The right ventricle in volume or pressure overload

Insights from novel imaging techniques

Aleksandra Trzebiatowska-Krzyńska

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To my family

“The more you know, the more you know you don't know.”

“Educating the mind without educating the heart is no education at all.”

Aristotle 400 BC

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ABSTRACT

This study is inspired by the gap in knowledge regarding the timing of cardiac surgery and interventions in adult patients with congenital heart disease. There are many parameters used assessing right ventricular function; however, most of them have pitfalls. Understanding the pathomechanisms by which the heart adapts to congenital defects is probably key to find the answer when it is time to intervene and start discussing treatment options.

Heart defects are the most frequently occurring congenital disorders. Less than 50% of individuals with moderate to severe congenital heart defects, e.g. transposition of the great arteries (TGA) or tetralogy of Fallot (TOF), survive to adulthood without intervention. Advances in cardiac surgery and better identification of individuals at risk for sudden cardiac death have increased survival rates. Currently, more than 96% of patients with congenital heart disease survive to at least 16 years of age; most undergo corrective surgery but are not cured, and only a few have normal physiology and anatomy. In many cases, the heart must develop mechanisms of adaptation to the changed conditions after surgery. Consequently, correction of the defect creates residual disease with a risk of future complications.

To prevent clinical deterioration and to identify the development of complications, patients need lifelong, regular follow up. The choice of follow-up modalities depends on the cardiac malformation.

The right ventricle (RV) plays an important role, as it is often part of the defect or is influenced by the surgery.

In the past, research was focused on assessment of left ventricular function (LV), and the RV was “the forgotten ventricle.” Observations and studies in the last few decades brought increased interest into the RV and revealed the importance of the RV in the prognosis of various cardiac diseases.

An understanding of RV morphology, pathophysiology and adaptive mechanisms is crucial for further studies of prognosis as well as for research linked to the use of particular diagnostic modalities.

When the RV is exposed to increased pressure load, e.g. in atrially corrected transposition of the great arteries (TGA), adaptation affects the cavity volume as well as the wall thickness. When the RV is volume overloaded, adaptation involves enhancement of the RV cavity volume while the wall thickness often remains unchanged under long time. RV ejection fraction (RVEF) gives some information about changes in RV function, but information on myocardial contractility and contractile reserve is also needed. New functional parameters

such as strain—also known as myocardial deformation—provide some information about intrinsic myocardial function.

In **Paper I**, we studied functional parameters such as ejection fraction and strain (radial and longitudinal strain for both ventricles) in patients with Tetralogy of Fallot (TOF) and TGA. Longitudinal RV strain was depressed in both patient groups in comparison with that in healthy individuals, and there were additional differences between the two patient groups.

In **Paper II**, we validated three-dimensional echocardiography (3DEcho) against the cardiac magnetic resonance (CMR) gold standard. The study population was limited to patients with TOF. In general, 3DEcho underestimated RV volumes but was able to identify patients with RV dilatation on CMR with high sensitivity. RV longitudinal free wall strain measured by CMR with a cut-off set at -14% identified patients with depressed exercise capacity and low peak oxygen uptake.

In **Paper III**, we studied a new CMR method to quantify and visualise turbulent flow in the heart and vessels. Turbulent flow can be harmful to tissue, blood cells, and endothelium and can contribute to tissue remodeling. In patients with TOF, turbulent flow can be seen as variance in 2DEcho color Doppler. In CMR, increased turbulent kinetic energy (TKE) could be seen with four-dimensional flow. The RV TKE was increased in patients with TOF with pulmonary regurgitation compared with that in healthy controls.

In **Paper IV**, we validated “knowledge-based reconstruction” (KBR), a novel method to calculate RV volume, against CMR in patients with various types of congenital heart defects. Two-dimensional echocardiogram-based three-dimensional RV reconstruction is a relatively uncomplicated method that creates a three-dimensional RV model based on a limited number of predefined points of interest (RV structures such as tricuspid annulus, RV free wall, or pulmonary valve).

KBR showed good agreement with CMR (intraclass correlation coefficient = 0.84 for RV end-diastolic volume and 0.89 for ejection fraction) but tended to underestimate RV volumes, which is in line with other methods based on ultrasound.

Conclusions:

3DEcho is an evolving modality that is able to identify patients with RV dilatation. It can be used clinically for the follow up of patients with congenital heart diseases, especially those with mildly to moderately dilated RVs. When an intervention seems likely, 3DEcho results should be verified by CMR.

CMR-derived measurements of longitudinal and radial strain provide a new understanding of RV remodeling and ventricular interdependence in patients with TOF and TGA. Depressed longitudinal strain may indicate a risk of depressed exercise capacity and, in patients with TGA, clinical deterioration.

Further studies in larger populations of patients with congenital heart defects are needed, as the altered RV morphology in such patients makes quantitative assessment especially challenging.

SVENSK SAMMANFATTNING

Hjärtfel är en av de vanligaste medfödda sjukdomarna. Tidigare nådde enbart hälften av dessa patienter med komplicerade hjärtfel vuxen ålder.

På grund av framsteg i barnhjärtkirurgi och bättre identifiering av risk för arytmi och plötslig hjärtdöd (SCD) har överlevnaden för patienter med Fallot tetralogy (TOF) eller transposition av de stora kärlen (TGA) ökat till 96 %.

De flesta patienter med komplicerade fel som har opererats i barndomen har ett resttillstånd som kan orsaka hjärtsvikt och komplikationer i vuxen ålder. Hjärtat anpassar sig till det postoperativa tillståndet vilket kan innebära ett ökat tryck eller volymsbelastning på kamrarna och därmed ändrade krav på pumpförmågan. Olika typer av korrigeringar leder således till olika typer av långtidseffekter.

För att förhindra klinisk försämring och för att identifiera tillkomst av komplikationer behöver patienterna livslång och regelbunden uppföljning.

Valet av uppföljningsmetod beror på typen av hjärtmissbildning och operationsmetoden.

Höger kammare (RV) spelar en viktig prognostisk roll hos patienter med medfödda hjärtfel eftersom den ofta är engagerad i defekten eller är påverkad av kirurgi. Tidigare forskning var fokuserad på bedömning av vänsterkammarfunktion (LV) medan RV var "den bortglömda kammaren".

Observationer och studier under de senaste årtiondena har påvisat höger kammares prognostiska betydelse vid olika typer av hjärtsjukdomar.

Förståelse av högerkammarens morfologi och adaptationsmekanismer är avgörande för förståelse av effekterna på prognos och för forskning gällande vissa diagnostiska metoder.

När RV utsätts för ökad tryckbelastning, t.ex. vid transposition av de stora artärerna (TGA), adapterar kammaren genom ökad volym och vägg tjocklek. Vid volymbelastning av höger kammare ökar kammarens volym medan vägg tjockleken kan under lång tid bli oförändrad. Ökade volymer kan skattas med hjälp av höger kammares slutdiastolisk volym och ejektionsfraktion (RVEF) men RVEF ger inte information om myokardiets kontraktilitet och kontraktila reserv. En ny funktionell parameter, strain - också benämnd myokarddeformation - ger ytterligare information om myokardfunktionen.

I **Delarbete I** studerades adaptationsmekanismer för RV in situationer med ökat tryck. Funktionella parametrar, som EF och strain (radiell och longitudinell RV och LV strain) bedömdes hos patienter med TGA och TOF. Dessa parametrar jämfördes mellan TGA, då RV utsätts för högt systemiskt tryck och TOF då RV arbetar med normalt eller endast lätt ökat tryck i lungcirkulationen. Korrelationer mellan parameter och arbetskapacitet bedömdes. Resultaten visar nedsatt longitudinell RV-strain i de två studerade grupperna jämfört med den friska befolkningen och även skillnader mellan patientgrupperna.

I **Delarbete II** genomfördes validering av 3-dimensionell ekokardiografi (3DEcho) mot CMR (guldstandard). Den undersökta gruppen bestod av patienter med TOF. RV-volymer underskattades med 3DEcho jämfört med CMR men 3DEcho kunde identifiera patienter med RV-dilatation med hög specificitet och sensitivitet. RV longitudinal strain i laterala väggen (RVLFWS) mätt med CMR med gräns vid -14% identifierade patienter med nedsatt arbetsförmåga och sänkt syreupptag.

I **Delarbete III** studerades CMR-metoden turbulent kinetisk energi (TKE) vilken kvantifierar och visualiserar turbulent flöde i hjärta och kärl. Turbulent flöde kan vara skadligt för blodkroppar och endotel och bidra till remodelering. Turbulent flöde kan ses som varians ("grönt") med färg Doppler vid 2DEcho. På CMR påvisades ökat TKE med 4D-flöde. Denna RV TKE var ökad hos TOF-patienter med pulmonell regurgitation (PR) jämfört med friska kontroller.

I **Delarbete IV** presenteras en ny metod för volymsbestämning av höger kammare, benämnd "Kunskapsbaserad rekonstruktion" (KBR), vilken validerades mot referens metoden CMR hos patienter med olika typer av medfödda hjärtfel. 2DEcho-baserad tredimensionell RV-rekonstruktion är en relativt enkel metod som skapar en 3-dimensionell RV-modell baserat på detektering av anatomiska landmärken (RV-strukturer såsom trikuspidaliseringen, högerkammarens fria vägg, pulmonalisklaffen etc.). KBR visar i likhet med övriga ultraljudsbaserade metoder en tendens till underskattning av RV-volymer jfr CMR.

Konklusion

3-dimensionell ekokardiografi är en metod under utveckling och validering. Den kan identifiera RV dilatation hos patienter med ToF och kan användas vid uppföljning av patienter med andra medfödda hjärtfel, särskild de med lätt till måttligt dilaterad högerkammare.

Vid misstanke om att det har tillkommit nedsatt systolisk funktion i höger kammare eller vid överväganden om kirurgisk intervention bör man verifiera 3DEcho fynd med CMR undersökning.

Longitudinell och radiell strain mätt med CMR ger ny inblick i höger kammars adaptativa mekanismer och gör det möjligt att identifiera patienter med nedsatt arbetskapacitet och TGA patienter med risk för hjärtsvikt och arytm.

Ytterligare studier med större antal patienter med medfödda hjärtdefekter behövs eftersom förändrad RV morfologi i denna population komplicerar kvantitativ bedömning.

