutamine-20 (3.2 ± 21.8%, see also Table 13). The correlation was strong during rest, dobutamine-10 and dobutamine-20 (Pearson=0.88, 0.84 and 0.84 respectively).

Table 13: Mean and Limits of Agreement in Normal Volunteers for Flow vs. Volumetric Parameters

Bland-Altman Category	Systemic antegrade output *LVSV vs. AO-FF (ml/beat/m2)*	Pulmonary antegrade output *RVSV vs. PA-FF (ml/beat/m2)*
REST		
• Mean difference	**-0.30**	**0.97**
• Upper limit of agreement	4.19	3.73
• Lower limit of agreement	-4.78	-1.79
DOBUTAMINE-10		
• Mean difference	**-2.14**	**-0.48**
• Upper limit of agreement	11.23	7.18
• Lower limit of agreement	-15.51	-8.14
DOBUTAMINE-20		
• Mean difference	**-0.53**	**1.35**
• Upper limit of agreement	5.60	5.65
• Lower limit of agreement	-6.66	-8.35

Table 14: Mean and Limits of Agreement in Fallot Patients for Flow vs. Volumetric Parameters

Bland-Altman Category	**Systemic antegrade output** *Volumetric (LVSV) vs. PC-Flow (AO-FF)* (ml/beat/m^2)	**Pulmonary antegrade output** *Volumetric (RVSV) vs. PC-Flow (PA-FF)* (ml/beat/m^2)	**Pulmonary regurgitant volume** *Volumetric (RVSV-LVSV) vs. PC-Flow (PA-BF)* (ml/beat/m^2)	**Pulmonary regurgitant fraction** *Volumetric (RVSV-LVSV / RVSV) vs. PC-Flow (PA-BF / PA-FF)* (%)
REST				
• Mean difference	**-0.8**	**-0.1**	**-3.6**	**-5.6**
• Upper limit of agreement	4.9	7.5	11.5	17.2
• Lower limit of agreement	-6.4	-7.2	-18.7	-28.3
• *Upper confidence interval*	*2.4 to 7.4*	*4.2 to 10.7*	*4.1 to 19*	*5.9 to 28.3*
• *Lower confidence interval*	*-8.9 to -3.9*	*-10.4 to -3.9*	*-26.1 to -11.2*	*-39.5 to -17*
DOBUTAMINE-10				
• Mean difference	**-3.1**	**2.4**	**-1.7**	**-3.8**
• Upper limit of agreement	14.8	26.3	22.3	15.5
• Lower limit of agreement	-20.9	-21.4	-25.6	-23
• *Upper confidence interval*	*6.3 to 23.2*	*15.7 to 36.8*	*10.4 to 34.1*	*5.95 to 25*
• *Lower confidence interval*	*-29.4 to -12.4*	*-31.9 to -10.8*	*-37.4 to -13.8*	*-32.5 to -13.5*
DOBUTAMINE-20				
• Mean difference	**5.2**	**6.8**	**5.4**	**3.2**
• Upper limit of agreement	35.8	28.3	29.4	25
• Lower limit of agreement	-25.5	-14.7	-18.6	-18.3
• *Upper confidence interval*	*21.2 to 50.3*	*18.7 to 37.8*	*17.6 to 41.3*	*14.2 to 35.8*
• *Lower confidence interval*	*-40 to -11*	*-24.2 to -5.2*	*-30.5 to -6.7*	*-29.5 to -7.9*

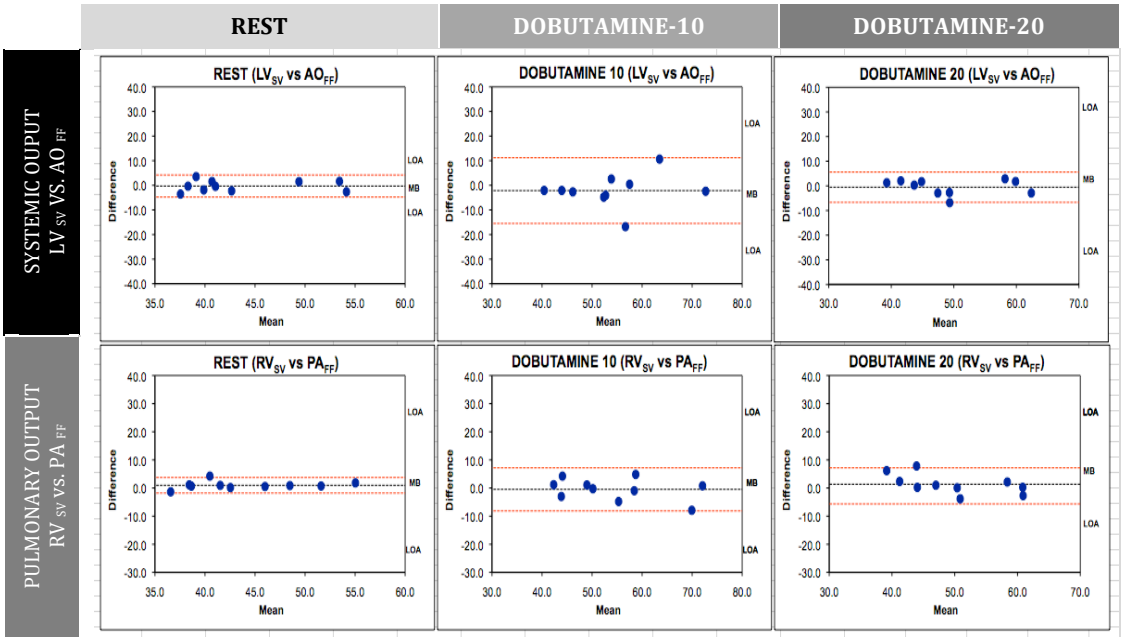


Figure 16: Systemic and Antegrade Flow Agreement between PC-Flow and Volumetric parameters in normal volunteers

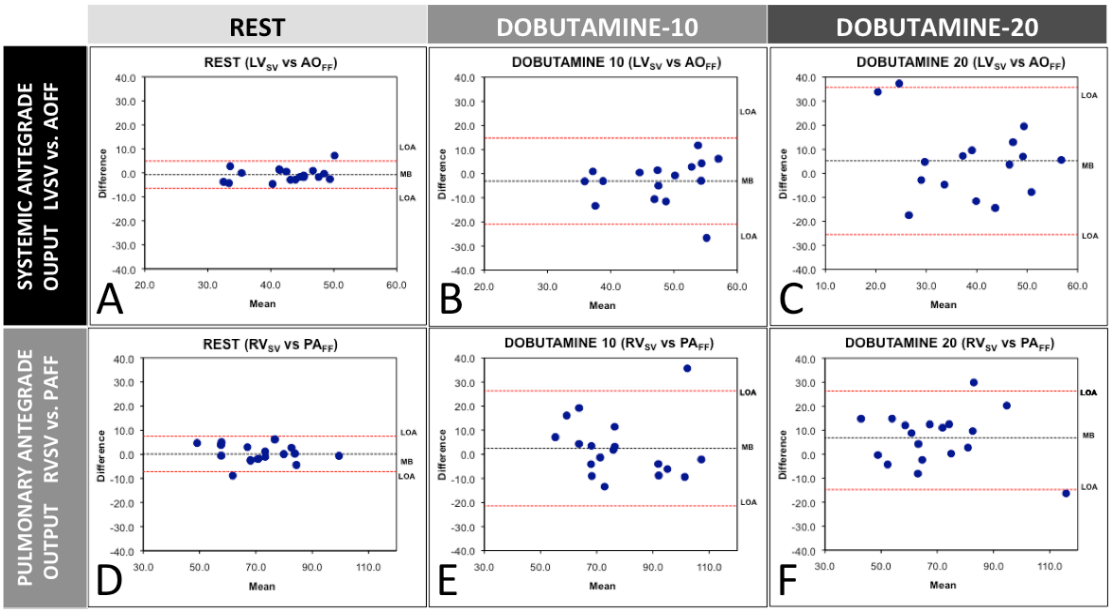


Figure 17: Systemic And Antegrade Flow Agreement Between PC-Flow And Volumetric Parameters In Fallot Patients

Bland-Altman plots of the mean bias (MB) and 95% confidence limits of agreement (LOA) between the volumetric vs. PC-flow assessment of the systemic antegrade output (A,B,C) and the pulmonary antegrade output (D,E,F) at the three different stages: rest (A, D), dobutamine-10 (B, E) and dobutamine-20 (C, F). Values are expressed as ml/beat/m^2.

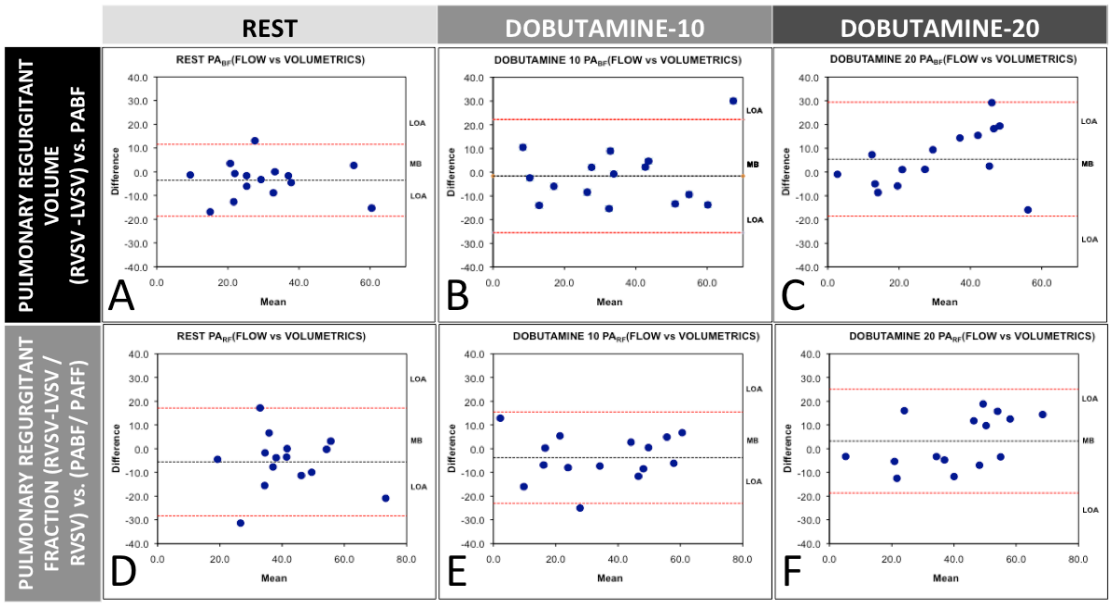


Figure 18: Pulmonary regurgitant volume and regurgitant fraction agreement between volumetric and PC-flow parameters
Bland-Altman plots of the mean bias (MB) and 95% confidence limits of agreement (LOA) between the volumetric vs. PC-flow assessment of the pulmonary regurgitant volume (A,B,C) and the pulmonary regurgitant fraction (D,E,F) at the three different stages: rest (A, D), dobutamine-10 (B, E) and dobutamine-20 (C, F). Values are expressed as ml/beat/m^2 for the pulmonary regurgitant volume and as percentage [%] for the pulmonary regurgitant fraction.

4.4 Summary

The results documented above clearly show that ventricular stroke volume at rest correlated extremely well with analogous PC-flow measurements. This is true even in the TOF patients who have a significant degree of regurgitation and is in line with previously published data. Of concern is how this agreement significantly deteriorated during stress in the TOF group although it appears to be maintained in the volunteers with normal cardiac anatomy. There are a number of factors, which are likely to influence the differences observed especially in the TOF group. All of the TOF patients had pulmonary regurgitation and are therefore more susceptible to abnormalities in flow dynamics and

conceivably this will be more pronounced at higher heart rates. Additionally image quality and accuracy of analysis needs to be considered specifically for the volumetric assessment. This will be explored further in the next chapter.

CHAPTER 5: ACCURACY OF CMR VOLUMETRIC ASSESSMENT

5.1 Overview

The previous chapters have shown the importance of volumetric and flow assessment during a CMR study [70, 73, 95, 96]. Conventionally volumes are measured using the short axis orientation, as this is optimal for the ellipsoid shape of the left ventricle. In patients with congenital heart disease, pathology often involves the right ventricle which in conditions such as surgically repaired TOF can become significantly dilated due to chronic volume loading from severe pulmonary regurgitation (PR). In these patients the ability to accurately measure ventricular size and function is essential for clinical decision making [21, 24, 108, 109]. Short axis assessment of volumes in these patients has been validated and used routinely in clinical practice. However it has been shown that assessment of volumes in TOF patients using axial slices is superior in terms of accuracy and observer variance [79]. This axial orientation allows better appreciation of the right-sided valve planes and right ventricular outflow tract dilatation. Although the assessment of RV volumes may contribute to the assessment of TOF patients with severe PR they do not fully predict which patients require PVR most urgently and or which patients with have the greatest improvement in RV function post PVR [21]. Volumetric assessment under stress testing conditions using agents such as dobutamine may provide new parameters of early right ventricular dysfunction [48, 65, 110, 111]. Short axis volumetric assessment during low dose dobutamine stress MR in a variety of congenital patients has been shown to be accurate and reproducible [61]. There are no data on the utility of axial volume

assessment during DS-MR imaging in volunteers or TOF patients. This chapter assesses the accuracy and reproducibility of axial and short axis volume assessment during dobutamine stress MR in the TOF patients and healthy volunteers. If significant changes in volumetric response are seen in either patients or volunteers it is essential to know whether these measurements are accurate and reproducible so that the information gained from stress imaging in patients can be used to guide clinical decision-making.

We also hypothesized that strict intra-institutional image reading training would yield acceptable observer agreement [94] underscoring the potential diagnostic value of higher dose DSMR in the early detection of right ventricular failure in this group of patients.

5.2 Accuracy of Volumetric Assessment

Left and right ventricular volumes were measured at rest and during stress MR for the TOF patients and normal healthy volunteers using the imaging parameters and exclusion criteria described in Chapters 2 and 4. The following description of quantitative and qualitative analysis will focus on the 18 TOF patients and 10 healthy volunteers who completed both levels of DS-MR, i.e. 10 and 20μg/kg/min of dobutamine (Chapter 4, Table 10). The detailed hemodynamic and volumetric response to dobutamine will be further described in Chapter 6.

5.2.1 Volumetric Quantitative Analysis

Volumetric analysis was performed as described in the methods of Chapter 2. For inter-observer analysis two independent experienced observers performed volumetric analysis on the TOF patients and the volunteers. For intra-observer analysis data was re-analyzed by a single observer 6 months after the initial assessment was performed.

Accuracy of volumetric assessment for both ventricles was analyzed by comparing the mean difference between the two observers together with the range of difference for each volumetric parameter. Further analysis by coefficient of variance (COV) showed there is good inter and intra-observer agreement for all parameters at rest observations with coefficient of variance <10% in both the volunteers and TOF patients (Figure 19&20, Table 15&16). With increasing concentration of dobutamine there continued to be good inter-observer agreement for end-diastolic volumes with a coefficient of variance for the LV-EDV in TOF patients of 1.6% and 4.6% (10, 20 respectively) and for RV-

EDV 4.2% and 3.7% (10, 20 respectively). However there was notably higher inter-observer variability for LV-ESV at stage 2 DS-MR. This is most significant for the LV-ESV in the TOF patients with a COV of 14.9% compared to 8.6% for RV-ESV for the same dobutamine stage (Figure 19, Table 15).

Intra-observer variability showed coefficient of variance levels below 10% for all ventricular parameters suggesting good reproducibility (Figure 20, Table 16).

Table 15:Inter-observer variability for ventricular parameters.

Parameter	Group	Coefficient of Variance (%)			Mean Difference [Range difference min; max]		
		Rest	10	20	Rest	10	20
LV-EDV	Fallot	3.5	1.6	4.6	0.99 [-6.5; 11.3]	1.39 [-8.9; 21.6]	-1.67 [-10.5;6.3]
	Normal	4.0	3.5	4.9	1.9 [-11.9;9.7]	-1.9 [-11.0;3.2]	1.3 [-10.1;9.6]
LV-ESV	Fallot	2.7	10.4	14.9	1.48 [-13.5;14.4]	0.66 [-6.9;7.8]	1.24 [-7.2;12.2]
	Normal	8.8	9.2	10.5	4.5 [-6.4;12.7]	4.5 [-2.9;9.5]	2.4 [-2.9;7.5]
RV-EDV	Fallot	2.9	4.2	3.7	-0.92 [-12.1;10.5]	1.01 [-18.7;15.4]	-2.97 [-18.6; 9.3]
	Normal	2.3	4.5	4.0	2.3 [-2.4:8.8]	-2.5 [-10.4:7.5]	0.6 [-7.1;6.7]
RV-ESV	Fallot	5.0	7.3	8.6	2.33 [- 6.2;9.8]	3.67 [-4.9;16.5]	2.9 [-9.9;15.5]
	Normal	7.8	8.5	9.1	3.5 [-4.0;10.4]	0.05 [-5.4;3.7]	-0.3 [-3.8;3.6]

Table 15: Agreement between the two observers for left and right ventricular volumes. Fallot patients: axial volume. Normal volunteers: short axis volume. Agreement was determined by coefficient of variance with levels of <10 considered to show good agreement.