LIST OF PAPERS

Paper I

Trzebiatowska-Krzynska A, Swahn E, Wallby L, Nielsen NE, Carlhäll CJ, Brudin L, Engvall JE.

Afterload dependence of right ventricular myocardial deformation: A comparison between tetralogy of Fallot and atrially corrected transposition of the great arteries in adult patients.

PLoS One. 2018 Sep 27; 13[1] e0204435 doi: 10.1371/journal.pone.0204435.

Paper II

Aleksandra Trzebiatowska-Krzynska, Eva Swahn, Lars Wallby, Niels Erik Nielsen, Carl Johan Carlhäll, Jan Engvall

Benefit of 3DEchocardiography for identifying RV dilatation in Fallot anomaly.

Manuscript

Paper III

Fredriksson A, Trzebiatowska-Krzynska A, Dyverfeldt P, Engvall J, Ebbens T, Carlhäll CJ

Turbulent kinetic energy in the right ventricle: Potential MR marker for risk stratification of adults with repaired Tetralogy of Fallot.

J Magn Reson Imaging. 2018 Apr; 47[2]:1043-1053 doi: 10.1002/jmri.25830. Epub 2017 Aug 2

Paper IV

Trzebiatowska-Krzynska A, Driessen M, Sieswerda GT, Wallby L, Swahn E, Meijboom F

Knowledge-based 3D reconstruction of the right ventricle: comparison with cardiac magnetic resonance in adults with congenital heart disease.

Echo Res Pract. 2015 Dec 1; 2(4):109-16 doi: 10.1530/ERP-15-0029.

ABBREVIATIONS

2CH view	two chamber view
3CH view	three chamber view
4CH view	four chamber view
AVPD	Atrioventricular plane displacement
BP	Blood Pressure
BSA	Body surface area
BMI	Body mass index
CCTGA	Congenitally corrected transposition of the great arteries.
CHD	Congenital heart defects
CMR	Cardiac Magnetic Resonance
CPET	Cardiopulmonary exercise test
DICOM	Digital Imaging and Communications in Medicine
ED	End diastole
ES	End systole
EDS	End-systolic volume
EDV	End-diastolic volume
EDVi	End-diastolic volume indexed
EF	Ejection fraction
FWLS	Free wall longitudinal strain
GLS	Global longitudinal strain
KBR	Knowledge based reconstruction
LV	Left ventricle
MAPSE	Mitral annular plane systolic excursion
NYHA	New York Heart <u>Association</u>
PAH	Pulmonary arterial hypertension
PR	Pulmonary regurgitation
RV	Right ventricle

SCD	Sudden Cardiac Death
SAX	Short axis view
SD	Standard deviation
SWLS	Septal wall longitudinal strain
SSFP	Steady-state free precession
TAPSE	Tricuspid annular plane systolic excursion.
TGA	Transposition of the Great arteries
THVV	Total Heart Volume Variation
TOF	Tetralogy of Fallot

Introduction

Adults with Congenital Heart Disease

Congenital heart defects are the most frequently occurring congenital disorders [1, 2]. Less than 50% of individuals born with moderate to severe heart defects, i.e. transposition of the great arteries (TGA), tetralogy of Fallot (TOF), or univentricular heart, will survive to adulthood without surgical intervention. Advances in cardiac surgery, successful treatment of arrhythmias, and better identification of individuals at risk of sudden cardiac death have increased survival rates in the past few decades. Today, more than 96% of patients with congenital heart disease live to at least 16 years of age. Residual lesions, ventricular dysfunction, and arrhythmias are common after surgery for congenital heart defects and often lead to increased mortality and morbidity in adulthood. Hence, patients with congenital heart defects need regular follow up and timely treatment throughout their lifetime [3] [4, 5]. The main target of follow up is assessment of ventricular function, especially right ventricular (RV) function, as the RV is often part of the congenital anomaly and plays an important role in the prognosis [6-8]. In the most of severe heart defects, the RV is exposed to increased pressure or volume loads, which initiate the development of compensatory mechanisms. A better understanding of those mechanisms will help determine the time point at which the compensatory adaptation becomes a harmful process and will enable better timing of surgery (if needed), especially in young people who face repeated interventions.

Even if the choice of follow-up modality depends on the cardiac pathology, echocardiography is the first choice for most anomalies [4]. Echocardiography is limited in its ability to visualize and assess RV function, especially in the case of RV dilatation, because of its reliance on certain geometrical assumptions. Cardiac magnetic resonance (CMR) is the reference method for measurements of RV volume [9, 10]. The RV ejection fraction (RVEF) determined by CMR has the best prognostic value among the measurable parameters [11-14] in cardiovascular disease.

There is a need for more efficient methods to assess RVEF. Three-dimensional echocardiography is emerging as a new modality to assess RV volume and RVEF, but it needs validation before it can be introduced into daily clinical praxis. Efforts to develop new functional parameters have revealed that myocardial deformation may be a good indicator of systolic ventricular function [15-18]. The aim of this thesis is to increase the knowledge about

adaptive mechanisms of the RV in adult patients with congenital heart disease and to investigate new parameters for the assessment of RV function.

Background

The most common heart defects

Transposition of the great arteries (TGA) and tetralogy of Fallot (TOF) are the most frequently encountered severe congenital heart defects. The cumulative survival rate of patients with TOF or TGA 25–30 years after Mustard repair is about 80%. The survival of such patients is limited mostly by a decline in right ventricular (RV) function. Along with residual lesions (baffle obstruction or leakage, residual ventricular septal defect, and pulmonary valve stenosis), RV dysfunction contributes to late morbidity and mortality manifested as reduced exercise capacity, heart failure, endocarditis, supraventricular arrhythmia, reoperation, and cardiac death [8].

Tetralogy of Fallot

TOF has three main components: an interventricular communication, a subpulmonary stenosis, and a biventricular origin of the aortic valve. Furthermore, the subpulmonary stenosis often leads to a fourth component: RV hypertrophy. The combination of defects results in high systolic RV pressure and low oxygenation of the blood transported to the systemic circulation. In corrective surgery, the interventricular connection must be closed and the obstruction in the RV outflow tract relieved, Fig 1-2. The most common long-term complication of TOF is the development of pulmonary valve regurgitation (PR), causing volume overload and dilatation of the RV [13, 19]. Hence, many patients with TOF need repeated replacements of the pulmonary valve. The time for intervention is determined by RV function and the regurgitant fraction in the RV outflow tract, both of which are difficult to assess with conventional two-dimensional echocardiography (2DEcho).

Figure 1. TOF before correction

Figure 2. TOF after correction

Transposition of the great arteries

In TGA, the systemic and pulmonary circulations are not serially connected, Fig 3. Intrauterine life is possible with TGA, because the placental circulation is connected to the systemic circulation by way of the arterial duct of Botalli; however, urgent neonatal surgery is required to sustain postnatal life. At the end of the twentieth century, the only possible correction for TGA was so-called physiological, atrial correction according to Mustard or Senning [20, 21], which redirects highly oxygenated blood to the body and desaturated blood to the lungs, Fig 4. After the correction, the RV supports the systemic circulation and is exposed to the systemic pressure. Associated lesions (ventricular septal defect, pulmonary stenosis) are common and complicate the course of the disease.

Associated lesions include a predisposition to arrhythmia and tricuspid valve regurgitation (TR) [22-24]. Patients with more than moderate TR and RV dysfunction have increased morbidity and mortality. TR is a significant independent predictor of outcomes and is strongly related to RV dysfunction. The question is whether TR leads to RV dysfunction or vice versa in a vicious circle. RV failure with ventricular enlargement results in worsening of the TR because of annular dilatation. Although the factors responsible for progressive failure of the systemic RV are not quite clear, it seems that the ventricular

geometry and the morphological features of the respective atrioventricular valves are important.

Some patients exhibit myocardial perfusion defects in the systemic RV after Mustard operation, suggesting inadequate coronary blood supply due to a supply/demand mismatch in the context of a severe RV hypertrophic response to systemic pressure loading [25].

Figure 3. TGA before correction

Figure 4. TGA physiological correction

The right ventricle

The RV, with its complex geometry and distinctive adaptive mechanisms in congenital heart disease, is a challenge to cardiologists. The RV is a crucial chamber, and its dysfunction—both systolic and diastolic—has clear implications to short-term and long-term outcomes. Reliable and accurate evaluation of the RV is very important clinically [26]. RV function is a well-known prognostic indicator, especially in congenital heart diseases, in which the RV is often involved in the pathology [27-29].

Right ventricular morphology

In contrast to the ellipsoidal shape of the left ventricle (LV), the shape of the RV is more complex. Viewed from the side, it appears triangular, and from the cross section it appears crescentic. The shape of the RV is influenced by the position of the interventricular septum. In adults, the volume of the RV is greater than that of the LV, whereas the muscle mass of the RV is only one sixth that of the LV. The two ventricles are closely interconnected through a three-dimensional network of common muscle fibers. The myofiber architecture of the RV is mainly composed of superficial, circumferential fibers and deep, longitudinal fibers oriented from the base to the apex. The superficial fibers of the RV continue as superficial fibers of the LV. The fiber continuity and the common fibers of the interventricular septum and common pericardium give the morphological basis for ventricular interdependence [30].

The RV can be divided into three compartments: the inlet compartment, the apical trabecular compartment, and the outlet compartment. Such division is particularly useful in analyses of congenitally malformed hearts. In addition, it is functionally convenient to divide the RV by the crista supraventricularis. Proximal to the crista supraventricularis is the RV sinus, which comprises >80% of the total RV volume. The infundibulum, situated between the crista supraventricularis and the pulmonary valve, comprises >20% of the RV volume but contributes <15% of the RV stroke volume [31].

Right ventricular physiology

The contraction pattern of the RV is serial, with the inlet and the infundibular parts contracting about 25–50 ms apart. Three mechanisms describe ventricular contraction: the inward movement of the free wall produces the “bellows effect”; the contraction of the longitudinal fibers draws the tricuspid annulus towards the apex; and, finally, the RV free wall displaces at the point of attachment to the interventricular septum secondary to LV contraction. The shortening of the RV is greater longitudinally than circumferentially and contributes the most important share of the RV stroke volume [32].

RV systolic function reflects contractility, preload, and afterload. About 20% of the RV systolic pressure and volume depends on LV contraction by way of ventricular interdependence [33, 34].