Table 16: Intra-observer variability

Parameter	Group	Coefficient of Variance (%)			Mean Difference [Range difference min; max]		
		DS-MR Stage			DS-MR Stage		
		Rest	10	20	Rest	10	20
LV-EDV	Fallot	2.7	1.7	1.8	-0.1 [-6.8 ; 6.5]	0.2 [-3.4 ; 3]	0.7 [-2.2 ; 4.1]
	Normal	4.4	4.7	5.0	-1.7 [-5.6;4.3]	-1.3 [-7.0;4.2]	-2.1 [-6.8;2.8]
LV-ESV	Fallot	5.8	6.2	6.4	-0.5 [- 7.0 ; 5.5]	-0.6 [-5.3 ; 2.6]	-0.6 [-3.6 ; 2.36]
	Normal	4.9	6.3	6.8	0.5 [-2.0;2.6]	-0.2 [-1.7;1.7]	-0.9 [-2.4;0.9]
RV-EDV	Fallot	1.7	2.4	2.1	0.1 [-5.8 ; 8.1]	0.2 [-3.9 ; 14.78]	2.1 [-6.78 ; 11.8]
	Normal	2.8	2.6	4.7	-0.7 [3.1;3.7]	-0.3 [-3.3;2.6]	-0.4 [-5.0;4.9]
RV-ESV	Fallot	1.7	2.3	3.8	-0.3 [- 3.1 ; 2.7]	0.4 [-4.6; 3.5]	-0.01 [-4.6 ; 6.7]
	Normal	4.4	6.5	6.9	-0.4 [-1.8;2.2]	-0.2 [-1.3;2.2]	-0.4 [-1.7;1.0]

Agreement between left and right ventricular parameters measured by a single observer 6 months apart. Fallot patients: axial volume. Normal volunteers: short axis volume. Agreement was determined by coefficient of variance with levels of <10 considered to show good agreement.

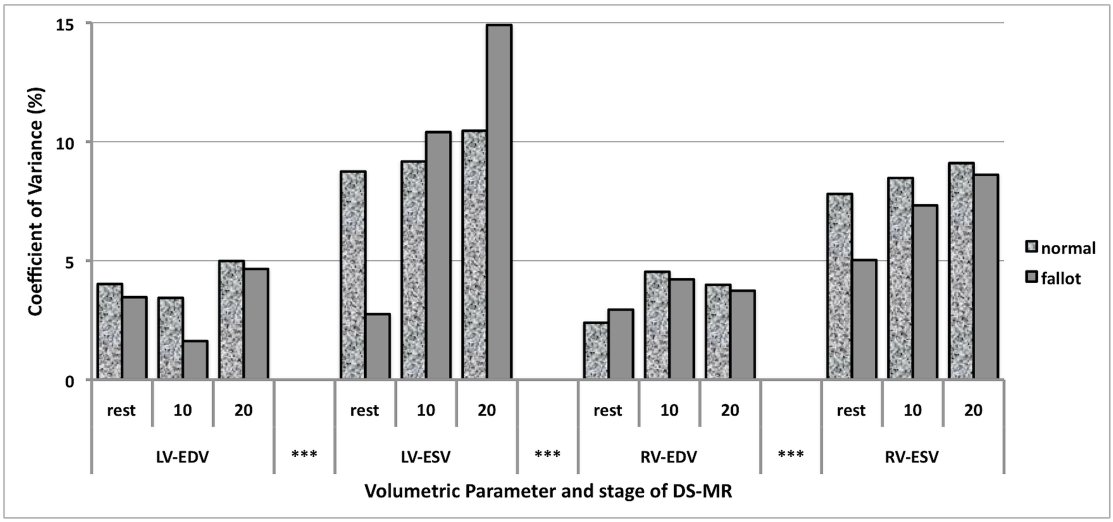


Figure 19: Inter-observer variability
Coefficient of variance calculated for right and left ventricular volumes at each level of dobutamine stress. Good agreement between observers was seen for all parameters except LV-ESV in the TOF patients at dobutamine 20ug/kg/min.

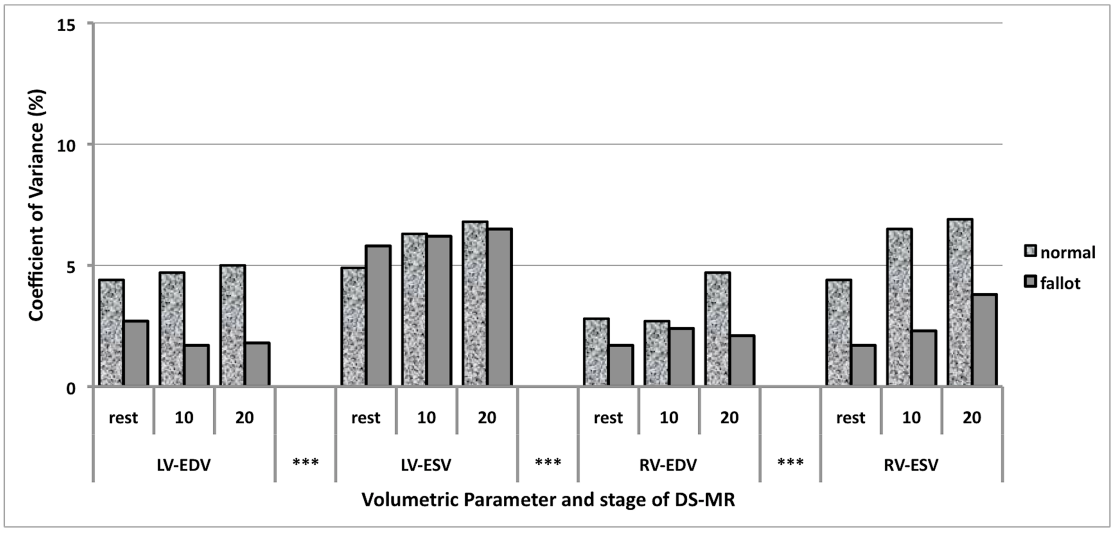


Figure 20: Intra-observer variability
Coefficient of variance results for intra-observer variance of ventricular volumes at each level of dobutamine stress. Good agreement (single observer) was seen for all parameters in TOF patients and volunteers.

5.2.2 Image Quality Assessment

Image quality scores were assessed as described in Chapter 2. In TOF patients and healthy volunteers image quality scores at baseline were excellent with mean score greater than 3 for both ventricles. There was a trend towards a small reduction in image quality with each stage of DS-MR and LV image quality scores in the TOF patients were slightly lower than the analogous RV scores, but these changes in image score did not reach statistical significance.

Volunteer Group: The mean score based on the visibility of the endocardial borders decreased [85] marginally with increase in DS-MR stage. In both ventricles scores at baseline were excellent with a mean quality score of 3.62 for the LV and 3.57 for the RV. There was a small reduction in image quality with each stage of DS-MR and scores of 3.23 and 3.15 for the LV and RV respectively by stage 2 dobutamine (Figure 21). These changes in image score were not statistically significant.

Fallot patient group: In this group there was also a decrease in image quality with escalation of the dobutamine protocol. At rest the mean image quality score for the RV was 3.56 and this reduced to 3.17 at stage 1 dobutamine and 3.11 at stage 2 dobutamine (Figure 21). The LV scores were slightly lower compared with the analogous RV scores. At dobutamine stage 2 for the LV the mean image quality score was 2.71 compared to 3.0 at rest. However, these changes in the image quality during DS-MR did not reach statistical significance using the Friedman's test, neither for the RV ($p=0.23$) nor the LV ($p=0.53$).

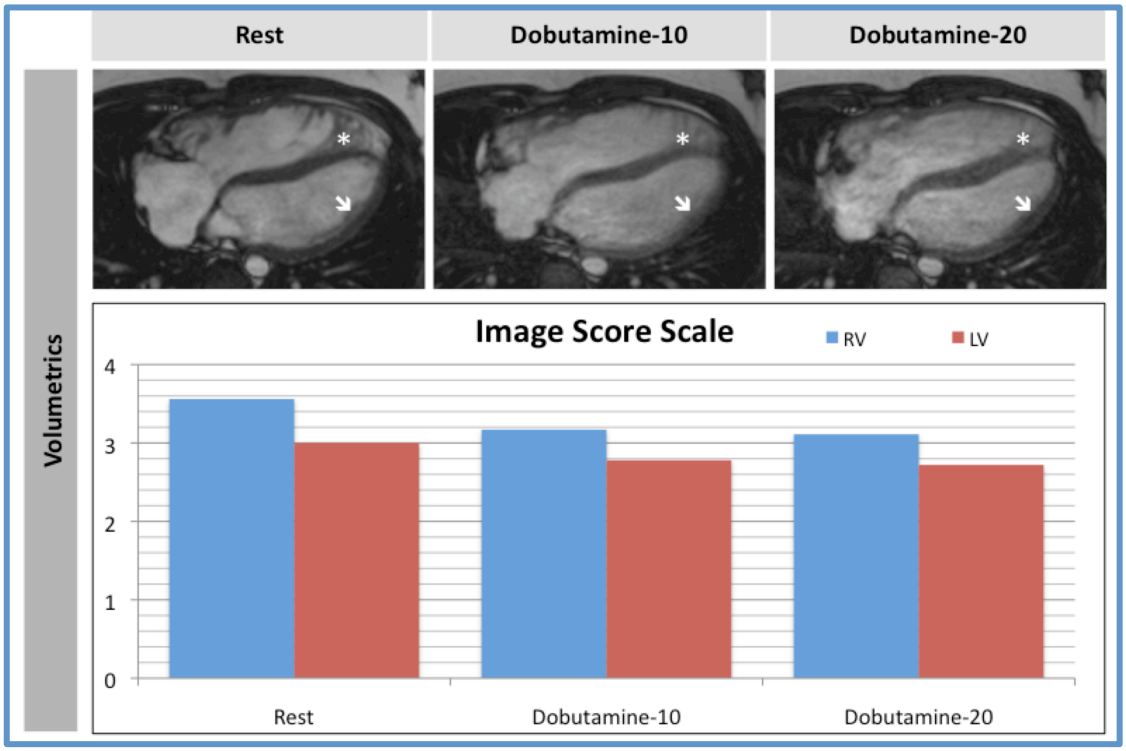


Figure 21: Image Quality Assessment
Volumetric image quality assessment for TOF patients. Mid-ventricular axial slices at rest, dobutamine-10 and dobutamine-20. The 2D-SSFP images were scored on a four-point scale based on the visibility of the endocardial borders for the right (*) and left (arrow) ventricles. Progressive (albeit not statistically significant) decrease of the image quality score (= extent of blurring of the endocardial borders) for the RV (blue bar) and LV (red bar), from rest to dobutamine-20.

5.3 Summary

This chapter has presented the assessment of accuracy of volumetric analysis in patients with corrected TOF and healthy volunteers both in the conventional short axis geometry and also axial geometry the preferred method for quantification of the right ventricle. Even at high doses of dobutamine, image quality is maintained and volumes can be quantified with fairly good inter-observer agreement and very good intra-observer agreement. However it is clear that at higher doses of DS-MR LV-ESV is susceptible to error. There are two potential causes for this poor agreement. Firstly the ventricular end-systolic size

is much smaller at this higher level of DS-MR. Small discrepancies between observers in volume measurement will be amplified when calculating the COV (as seen in previous study [61]). Therefore even a small difference between observers will result in a much greater variance and suggest poor agreement. Secondly the images in TOF patients were acquired in the axial plane and although this is known to allow better visualization for the RV this is prone to error in the LV due to partial volume effect in the most apical slices of the ventricle [79]. In comparison the normal group have better agreement between observers at higher DS-MR stages with a COV of 10.5 at stage 2 DS-MR and these images were acquired using a short-axis geometry. Although volumetric assessment of the LV using transverse slices has been validated [79, 95] and is thought to be comparable to short axis imaging at rest it is likely that the potential for error is greater during DS-MR.

In the RV the ESV in both TOF patients and the normal volunteers showed good agreement suggesting good reproducibility. In the TOF group this superiority in comparison to the LV-ESV is likely to be due to the larger baseline ESV reducing the potential errors of small volumes. Additionally the axial geometry allows better visualization of the valve planes which may improve accuracy when assessing volumes as seen previously [79]. In comparison the normal group also showed good agreement between observers in RV-ESV assessment at higher stages of DS-MR suggesting that both short axis and axial assessment of the RV yield reproducible results. Overall the data show good agreement between observers for volume assessment during DS-MR. This is only possible with good

institutional training and adherence to strict reporting guidelines [94]. This should be taken into consideration when performing and analyzing DS-MR volumes.

CHAPTER 6: DOBUTAMINE STRESS MR IN TETRALOGY OF FALLOT

6.1 Overview

The previous chapters have shown the importance of volumetric and flow assessment and how these can be affected during stress imaging. In this chapter the focus is on the haemodynamic and volumetric changes seen during dobutamine stress MR, and how these may reflect underlying ventricular dysfunction.

In repaired TOF chronic severe PR is associated with progressive RV dilatation and dysfunction and an increased risk of exercise intolerance, arrhythmia, and sudden death [97]. PVR is beneficial in reducing RV size as quantified by CMR [22, 98] but may not lead to recovery when performed late, i.e. in patients with prolonged and severe ventricular dilatation and dysfunction [99, 100]. Hence, there is accumulating evidence to support PVR before clinical symptoms and ventricular dysfunction occur, but controversy remains on appropriate timing criteria [22, 101, 102]. A recent CMR study has demonstrated that even moderate reduction of right (RV-EF<45%) and left ventricular ejection fraction (LV-EF<55%) in addition to severe RV dilatation (RV-EDV z-score >7) predicted major adverse events such as death, increase in NYHA class to III or IV, or sustained ventricular tachycardia [103]. This suggests a need to focus on early markers of impaired ventricular systolic function when selecting asymptomatic TOF patients for early PVR [103, 104].

Stress imaging may provide early markers of ventricular dysfunction. To date low-dose DS-MR up to 7.5 μg/kg/min [105] has identified abnormalities of diastolic

function in TOF with chronic PR [59] but has failed to identify RV systolic dysfunction not already evident at baseline [106].

Therefore, this study tested the hypothesis that DS-MR at a higher dose level may provoke ventricular systolic dysfunction amongst a group of TOF patients with chronic severe pulmonary regurgitation, RV dilatation, and preserved baseline ventricular systolic function. We also sought to provide reference values of 'normal' ventricular response from healthy adult volunteers using our staged DS-MR protocol (baseline, 10 and 20 μg/kg/min of dobutamine) for comparison with patient data. An additional goal was to define parameters of ventricular systolic dysfunction in response to stress that might be more sensitive than ejection fraction at rest, in order to design future clinical research in larger series.

The following chapter will discuss the volumetric changes seen in TOF patients and healthy volunteers and how this may reflect underlying RV dysfunction.

6.2 Results Of Haemodynamic And Volumetric Changes During DS-MR

As previously described, of the 28 TOF patients recruited for the study only 24 completed full volumetric and flow assessment at 10μg/kg/min of dobutamine and 18 continued to complete the higher dose of dobutamine at 20μg/kg/min, stage 2 (Chapter 4, Figure 13). This chapter will describe the haemodynamic consequences of dobutamine stress. The volumetric analysis will initially review the changes observed during low dose dobutamine as 24 of the patients completed this section. The comparative data at both levels of DS-MR and the trends observed includes only the 18 patients who completed the full protocol.

6.2.1 Haemodynamic Parameters

At stage 1 DS-MR heart rate increased by 29% in the TOF patients and by 27% for the control group. Heart rate continued to increase at stage 2 DS-MR by 34% for TOF patients and 33% for controls. Mean arterial blood pressure also increased with each level of DS-MR (Stage 1 TOF patients: 10%, controls: 8%, Stage 2 TOF patients: 6%, controls: 4%). Both groups had a significant ($p<0.05$) and similar increase in heart rate and mean arterial blood pressure at each level of dobutamine, confirming the reproducibility of the dobutamine stress protocol (Fig. 22).