The RV afterload represents the load the RV needs to overcome during ejection. When the RV ejects into the pulmonary circulation, afterload can be simplified as the load caused by pulmonary vascular resistance [19] which is highly variable under physiologic conditions. The pulmonary systolic pressure is much lower than the systemic pressure, which enables the RV to pump the same stroke volume as the LV using only 25% of the LV stroke work.

The RV preload represents the load before contraction. According to the Frank Starling mechanism, increases in preload within the normal range increase RV stroke volume.

An important aspect of RV physiology is myocardial perfusion, the coronary flow pattern differs between the right coronary artery (RCA) and the left coronary artery (LCA). In contrast to the LCA, in normal loading conditions, coronary flow in the proximal RCA occurs in both diastole and systole. The RV has a relatively low rate of oxygen consumption, which makes it relatively resistant to irreversible ischemic injury compared with the LV. The RCA perfuse parts of the RV and the inferior wall of the LV. The RCA often has a more extensive collateral system including, for example, the moderator band artery.

Figure 5. Pathophysiology of RV failure

Right ventricular adaptation to changes in load

Pressure overload

The initial adaptive response of the RV to increased pressure load is myocardial hypertrophy followed by progressive contractile dysfunction [23]. Subsequently, RV chamber dilatation develops to maintain stroke volume despite the contractile dysfunction. Pathophysiology of RV failure Fig 5. The increase in size and the pressure overload of the RV influence the position of the interventricular septum, which influence LV filling and compliance and thus contributes to diastolic dysfunction of the LV, Fig 6 A-B.

Figure 6. (A) Normal RV pressure. (B) High RV pressure. (C) RV volume overload.

Volume overload

The RV is more able to adapt to volume overload than to pressure overload. It can tolerate volume overload for a long time without a significant decrease in systolic function [35]; however, long-standing RV volume overload leads to morbidity and mortality. Progressive TR with worsening of RV function leads to clinical symptoms of right heart failure.

Dilatation of the RV shifts the interventricular septum towards the left side of the heart, changing the LV geometry, which may contribute to low cardiac output by decreasing the LV preload, Fig 6C.

Exercise capacity in adults with congenital heart disease

Patients with congenital heart disease generally have a depressed exercise capacity, defined as <90% of the reference capacity, expressed in terms of maximal workload in Watts and peak oxygen uptake [36-38]. Adult females with congenital heart disease have lower peak oxygen consumption (VO₂) than adult males with congenital heart disease, which is in line with what is found in the healthy population. The degree of impairment depends on the type of malformation and the type of corrective surgery [39] and is predictive of morbidity and hospitalization [40].

Methodological background

Assessment of RV function

Cardiac magnetic resonance

CMR is the most accurate method to measure RV volumes. It enables the assessment of valve flows, which is the basis for the calculation of regurgitant volumes and shunt fraction. In addition, CMR has several features that are not evaluated in this thesis, such as the ability to differentiate among myocardial edema, necrosis, and fibrosis. CMR can also be used to quantify myocardial perfusion.

General principles of CMR

CMR is based on the distribution of water in the body. It detects the motion (i.e. “spin”) of positively charged protons while the patient is inside a CMR scanner. All of the protons are exposed to a powerful external magnetic field, which causes the proton spins to align with (parallel to) or against (antiparallel to) the direction of the magnetic field. The brief application of a radiofrequency signal causes the spins to flip to a certain degree from the direction induced by the main magnetic field. As the protons return to the basal state, they produce a signal, which can be characterized by two parameters: T1 relaxation time and T2 relaxation time. The relaxing spins produce different gradients of magnetic field, allowing spatial information to be detected by receiver coils in the scanner. Different tissues have different relaxation times, and T1-dominated or T2-dominated image contrast can differentiate among tissues.

Balanced steady-state free precession imaging (SSFP)

SSFP is the most widely used technique for the assessment of cardiac morphology. It allows the acquisition of images of the heart throughout the cardiac cycle in imaging planes similar to those used in echocardiography or along the x-y-z grid of the scanner. SSFP produces a high contrast between the bright signal of the blood and the dark signal of the myocardium.

Late gadolinium enhancement (LGE)

Gadolinium is a contrast agent that distributes in the extracellular space without entering intact myocytes. In areas where the myocyte membranes are injured (such as in myocardial infarction with necrosis) or the extracellular space is increased (e.g. due to amyloid protein or fibrosis), the gadolinium concentration is increased and persists for a longer time compared with that in healthy myocardium. Pathological areas thus appear bright on imaging scans, which is the basis for the expression that scarred tissue presents “late” gadolinium enhancement, or LGE [10, 41].

Echocardiography

Two-dimensional echocardiography can be used to measure the length and area of the cardiac chamber and to perform linear measurements perpendicular to a chosen axis (M-mode). It is possible to measure movements of the blood and tissue using various techniques based on the Doppler principle, including pulsed wave Doppler, continuous wave Doppler, color Doppler, and tissue Doppler. Doppler-based methods can be used to assess both the direction and the velocity of blood flow. 2DEcho measurements can only be performed within a particular cut plane/slice. Because Doppler velocity measurements are dependent on the accurate alignment of the ultrasound beam along the intended flow direction, they may underestimate the flow velocity if the angle between the ultrasound beam and the flow is in excess of 20 degrees [42]. That feature limits the usefulness of 2DEcho, because more complicated structures are often difficult to measure in a standardized slice. Echocardiography is continuously evolving, however. The use of 3DEcho is increasing in research and is slowly entering the clinical realm because of its ability to visualize cardiac structures and provide improved volume calculations [43].

Cardiopulmonary exercise testing (CPET)

CPET is usually performed on a bicycle ergometer or a treadmill. Measurements of airflow, CO₂ production, and VO₂ allow the simultaneous assessment of metabolism and cardiovascular response.

Maximal VO₂ (VO₂ max) is the objective measure of the maximal aerobic capacity of the individual as demonstrated from reaching a plateau during incremental exercise. Peak VO₂ is the highest value measured, without regard to reaching a plateau and often indexed by body mass and time (e.g. ml × kg⁻¹ × min⁻¹). Indexed values allow comparison among individuals of different body sizes; however, they can underestimate the capacity in individuals with large body mass.

Specific methodologies used in the current study

Flow measurement with cardiac magnetic resonance

Flow measurement with CMR is performed with a technique called phase contrast. When a magnetic gradient is applied in a certain direction, the frequencies of nuclear spins change in proportion to the strength of the magnetic field. Consequently, their relative phase constantly changes as long as the gradient is applied. From that information, the mean flow velocity within a certain area can be calculated and multiplied by a number of time steps, which creates information about volume flow, as in the calculation of the stroke volume of the aorta or the pulmonary artery.

By combining the flow velocity-encoding information in all three spatial directions inside a three-dimensional sample volume throughout the cardiac cycle, the flow velocity and flow directions can be calculated for a location anywhere inside the volume. Because the method combines three-dimensional velocity information and time, it is often referred to as four-dimensional phase contrast imaging, or 4D flow CMR. This method allows for non-invasive visualization and quantification of blood flow patterns inside vessels and the heart.

Turbulence is a property of gases and liquids, even the blood in the human cardiovascular system. A special application of CMR allows the calculation of the presence and magnitude of small variations in velocity, also called “turbulent kinetic energy” (TKE). Research on TKE originated in Linköping and has been applied to several cardiac conditions [44, 45].

Measurement of right ventricular volume by cardiac magnetic resonance

The most common algorithm used with CMR to calculate RV volume and the RVEF is the disk summation method. With CMR, slices of the thorax can be acquired in any direction. Thus, the heart can be assessed from a stack of time-resolved slices acquired in the axial direction (sometimes denoted “trans-axial” or from slices acquired with reference to the long axis or the short axis of the cardiac ventricles, Fig 7. Analysis is most often performed manually and offline, despite available methods to automatically analyze slices “on the fly,” as in the “inline ventricular function” promoted by one vendor. On every slice, endocardial contours are manually traced at end diastole and end systole, identified on the basis of tricuspid and aortic valve closure and maximal/minimal RV cavity size. On the most basal slices, it is difficult to detect the border between the right atrium (RA) and the RV. If more than 50% of a segmented slice cavity area is assigned to the RV (based on wall thickness and cavity size), the area is included in the RV volume. Endocardial trabeculae are included in the RV cavity [46, 47].

Figure 7. CMR based RV volume calculation

Fig 7.1 Right ventricular end systole (RVES). Fig 7.2 Right ventricular end diastole (RVED).
A: Segmentation in the short axis view (SAX), B: Three-chamber view (3CH),
C: Four-chamber view (4CH) - control of RV endocardial tracking.

Echocardiography

Two-dimensional echocardiography is the initial modality for RV evaluation. Current guidelines prescribe how to perform a comprehensive 2DEcho cardiac scan [48]. In the current study, images were acquired from several scanning positions: the apical four-chamber position; the RV-focused apical four-chamber position, Fig 8-9; the left parasternal long axis Fig 10-11; short axis positions, the left parasternal RV inflow position; and the subcostal position for assessment of RV size, systolic and diastolic function, and RV systolic pressure—when possible.

Figure 8. TGA 4CH RV size

Figure 9. ToF 4CH RV size

ToF = tetralogy of Fallot, TGA = transposition of the great arteries, PLAX = parasternal long axis, 4CH = four-chamber view, RV = right ventricle, D = diameter, RVD1 (basal RV linear dimension) = maximal transversal dimension in the basal third of RV inflow at end diastole in the RV-focused view, RVD2 (mid-cavity RV linear dimension) = transversal RV diameter in the middle third of RV inflow, approximately halfway between the maximal basal diameter and the apex, at the level of papillary muscles at end diastole.

Figure 10. ToF PLAX RV size

Figure 11. TGA PLAX RV size

RVOT prox = measured from the anterior RV wall to the interventricular septal-aortic junction. ToF = tetralogy of Fallot, TGA = transposition of the great arteries, PLAX = parasternal long axis, 4CH = four-chamber view, RV = right ventricle, RVOT = right ventricular outflow tract.

Three-dimensional echocardiography

We attempted 3DEcho on all of the participants in the current study [43]. The participants were in the same position for 3DEcho as they were for the 2DEcho examination. The image sector was optimized to encompass the whole RV within the ultrasound sector. During a single end-expiratory breath-hold, four or six wedge-shaped sub-volumes gated to the R wave were acquired to be stitched together to create a dataset representing the whole RV. The optimal frame rate was 25–55 frames per cardiac cycle.

Dilated or hypertrophic RVs; for example, after an atrial switch procedure for TGA; may be difficult to visualize completely with acceptable image quality.

In patients with TOF, the RV outflow tract may be dilated via the surgical insertion of a patch to relieve RV outflow tract obstruction. In patients with moderately dilated or hypertrophic ventricles, the long axis of the RV is often tilted towards the horizontal plane, and the sternum compromises the image quality to a lesser extent, enabling imaging of the entire RV.

Three-dimensional echocardiography image analysis

We analyzed the RV dataset using dedicated software (4D RV-Function, TOMTEC Arena, TomTec Imaging Systems, Germany) that allowed semiautomatic contour detection of the endocardial borders, Fig 12. The program calculated RV volumes and RVEF with the possibility of manual contour revision, Fig 13 [49, 50]. The RV is displayed as an end-diastolic mesh defining the RV endocardium in Fig 14.

Figure 12. How to define the anatomical extent of the left ventricle (LV) and the right ventricle (RV), A=apical, 4CH=four-chamber view, 2CH=two chamber view, 3CH=three chamber view, SAX=short axis view, MV=mitral valve, AJL=anterior junction, PJL=posterior junction.

Figure 13. Three-dimensional analysis of the RV. After positioning anatomical landmarks in the acquired 3DEcho data set, a short-axis (SAX) view and a four-chamber (4CH) view were extracted. The endocardial border had to be manually adjusted in both end diastole and end systole. After acceptance by the observer, the three-dimensional endocardial surface was calculated and rendered, EDV=end diastolic volume, ESV=end systolic volume,

Figure 14 A and B. End-diastolic mesh defining the RV cavity volume. PV = pulmonary valve, TV = tricuspid valve, AoV=aortic valve, TGA=Transposition of the great arteries, TOF=Tetralogy of Fallot.

Analysis of patients who have an enlarged RV that functions as a systemic ventricle, e.g. patients with congenitally corrected TGA (CCTGA) or TGA after Mustard or Senning repair, is difficult. Modelling of the RV volume is frequently not reliable in such patients.

Knowledge-based reconstruction (KBR)

KBR is based on a standard 2DEcho examination with some modification to the RV views to visualize the pulmonary valve and the posterior tricuspid leaflet [51-53].

We stored the acquired two-dimensional images of the RV and their spatial information on a VentriPoint Medical System computer attached to the ultrasound scanner, Fig 15. To account for the fact that RV shapes vary with different diseases, the KBR software provides different references for RV reconstruction in specific malformations. Thus, before start of the data analysis, the kind of pathology under examination needs to be entered into the software.

VentriPoint Diagnostic System

Figure 15 VentriPoint Diagnostic System. Ref. VMS user guide, 2011

Reprinted from VMS user manual with permission of the VMS Company, California.

The integrated system contains the hardware necessary to capture ultrasound images, track the three-dimensional coordinates of the ultrasound transducer, and complete the reconstructions.

The first step of image analysis is the definition of end diastole, which is based on electrocardiogram (ECG) and visual assessment, taking into account the largest RV cavity size and the opening and closure of the tricuspid and pulmonic valves (if visible).

In the next step, 15 to 35 points are placed on predefined crucial anatomical structures, Table 1, Fig 16. The procedure must be performed on images of end diastole and end systole.

Combining data from two-dimensional cross-sections and their location in three-dimensional space, and after comparison with the reference database, the VentriPoint system reconstructs a three-dimensional model of the RV using piecewise smooth subdivision surface reconstruction (PSSR) technology, Fig 17 [54].

Table 1. Ventripoint Medical System image acquisition protocol

View	Region of Interest
Parasternal Long Axis	Axis RV Anterior Free Wall, Septum, MV, AoV
Parasternal Long Axis	RV inflow Anterior / Posterior TV Annular Insertions, RVE
Parasternal Long Axis	RVOT/PA PV Annular Insertions
Parasternal Short Axis	RVOT/PA PV Annular Insertions, RVOT, Conal Septum
Parasternal Short Axis	Mitral Valve Annular Level
Parasternal Short Axis	Papillary Muscle Level, RVE, RVS, Crux of RV Inf/Ant Free Wall and septum
Parasternal Short Axis	Apex RVE, RVS, Crux of RV Free Wall and Septum
Apical 4 Chamber – Focusing on RV	Anatomical Structures Anterior and Septal TV Annular Insertion
True RV Apex	Oblique Apical True RV apex, RVS, RVE
Apical RV 2Chamber, Counter Clockwise from 4 CH	RVE, RVS
Foreshortened Apical	RV Inflow/Outflow RV LAT/ANT Free Wall, RV Inflow, RVOT

RV = right ventricle; MV = mitral valve; AoV = aortic valve; RVE = RV endocardium; PA = pulmonary annulus; TV = tricuspid valve; RVS = RV septum, RVOT=Right ventricular outflow tract; PA PV = pulmonary valve, pulmonary annulus; RV LAT=RV lateral wall; RV ANT = RV anterior wall;

Figure 16. Result of the first reconstruction

Figure 17. Final result

Colors represent anatomical structures: blue=ventricular septum; red=RV myocardium, light brown=pulmonic annulus; violet=tricuspid valve; green=RV septal edge; yellow=apex.

Reviewing the three-dimensional model

The first step in reviewing the results of a three-dimensional model construction is to examine how the borders on the three-dimensional model intersect and align with the anatomical structures displayed on the two-dimensional images. Next, the border intersections of the three-dimensional model should be revised to confirm adequate coverage of the RV. Finally, all the points on the three-dimensional model need to be controlled. If the points adhere to the surface of the three-dimensional model, then the model is most likely an accurate representation.

Cardiopulmonary exercise test CPET

CPET was performed on a cycle ergometer (Monark Ergonomic 839E, Monark Exercise AB, Vansbro, Sweden) with the patient in an upright position. Depending on the expected individual physical work capacity, a protocol was devised that began with 5 min of steady-state load at 30/50 W followed by load increases in increments of 10/20 W/min with the goal of reaching maximal exercise capacity within 8–12 min. The test was maximum-symptom limited; exercise was interrupted at Borg scale of perceived exertion ≥ 17 . Breath-by-breath respiratory gas analysis was performed using a Jaeger Oxycon Pro (Vyaire Inc., Mettawa, IL, USA). Peak VO_2 was calculated as the mean of VO_2 values measured during the last 60 s of exercise and was expressed as $\text{ml} \times \text{kg}^{-1}$ and $\text{ml} \times (\text{kg}^{-1} \times \text{min}^{-1})$. Patients were considered to have achieved maximal exercise capacity if the respiratory exchange ratio exceeded 1 continuously for 3 min or longer. Patients were monitored by continuous 12-lead ECG. Blood pressure was measured using a cuff manometer at rest and at 3 min intervals during exercise. Spirometry was performed in all patients immediately before the CPET to obtain forced vital capacity and forced expiratory volume in 1 s measurements.

Right ventricular functional parameters

A comprehensive examination of the RV should be performed using multiple acoustic windows to assess functional RV parameters [42, 55].

Linear measurements

The most frequently used linear measurements are fractional area change (FAC), tricuspid lateral annular systolic velocity (S'), and tricuspid annular plane systolic excursion (TAPSE). The quantitative assessment of RV function based on 2DEcho parameters recommended by cardiology guidelines has some method-related limitations but can still be used to distinguish between normal and abnormal RV function [56]. The categorization of RV dysfunction is hampered by relatively high inter-observer variability, especially in cases of mild to moderate RV dysfunction. The correlation between 2DEcho linear parameters and RVEF has been studied, and some authors recommend using the correlation between TAPSE and CMR-assessed RVEF [57]. In patients with TGA, there was a weak correlation between linear parameters of RV function (measured by 2DEcho) and CMR [58]. Loading conditions should always be taken into consideration when normal values of longitudinal parameters and FAC are interpreted [59].

Ejection fraction

EF is a volume-based parameter calculated as the difference between the end-diastolic and end-systolic RV volumes, expressed as a percentage: $EF = (EDV - ESV) / EDV \times 100 \%$. EF is a load-dependent parameter influenced by LV function and interventricular septum configuration.

Even if CMR is recommended for the assessment of RV volumes and RVEF, it is important to recognize some critical points in CMR imaging of the RV for a correct interpretation of the results. A main difficulty in the calculation of volume is the determination of the separation between the RV and the right atrium (RA).

Equally important is the correct determination of the levels of the infundibulum and the pulmonary valve, especially in patients with TOF after cardiac surgery and patch placement in that region. As previously mentioned, the infundibulum represents about 20% of the RV volume [60].

Interobserver variability is high for the tricuspid valve region (42%) and the infundibulum and the pulmonary valve (34%). In relative terms, interobserver variability is the greatest in the infundibular region. In the current study, the overall interobserver variability for volume estimation with CMR was 10%, which is in agreement with other studies [61] [62, 63].

Ejection fraction measured by three-dimensional echocardiography

During the past decade, many studies have been conducted to validate 3DEcho in comparison with the gold standard CMR. Most research found that 3DEcho significantly underestimates RV volumes [2] [64]. The same studies revealed high intraobserver and interobserver variability.

In the study by Grewal, RV end-diastolic volume (EDV) and end-systolic volume (ESV) measured by 3DEcho were underestimated by 12–36% when EDV was >250 ml and ESV was >150 ml. By contrast, those values were underestimated by only 5–15% when RVEDV was <250 ml. In the study by Gopal [65], which used the disc summation method, the underestimation of RV volumes by 3DEcho was not significant in relation to CMR values, but the studied population had normal or only slightly dilated RVs.

Recently, new software solutions have become available that increase the reliability of 3DEcho. (TOMTEC v 2.0 and newer versions of Knowledge based reconstruction (KBR) system, Ventripoint Medical Systems (VMS+).

Global longitudinal strain (GLS), circumferential and radial right ventricular strain

Lagrangian strain is defined as the change in the length of an object in a certain direction relative to a baseline length, Figure 18.