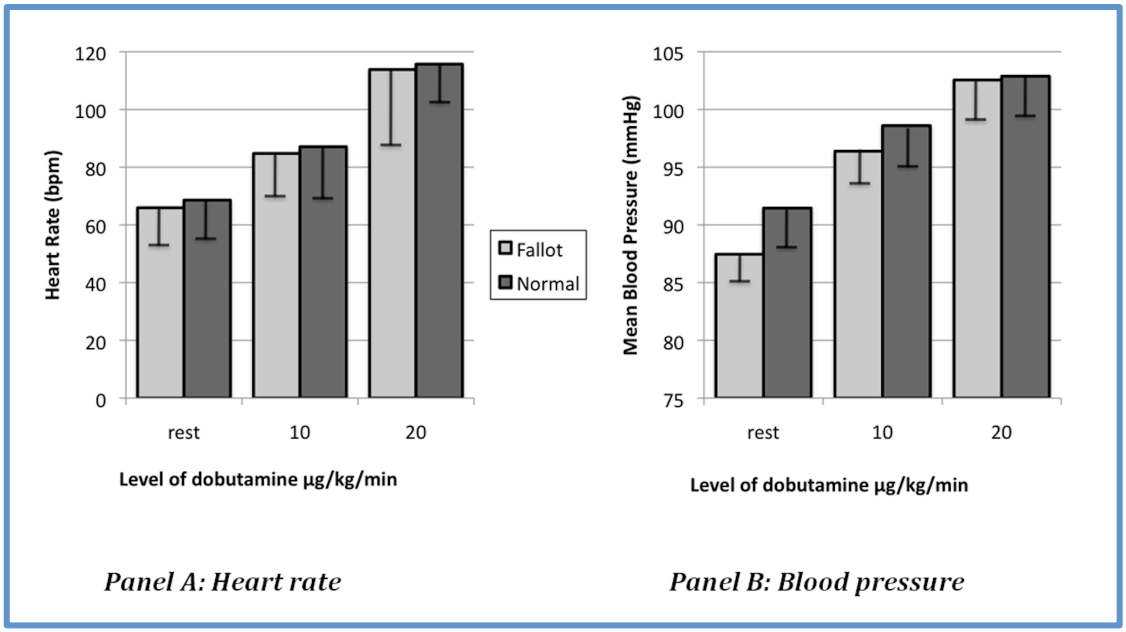


Figure 22: Haemodynamic changes during DS-MR
Change in mean heart rate and mean arterial blood pressure related to level of dobutamine, rest, 10 or 20 µg/kg/min for patients and normal healthy volunteers. Values expressed as mean with standard deviation shown. There was a statistically significant increase in heart rate and blood pressure from baseline to 10 µg/kg/min and also between 10 and 20 µg/kg/min for both TOF patients and controls (all p-values <0.05)

The LV and RV cardiac index increased significantly with each dobutamine dose in both the TOF group and normal controls. The magnitude of this increase was greater in the control group compared with the TOF group. The percentage increase in RV-CI in the control group for stage 1 and stage 2 dobutamine was 56% and 23% respectively compared with 44% and 20% for the TOF group (Table 17). The RV-CI is greater within the TOF group as this includes the additional volume from the PR hence the marked difference in CI for LV vs RV.

These haemodynamic changes observed correlate well with published data on stress imaging (echo and CMR) and confirm the physiological effects of dobutamine on the myocardium. This is important, as it is necessary to ensure effective stress conditions to enable interpretation of volumetric and flow

measurements acquired. The volumetric parameters will now be further examined.

Table 17: Cardiac Index During DS-MR

Parameter		Stage of DS-MR			% Change in CI	
		Rest	10	20	Rest-10	10-20
LV-CI (l/min/m²)	Fallot	2.8±0.5	3.9±0.8*	4.4±1.0§#	40	13
	Normal	3.0±0.6	4.8±0.8*	5.7±0.8§#	60	19
RV-CI (l/min/m²)	Fallot	4.5±0.9	6.5±1.5*	7.8±1.9§#	44	20
	Normal	3.0±0.6	4.7±0.8*	5.8±4.0§#	56	23

Table 17: Values are expressed as mean ± standard deviation for TOF patients (n=18) and normal healthy volunteers (n=10). The significance of these changes is denoted by the following: (*) change from rest to 10 dobutamine, p<0.05, (§) change from 10 to 20 dobutamine, p<0.05, (⌘) change from rest to 20, p<0.05.

6.2.2 Ventricular function

Volumetric analysis included quantification of bi-ventricular EDV, ESV, SV and derived EF as described in Chapter 2.

6.2.2.1 Dobutamine Stress MR Stage 1 – Dobutamine 10 µg/kg/min

Volunteers

Previous study has reported that during dobutamine stress imaging in healthy volunteers there is little change in ventricular EDV and a reduction in ESV at low dose dobutamine. This pattern of ventricular volumetric change was seen clearly in the volunteer group in this study.

During stage 1 DS-MR there was a reduction in ESV with no change in EDV. Hence, the increase in SV related to unchanged EDV, with significant increase in bi-ventricular EF, reflecting normal contractile reserve.

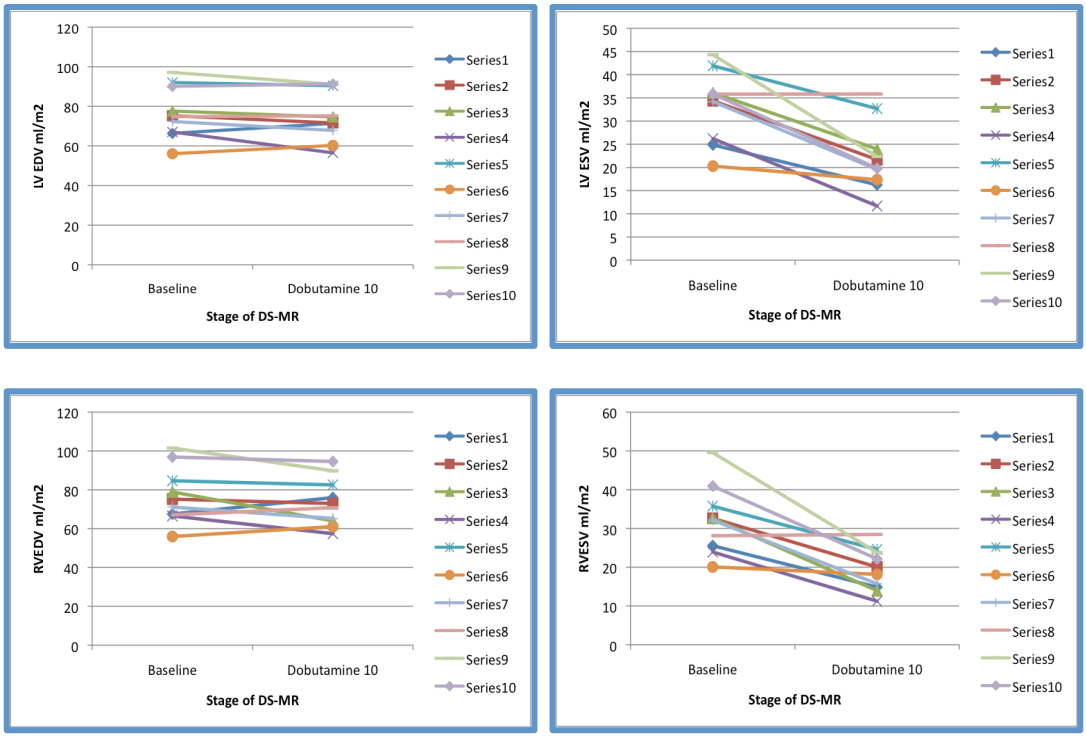


Figure 23: Normal volunteers, volumetric parameters during Stage 1 DS-MR

TOF Patients

Of the 28 TOF patients recruited, 24 completed the first stage of DS-MR; data for the volumetric changes is shown in figures 23 and 24 (mean results are displayed later in this chapter). In the majority of TOF patients the expected trend in volumetric measurements is observed. There is a decrease in end-systolic volume for the LV and RV during stage 1 of the DS-MR protocol. However there are 3 patients, whose LV parameters do not follow the typical pattern of response. In the LV-EDV response figure, patients 7,19 and 20 show an increase

in LV-EDV during stage 1 DSMR. The same patients also have no reduction in LV-ESV during the same stage. The significance of this is difficult to put into context in such a small data set but may show correlation with abnormal ventricular response at stage 2 DS-MR.

Two patients (11 and 12) show an increase in RV-EDV increase during DSMR stage 1 and a slight increase in RV-ESV. This data shows that although when averaged it appears the patient group respond to dobutamine 10μg/kg/min as expected, on an individual basis there are some patients have an abnormal response even at low dose DS-MR

Of the four patients who could not continue to stage 2 DS-MR, three had an appropriate reduction in ESV and appropriate increase in EF at stage 1. One patient had a very dilated RV at baseline and very abnormal response to dobutamine stage 1 (series 11, figure 24).

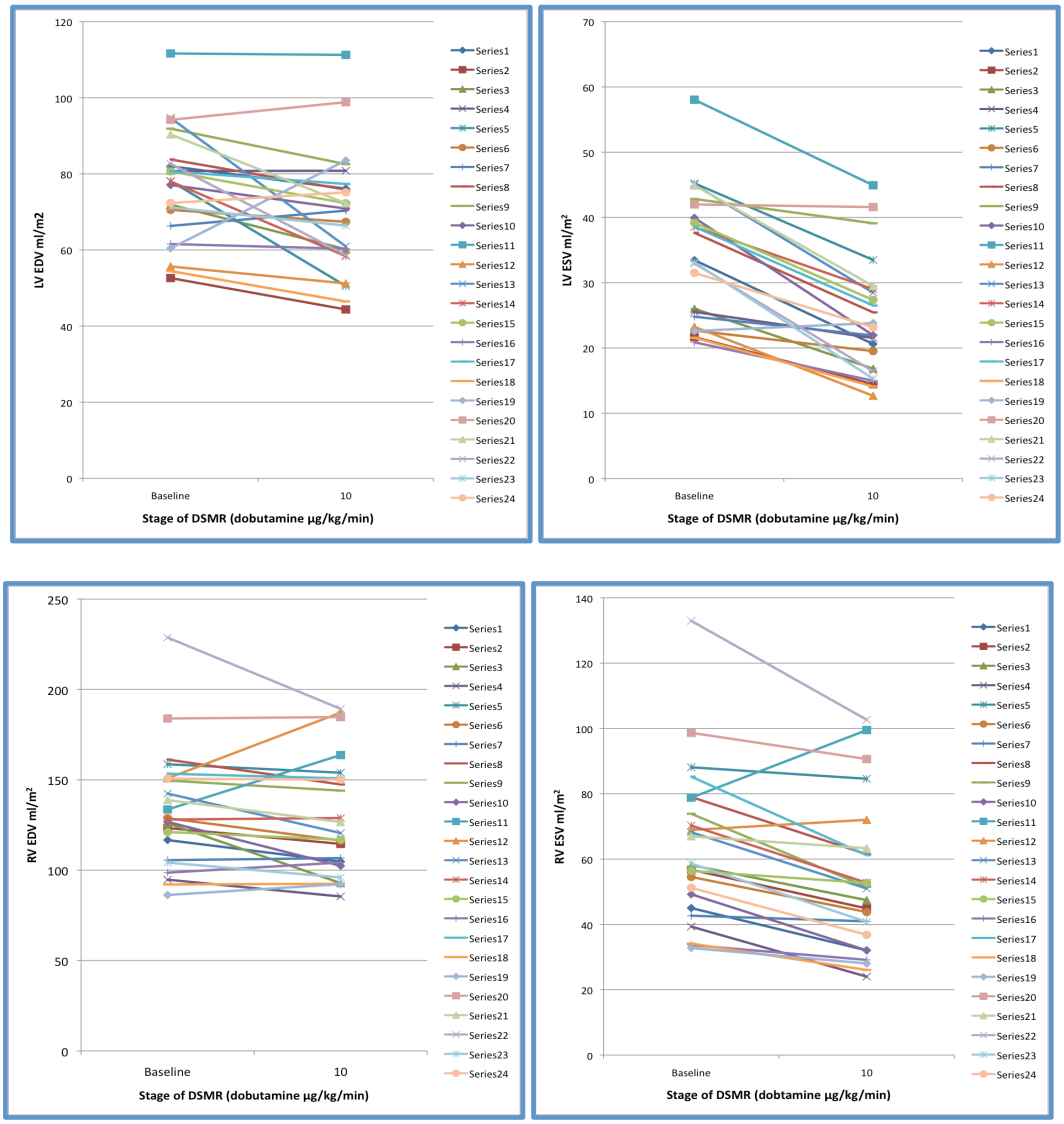


Figure 24: Fallot patients volumetric parameters during DSMR Stage 1

6.2.2.2 Dobutamine Stress MR Stage 2 – Dobutamine 20 µg/kg/min

Volunteers

During the second stage of the DS-MR protocol, dobutamine concentration was increased to 20µg/kg/min. At this level there was marked reduction in EDV and ESV for both ventricles with no significant change in SV (Figure 25 & 26). Resulting in a further significant increase in EF - normal contractile reserve.

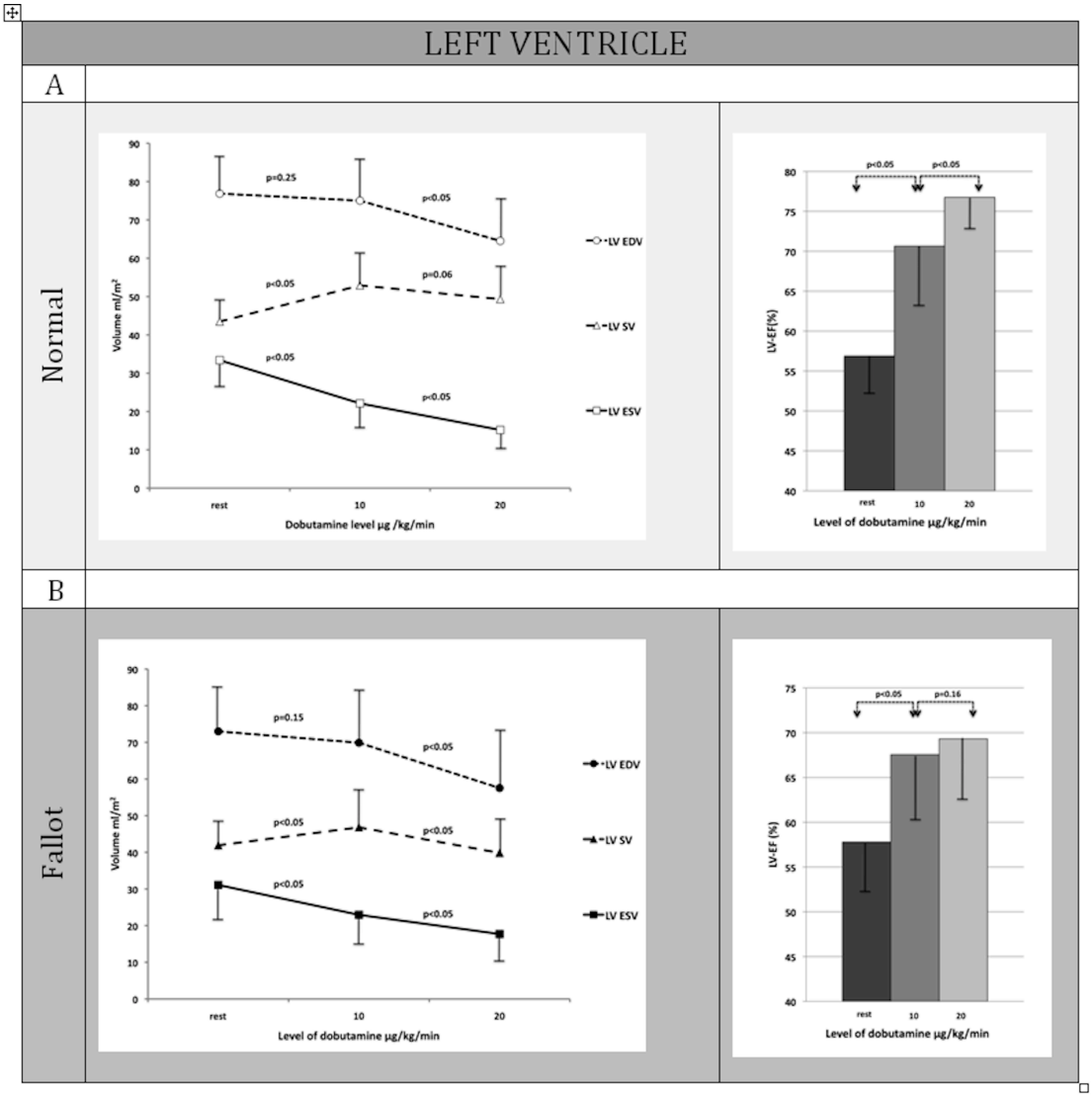


Figure 25: Volumetric changes in Left Ventricle during DS-MR
Normal volunteers (A) and Tetralogy of Fallot patients (B)
Mean ejection fraction for each ventricle is shown in the panel to the right of the volumetric data. Values expressed as mean with standard deviation.
P values denote significant difference between each level of dobutamine protocol.