Strain % = $(L_t - L_o) / L_o$, where L_t is the length at time t , and L_o is the initial length at time zero. Strain can be described as the change in length divided by the original length.

Figure 18. Strain concept

A positive strain value represents an increase in dimension, whereas a negative strain value describes a decrease in dimension (shortening). The average strain in different myocardial segments is calculated by the software (CMR or Echo) and presented numerically and in the form of time-resolved graphs [66].

Assessment of deformation parameters

Recent studies reported the importance of novel parameters (i.e. strain and strain rate) in the assessment of RV function and prognosis in cardiovascular disease [67]. The use of LV and RV strain is recommended in patients with ventricular dysfunction. Interventions that cause hemodynamic improvement are usually followed (or preceded) by improvement in longitudinal strain of the right or left ventricle [68]. As the longitudinal fibers are preferentially subendocardial [31][29], pathological processes of the endocardium can be detected as a reduction in longitudinal strain values, as in ischemia and in increased afterload of the LV and RV. If it is mainly the epicardium that is engaged in the disease or pathological process, differences in circumferential strain may be more obvious than changes in longitudinal strain. Circumferential strain may increase as a compensatory mechanism in situations with reduced longitudinal strain to preserve stroke volume, as in the case of LV hypertrophy in response to increased afterload [67, 69]. As the LV is composed of three layers including circular fibres, increased LV afterload can transform circular fibres as well. Some studies suggest that in hypertrophic cardiomyopathy, radial strain decreases in parallel to the longitudinal strain [70]. Both ventricles share myocardial fibres, and the changes in RV strain correspond to changes in LV function. Thus, LV strain modifications [71] could reflect ventricular interdependence [72].

Modalities to assess strain are echocardiography (speckle tracking) and several principles in CMR such as “feature tracking” (related to speckle tracking), tagging, displacement encoding with stimulated echoes [73], and strain encoding [74] [75].

Echocardiography

Post processing analysis of files was performed offline using commercially available software (EchoPac, GE Healthcare, Horten, Norway). To measure RV global longitudinal strain (RVGLS), the RV endocardial border was manually traced in the four-chamber view and divided into three septal and three free wall segments. After analysis of the segmental tracking quality and subsequent manual adjustment, longitudinal strain curves were generated for each RV segment. Peak RVGLS was calculated by averaging values obtained from all six RV segments, Fig 19. RV free wall longitudinal strain (RVFWLS) was calculated using the same tracking as global RV strain by averaging the strain value of the three lateral wall segments.

Longitudinal RV strain assessed with speckle tracking

Figure 19. 2DEcho RV speckle tracking.

Longitudinal Strain analysis of the right ventricle (RV). In the first step, the user sets the points in the posterior and septal RV wall at the level of the tricuspid valve and in the RV apex, starting the tracking of the RV endocardial border in the apical four-chamber view (A4CH) (**left top**). The strain curves are generated by the software (**right top**). A color map of segmental strain over the cardiac cycle is produced with the segments arranged in a linear fashion, allowing visual assessment of the contraction pattern (**right bottom**). After approval of the endocardial tracking by the user, peak systolic strain values are displayed for all six RV segments and for global systolic RV strain (**left bottom**). AVC, aortic valve closure

Many studies have found depressed global longitudinal strain (GLS) in the systemic RV in patients with atrially corrected TGA. Kalogeropoulos in 2012 showed that patients with GLS $< -10\%$ (less negative) have increased risk of heart failure and ventricular arrhythmia [76].

Cardiac magnetic resonance-derived myocardial feature tracking (FT-CMR)

FT-CMR provides deformation parameters from routinely available steady-state free precession (SSFP) cine sequences [77].

In the current study, FT-CMR was performed using dedicated software provided by TomTec Imaging Systems (2D CPA MR, Cardiac Performance Analysis). The endocardial border was drawn manually in an end-diastolic frame in the four-chamber view. The RV strain curves are demonstrated in Fig 20-21. The software is user friendly with a short learning curve and has high

interobserver correlation for RV longitudinal and circumferential strain, intraclass correlation coefficient (ICC) = 0.75–0.97; ICC was somewhat lower (0.66) for radial RV strain and mid-ventricular strain [78]. Radial and circumferential FT-CMR is based on a midventricular RV slice in the short-axis view.

Figure 20. FT-CMR measurement of longitudinal RV strain (**bottom left** - numerical values; right, **bottom right** - strain curves, FT-CMR=feature tracking CMR).

Figure 21. FT-CMR, Radial (**upper**) and circumferential (**bottom**) RV strain (left, numerical values; right, strain curves per segment), FT-CMR=feature tracking CMR.

Cardiopulmonary exercise test in the patients with congenital heart defects

Patients with congenital heart disease generally have depressed exercise capacity, expressed in maximal workload in Watts and peak oxygen uptake [36, 37, 80]. The degree of impairment depends on the type of malformation and is predictive of morbidity and hospitalization [40].

Statistical analysis

We tested the normality of the data by visual inspection of histograms and by Shapiro-Wilk test. Continuous data were expressed as the mean $\pm$ standard deviation (SD) or as the median and range. Confidence intervals were used where appropriate. We considered P values < 0.05 to be statistically significant. We tested the differences between the results of 3DEcho and CMR by paired-samples t-test. We constructed Bland-Altman plots to assess bias between methods [81]. We tested the relationships between variables by bivariate correlation analysis, with calculation of Pearson correlation and linear regression. We calculated the ICC for single and average measurements for interobserver and intraobserver variability in an absolute agreement two-way mixed model. All calculations were performed with IBM SPSS Statistics 23.

Aims of the thesis

The aim of this thesis was to study the remodelling of the RV in response to increased pressure and volume loads. Specifically, our goals were to:

- study the applicability of new parameters for the assessment of RV function (radial and longitudinal strain) measured by CMR
- evaluate the applicability of 3DEcho for volumetric analysis of RV function in adult patients with TOF and TGA in comparison with the CMR gold standard
- investigate the new CMR modality TKE when applied to blood flow in patients after TOF correction
- study the new 2DEcho-based technique for three-dimensional RV Knowledge based reconstruction (KBR) and its applicability in adult patients with congenital heart disease

RESULTS

Papers I and II

Patient population

Forty-four adult patients with corrected congenital heart disease underwent CMR and echocardiography examinations within 4 h of each other. For inclusion criteria see additional files, flow charts in Figure 23 (Paper I) and Figure 24 (Paper II) included at the end of the thesis. Seven cardiovascular healthy participants in another study served as the control group for CMR measurements. The patients also performed a CPET after the imaging examinations. There were two subgroups of patients: those with the RV in a sub-pulmonic position (TOF) and those with the RV in a systemic position (TGA). The basic clinical parameters (Table 3) were similar between the subgroups. The QRS duration on the electrocardiogram was significantly longer in the patients with TOF than in those with TGA. Systolic RV pressure was at the systemic level in the patients with TGA, whereas it was normal or slightly increased in the patients with TOF. According to the New York Heart Association (NYHA) functional classification, the patients were moderately affected by their cardiac condition; none of the patients was rated in NYHA class IV. The patients with TOF generally had higher NYHA functional classification than those with TGA, with 61% of the former and 38% of the latter rated in NYHA class I, Table 2.

In paper II, the patients with TGA were excluded from the analysis because of poor image quality on 3DEcho.

Table 2 Patient characteristics

Variable	RV systemic position N=8	RV subpulmonic N=36	P Value	Control Group N=7
Age	36 ($\pm$ 7)	34 ($\pm$ 11)	ns	37($\pm$ 14)
BMI kg/m ²	26 ($\pm$ 2.9)	24 ($\pm$ 4)	ns	24 ($\pm$ 3)
BSA m ²	1.9 ($\pm$ 0.26)	1.9 ($\pm$ 0.25)	ns	1.9 ($\pm$ 0,2)
SBP mmHg	116 ($\pm$ 14)	116 ($\pm$ 14)	ns	120 ($\pm$ 10)
DBP mmHg	73 ($\pm$ 8)	74 ($\pm$ 12)	ns	75 ($\pm$ 9)
Systolic RV pressure	116 ($\pm$ 14)	25 ($\pm$ 10)	sign.	n/a
Heart rate beats/min	60 ($\pm$ 6)	71 ($\pm$ 13)	ns.	65 ($\pm$ 14)
QRS msec	105 ($\pm$ 24)	139 ($\pm$ 29)	0,004	98 ($\pm$ 10)
NYHA FC I/II/III/IV (%)	38/50/12/0	61/23/16/0		100/0/0/0

Nine of the 36 patients with TOF displayed moderate to severe pulmonary regurgitation (PR). All of the patients with TOF had undergone one to three (mean 1.5) surgical treatments. The mean age at the time of surgical correction for TOF was 4 years. Among the eight patients with TGA, four had received a Senning atrial correction, and two had received a Mustard correction. The remaining two patients with TGA had CCTGA.

Strain in the RV and LV

Compared with the patients with TOF, the patients with TGA had significantly increased RV wall thickness [5.3 mm ($\pm$ 0.8 mm) versus 3.5 mm ($\pm$ 0.5 mm), $p < 0.0001$] and a tendency for higher midventricular radial strain [+22.2% ($\pm$ 6.7%) versus 18.5% ($\pm$ 5%)], although the difference in midventricular radial strain was not significant.

The patients with TGA had less RV atrioventricular plane displacement (RVAVPD) than the patients with TOF ($p < 0.05$), and both groups had less RVAVPD than healthy controls ($p < 0.001$), Figure 22.

Both groups of patients had significantly depressed RV global longitudinal strain (RVGLS) compared with the controls ($p < 0.001$). That finding is in agreement with the significantly depressed RVAVPD in the patients with TGA ($p < 0.0001$)

Figure 22. Box plots with correlations for Radial midventricular LV strain; Radial midventricular RV strain; Global longitudinal RV strain; RV atrioventricular plan displacement; LV ejection fraction.

TGA = transposition of the great arteries; TOF=Tetralogy of Fallot; LV = left ventricle, RV = right ventricle, * = significant difference, ns = non-significant difference

Right ventricular volume and ejection fraction

In Paper I and Paper II RV volumes were measured with CMR and three-dimensional echocardiography respectively. Comparison between methods was performed in Paper II.

The mean RV volumes (end diastolic and end systolic) in the patients with TOF and TGA were somewhat greater than those in the controls and were also greater than the reference value for the respective method, CMR according to ref. Maceira [82] and 3DEcho ref. Tamborini [83]. There was no significant difference in RV volumes between the patients with TOF and those with TGA. LVED volumes were smaller than RVED volumes in patients while in controls RV and LV end diastolic volumes did not differed.

Compared with CMR, 3DEcho produced smaller estimates of RV end-diastolic volume and RV end-systolic volume.

Among the LV volumetric measurements, LVEF was lower in the patients with TOF than in those with TGA 49% ($\pm 6\%$) versus 55% ($\pm 7\%$), $p < 0.05$.

CMR and 3DEcho correctly identified 68% and 95% of the females and 94% and 100% of the males with RV dilation, respectively, Table 3 and Table 4.

Table 3. RV volume in comparison with reference values for CMR and 3DEcho.

RVEDV ml	CMR	CMR	CMR	3DEcho	3DEcho	3DEcho
	Maceira ¹ RVEDV mean $\pm$ SD	Patients Mean $\pm$ SD	RVEDV > ref. (N, %)	Tamborini ² RVEDV mean $\pm$ SD	Patients Mean $\pm$ SD	RVEDV > ref. (N, %)
RVEDV						
Male	169 $\pm$ 25	212 $\pm$ 59	13 (68)	99 $\pm$ 22	198 $\pm$ 27	18 (95)
Female	133 $\pm$ 22	182 $\pm$ 49	16 (94)	79 $\pm$ 11	176 $\pm$ 49	17 (100)
RVESV						
Male	62 $\pm$ 15	126 $\pm$ 35	19 (100)	35 $\pm$ 10	110 $\pm$ 33	18 (95)
Female	49 $\pm$ 13	101 $\pm$ 34	17 (100)	25 $\pm$ 7	89 $\pm$ 23	17 (100)

RV=Right ventricle; EDV=end-diastolic volume; ESV=end-systolic volume; SD=standard deviation; CMR=Cardiac magnetic resonance

¹ Right ventricular volume by gender and age < 60 years

² Right ventricular volume by gender and age between 30 – 39 years

There was no significant difference in RVEF between the patients with TOF and those with TGA. RVEF in patients was lower than in controls but the difference was not significant. Table 4.

Table 4. CMR-assessed RV and LV volumes and ejection fraction

Variable	RV TGA N=8 (SD)	RV TOF N=36 (SD)	<u>P value</u> <u>TGA v. TOF</u>	Control group N=7
LV EDV ml				
Mean (SD)	153 ($\pm$ 57)	156 ($\pm$ 31)	ns	190 ($\pm$ 35)
Median (min-max)	145 (86-235)	155 (107-222)		196 (141-229)
LV ESV ml				
Mean (SD)	71 ($\pm$ 34)	80 ($\pm$ 18)	ns	92 ($\pm$ 26)
Median (min-max)	60 (35-129)	78 (51-122)		82 (67-138)
LV EF %				
Mean (SD)	55 ($\pm$ 7)	49 ($\pm$ 6)	0.009	54 ($\pm$ 6)
Median (min-max)	57 (40-62)	50 (37-60)		53 (48-61)
RV EDV ml				
Mean (SD)	220 ($\pm$ 82)	197 ($\pm$ 56)	ns	195 ($\pm$ 40)
Median (min-max)	167 (146-350)	182 (111-339)		205 (140-248)
RV ESV ml				
Mean (SD)	129 ($\pm$ 61)	114 ($\pm$ 41)	ns	101 ($\pm$ 25)
Median (min-max)	98 (69-246)	107 (62-260)		108 (63-128)
RV EF %				
Mean (SD)	43 ($\pm$ 6)	43 ($\pm$ 8)	ns	49 ($\pm$ 4)
Median (min-max)	43 (30-53)	43 (23-60)		48 (44-55)

RV volumes from 3DEcho and CMR, with reproducibility measurement

Correlations and limits of agreement between 3DEcho and CMR were assessed with Pearson correlation, regression analysis, ICC, and Bland Altman plots. There was high intraclass correlation in the assessments of RV end-diastolic volume between 3DEcho and CMR. The intraclass correlation was somewhat lower for RV end-systolic volume, and poor for RVEF, Table 5. The Bland Altman plots showed relatively small bias but wide confidence intervals.

Table 5. Comparison of CMR and 3DEcho measurements of RV end-diastolic volume, RV end-systolic volume, and RV ejection fraction.

Table 5. Intertechnique comparison

	Pearson correlation, r	Regression analysis, R ²	Intraclass correlation for average measurements, ICC
RVEDV ml CMR/3DEcho	r=0,82 p<0.05	R ² =0.67	ICC = 0.90 p<0.05
RVEDVI ml/m ² CMR/3DEcho	r=0.75 p<0.05	R ² =0.56	ICC = 0.86 p<0.05
RVEDV interobs. 3DEcho	r=0.54 p<0.05	R ² =0.29	ICC = 0.76 p= 0.05
RVESV ml CMR/3DEcho	r=0.72 p<0.05	R ² =0.51	ICC = 0.81 p<0.05
RVEF % CMR/3DEcho	r=0.42 p<0.05	R ² =0.18	ICC= 0.60 p<0.05

RVEDV= Right ventricular end-diastolic volume, RVEDVI= Right ventricular end-diastolic volume indexed per body area, RVESV=Right ventricular end-systolic volume, CMR=Cardiac Magnetic Resonance, 3D Echo=Three dimensional echocardiography, RVEF=Right ventricular ejection fraction, SD=Standard deviation.

Cardiopulmonary exercise test in adults with congenital heart defects

Patients with heart defects have impaired exercise capacity in comparison with healthy individuals, and females generally have lower peak VO₂ and maximal workload in Watts than males. The exercise intolerance in the patients in our study is similar to that presented in other papers, Table 6 [80] [38, 40].

Table 6. Peak VO₂ in the study by Kempny et al. and in the current study.

Diagnosis	Male ¹	Female ¹	Male ² N 3	Female ² N 5
TGA atrial	27.4±7.3	21.8±6.5	25.7± 1.8	21.4±5.8
			Male N 19	Female N 17
TOF	27.2±9	22.5±6.8	29.3±8.1	24.8±4.8

¹ Kempny [40], the total numbers of patients with TGA and TOF were 98 and 568, respectively. ² Current study

Because the number of patients with TGA in our study was small, we excluded those patients from our assessment of the correlation between RV free wall longitudinal strain and exercise capacity. Among the patients with TOF, those with decreased exercise tolerance had longitudinal free wall strain less negative than -14% Table 7. The patients with reduced RV longitudinal free wall strain also had reduced tricuspid annular plane systolic excursion measured by echocardiography (2D and 3D), Table 8.

Table 7. RV free wall strain and exercise capacity above and below -14%

RVFWLS > - 14 %		
Parameter	Female N 12	Male N 9
	Mean ± SD [C I]	Mean ± SD [C I]
CPET Wat max	138 ±33 [73; 203]	227 ±54 [121; 332]
CPET VO ₂ ml x kg ⁻¹ x min ⁻¹	26 ± 4 [18; 34]	32 ±8 [16; 48]
TAPSE 3D Echo	17 ±5 [7;27]	14 ±6 [2;26]
TAPSE 2 D Echo	16 ±4 [9;23]	14 ±4 [7;21]
RVFWLS ≤ - 14 %		
Parameter	Female N 5	Male N 10
	Mean ± SD [C I]	Mean ± SD [C I]
CPET Wat max	96 ±26 [43;149]	186 ±51 [86;286]
CPET VO ₂ ml x kg ⁻¹ x min ⁻¹	22 ±5 [12;33]	27 ±8 [12;42]
TAPSE 3D Echo	14 ±3[9;19]	12 ±4 [5;20]
TAPSE 2 D Echo	14 ±1[12;17]	13 ±2 [8;18]

RVFWLS= Right ventricular free wall longitudinal strain, CPET=Cardio pulmonary exercise test, TAPSE=Tricuspid annular plane systolic excursion, SD=standard deviation, CI=Confidence interval

In patients with TOF, longitudinal LV strain was higher (i.e., more negative; $p < 0.05$) in those with RV free wall strain more negative than -14% than in those with RV free wall strain less negative (lower) than -14%. Table 8

Table 8 Free wall longitudinal strain and other functional parameters of RV and LV function

Female			Male	
Parameter $\pm$ SD	RVFWLS $\leq$ -14 % N 5	RVFWLS $>$ -14 % N 12	RVFWLS $\leq$ -14 % N 10	RVFWLS $>$ -14 % N 9
LVGLS %	-19.6 $\pm$ 4.9	-24 $\pm$ 5.2	-17.8 $\pm$ 3	-22.3 $\pm$ 3.7
LVEF %	47 $\pm$ 8	44 $\pm$ 8	39 $\pm$ 8	45 $\pm$ 6.4
RVEF %	53 $\pm$ 5	49 $\pm$ 5	43 $\pm$ 5	52 $\pm$ 5
RVEDV ml	158 $\pm$ 35	191 $\pm$ 52	214 $\pm$ 69	208 $\pm$ 49
RVESV ml	84 $\pm$ 25	109 $\pm$ 36	134 $\pm$ 36	117 $\pm$ 32
TAPSE mm	13.8 $\pm$ 2.6	16.8 $\pm$ 4.8	12.4 $\pm$ 3.7	14 $\pm$ 6
Watt max	96 $\pm$ 27	138 $\pm$ 33	186 $\pm$ 51	227 $\pm$ 54
Peak VO ₂ ml $\times$ kg ⁻¹ $\times$ min ⁻¹	22 $\pm$ 5.4	26 $\pm$ 4.3	27 $\pm$ 7.6	32 $\pm$ 8.2
PA pr. mmHg	23 $\pm$ 14	12 $\pm$ 16	26.7 $\pm$ 16	22 $\pm$ 17

RVFWLS=right ventricular free wall longitudinal strain, LVGLS=left ventricular longitudinal strain, LV=left ventricle, RV=right ventricle, EF=ejection fraction, EDV= end-diastolic volume, ESV = end-systolic volume, PA pr. = pulmonary artery pressure, Peak VO₂ = peak oxygen uptake during the test, TAPSE = tricuspid annular plane systolic excursion, SD = standard deviation

Paper III

Study population

This study included 16 patients with corrected TOF and existing PR who were not subjected to pulmonary valve replacement (PVR) and one patient that had PR despite previous PVR. The patients were divided into two groups based on the PR fraction: those with a lower PR fraction ($\leq 11\%$) and those with a higher PR fraction ($>11\%$).