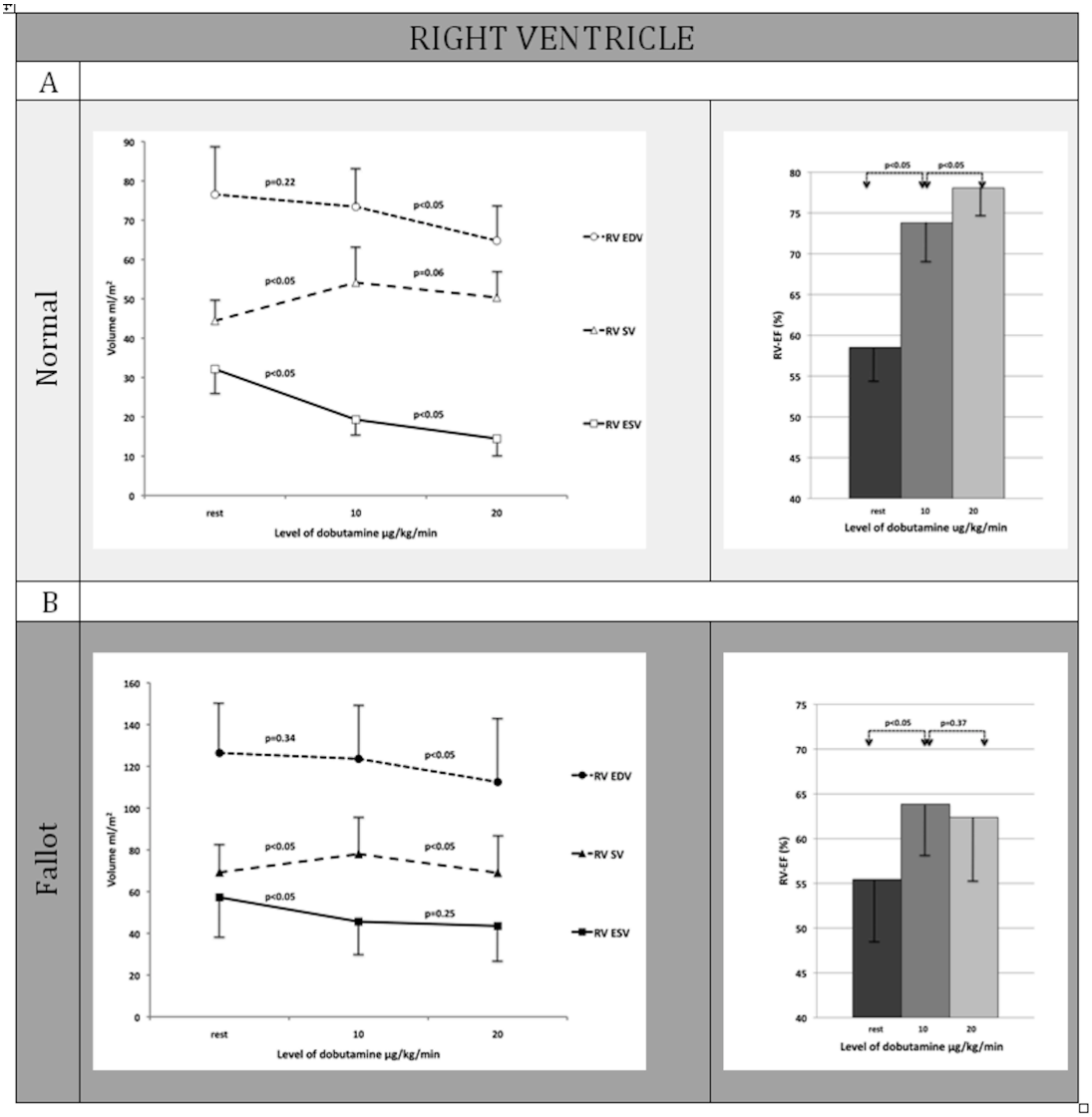


Figure 26: Volumetric changes in the Right Ventricle during DS-MR
Normal volunteers (A) and the Tetralogy of Fallot patients (B)
Mean ejection fraction for each ventricle is shown in the panel to the right of the volumetric data. Values expressed as mean with standard deviation.
P values denote significant difference between each level of the dobutamine protocol.

TOF patients

In the TOF patients for the LV (Figure 25), the same pattern of response was observed for LV-EDV and LV-ESV as described above for the volunteers, although the improvement in EF at 20μg/kg/min dobutamine failed to reach statistical significance.

There was a reduction in RV-EDV, which reached statistical significance (Figure 26, panel B). However the degree of this reduction was relatively smaller than that observed for the LV volumes (LV-EDV 18%, RV-EDV 9% at stage 2 DS-MR).

The most striking result was the change in the RV-ESV during stage 2 DS-MR. The higher dose dobutamine did not universally result in the expected decrease in RV-ESV in the TOF group, but produced two distinct types of response: A proportion of patients had a further decrease in RV-ESV (responders), whilst others had increased or unchanged RV-ESV (non-responders) (Figure 27 panel A).

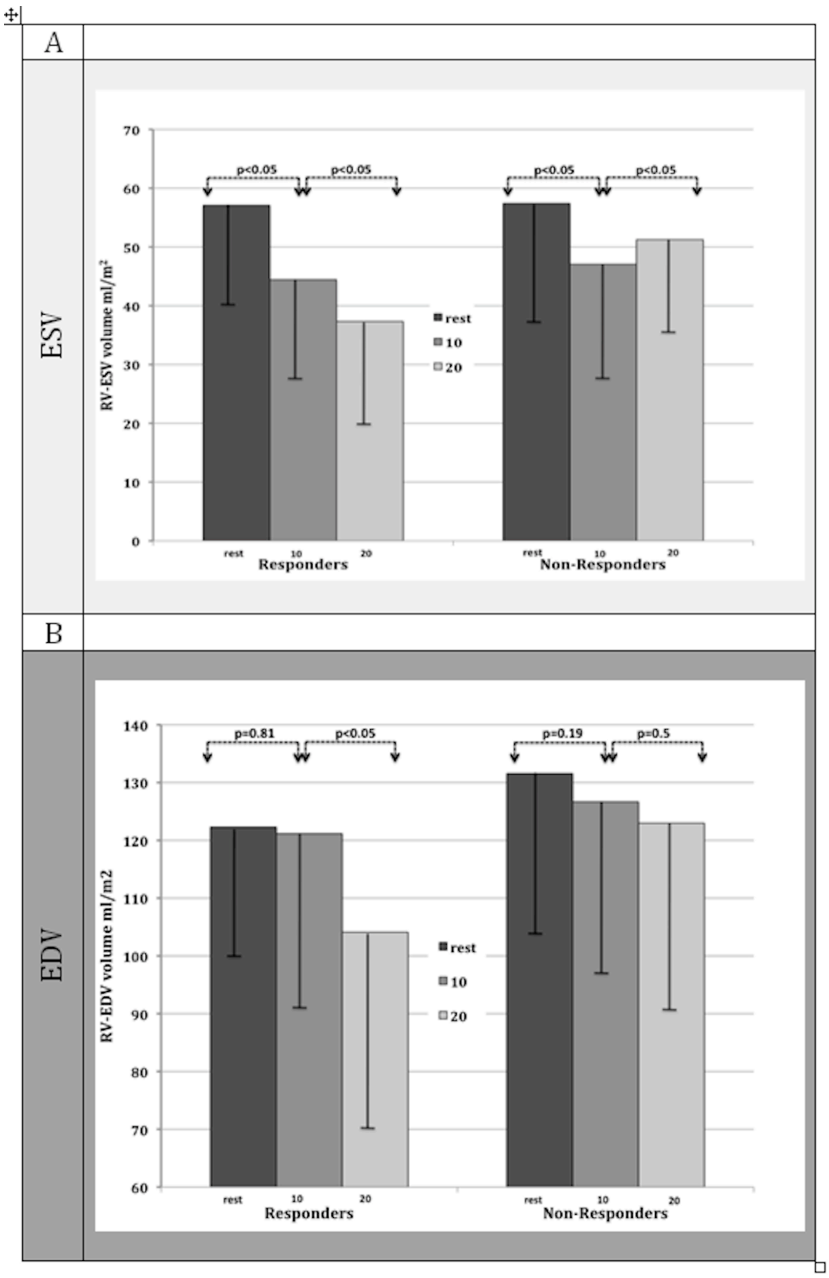


Figure 27: Sub-group analysis determined by RV-ESV response
(A) Dobutamine effect on RV-ESV, subgroups defined by response to dobutamine from 10 to 20 µg/kg/min. The responders (n=9) showed a further reduction of RV-ESV on increasing from 10 to 20, which is comparable to that seen in the control group (RV-ESV rest 32.1ml/m^2, DS-MR 10: 19.3ml/m^2, DS-MR 20: 14.5ml/m^2, p<0.05). The non-responders showed either an increase or no change in RV-ESV.
(B) Dobutamine effect on RV-EDV by subgroups defined by response in RV-ESV. The responders, showed a minimal reduction of RV-EDV from baseline to dobutamine 10 whilst there is a more significant reduction in RV-EDV from 10 to 20. In the non-responders there is also only a minimal decrease in EDV from rest to 10 and little further reduction from 10 to 20.

6.2.2.3 Responders vs. non responders

The possibility of correlating the RV-ESV response with an underlying baseline characteristic or stress parameter was further explored. Table 18 shows a comparison of some of these parameters with t-test analysis. The only parameter that showed a difference between the sub-groups was baseline heart rate ($p=0.04$) with a slightly lower heart rate in the non-responder group. However during DS-MR a comparable increase in HR at each level of stress was seen in each sub-group. The responders had a HR at rest of 70bpm, DS-MR 10, 89bpm and DS-MR 20, 113bpm. The non-responders had a heart rate at rest of 62bpm, DS-MR 10, 80bpm, DS-MR 20: 114bpm. Therefore the abnormal volumetric response seen at 20 μg/kg/min could not be predicted from baseline characteristics.

The responder and non-responder sub-groups also showed trends in RV-EDV response. In the responder group the baseline RV-EDV was slightly less than in the non-responder group (not statistically significant). During DS-MR there was a significantly greater reduction in RV-EDV in the responder sub-group (Figure 27 panel B) especially at stage 2 DS-MR. These changes within the sub-group are important as they reflect changes in overall ventricular EF and therefore determine RV contractile reserve (Figure 28).

Table 18: Baseline characteristics of RV-ESV responders and non-responders

Parameter	**Group 1** *RV-ESV Responders* **n=9**	**Group 2** *RV-ESV Non-responders* **n=9**	**T test** *Difference between 2 groups (p values)*
Age at CMR (yr)	32.8 (19.8-60.1)	30.7 (16.2-59.7)	0.88
Sex (M/F)	**F=6 M=4**	**F=3 M=5**	N/A
NYHA classification	2.0±0.6	1.8±0.4	0.32
BSA	1.77±0.16	1.72±0.16	0.54
Age at TOF correction (yr)	4.1 (1.3-20.2)	4.9 (1.5-15.5)	0.73
QRS duration (ms)	150±7.6	151±7.3	0.81
Heart rate (bpm)	68.3±9.09	63.0±8.4	**0.04**
Mean BP (mmhg)	86.1±7.6	89.2±2.9	0.34
LV-EDV	70.1±12.0	76.7±11.1	0.27
LV-ESV	29.4±7.2	33.2±8.3	0.34
LV-SV	40.6±7.3	43.5±5.2	0.4
LV-EF	58.2±5.3	57.2±6.8	0.73
RV-EDV	122.3±24.3	131.6±28.1	0.48
RV-ESV	57.1±17.7	57.4±19.07	0.97
RV-SV	65.2±11.0	74.2±13.3	0.16
RV-EF	54.1±7.6	57.1±6.1	0.41

Table 18: The subgroups are defined by response of RV-ESV to dobutamine from 10 to 20 µg/kg/min, showing no significant difference (except for gender and heart rate) between the two subgroups for baseline volumetric or clinical parameters.

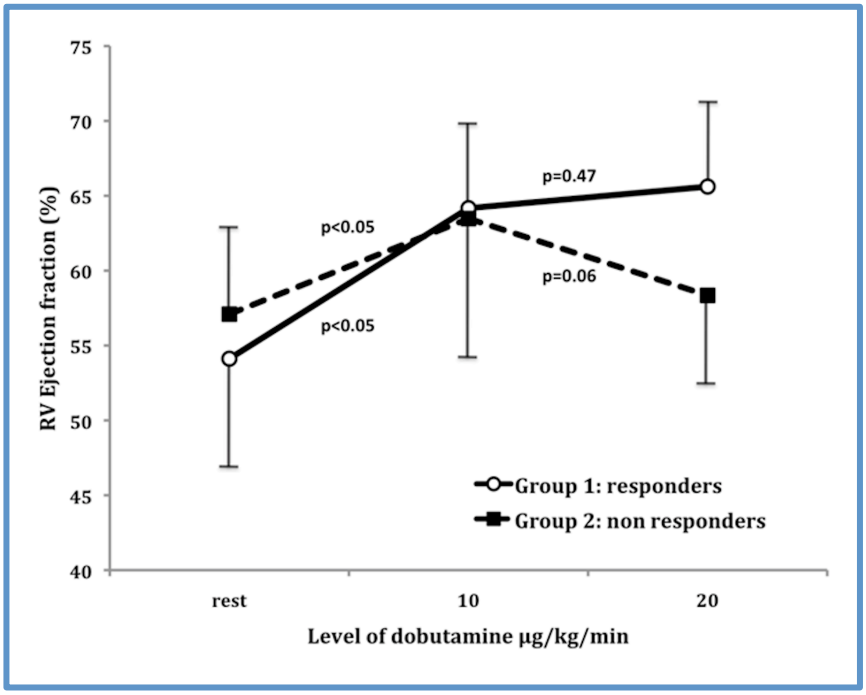


Figure 28: Change in RV-EF by subgroup.
The responders have a significant increase in RV-EF from rest to 10 and there is a non-significant further small increase at higher levels of dobutamine. The non-responders have an initial increase in RV-EF but with higher levels of dobutamine there is a reduction in RV-EF.

6.2.3 Contractile reserve

Contractile reserve is determined by change in ventricular EF, and can therefore be measured by any imaging modality that quantifies EF. An increase of greater than 5% during stress is considered to indicate the presence of contractile reserve. The RV-ESV non-responders had a reduction in RV-EF at 20µg/kg/min indicating abnormal contractile reserve (Figure 29). As demonstrated in Figure 29, the changes in RV-EDV showed no correlation with changes in RV-EF whilst RV-ESV showed a good relationship. This suggests that the response of RV-ESV at 20µg/kg/min contributed most to abnormal RV contractile reserve in this patient group.

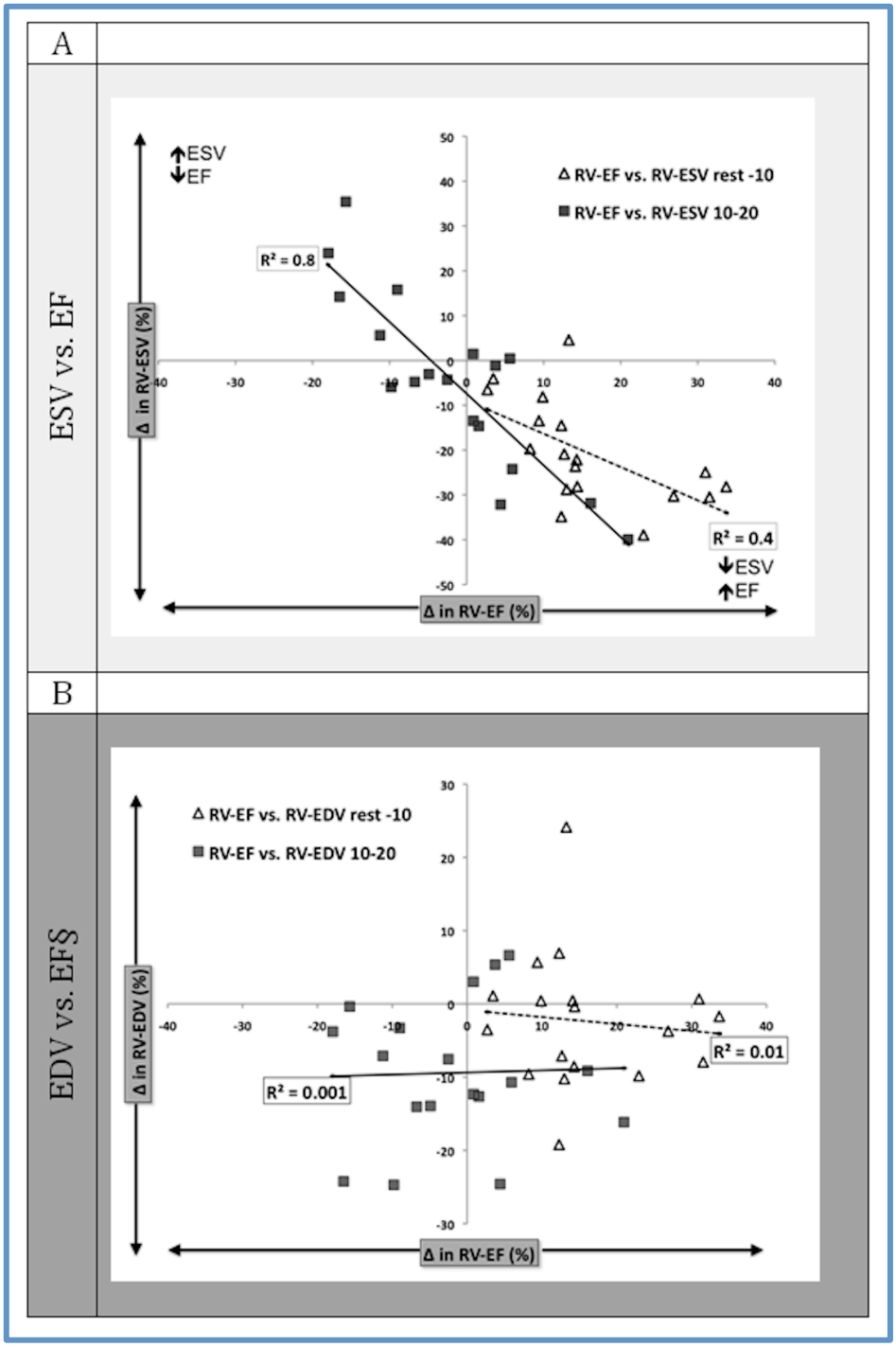


Figure 29: Correlation of contractile reserve and volumetric changes in TOF patients during DS-MR.

Scatter plots showing percentage change in RV-EF (=contractile reserve) compared to percentage change in RV-ESV (Panel-A) and RV-EDV (Panel-B) from rest to dobutamine 10 (triangles) and from 10 to dobutamine 20 (squares).

In Panel-A, the upper left quadrant in the RV-ESV vs. RV-EF image incorporates the abnormal responders, as RV-ESV either increases or is static with a reciprocal reduction in RV-EF. The lower right quadrant shows a normal response with a decrease in RV-ESV and comparable increase in RV-EF. Regression analysis shows a good correlation between change in RV-EF and ESV (Panel-A) whereas there is no discernable agreement with EDV (Panel-B).

6.3 Long term follow up

The patients involved in this study have been under continuing care with St Thomas' ACHD team. Unfortunately due to budgeting and time restraints during the research period it was not possible to follow up all patients with repeat CMR at a specific interval from their initial research CMR. The proposal at the start of the research period was to perform serial CMR at 1 year intervals if no PVR was performed and at 6 months post PVR then annual review if PVR was arranged. Although it was not possible to collect this data as anticipated it has been possible to review all patients over a 5 year interval to determine which of the went on to PVR and which have continued with medical management. Table 20 shows the patient follow up data.

Of the original 28 patients recruited into the study, 11 had PVR. The median interval for PVR following the DS-MR protocol was 3 years. Of those, 4 patients completed the first stage of DS-MR only due to mild side effects from the dobutamine. The remaining 7 completed both stages of the DS-MR protocol with 4 of these patients falling into the "responder" category as determined by the RV-ESV response to dobutamine. 2 patients had an abnormal RV-ESV response to higher dose of dobutamine and were considered "non responders" (1 data set was not included in the final volumetric analysis due to poor image quality). All PVR procedures were completed without significant cardiovascular morbidity or mortality. Within the group of patients who underwent PVR (i.e. the 11 patients) 4 had follow up CMR at 6 months post procedure and the results are shown in Figure 30. There is a reduction in RV-EDV and RV-ESV in patient 1 and 2 but little change in volumes for patient 3. Patient 4 only has a small reduction in RV-ESV post PVR. Regarding the response to dobutamine pre operatively, patients 1 and

4 both had a normal RV-ESV response at stage 2 DS-MR and therefore considered responders. Patients 2 and 3 only completed the first stage of DS-MR and therefore data for higher level of dobutamine is not available.

Table 19: Follow Up Data for TOF patients

No	DS-MR stage	Responder vs. non responder	PVR
1	2	Responder	Y
2	2	Responder	Y
3	0		
4	2		Y
5	1		Y
6	2	Responder	
7	1		Y
8	2	Non responder	
9	2	Non responder	
10	0		
11	2	Responder	
12	0		
13	2	Non responder	
14	2	Non responder	Y
15	1		Y
16	2	Responder	Y
17	1		
18	2	Responder	Y
19	2	Non responder	
20	2	Non responder	
21	2	Responder	
22	2	Responder	
23	2	Non responder	
24	2	Non responder	Y
25	1		
26	1		Y
27	2	Responder	
28	2	Non responder	

Table 19: Follow up data for the TOF patients. The 28 patients are listed with level of DS-MR achieved i.e. stage 1 or stage 2, whether they were considered to be "responders" or non-responders determined by RV-ESV response and follow up in terms of PVR

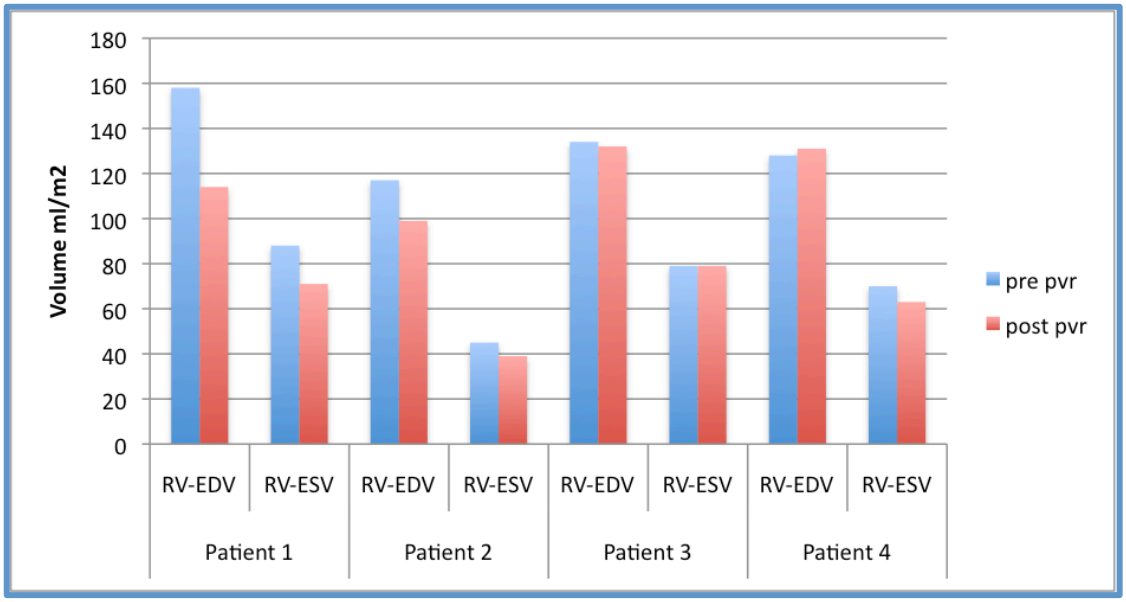


Figure 30: Pre and Post PVR Right Ventricular Volumes
Of the 11 patients who went on to PVR, 4 had follow up CMR with volumetric assessment. The graphs above show that for these patients there was a change RV-EDV and RV-ESV following PVR in patients 1,2 and 4 with little change in volumetric parameters for patient 3.

Nine of the patients who did not proceed to PVR had serial CMR assessment. Volumetric parameters at follow up scan are shown in Figure 31. There is no change in the RV-EDV or RV-ESV of these patients on repeat CMR. Seven of these patients during DS-MR stage 2 had an abnormal RV-ESV response and therefore considered to be "non-responders". The fact that these patients have required repeat CMR compared to the other 8 non-PVR patients suggests that they continue to be symptomatic. It is possible that these patients have a degree of restrictive RV physiology and that is what determines the abnormal RV-ESV response. Whether restrictive physiology results in abnormal systolic response to dobutamine cannot be determined from this small study and it is hoped that with larger patient cohorts this hypothesis can be further explored.

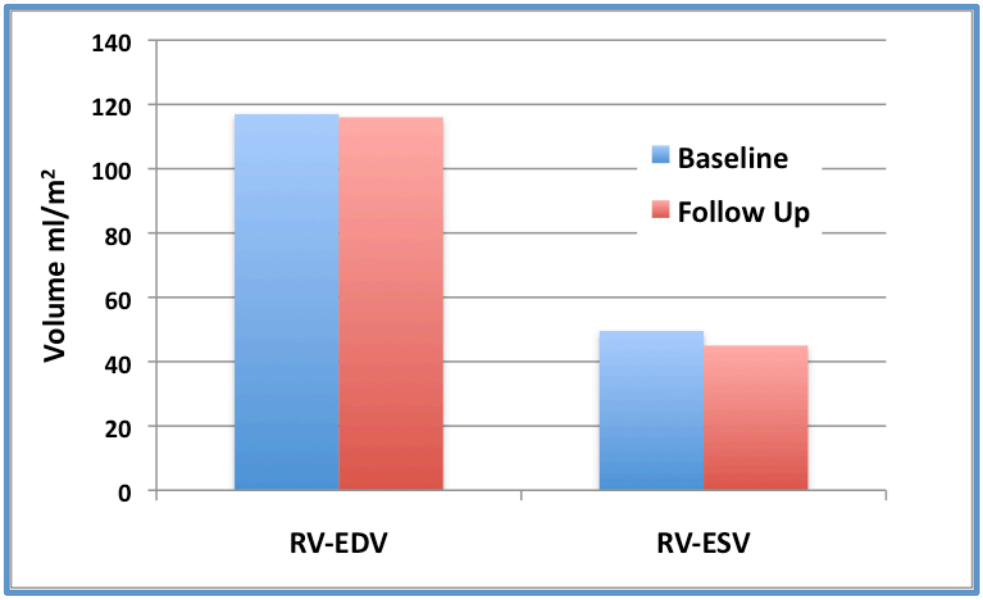


Figure 31: Follow up CMR volumes for non-PVR TOF patients
Right ventricular volumes at baseline during research protocol CMR and at follow up CMR in patients who did not go forward to PVR (n=9).

6.4 Summary

The normal haemodynamic and volumetric response to a staged dobutamine protocol has been demonstrated for the first time in healthy volunteers.

The data clearly show that within a small cohort of TOF patients with significant PR there are a group of patients with an abnormal ventricular response to dobutamine. The most significant abnormality is the change in RV-ESV at dobutamine 20 that correlates with abnormal contractile reserve. We hypothesise that at higher levels of DS-MR this abnormal RV-ESV response may be a discriminating factor in the assessment of patients awaiting PVR.

CHAPTER 7: DISCUSSION AND FUTURE DIRECTION

The previous chapters have highlighted the importance of CMR assessment in repaired TOF patients. The roles of ventricular volume and arterial flow assessment have been explored together with the importance of accurate quantification. The results will now be put into the clinical context with particular reference to the timing of PVR and potential new strategies to evaluate TOF patients in the future.

7.1 Stress magnetic resonance imaging in TOF

One of the main aims of this study was to determine the haemodynamic effects and volumetric changes during dobutamine stress MR imaging in TOF patients. This was achieved by the direct comparison of DS-MR in healthy adult volunteers and TOF patients with preserved biventricular function, moderate RV dilatation and severe PR. Overall a normal response in LV and RV volumetric response was found at a low level of dobutamine stress (10μg/kg/min) in the TOF patient cohort. The volumetric changes seen were similar to that seen in the healthy volunteer group and are in line with previously published data by Van de Berg et al, which also demonstrated normal systolic function in TOF patients during low dose dobutamine stress assessment [106] . Therefore this dose is unlikely to unmask systolic dysfunction compared with controls when using volumetric CMR

On increasing from 10 to 20 μg/kg/min of dobutamine, changes in RV and LV systolic function were observed. There was a significant further reduction LV

volumes (normal response) but the increase in LV-EF in TOF patients failed to reach statistical significance. This may be due to the small sample size and in a larger cohort of patients this effect may become more prominent. Recent study has suggested that there is significant adverse ventricular-ventricular interaction when TOF patients have greater RV volumes [107] and therefore in a larger cohort, especially one which included patients with significant RV dilatation, this effect may become more apparent.

More impressive is the abnormal RV-EF response observed in a sub-group of TOF patients, who failed to further increase RV-EF when increasing from 10 to 20μg/kg/min of dobutamine, due to either failure of reduction or increase of RV-ESV. The remainder of TOF patients had normal reduction of volumes at 20μg/kg/min although the increase in RV-EF did not reach statistical significance. The difference in incremental stress response within the TOF cohort could not be predicted by clinical or baseline CMR parameters. In comparison the healthy volunteers had a normal response to dobutamine throughout the clinical protocol and therefore a significant increase in bi-ventricular EF demonstrating normal contractile reserve.

7.1.1 Mechanics of impaired RV contractile reserve

The response of RV-ESV to stress contributed most to the degree of change of EF, (Figure 29). The importance of RV-ESV was highlighted recently by Uebing et al. [108] using conductance catheter technology to analyze pressure-volume relations under dobutamine stress in a similar cohort of TOF patients. They observed that increased RV-ESV was associated with reduced end-systolic elastance (Ees), a load-independent marker of myocardial contractility, and that RV-ESV correlated more closely with Ees than either RV-EDV or RV-EF [108]. Hence, although load-

dependent, RV-ESV may still be regarded as a non-invasive marker of contractility as it seems to reflect not only RV volume loading but also intrinsic myocardial contractility [108]. Moreover, a RV-ESV >50 ml/m^2 was a strong predictor of major adverse events in TOF in the study of Knauth et al [103]. For these reasons, the impact of RV-ESV change on contractile reserve is a noteworthy extension of these previous findings highlighting the importance of RV-ESV in the interpretation of systolic function.

7.1.2 Clinical implications of volumetric changes seen during DS-MR

These findings are relevant as it has been reported that ventricular systolic function is of great prognostic importance in TOF patients with significant RV dilatation and chronic severe PR as even moderate ventricular systolic dysfunction (RV-EF<45%, LV-EF<55%) is associated with impaired clinical status [104] and can predict major adverse events [103]. If DS-MR is able to provoke abnormal contractile reserve within a cohort with only moderate RV dilatation (126.4±27.2 ml/m^2 BSA) and preserved biventricular function at baseline as observed in this study, then this pattern of response may identify those TOF individuals at higher risk of adverse long-term outcome. Clearly this may also therefore elucidate which patients may require PVR or even which patients are being offered PVR too late.

7.2 Relationship between Flow And Volumes during DS-MR

As has been previously discussed in chapter 4, assessment of great artery flow and documentation of PR is an essential component of the clinical CMR assessment in TOF. All of the patients in this study had a degree of pulmonary

regurgitation and one of the initial aims of the thesis was to document the changes in flow dynamics that occur during DS-MR and also to look at the association between great artery flow and volumetric analysis.

7.2.1 Response of pulmonary regurgitant flow during DS-MR

The study showed that there is a significant increase in total pulmonary forward flow at 10μg/kg/min DS-MR, which could not be maintained at 20μg/kg/min DS-MR. This is in agreement with the increase in RV-SV seen by volumetric assessment during DS-MR. The PR volume (PA-BF) increased at stage 1 DS-MR but then decreases at stage 2 DS-MR possibly due to shorter diastole at higher heart rates. However these changes in flow dynamics were not reflected in the calculated regurgitant fraction, which remained constant throughout DS-MR. Clinically in addition to other clinical and volumetric parameters, pulmonary regurgitant fraction remains one of the criteria used to determine PVR timing in TOF patients. However Wald et al have suggested that the use of PR expressed volumetrically, rather than as a percentage of antegrade MPA flow, is a more appropriate method for quantification in the assessment of TOF patients [109]. This would appear to be true in this TOF patient cohort as PR-RF does not reflect the important changes in PR volume observed during flow imaging under dobutamine stress conditions.