Results

The patients with a higher PR fraction had a greater RV end-diastolic volume than those with a lower PR fraction; however, the RV end-diastolic volume was below the threshold for PVR in both groups [7, 68]. There was no difference between the two groups in QRS duration, which was previously linked to RV end-diastolic volume [84].

Higher TKE values were related to the magnitude of PR. Four-dimensional flow-specific TKE markers had slightly stronger association with RV remodeling than conventional two-dimensional flow PR parameters. Patients with a higher PR fraction had larger RVs. The patients with a higher PR fraction had markedly increased TKE levels, both globally and locally, despite the absence of a clear indication for reintervention.

Conclusions

We hypothesized that there are factors other than progressive PR and RV volume overload that contribute to RV dilation. Increased kinetic energy in the right ventricular outflow tract (RVOT) in both systole and diastole, which is equivalent to increased turbulence, could be one of several factors contributing to RV remodeling. Disturbed flow has been linked to endocardial dysfunction and may potentially increase the risk of fibrosis development.

These findings suggest novel mechanisms responsible for the development of late complications after TOF repair. TKE has potential to serve as marker for risk stratification.

Paper IV

The aim of this paper was to assess the feasibility and accuracy of knowledge based reconstruction (KBR), a new, knowledge-based approach to RV volume measurement. Patients with congenital heart disease from the outpatient clinic at the University Hospital in Utrecht were included in the study.

Patient population

Nineteen unselected adult patients with congenital heart disease (six females and 13 males) were included in the study. The diagnoses were TOF with stenosis or insufficiency in a pulmonary homograft, TGA after atrial switch, TGA after arterial switch, and TGA after Rastelli correction. One patient suffered from pulmonary hypertension not related to congenital heart disease. The mean age of the patients was 28 years (range = 43 years).

Results

RV volumes assessed with KBR were smaller than RV volumes measured with CMR however for RVESV the difference was not significant.

$EDVi_{(KBR)} 114 \pm 17$ ml versus $EDVi_{(CMR)} 121 \pm 19$ ml ($p < 0.05$), $ESVi_{(KBR)} 63 \pm 14$ ml versus $ESVi_{(CMR)} 64 \pm 16$ ml ($p = 0.5$) and $RVEF_{(KBR)} 45 \pm 8\%$ versus $RVEF_{(CMR)} 47 \pm 9\%$, respectively ($p < 0.05$).

The correlation between both methods assessed with ICC was 0.84 for RV EDVi, 0.90 for RV ESVi, and 0.89 for RVEF ($p < 0.001$).

Table 9. Comparison between KBR and CMR

	Mean	SD	CI	df	Sig.
EDV	-12.63	12.93	[-20.58; -4.67]	15.00	0.004
EDVi	-7.13	8.09	[-11.44; -2.81]	15.00	0.003
ESVi	-1.25	6.97	[-4.96; 2.46]	15.00	0.48
SV	-9.94	8.09	[-14.63; -5.25]	15.00	0.000
EF	-2.0	3.56	[-3.90; -1.04]	15.00	0.04

EDV = end-diastolic volume, ESV = end-systolic volume, SV = stroke volume, EF = ejection fraction
i=indexed volume per body surface area

Conclusion

KBR underestimates RV volumes. The difference between KBR and CMR is significant for end-diastolic volume ($p < 0.05$) and RVEF ($p < 0.05$) but not for end-systolic volumes. RVEDV underestimation by 12.6ml and RVEDVi 7

ml seems to be acceptable from a clinical point of view, especially taking into consideration variation of the RV pathology in the studied group.

DISCUSSION

The first two papers in this thesis examined the determination of RV volumes and strain with the aim to increase our understanding of RV remodeling and adaptation. The third paper introduced CMR TKE and examined the feasibility of using TKE to investigate RV remodeling. In the last paper we applied the Knowledge Based Reconstruction (KBR) to a group of patients with congenital malformations to test its feasibility for volume measurements in this population.

RV volumes

It is well known that echocardiography underestimates RV volumes in comparison with CMR, especially in patients with dilated RVs, such as those with congenital anomalies [64].

RV volumes in adult patients with congenital heart defects were increased in comparison with reference values for all assessment methods (CMR, 3DEcho, and KBR), which is in line with previous findings [85] [82, 83]. In patients with repaired TOF, the RV remodels and enlarges in an unpredictable way. The apical part of the RV dilates, the diameter in the cross-section changes from crescent-shaped to rectangular, and the bulging base of the ventricle makes it challenging to define the RV borders. Only 25% of the patients with TOF presented with moderate or severe PR at the start of the study (Paper I and II). All of the patients had indexed RV volumes below 150 ml/m^2 , which is the threshold for consideration of PVR. The small RV volumes in the study population might have been the most important factor behind the high feasibility of 3DEcho found in our studies. Smaller volumes allow a complete acquisition of the full RV volume, reducing the issue of volume underestimation by three-dimensional ultrasound.

In normal hearts, the RV outflow tract accounts for 20% of the RV volume. In the hearts of patients with TOF and a dilated RV outflow tract, that figure is probably even higher [86, 87]. An enlarged, abnormal, and often aneurysmal outflow tract is common in repaired TOF and is especially difficult to visualize. The RV outflow tract is often surgically reinforced with prosthetic material, which frequently has different physical properties than the surrounding tissues, making border delineation problematic. Twenty of the patients with TOF had transventricular surgery, while 12 had trans-annular surgery, and

two had trans-atrial corrections. Transventricular and trans-annular surgeries contribute to progressive RV dilatation. Furthermore, trans-annular surgery also contributes to the development of PR as well as an increased risk of RV outflow-tract aneurysm [88]. Because most of the patients in our studies had been subjected to those surgical techniques, the substrate for RV and RV outflow-tract dilatation was present, which could contribute to high interobserver variability [89]. Our results regarding the total RV volumes agree with the results from previous studies of similar populations [64, 90]. Another condition frequently used to study the response of the pressure-loaded RV is pulmonary arterial hypertension; however, the RV volume, in patients with that condition is usually smaller than that in patients with congenital heart defects and hence interobserver variability is lower. Smaller RVs more easily fit into the image sector than larger RVs, which facilitates assessment of the presence and extent of RV remodeling [91].

The TomTec software does not include the RV outflow tract in its delineation of the endocardial border. The wall tracking is based on the algorithm for the normal RV. This may lead to underestimation of the RV volume by 3DEcho. Medvedofsky used the same TomTec version and reported RV volumes comparable to ours but with higher correlation with CMR assessed volumes and with lower interobserver and intraobserver variability. That report however did not include RVs with postsurgical anatomic distortion [49, 50].

SonoVue is an echo contrast used for delineation of the myocardial border and assessment of perfusion defects [92]. We could not corroborate previous reports of improved agreement between 3DEcho and CMR for the determination of RV volumes after the application of echo contrast [93]. The previous studies did not include patients with altered anatomy, however, and only 10% (three patients) of the patients in one study had a simple form of congenital pathology [89]. Therefore, we regard the addition of contrast to 3DEcho as insufficient to improve the anatomical delineation of complex congenital anomalies.

Most studies that assess the feasibility and reliability of 3DEcho in patients with congenital heart disease involve relatively small patient populations. In general, they emphasize difficulties with endocardial border delineation and show a tendency to underestimate volumes, especially in large RVs [94]. An important factor is the experience of the examiners in the acquisition and assessment of 3DEcho and in congenital heart disease in general. A low level of 3DEcho experience might have contributed to the high interobserver variability of the 3DEcho measurements in our study.

CMR is often used as a gold standard in research. However, there are some drawbacks to the application of CMR: scanner time may be unavailable; the evaluation of images requires a long time in comparison with that of 3DEcho images; and interobserver variability is fairly high in patients with complicated anatomy. We suggest that the combination of 2DEcho linear parameters with 3DEcho in experienced hands often is sufficient for routine follow up, but CMR should be applied frequently when the anatomy is difficult.

Deformation parameters, right ventricular strain

A previous study showed that in physiological conditions, longitudinal displacement of the RV (i.e., RVAVPD) produces a higher contribution to the total variation in heart volume than radial contraction. The same study reported that longitudinal shortening is a greater contributor to RV stroke volume than circumferential shortening; and RVAVPD is responsible for about 80% of the RV stroke volume, while LV atrioventricular plane displacement (LVAVPD) is responsible for about 60% of the LV stroke volume [32]. The authors concluded that in the normal LV, radial function contributes a larger share of the total variation in heart volume than it does in the normal RV (40% versus 20%). Several studies have described a reduction of longitudinal and circumferential strain in TGA, TOF, and hypertrophic cardiomyopathy [67] [95-98]. We could speculate whether there is a coupling between low AVPD and depressed RVGLS.

Transposition of the great arteries

RV longitudinal strain was ($-16 \pm 2.9\%$) lower (i.e., worse) in the systemic ventricle than in TOF group ($-19.5 \pm 5.6\%$), and control group ($-28 \pm 5.5\%$).

Previous studies have shown that lower RV longitudinal strain in patients with TGA is related to functional capacity and thus predictive of adverse outcomes [99]. Our results partly confirmed that observation. Both patient groups presented with lower longitudinal strain than the control group, and their exercise tolerance was depressed to the level described in previous studies of exercise tolerance in patients with TOF or TGA [38, 40]. However, we did not have records of adverse events at the start of the study, and we made no formal longitudinal follow-up observations (Paper I).

The RV in patients with TGA responds to increased afterload by developing hypertrophy [23, 100]. We hypothesize that the high radial RV strain in the patients with TGA in our study mirrors adaptation to increased pressure load

and is related to an increase in wall thickness. In analogy, if high longitudinal strain corresponds to an increase in preload, it would be important to search for a cutoff value of strain that indicates irreversible myocardial changes and progression of fibrosis [15]. The interpretation of changes in RVGLS and RVAVPD in patients with TGA needs to take the long-term effects of cardiac surgery into consideration and not only the effects of myocardial hypertrophy. In patients with TGA, circumferential RV strain correlates moderately with ejection fraction of the systemic RV after atrial correction (Mustard or Senning) [88]. We could not confirm that observation, possibly because the number of patients with TGA in our study was small.