7.2.2 Disparity of flow vs volume during DS-MR

CMR flow assessment at rest is reproducible and in previous studies has been shown to correlate well with analogous volumetric parameters. However little is known about how robust and comparable these are relative to volumetric parameters [110] during stress imaging, particularly at higher doses up to 20 μg/kg/min dobutamine [105]. Therefore, simple parameters derived from flow and

volume data, such as stroke volumes, and also more calculated parameters such as the absolute PA-BF and PA-RF were compared and the full results are available in Chapter 4.

This study showed that for simple parameters, under resting conditions an excellent agreement of ventricular volumetric SV by CMR with their respective aortic and pulmonary total forward flow volumes by PC-flow as is commonly reported [83]. This agreement however deteriorated markedly under dobutamine stress. For the calculated parameter PA-RF, there was considerable disagreement; both at rest and during stress. As mentioned previously this again questions the utility of PR-RF as a useful marker of pulmonary regurgitation severity. In this study the pulmonary regurgitant volume (PA-BF) showed acceptable agreement at rest between the stroke volume difference method (RV-SV minus LV-SV) and pulmonary backward flow by PC-flow (PA-BF) but there was deterioration of agreement during stress.

Reasons for disagreement during DS-MR

These results clearly suggest that during stress flow and volumetric measurements cannot be used interchangeably. The reasons why there is such variability in the results are numerous.

During pharmacological stress motion artefacts may occur to some degree due to tachycardia, increased myocardial wall motion velocities and presence of ventricular ectopics. The volumetric images were quality scored and a moderate (albeit not significant) reduction in image quality score and slight increase in observer variance at stress was found. Another confounding factor may be differences in expiratory breath hold diaphragm positions as patients become

more uncomfortable during dobutamine exposure. This may result in inconsistent coverage of the ventricles and slight bias in volumetric numbers. With flow imaging, the more important potential limitations include low temporal resolution at higher heart rates (up to 160 bpm) and increased turbulence and velocities, particularly in the main pulmonary artery, during stress. Turbulent flow may not be perpendicular to the imaging plane and lead to flow underestimation from intra-voxel phase dispersion [111].

In order to achieve sufficient temporal resolution in DS-MR flow imaging a free-breathing protocol was chosen. The PA flows would have been difficult to acquire within a reasonable breath-hold. However there are disadvantages to free-breathing scanning, namely propensity for arrhythmia affecting retrospective phase reordering, background phase offset errors [112] and susceptibility to irregular breathing patterns during stress[111] which may impact on the correlation between volume and flow measurements.

7.2.3 Clinical impact of flow imaging during DSMR

In repaired TOF with chronic severe PR, agreement between CMR PC-flow and volumetry was excellent for stroke volumes and acceptable for absolute PA-BF under resting conditions. Under stress there was considerable disagreement for all of these parameters, and for PA-RF this was even true at rest. Although image quality suffered to some degree, there was little observer variance in volumetrics during increasing levels of dobutamine stress as intra-institutional strict reading criteria were consistently applied. These results suggest that measures of RV and LV SV, absolute PA-BF and importantly PA-RF during DS-MR should be interpreted with caution and should not be used interchangeably. For DS-MR in

TOF patients the focus should be on simple parameters such as response of ventricular end-systolic and end-diastolic volumes to dobutamine stress.

7.3 Reproducibility and observer variance

The difficulties seen when comparing volumetric and flow data highlight the importance of reproducibility of CMR measurements and how this may be affected during DS-MR. The accuracy and reliability of resting CMR volumes has been well-published [94]. However as seen in this study resting imaging may not truly reflect underlying ventricular dysfunction and there is increasing interest in the development of better determinants of ventricular systolic and diastolic function and contractile reserve through stress imaging especially in congenital conditions such as TOF [65]. Published data suggests that there is a risk of error when assessing ESV response during DS-MR and this questions the utility of such a parameter in the assessment of ventricular systolic function [61].

An additional aim of this thesis was to assess the reproducibility and accuracy of stress imaging analysis. Reproducibility was determined by coefficient of variance and image quality was also taken into consideration. The study showed that in TOF patients and the healthy volunteers inter and intra-observer agreement of end-diastolic volumes was excellent at all stages of DS-MR. In the TOF patient group at 20μg/kg/min of dobutamine there was abnormal RV-ESV response in comparison to the normal volunteers. The inter- and intra-observer analysis of this parameter shows good agreement between observers and good reproducibility of this parameter at higher levels of stress. In comparison LV-ESV

in the TOF group has a greater COV, of 14.9%, suggesting less good agreement between observers during stage 2 DS-MR. There are 2 potential causes for this poor agreement. Firstly the ventricular end-systolic size is much smaller at this higher level of DS-MR. Small discrepancies between observers in volume measurement will be amplified when calculating the COV (as seen in previous study [61]) so even a small difference between observes will result in a much greater variance and suggest poor agreement. Secondly the images in TOF patients were acquired in the axial plane, which may result in partial volume effect in the most apical slices of the ventricle [79]. In comparison the normal healthy volunteer group have better agreement between observers at higher DS-MR stages with a COV of 10.5 at stage 2 DS-MR; these images were acquired using a short-axis geometry, which is a more standardized method of LV assessment. Although volumetric assessment of the LV using transverse slices has been validated [79, 95] and is thought to be comparable to short axis imaging at rest it is likely that the potential for error is greater during DS-MR.

The RV-ESV in both TOF and the normal volunteer group showed good agreement suggesting good reproducibility. In the TOF group this superiority in comparison to the LV-ESV is likely to be due to the larger baseline ESV reducing the potential errors of small volumes. Additionally the transverse geometry used in the TOF allows better visualization of the valve planes which may improve accuracy when assessing volumes [79]. In comparison, the volunteer group also showed good agreement between observers in RV-ESV assessment at higher stages of DS-MR suggesting that both short axis and axial assessment of the RV yield reproducible results.

Image quality should also be taken into consideration as it is anticipated that at higher heart rates this be will affected due to motion and respiratory artefacts [61]. Although image quality reduced marginally with increased DS-MR stage, all images were of a high enough quality for analysis and this is unlikely to have caused significant error in analysis for either the TOF patients or the volunteers.

The data showed good agreement between observers for volume assessment during DS-MR. This is only possible with good institutional training and adherence to strict reporting guidelines [94]. This should be taken into consideration when performing and analyzing DS-MR volumes.

Overall, especially for the RV parameters the reproducibility was good. Previous work has suggested the ESV parameter to be most at risk and this appeared to be true for the LV in the TOF groups although the reasons for this have been well explained. The stress data suggested that changes in RV-ESV at higher dobutamine concentrations may have clinical application and therefore the good reproducibility of this parameter supports its clinical utility.

7.4 Safety

Safety is paramount when performing DS-MR and this study has shown that a dose of 20mcg/kg/min is safe and well tolerated in this particular TOF study population. Only 2 patients experienced minor side effects and there were no documented serious adverse reactions. Major side effects although infrequent were reported from studies using higher doses up to 40mcg/kg/min in patients with coronary artery disease [50], whereas echocardiographic studies using up to 40mcg/kg/min in TOF have only reported one case of non-sustained ventricular

tachycardia at a dose of 20mcg/kg/min [66, 67]. This potential risk of arrhythmias although rare has resulted in cautious dobutamine administration in congenital heart disease patients. Currently, a dose of 7.5mcg/kg/min has been considered to be the safest and most effective [61]. However, the concern with this low dose approach is that there are potential changes in cardiac response to dobutamine as demonstrated in this investigation, which are not seen at low doses.

The higher-dose protocol up to 20μg/kg/min was well tolerated in all controls and our strictly selected TOF patients where only 4 of 24 patients were unable to proceed to full dose due to minor symptoms. It is mandatory that resuscitation equipment and trained staff are available when performing DS-MR.

7.5 Study Limitations

Due to very strict exclusion criteria for safety reasons, this exploratory study included a relatively small number of patients, and therefore the conclusions (including safety considerations) are not applicable to TOF with severe RV dilatation, arrhythmia, additional pulmonary stenosis and additional cardiac defects. Volunteers and TOF patients were not age-matched, but this small difference in age is unlikely to have caused a major bias. Short-axis volumetry was used for controls and transverse acquisition for TOF patients. However the two approaches have been shown to be comparable [94, 113] and changes in parameters rather than absolute volumes were the focus of the study. It would however be beneficial to perform the DS-MR protocol with both axial and short axis assessment in a TOF patient or volunteer group to get a better understanding of these potential limitations during DS-MR.

The limitations of a single centre study with limited number of patients must be acknowledged. However from this work the protocol has been adapted to form part of the assessment in TOF patients in a large multi-centre study in Germany (German Competence Network). It is hoped that future results from this research will confirm the trends observed in the small TOF patient cohort described in this thesis.

7.6 Future perspective

This thesis has evaluated the safety and utility of dobutamine stress imaging in patients with TOF. The most important observations were that at higher doses of dobutamine RV contractile reserve is abnormal in some TOF patients due to abnormal change in RV-ESV. How this change relates to clinical need for PVR is difficult to interpret in this small patient cohort. There are a number of questions that currently remain unanswered and through future study could reveal important features of early systolic dysfunction in this group of patients.

Load independent assessment

This study has focused on RV-ESV and contractile reserve as potential markers of RV dysfunction. These are both load dependent parameters significantly influenced by regurgitant volumes. Other parameters may better reflect true myocardial dysfunction for example deformation imaging using tagging or speckle tracking and the relationship with strain and strain rate analysis from MR imaging could potentially offer load-independent markers of ventricular dysfunction which may prove to be more predictive of outcome.

Stress echo assessment

The initial research protocol applied to the TOF patients included an extensive echo protocol including tissue velocity imaging and 3D volume assessment. In the patient cohort 3D volume assessment proved to be technically challenging due to the significant dilation of the RV in many cases. Post processing of these large volumes resulted in underestimation of volume measurements, this has also been observed in published data [33]. Therefore echo assessment could not be assumed to be comparable to CMR volume assessment. Although CMR remains the gold standard for volumetric assessment, with improvement in 3D echo technology it is possible in the future that similar stress studies could be carried out with echocardiography. Benefits of this would include accessibility, faster acquisition of images and reduction of patient's dobutamine exposure. It would also facilitate the study of patients with contraindications to CMR imaging and could be applied to exercise echo thereby removing the need for pharmacological agents.

Fast CMR scanning

Chapter 3 reports the results of a faster 3D ventricular assessment. The aim of this part of the project was to determine whether there are methods to achieve full ventricular assessment in a single breath hold. Because of the extensive imaging protocol undertaken by the patients and volunteers in this study this fast 3D sequence was not examined under stress conditions. However future study could implement fast imaging methods such as this to minimize the duration of dobutamine exposure and improve image quality related during DS-MR. Utilization of blood-pool contrast agents may also reduce error by allowing better blood-pool endocardial definition.

DS-MR Pre and Post PVR

The observation that some patients have an abnormal RV-ESV response during stress needs to be explored further in the context of ventricular function pre and post PVR. Repeating the stress protocol following pulmonary valve surgery would give a good insight into how the volumetric parameters change once the volume load of PR has been eliminated. It would also allow confirmation of whether abnormal RV-ESV response during stress truly reflects systolic dysfunction. As mentioned previously this study is currently being performed using the protocol described in this thesis as part of a multi-centre long term study created by the German Competence Network and the results are awaited.

Future study should also focus on more refined analyses of ventricular sub-compartment response[114] and regional wall motion behavior[115] between rest and stress as this may add relevant information on the mechanics of ventricular dysfunction. Correlation with ventricular scarring[116] and fibrosis imaging[117] might further improve the understanding of progression of ventricular dysfunction and its association with major adverse events such as clinical dyssrhythmia and sudden cardiac death.

7.7 Conclusions

In TOF patients with chronic PR and preserved baseline ventricular systolic function, DS-MR at 20 μg/kg/min revealed abnormal RV contractile reserve in a proportion of patients. This was due to paradoxical change in RV-ESV, leading to significant worsening of RV-EF, whilst controls showed further reduction of volumes at this dose level. These differences in stress response were not predictable from baseline parameters. In contrast, low-dose DS-MR at 10 μg/kg/min demonstrated a normal biventricular contractile reserve compared with volunteers. Hence this dose is unlikely to unmask systolic dysfunction using volumetric CMR. Therefore, the staged higher-dose DS-MR protocol used in this study may have the potential to select those at risk for systolic dysfunction when baseline RV-EF is still within the normal range and therefore determine which patients will benefit most from pulmonary valve replacement.

APPENDIX 1

Consent

Guy's and St Thomas' Hospital NHS
NHS Trust

Guy's Hospital
St Thomas' Street
London SE1 9RT
Tel: 020 7188 7188

Department of Congenital Heart Disease

Cardiac Magnetic Resonance Imaging

LREC Study Number: **03/06/15**
Patient Identification Number for this trial:

CONSENT FORM

Title of Project: **Comparison of Tissue Doppler and Magnetic Resonance Imaging for assessment of right ventricular function in patients with Tetralogy of Fallot and Pulmonary Regurgitation.**

Name of Researcher: Prof Reza Razavi

Please initial box

1. I confirm that I have read and understand the information sheet (Version.2, 26 August 2006) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that images collected will be stored on computer system, and, after my name and address have been removed, may be available to researchers at other institutions or the manufacturer of the scanner (Philips Medical Systems). ☐
4. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Guy's and St Thomas' Hospital NHS
NHS Trust
Department of Congenital Heart Disease
Tel: 020 7188 7188

Cardiac Magnetic Resonance Imaging

PATIENT INFORMATION SHEET

Study Title:

Comparison of tissue Doppler and magnetic resonance imaging for assessment of right ventricular function in patients with tetralogy of Fallot and pulmonary regurgitation

TO THE PATIENT:

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. Please ask us for a copy, or if you wish, a copy may be obtained from CERES, PO Box 1365, London N16 0BW.

Purpose of the Study:

You are invited to take part in a research study that is being done at Guy's and St Thomas' Hospital NHS Trust. The reason for this research study is to compare the findings of MRI of your heart with those of echocardiography, in particular the function of your pulmonary valve, which over time may leak. The aim is to try and establish if echocardiography and MRI can help define the timing of any future operations for repair of leaking pulmonary valves in patients with repaired tetralogy of Fallot.

Why I have been chosen and what will happen if I take part in the study:

You are due to have a routine cardiac MRI (Magnetic Resonance Imaging) to assess your heart. In addition to this routine scan, we will perform a tissue Doppler echocardiogram and a stress MRI. This assessment will be performed in one sitting at Guy's Hospital. Images of your heart will be taken with MRI, you will then be removed from the MR scanner, have a tissue Doppler echocardiogram, and then be slid back in the MR scanner to complete the scan. During this second MR scan you will be given a low dose of a drug called Dobutamine, which will make your heart work a little harder (stress). This is a way of mimicking exercise within the MR scanner. Dobutamine in low doses is a safe drug, though you may experience headache, flushing and palpitations. The total time for both examinations would be about 1 hour. This is about 30 minutes longer than a standard scan would take if you were not taking part in this study.

As you may know, MRI is a way of looking at your heart and blood vessels and is risk-free (except some patients who should not have scans because they have things like heart pacemakers). The MRI would be made up of a number of scans each taking a few seconds (where you have to hold your breath) or a few minutes (where you won't have to hold your breath). As part of this examination you may be given an injection of a contrast agent (similar to a dye) called Gadolinium.
Some people undergoing MRI scans (approximately 5%) develop feelings of claustrophobia (distress at being in an enclosed space). If you feel claustrophobic then you can ask for the scan to be stopped.

A tissue Doppler echocardiogram is a special way of looking at echo images, but the images will be taken in the same way as the echocardiograms you have had in the past.

Do I have to take part in the study?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the care you receive.

What if something goes wrong?
If you are harmed by taking part in this research project there are no special compensation arrangements. If you are harmed due to someone's negligence then you may have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain about any aspect of the way you have been approached or treated during the course of this study the normal NHS complaint mechanism may be available to you.

Will my taking part in this study be kept confidential?
All information, which is collected about you during the course of the research, will be kept strictly confidential. Any information or pictures about you which leaves the hospital, will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
The images collected will be stored on a computer system and, after your name and address has been removed, may be made available to researchers at other institutions or to the manufacturer of the scanner.
We plan to publish the results of this study in a medical journal once the study has been completed and the results analysed. None of the patients will be identified in any report or publication.

Who is organising and funding the research?
This study is being organised by the cardiac MRI department of the department of congenital heart disease of Guy's and St. Thomas' Hospital.

This study has been reviewed and approved by the Guy's Hospital Research Ethics Committee. You will be given a copy of this information sheet and a signed consent form to keep for your records.

Contact for further information:

Prof Reza Razavi
Division of Imaging Sciences
Rayne Institute, 4th Floor Lambeth Wing,
St Thomas' Hospital
London SE1 7EH
Tel: (+44)/(0)20 718 85440
Fax: (+44)/(02)0 718 85442

Dr Victoria Parish
Division of Imaging Sciences
Tel: (+44)/(0)20 718 88382
Fax: (+44)/(0)20 718 85442

Patient Information Sheet Version 2. 29 August 2006.

Ethics

i) Ethics application

Guy's Research Ethics Committee **R&D NO:**

APPLICATION FORM

Application for approval of an investigation for teaching or research involving human subjects

1.	Brief title of Project	Comparison of Tissue Doppler and Magnetic Resonance Imaging for assessment of right ventricular function in patients with Tetralogy of Fallot and Pulmonary Regurgitation		
2.	Personnel involved			
	Department:	Medical Imaging Science		
	Head of Department:	Dave Hawkes		
	Applicant (main investigator) name/appointment	Dr Reza Razavi Honorary Consultant in Paediatric Cardiology		
	Supervisor (if relevant)			
	Principal assistants and their responsibilities	Dr Michael Vogel Senior research fellow in Congenital Heart Disease Dr Derek Hill Reader Radiological Science Dr Andrew Taylor Research Fellow in Cardiac MRI		
3.	State your personal experience in this field in terms of extent and duration	I am a paediatric cardiologist in charge of the cardiac MR service at Guy's and St Thomas' and direct and report the three weekly sessions of cardiac MR at Guy's (1 for children, 2 for adults). I also perform diagnostic and interventional cardiac catheterisations in children and adults with congenital heart disease. I have been involved with acquisition and reporting of cardiac MR at Guy's and St Thomas' over the last 6 years and cardiac catheterisation over the last 8 years. I am part of group of scientists and clinicians who been successful in obtaining over £3.8 M of funding from HEFCE, research councils, charities and industrial sources for a research MR centre at Guy's with a strong emphasis on cardiac MR and MR guided intervention were this work is going to be carried out.		
4.	Are you a member of a defence organisation (MPS/MDU)? If so please give registration number	MDU 232105J		
5.	Contact numbers:	Telephone	Fax	Email
		020 7955 3196	020 7955 4614	reza.razavi@kcl.ac.uk

PROJECT DETAILS

6.	Purpose of investigation (please indicate what information you hope to obtain, and what you believe will be the benefits).	**Patients with congenital heart disease who have had surgery to their right ventricular outflow tract or pulmonary valve or who have pulmonary homografts or conduits may develop pulmonary incompetence. These patients may develop right ventricular dilation and dysfunction, and be prone to ventricular arrhythmias. They may therefore require intervention to replace the regurgitant pulmonary valve. There are currently no data on the optimal timing of intervention. If the intervention is performed too early, there are concerns about the requirement of future re-interventions, as the life span of currently used pulmonary homografts is limited to an average of 5-7 years. On the other hand, there is a limit to the number of re-operations that can be performed in a single patient. Delaying the intervention carries the risk that the RV dysfunction will not fully recover. The potential of recovery of RV function is difficult to assess. Data from patients with ischaemic heart disease suggest that evaluation of contractile reserve is a good surrogate of recoverability of ventricular function. However, this has so far not been assessed in patients with pulmonary regurgitation. While echocardiography is most commonly used for routine assessment of ventricular function it has severe limitations in the RV, because of its difficult geometry. Cardiac magnetic resonance allows accurate assessment of right ventricular volumes and function. However, this is load dependent and therefore has its limitations when evaluating procedures characterised by rapid changes in loading conditions. Recently, novel tissue Doppler techniques have been shown to measure RV contractile function independent of loading conditions. This is done by measuring myocardial tissue acceleration during the iso-volumetric phase of ventricular contraction. The technique has been experimentally validated but validation in a larger clinical setting has not yet been performed. It is possible to measure myocardial tissue acceleration by CMR tagging techniques. This has not yet been used to assess load independent ventricular function, however it has the advantage of allowing assessment of myocardial tissue acceleration in 3 planes rather in a single plane as obtained by tissue Doppler.** **We will compare standard parameters of RV function by CMR, pulmonary regurgitation by phase contrast flow and three-dimensional myocardial acceleration obtained by tagging with the new tissue Doppler techniques. Tissue Doppler imaging has the potential advantage of being applicable on the intensive care unit, in the operating theatre, and outpatients. Data can be acquired during routine echocardiographic examinations within a few minutes without any extra discomfort for the patient.** **In addition, these load independent methods of measuring ventricular function allow assessment of RV contractile reserve. This can be achieved by acquiring data at rest and during infusion of dobutamine. We will assess the ventricular function and tissue doppler indices with MRI and echocardiography at rest and whilst the patients are exposed to dobutamine an intravenous cardiac inotrope. This will enable accurate assessment of contractile reserve and may unmask features of myocardial dysfunction which are not detected during resting conditions.**

		The principal goals of this project are: to devise a technique for measuring load-independent RV function using MRI tagging to assess the feasibility and safety of dobutamine stress MRI in patients with Tetralogy of Fallot Compare load-independent techniques with more established load-dependent measures of ventricular function and the degree of pulmonary regurgitation To look for early markers of ventricular dysfunction in patients with Tetralogy of fallot prior and significant pulmonary regurgitation
7.	Provide a concise description of what is to be done (the protocol) *Expand the box as necessary when giving your description*	This study will be carried out at the new MR research centre of Guy's hospital. Adults and adolescents will be studied. The patient will be moved into the MR scanner and imaging of the area of interest will be performed as per usual cardiac MR scan of patient with congenital heart disease. The scans will be performed with breath-holds lasting 10-25 secounds. This will involve 1- a plan scan 2- a SENSE reference scan. 3- an interactive real-time scan to plan the planes of right ventricular short axis, long axis and also a short axis plane through the pulmonary artery and aorta. 5- a phase contrast through plane velocity image in the short axis plane through the pulmonary artery and aorta. 6- 3D Balanced Fast Field Echo short axis through the right ventricle 7- a series of spiral C-SPAM tagging imaging in the short axis, and long axis. The cardiac MR examination will take 30 minutes. Following the CMR acquisition patient will be moved out of the scanner on the interventional table and the tissue Doppler echocardiography will subsequently be performed in the same room without moving the patient. (10 minutes). We will then start an infusion of Dobutamine 10μg/kg/min. We will repeat the phase contrast through plane velocity of the pulmonary artery, 3D Balanced Fast Field Echo short axis through the right ventricle and spiral C-SPAM tagging imaging in the short axis, and long axis. (10 min) The patient will then have repeat tissue Doppler examination.(10 min). We will increase the Dobutamine to 20μg/kg/min and repeat the cardiac MR (10 min) and tissue Doppler echocardiography. (10 min).
8.	(a) State potential hazards (if any), including the degree of apprehension, pain and disturbance.	MRI has been performed on millions of human subjects (and at Guy's specifically since 1986) without ill effect. There are well-established contraindications for MRI, including pacemakers and other implanted devices and metallic foreign bodies. Screening procedures are in place in the MR unit to exclude such subjects, and will be adopted in these studies. Dobutamine is routinely used as an agent to increase myocardial contractility during imaging studies and with the low dose being

		used in this study and as the patients do not have ischaemic heart disease we do not expect any problems. Patient however will be monitored with ECG and BP monitoring and the infusion will be stopped if there are any adverse effects or symptoms.	
	(b) State how the proposed protocol would differ from the routine management.	Patients with tetralogy of Fallot routinely undergo MRI assessment and echocardiography. However, in this study both procedures will be performed concurrently and repeated following the infusion of low dose dobutamine.	
9.	State the likely duration of the project	6 months	
10.	Where will the project be done?	MRI research centre at Guy's Hospital	
11.	What individual benefit (if any) will a patient have if he/she participates in the study?	The MRI scan will be used for routine assessment of patient and in deciding need for further treatment. There will be no immediate individual benefit form the measurement of contractile reserve and compression with Tissue Doppler.	
	PATIENTS /VOLUNTEERS		
12.	(a) State the number, age and type of patients/subjects likely to be involved. Give the size of any differences that you are hoping to show between groups	We will study 30 patients with tetralogy of Fallot who are referred for cardiac MRI assessment.	
	(b) Have you obtained statistical advice on either of the following? *(Delete as applicable)* The number of subjects required in order to demonstrate results of clinical value Methodology and statistical analysis	No	
	If YES, <u>please indicate from whom:</u>		
13.	Do these include women who are pregnant or likely to become pregnant? How will pregnancy be excluded (if relevant)?	No, patient population is unlikely to include pregnant women and pregnant women will be excluded by the MR/X-ray questionnaire filled in prior to scanning	
14.	How will patients/volunteers be recruited?	We will write to patients with tetralogy of Fallot on the waiting list for cardiac MRI with an invitation letter, information sheet and consent form.	
15.	Informed consent must be obtained in all cases. Whether written or oral consent is sought, written information should be provided for the patient/volunteer, and this must be included with this application. Please indicate if consent will be:	a) Oral	
		b) Written	Yes
		c) Obtained in the presence of a disinterested third person	
16.	Give details of any payment to be made to the patient/subject	None	

	COMMUNICATION			
17.	Please indicate what (if any) information will be sought from general practitioners, and what information will be supplied to them and in what form. Note that written information should indicate how experimenters can be contacted by telephone in emergencies	N/A		
18.	When a drug is being administered will the patient/subject have on his person some means of this being known in case of a sudden illness/accident?	N/A		
	DRUGS			
19.	Please state briefly the known pharmacology of drugs to be used, indicating activity and important side effects	Standard MR contrast agent if clinically indicated Dobutamine is an inotropic agent which acts by increasing myocardial contractility and arterial vasodilation. Side effects at low dose may include, headache, flushing, palpitations.		
20.	Has approval been obtained from the Committee for Safety in Medicine:	Yes	No	Not Applicable
				N/A
21.	Are radioactive substances/ionising radiation to be used?	no :		
	a) give estimated radiation doses from the procedure;			
	b) if the applicant is not a consultant radiologist or nuclear medicine physician, please append a letter from radiation protection adviser or delegate;			
	c) has an ARSAC certificate been obtained or applied for? (please append a copy of the certificate to this application);			
	d) is the investigation using ionising radiation/radioactive substances intended to benefit the patient?			
	SPONSORSHIP			
22.	Is this study being performed with commercial sponsorship, or sponsorship from some outside body (e.g. the MRC)? If so, please state from whom.	No		
23.	If this project involves participation/sponsorship by a pharmaceutical company, has indemnification or no fault liability been obtained?	N/A		
24.	Is there any other form of indemnification?	No		
25.	Please add (or append) any other relevant information			

ii) Original Ethics Approval

South East London NHS
Strategic Health Authority

27 June 2003
Ref: 03/06/15

Quote reference in all correspondence

Guy's Research Ethics Committee
3rd Floor Nuffield Annexe
Henriette Raphael House
Guy's Hospital, London SE1 9RT

Chair: Professor Steven H Sacks
Administrator: Mrs Valerie Heard
Direct line: 020 7955 4559
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Website: www.corec.org.uk

02 JUL 2003

Dr Reza Razavi
Radiological Sciences
5th Floor
Thomas Guy House
Guy's Hospital

Dear Dr Razavi

Re: Ref: **03/06/15 Comparison of tissue doppler and magnetic resonance imaging for assessment of right ventricular function in patients with tetralogy of fallot and pulmonary regurgitation.**
Application Form signed 9 June 2003
Patient Information Sheet and consent form V.1 dated 9 June 2003

The Ethics Committee, at its meeting held on Wednesday 25 June 2003 considered your application and will be willing to approve it subject to the following. **Please highlight the changes in the new documents wherever possible (bold text or coloured highlighter).**

- Section 8a of the application should clarify whether patients will be given Gadolinium; if so the risks should be included in the information sheet.
- What type of statistical analysis will you be using for this study in order to arrive at your endpoint?

Please send an amended information sheet, taking into account the following:

- How much additional time patients will spend in this study.
- Please explain MRI.
- In the section 'Why have I been chosen?' express "slid out of the MRI scanner" as "removed from the MRI scanner".
- 'We intend to publish the results .. . . .' should be changed to "we plan to publish . . . . "

Once the Committee has received written assurance that the above requirements have been met, a confirmation of approval will be issued. If you send amended documents they should be given a new version and date. Patient Information Sheet/Consent Form should be on departmental headed notepaper. Please remember to complete points 1 and 3 of the consent form.

A list of members at the meeting is enclosed.

Yours sincerely

Steven H Sacks
Chairman of the Guy's Hospital Research Ethics Committee

NHS
National Research Ethics Service

Guy's Research Ethics Committee
(South London REC Office 3)
Governor's Hall Suite
St Thomas' Hospital
SE1 7EH

Tel: 020 7188 2260
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17 June 2009

Professor Reza Razavi
Professor of Paediatric Cardiovascular Science
Division of Imaging Sciences
The Rayne Institute
4th Floor, Lambeth Wing
St Thomas' Hospital

Dear Professor Razavi

Study title:	**Comparison of tissue doppler and magnetic resonance imaging for assess**
REC reference:	**03/06/15**
Protocol number:	**Protocol Ref N/A**
Amendment number:	**Minor**
Amendment date:	**04 March 2009**
Details:	*Amendment to extend the study until October 2010 and administrative changes to the contact details on the information sheet*

Thank you for your letter of 04 March 2009, notifying the Committee of the above amendment.

The Committee does not consider this to be a "substantial amendment" as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Document	Version	Date
Notification of a Minor Amendment	Minor	04 March 2009
Participant Information Sheet	3	21 July 2008
Participant Consent Form	3	21 July 2008

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

03/06/15: **Please quote this number on all correspondence**

Yours sincerely

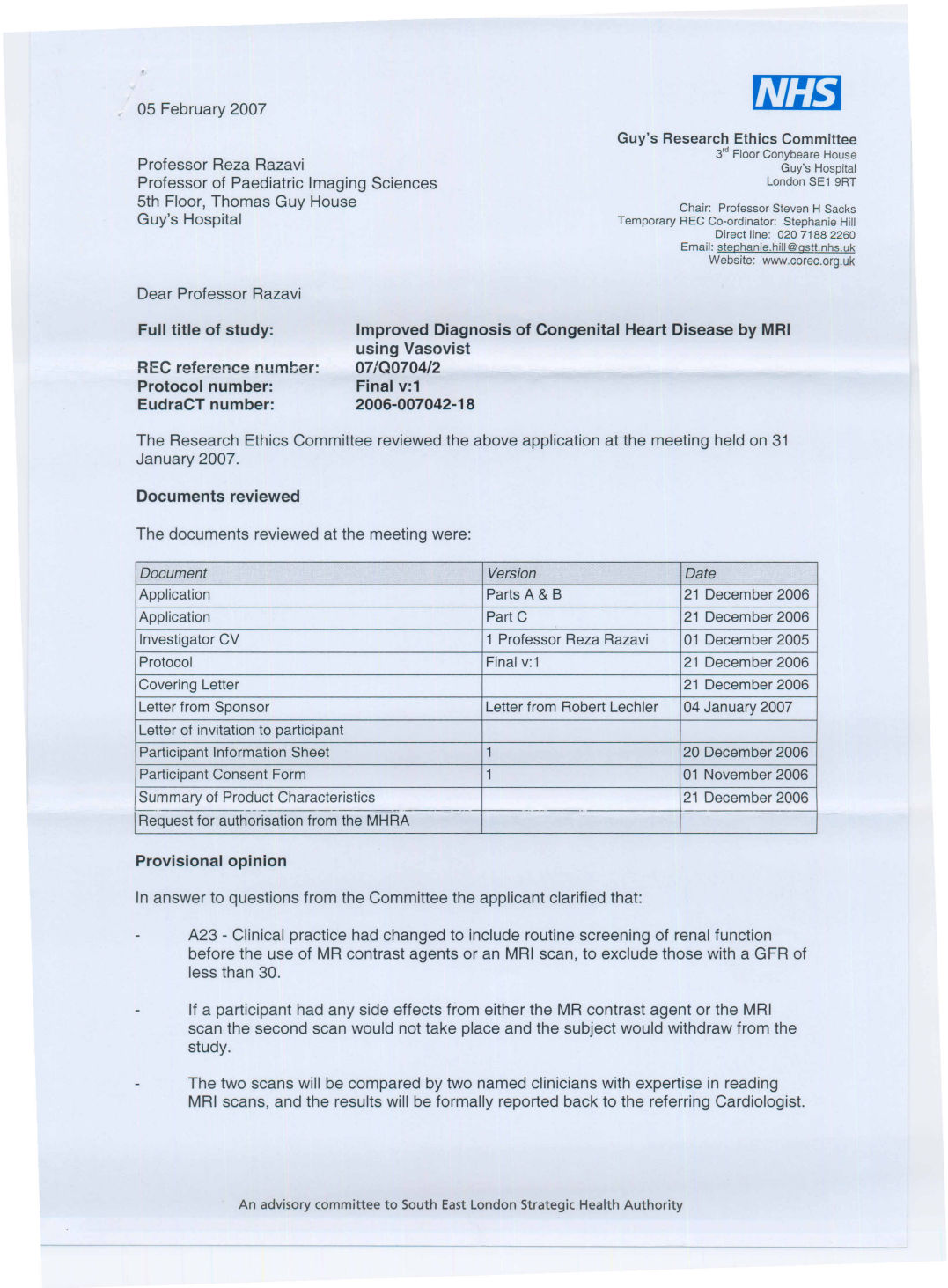
Stephanie Hill
Committee Co-ordinator

E-mail: stephanie.hill@gstt.nhs.uk

Copy to: *R&D office, GSTFT*

iii) Ethics for Fast 3D Imaging

The fast 3D protocol (described in chapter 2 and 3) was devised as part of a larger project looking at the utility of new contrast agents in the assessment of congenital heart disease.