TR has adverse prognostic value in TGA, because it contributes to RV volume overload in situations with a high-pressure load. Several questions need to be addressed. First, how should longitudinal RV strain be interpreted in the situation with chronic pressure overload and increased volume load, or in other words, is an increase in RVGLS to be expected? Second, is the lack of increase in strain in response to increased volume load a poor prognostic factor? Werther et al. discussed RVGLS in patients with pressure and volume overload, but their study included only patients with normal anatomy. Patients with high RV pressure (>70 mmHg) were excluded, which limits the applicability of their findings in relation to our population.

Radial LV strain in the patients with TGA was significantly lower than that in the patients with TOF and in the control individuals. That result could be the effect of adverse remodeling of the LV in TGA, which is no longer exposed to high afterload, in analogy to what occurs in the RV during the first weeks after birth [101].

Tetralogy of Fallot

The patients with TOF had significantly lower (less negative) longitudinal CMR-derived RV strain than the control individuals [-20% ($\pm$ 4%) versus -28% ($\pm$ 7%)]. This is in line with previous reports that impaired longitudinal strain is predictive of adverse clinical outcomes independently of the ejection fraction and is related to subpulmonary ventricular function [72, 99].

RVAVPD was also significantly lower in the patients with TOF than in the controls 11 mm ($\pm$ 2.5 mm) versus 16 mm ($\pm$ 1.6 mm), $p < 0.001$. RVEF was also lower in the patients with TOF than in the controls, but the difference was not significant 43% ($\pm$ 8%) versus 49% ($\pm$ 4%).

In TOF, LV dysfunction is a risk factor for SCD. Therefore, assessment of LV function is just as important as assessment of RV function [102]. The patients with TOF in our study had significantly lower LV ejection fraction than the patients with TGA and the controls. The patients were in sinus rhythm and without clinical symptoms of heart failure. The RVEF in the patients with TOF was also depressed in comparison with normal values [82][71]. We can only speculate whether the depressed LV ejection fraction in those patients was an effect of adverse remodeling in response to impairment in the RVEF and thus an expression of interventricular dependence. Impairment of the LV ejection fraction is classified as mild if the ejection fraction is between 40% and 59% [102]. Therefore, the impairment of LV ejection fraction in our population was mild, with an LV ejection fraction of $49\% \pm 6\%$. The risk of SCD is greatest in patients with moderate to severe impairment of the LV ejection fraction, especially in combination with a QRS duration exceeding 180 ms [100].

Myocardial deformation parameters are predictive of outcomes in patients with TOF [103]. Previous studies have reported that patients with TOF who experience adverse outcomes have lower (less negative) RV and LV longitudinal strain [104], and it has been suggested that longitudinal RV strain and circumferential LV strain should be included in risk assessment of patients with TOF [105]. In our study, there was no significant difference in left ventricular global longitudinal strain (LVGLS) between the patients with TOF and the controls. We did not have records of adverse outcomes at the time that patients were enrolled in the study, and all of the participants were in good clinical condition without signs of heart failure. However, we observed that, when the patients were stratified by gender and right ventricular free wall longitudinal strain (RVFWLS), LVGLS was higher in patients with higher peak

oxygen uptake and better exercise capacity expressed in Watts. Lower RVGLS ($>-14\%$) was indicative of patients with a low exercise capacity (Paper II).

Our sample size only allows speculation about whether higher LV strain reflect ventricular interdependence, as patients with higher exercise tolerance also had higher (i.e., more negative) RVFWLS [33], or if it simply depends on better bilateral ventricular function.

A correlation between LVGLS and LV ejection fraction in patients with heart disease was reported previously [106]. We did not find such a correlation between longitudinal strain and ejection fraction in either ventricle. That discrepancy can be explained by the fact that patients that had undergone surgery for congenital heart defects were not included in the previous study. As surgery (e.g., patch placement in the ventricular septum) often causes regional abnormalities in wall motion, the results of the previous study cannot be extrapolated to the population with congenital heart defects in general.

The interesting observation in our study is the correlation between right and left ventricular longitudinal strain and right and left ventricular ejection fraction in TOF population, this observation needs confirmation in a studies in a larger group of patients.

Based on results of our study we recommend that strain measurements be introduced into clinical practice as a complement to calculations of RVEF in patients with congenital heart defects. Further development of software that allows a reliable assessment of deformation parameters with both echocardiography and CMR will facilitate higher reproducibility and more reliable assessment of RV function.

Cardiopulmonary exercise test

Teratology of Fallot

Our results are consistent with previous studies describing impaired exercise tolerance in patients with heart defects [38] [107]. Exercise capacity was depressed in our whole study population, and there was a difference between genders. There are several possible explanations for those results, including the influences of cardiac reserve, lung function, and age [108]. In our study, males with TGA had slightly lower peak VO_2 than in study by Kempny. However, as there were only three males in our sample, the results are not representative for the TGA population. The results from Kempny for the TOF population are in line with our results. We observed the effects on LV longitudinal strain in males and females with RVFWLS above and below a

cutoff of -14%, which is in line with previous findings, but the correlation may be non-linear. Our sample included only five females with negative strain values $\leq -14\%$, which precluded statistical analysis.

RV lateral wall strain has been shown to have higher prognostic value than global RV strain, which is in line with our findings that the difference in exercise capacity relates to RVFWLS.

Knowledge-based reconstruction

KBR was feasible in RVs with different anatomy, because it does not require visualization and tracking of the endocardial border of the RV but instead relies on the detection of predefined anatomical structures. In many malformations, the RV has an unpredictable shape, which makes the use of commonly used parameters and views impractical.

We found that KBR consistently underestimated RV volumes by a small amount. In a recently published study by Pieterman [109], KBR overestimated RV volumes. The largest difference in the previous study was in patients with right ventricle-pulmonary artery (RV-PA) pathology, a group whose anatomy is difficult to visualize. The study population was younger and more heterogeneous and had smaller body surface area than the population in our study.

Factors influencing image quality

In a previous study, Laser reported a small underestimation of RV end-diastolic volume and an overestimation of RV end-systolic volume by KBR. The patients in that study were younger than the patients in our study. The differences between our study and the previous one might be related to the number of points defined for the reconstruction, which was higher in the study by Laser [51], thus allowing a more exact anatomical definition to be calculated (64 points in average).

KBR has high feasibility and works best in younger patients with better image quality. When differences among KBR studies are assessed, the high variability of RV shapes should be taken into consideration. The diagnostic method should be tailored for each patient [110].

Limitations

Our study had a small number of participants. The RV dysfunction varied in severity and was based on different pathologies among the patients. Many studies of congenital heart defects include children and adolescents. Differences in the selection of patients complicate comparisons of results among research papers.

We did not use gadolinium-enhanced images, which would have provided T1 measurements and values for extracellular volume to enable the assessment of the presence of diffuse fibrosis.

Future directions

Future studies should address whether changes in radial strain correspond to changes in RV wall thickness and RVEF in patients with TGA. Additionally, a future study with gadolinium-enhanced CMR should identify the level of myocardial fibrosis beyond which the amelioration of fibrosis and adverse functional changes is no longer possible.

FT-CMR showed appropriate reproducibility in our study and may be feasible in a larger, multicenter longitudinal study for the assessment of prognostic information based on various expressions of strain.

CONCLUSIONS

RV volumes derived from 3DEcho in patients with congenital heart defects showed larger right ventricular end diastolic volumes and higher interobserver variability compared with those in individuals with normal hearts. Variation within and between observers and operators remains an important issue in the evaluation of volume measurements, especially when decisions about and the timing of (re)interventions depend on indexed volumes, as they do in patients with congenital heart defects.

CMR measurements remain the gold standard, but even with CMR, a high level of operator experience and standardized protocols are necessary to keep interobserver variability low.

Deformation parameters assessed by CMR correlate with RV function and exercise capacity in patients with TOF and TGA. Reproducibility and agreement between CMR and 2DEcho measurements are high for anatomically normal ventricles. Larger differences are seen when the RV morphology is altered after repeated surgeries, which requires a re-assessment of the reproducibility of the measurements.

Knowledge-based, “three-dimensional RV reconstruction based on two-dimensional imaging” also known as “knowledge-based reconstruction”, “KBR”, acquisition facilitates the standardization of investigative protocols. The idea of reconstruction based on comparison with a large database of patients with corresponding pathology is in line with other methods for “multi-atlas segmentation.” Those methods and other approaches to machine learning seem to have the potential to improve segmentation of the RV in patients after surgery for complicated congenital heart diseases.

GENERAL CONCLUSIONS

Myocardial deformation parameters (i.e., longitudinal and radial RV strain) have prognostic value in patients with TOF and TGA. When they are assessed with CMR, they have high reproducibility and feasibility. The reproducibility is somewhat lower if the measurements are based on echocardiography. Our results show some differences between groups of patients, but the small group sizes make it difficult to show statistical significance. Larger longitudinal studies are needed to validate the prognostic value of strain in both TOF and TGA.

It is highly feasible to use 3DEcho to assess patients with TOF with mild to moderate RV dilation. However, we cannot confirm the feasibility of using 3DEcho for volume calculations in patients with TGA. The altered morphology in patients with TGA prevents reliable three-dimensional reconstruction and volume determination. At times, 3DEcho has high interobserver variability, and its accuracy seems to be related to the experience of the operator. CMR verification is needed in cases with complicated anatomy.

The visualization of turbulent blood flow is a new modality and needs further validation in patients with TOF and PR. We could only test it in a small group of patients in the current study, but our results show that the method introduces some new information to our understanding of the cardiac remodeling process.

The new concept, “three-dimensional RV reconstruction based on two-dimensional imaging,” is a method with high reproducibility that produces a more exact estimation of RV volumes than conventional 3DEcho. It has high feasibility and allows patient-tailored volume reconstruction. The method is still under development and requires further validation in different pathologies.

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Additional file.

Figure 23. Flow chart, inclusion Paper I

1* inability to cooperate, AF atrial fibrillation, PM Pacemaker, TGA Transposition of the Great Arteries, ccTGA congenitally corrected transposition of the Great Arteries, ToF Tetralogy of Fallot, PS pulmonary stenosis

Additional file.

Figure 24. Flow chart, inclusion. Paper II

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