05 February 2007

NHS

Guy's Research Ethics Committee
3rd Floor Conybeare House
Guy's Hospital
London SE1 9RT

Chair: Professor Steven H Sacks
Temporary REC Co-ordinator: Stephanie Hill
Direct line: 020 7188 2260
Email: stephanie.hill@gstt.nhs.uk
Website: www.corec.org.uk

Professor Reza Razavi
Professor of Paediatric Imaging Sciences
5th Floor, Thomas Guy House
Guy's Hospital

Dear Professor Razavi

Full title of study: **Improved Diagnosis of Congenital Heart Disease by MRI using Vasovist**
REC reference number: **07/Q0704/2**
Protocol number: **Final v:1**
EudraCT number: **2006-007042-18**

The Research Ethics Committee reviewed the above application at the meeting held on 31 January 2007.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Application	Parts A & B	21 December 2006
Application	Part C	21 December 2006
Investigator CV	1 Professor Reza Razavi	01 December 2005
Protocol	Final v:1	21 December 2006
Covering Letter		21 December 2006
Letter from Sponsor	Letter from Robert Lechler	04 January 2007
Letter of invitation to participant		
Participant Information Sheet	1	20 December 2006
Participant Consent Form	1	01 November 2006
Summary of Product Characteristics		21 December 2006
Request for authorisation from the MHRA		

Provisional opinion

In answer to questions from the Committee the applicant clarified that:

- A23 - Clinical practice had changed to include routine screening of renal function before the use of MR contrast agents or an MRI scan, to exclude those with a GFR of less than 30.
- If a participant had any side effects from either the MR contrast agent or the MRI scan the second scan would not take place and the subject would withdraw from the study.
- The two scans will be compared by two named clinicians with expertise in reading MRI scans, and the results will be formally reported back to the referring Cardiologist.

An advisory committee to South East London Strategic Health Authority

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to The Chair.

Further information or clarification required

Information sheet/consent form(s)

Please state the most common side effects of Vasovist (ie more than 1 in 100) in the information sheet.

Please include the offer of travel expenses.

When submitting your response to the Committee, please send revised documentation where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 05 June 2007.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

07/Q0704/2	**Please quote this number on all correspondence**

Yours sincerely

Professor Steven Sacks
Chair
Email: stephanie.hill@gstt.nhs.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments.*

Copy to: R&D Department, GSTFT

APPENDIX 2

Echocardiography

Echo data were collected for all TOF patients as part of the full research protocol and details of the measurements obtained are described in Chapter 2.

With the utility of an XMR unit (combined X-ray and CMR table) it was possible to perform echocardiography within the scanning room just prior to CMR and then also perform stress echocardiography whilst the dobutamine at peak dose of 20ug/kg/min immediately after completion of the DS-MR protocol.

Within this appendix the echo data will be described and documented. It has not been included within the man thesis as although baseline data is available, stress echo data was extremely difficult to achieve and therefore the data is relatively incomplete. 3D data acquisition was collected in the majority of patients. At the time of performing the study, 3D analysis software was still a relatively new entity, especially with the dilated right ventricle and volumetric measurements proved to be difficult to measure and assess accurately.

Echocardiography was not performed on the healthy volunteers.

Baseline Echo parameters

Table 20 documents the mean baseline echo parameters acquired for all TOF patients. These results clearly show that the TOF patients had well functioning but dilated RV's with at least moderate PR. All patients had good LV function on echo.

Table 20: Baseline Echo Parameters in TOF

Parameter	Mean ± SD
LV End-diastolic dimension (cm)	4.4±0.5
LV End-systolic dimension (cm)	3.1±0.5
Estimated LV EF (%)	55±5
RV End-diastolic dimension (cm)	4.7±0.7
PV Vmax (m/s)	1.9±0.6
PV Pressure Half Time (ms)	105±28
TAPSE (cm)	19±3.0
RV TDI S wave (m/s)	0.11±0.03

PV V max, peak velocity through the pulmonary valve, TAPSE tricuspid annular plane systolic excursion, TDI S wave, peak velocity of the systolic wave on tissue velocity imaging

3D volumetric assessment

Due to the technical problems already mentioned only twelve 3D data sets were available for comparison with CMR volumes. The figures below show that although RV-EDV measures tend to have modest agreement comparing CMR with Echo, there is poor agreement for RV-ESV, RV-SV and RV-EF. In general echo volumes tended to be smaller than equivalent CMR volumes and this is likely to be due to poor endocardial definition of the lateral RV wall and RVOT on echo imaging (Figure 32).

Stress echocardiography

The focus of this aspect of the protocol was to acquire 3d and TDI images to assess tissue velocity measurements using peak S wave at the RV lateral wall, septum and LV lateral wall (Figure 33). Strain and strain rate was not calculated. 3D data was collected at stress but due to high heart rates and significant RV dilatation many data sets were unsuitable for analysis

Tissue velocity imaging

These data showed that during stress there is an increase in peak S wave velocity at the RV lateral wall, septum and LV lateral wall. It appears that there is a greater increase in peak LV S wave but the increase is significant in all three positions. This is in keeping with previously documented studies that have shown an increase in all TVI measurements during dobutamine stress in TOF patients.

Summary

Echo remains an essential tool for assessing patients with TOF but direct comparison of echo parameters with CMR is difficult in these patients. CMR remains the gold standard for volumetric assessment due to the anterior position of the RV in the chest and the underestimation of volumes by echo in patients with dilated RV's. As echo technology improves it is likely that image quality and therefore endocardial definition will improve and this will allow utilization of 3D scanning in a variety of congenital heart disease patients.

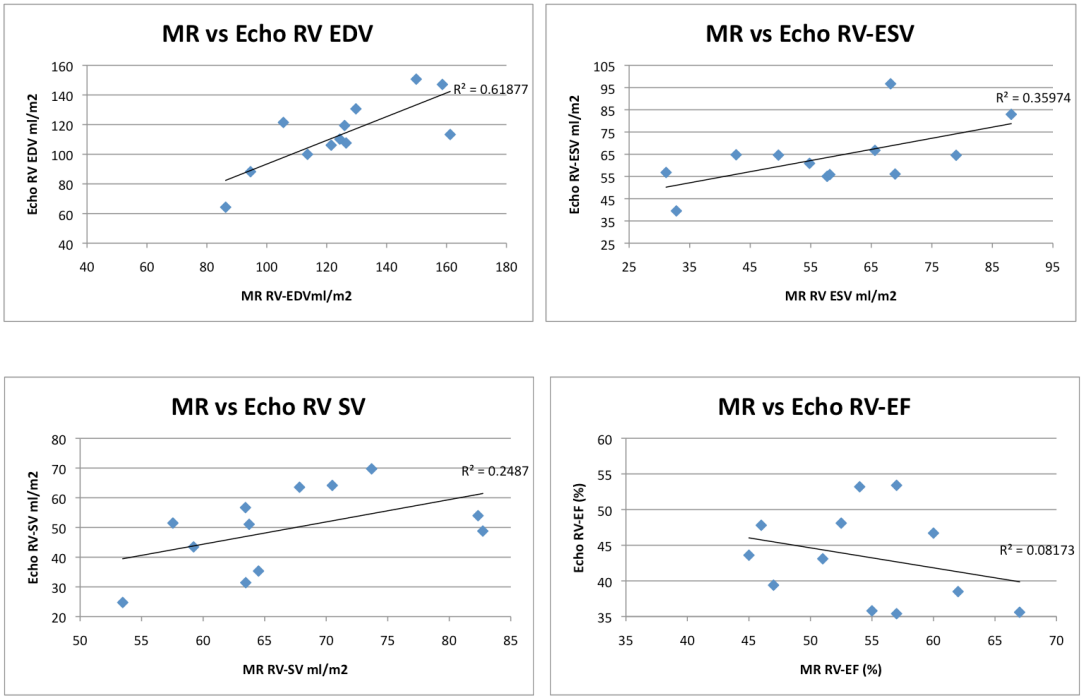


Figure 32: Comparison of 3D Echo and CMR parameters at rest

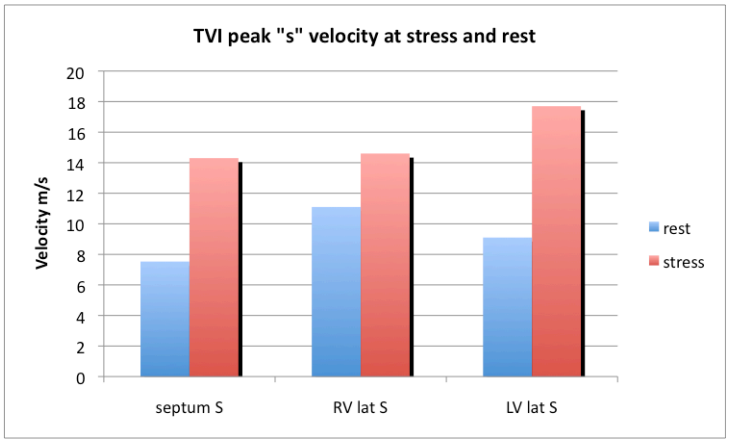


Figure 33: TVI peak S wave during dobutamine stress

APPENDIX 3

Publications

1. Single breath-hold assessment of cardiac function using an accelerated 3D single breath-hold acquisition technique – comparison of an intravascular and extra vascular contrast agent.

   Markowski MR, Wiethoff AJ, Jansen CH, Uribe S, Parish V, Shuster A, Botnar RM, Bell A, Kiesewetter C, Razavi R, Schaeffter T, Greil GF. Journal of cardiovascular Magn Reson 2012 Jul 31;14:53

2. Cardiac magnetic resonance myocardial feature tracking correlates with natural radial strain and corresponds to inotropic stimulation.

   Schuster A, Kutty S, Padiyath A, Parish V, Gribben P, Danford DA, Makowski MR, Bigalke B, Beerbaum PB, Nagel E. J Cardiovasc Magn Reson. 2012 Feb 1;14 Suppl 1:O50

3. Dobutamine stress MRI in repaired tetralogy of Fallot with chronic pulmonary regurgitation. A comparison with healthy volunteers.

   Parish V, Valverde I, Kutty S, Head C, Qureshi SA, Sarikouch S, Greil G, Schaeffter T, Razavi R, Beerbaum P. Int J Cardiol. 2011 Dec

4. Cardiovascular magnetic resonance myocardial feature tracking detects quantitative wall motion during dobutamine stress.

   Schuster A, Kutty S, Padiyath A, Parish V, Gribben P, Danford DA, Makowski MR, Bigalke B, Beerbaum P, Nagel E. J Cardiovasc Magn Reson. 2011 Oct 12;13:58.

5. Congenital heart disease: cardiovascular MR imaging by using an intravascular blood pool contrast agent.

   Makowski MR, Wiethoff AJ, Uribe S, Parish V, Botnar RM, Bell A, Kiesewetter C, Beerbaum P, Jansen CH, Razavi R, Schaeffter T, Greil GF. Radiology. 2011 Sep;260(3):680-8.

6. Cardiovascular MR dobutamine stress in adult tetralogy of Fallot: disparity between CMR volumetry and flow for cardiovascular function.

   Parish V, Valverde I, Tzifa A, Head C, Sarikouch S, Greil G, Schaeffter T, Razavi R, Beerbaum P. J Magn Reson Imaging. 2011 Jun;33(6):1341-50

7. Cardiovascular MRI in childhood.

Attili AK, Parish V, Valverde I, Greil G, Baker E, Beerbaum P. Arch Dis Child. 2011 Dec;96(12):1147-55.

8. Cardiovascular MR imaging of conotruncal anomalies.

   Frank L, Dillman JR, Parish V, Mueller GC, Kazerooni EA, Bell A, Attili AK. Radiographics. 2010 Jul-Aug;30(4):1069-94

9. Planning of catheter interventions for pulmonary artery stenosis: improved measurement agreement with magnetic resonance angiography using identical angulations.

   Valverde I, Parish V, Hussain T, Rosenthal E, Beerbaum P, Krasemann T. Catheter Cardiovasc Interv. 2011 Feb 15;77(3):400-8.

10. Single breath-hold assessment of ventricular volumes using 32-channel coil technology and an extracellular contrast agent.

    Parish V, Hussain T, Beerbaum P, Greil G, Nagel E, Razavi R, Schaeffter T, Uribe S. J Magn Reson Imaging. 2010 Apr;31:838-44.

11. Pharmacokinetic modeling of delayed gadolinium enhancement in the myocardium.

    Knowles BR, Batchelor PG, Parish V, Ginks M, Plein S, Razavi R, Schaeffter T. Magn Reson Med. 2008 Dec;60(6):1524-30

12. Atypical atrial septal defects in children: non-invasive evaluation by cardiac MRI.

    Beerbaum P, Parish V, Bell A, Gieseke J, Körperich H, Sarikouch S. Pediatr Radiol. 2008 Nov;38(11):1188-94.

13. Volumetric cardiac quantification by using 3D dual-phase whole-heart MR imaging.

    Uribe S, Tangchaoren T, Parish V, Wolf I, Razavi R, Greil G, Schaeffter T. Radiology. 2008 Aug;248(2):606

Abstract Presentations

1. AEPC, Annual Scientific Congress, Innsbruck, May 2010

- Oral presentation: Dobutamine Stress MR in Tetralogy of Fallot with Severe Pulmonary regurgitation: Is RV-ESV Response Important? (Paediatric Cardiology 2010)
- Poster presentation: Dobutamine Stress-Magnetic Resonance Imaging in repaired Tetralogy of Fallot: Agreement of flow- versus volumetric-derived parameters of cardiac function
- Poster presentation: Higher dose Dobutamine stress MR in Tetralogy of Fallot: Right ventricular end-systolic volume (RV-ESV) is a reliable parameter of systolic RV function with low observer

2. SCMR, Annual Scientific Congress, Phoenix, January 2010

- Poster Presentation: Safety, feasibility and haemodynamic effects of dobutamine stress MRI in corrected Tetralogy of Fallot (JCMR 2010)

3. European Society of Cardiology, Scientific Congress, Barcelona, August 2009

- Poster Presentation: Assessment of right ventricular contractile reserve in corrected Tetralogy of Fallot by dobutamine stress MRI (European Heart Journal 2009, 30, 807)

4. Euro CMR, Annual Scientific Meeting, Athens, May 2009

- Oral Presentation – Nominated for best abstract award: Single breath-hold assessment of ventricular volumes using 32-channel coil technology and an extracellular contrast agent

5. ISMRM, Annual Scientific Congress, Hawaii April 2009

- Oral presentation: Single breath-hold assessment of ventricular volumes using 32-channel coil technology and an extracellular contrast agent (JMRI 2009)

6. SCMR, Annual Scientific Congress, Orlando January 2009

- Poster Presentation: Imaging of Aortic Coarctation Using Gd-DTPA and Gadofosveset: A Comparative Study (SCMR 2009)

7. British Cardiac Society, Manchester June 2008

- Poster Presentation: Dobutamine Stress MRI in Tetralogy of Fallot with Severe pulmonary regurgitation: A prospective Pilot study (Heart 2008)

8. Association of European Paediatric Cardiology (AEPC), Venice May 2008

- Poster Presentation: Dobutamine Stress MRI in post repair Tetralogy of Fallot with severe pulmonary regurgitation: Preliminary results

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