Outcome Late After Repair of Tetralogy of Fallot

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Outcome Late After Repair of Tetralogy of Fallot

Uitkomst lange tijd na operatie in verband met tetralogie van Fallot

Proefschrift

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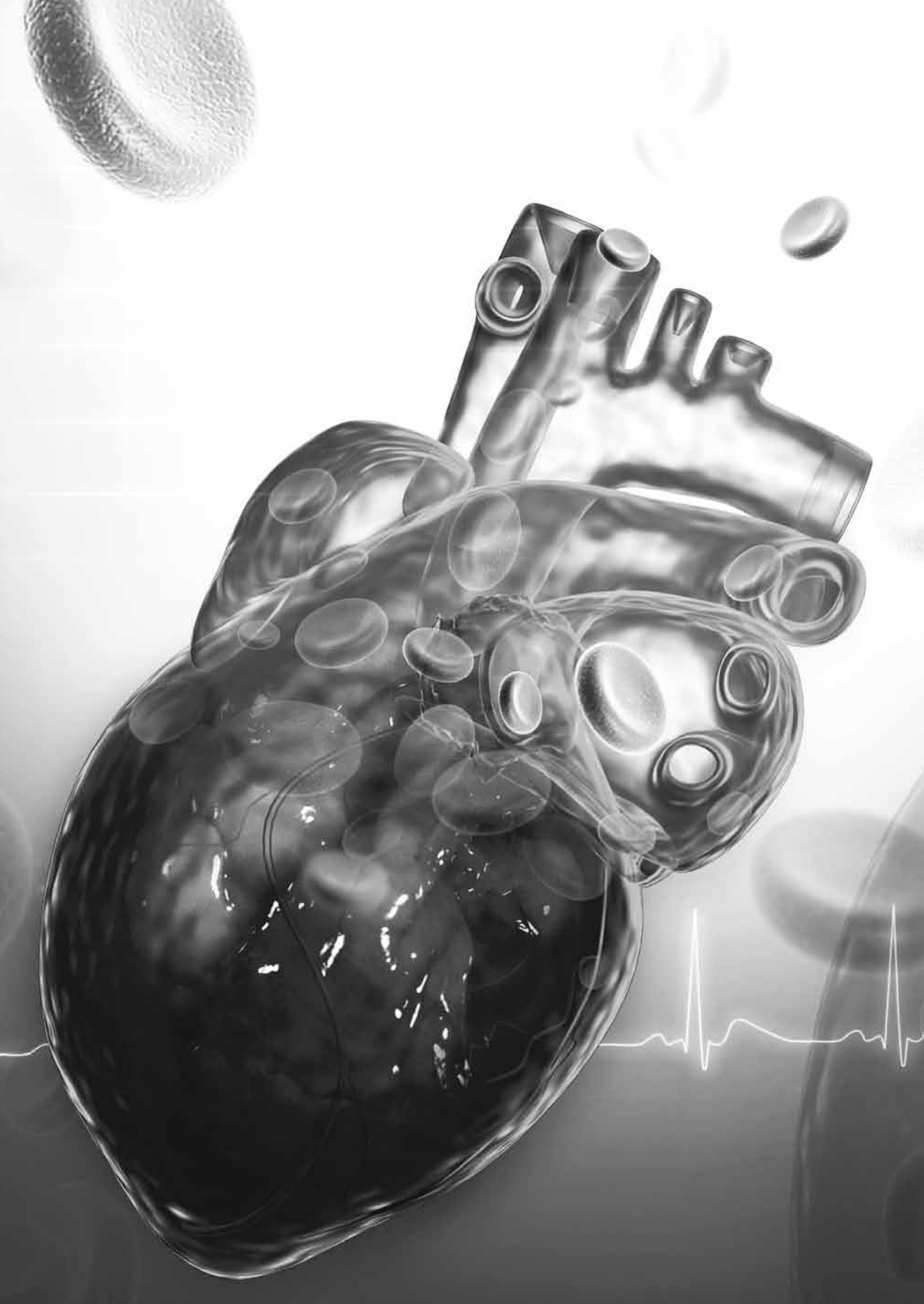


Chapter 1

General introduction and outline of the thesis

In this first chapter, an overview is given on congenital heart disease in general and on tetralogy of Fallot (TOF) more specifically. Etiology and birth prevalences will be discussed, as well as treatment options and long-term outcome in TOF patients with regard to ventricular function and clinical condition. Since the right ventricle (RV) is the most affected ventricle in patients after TOF repair, more detailed information is given on RV anatomy, physiology, and function. Imaging techniques to assess systolic and diastolic function, in particular magnetic resonance imaging (MRI), will be discussed. The use of biomarkers in patients with heart failure and after TOF repair is described. Finally, the aims and outline of this thesis will be presented.

Congenital heart disease

A congenital heart defect (CHD) has been defined as a gross, structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance[1]. There is considerable variation in the reported birth prevalences of CHDs in the literature[2-3]. Reasons for the reported differences in these patient populations include: age of detection and follow-up duration of the included patients, inclusion or exclusion of certain diagnosis, and use of (fetal) echocardiography[2]. A significant part of tiny ventricular septal defects (VSD) will close spontaneously during childhood, and inclusion of newborns only will lead to a higher birth prevalence for VSDs. Differences in birth prevalences could also be caused by the inclusion or exclusion of certain diagnosis, like for example bicuspid aortic valve. Furthermore, the increasing use of (fetal) echocardiography has increased the number of CHDs that have been detected. In contrast, increased prenatal screening have lead to an increased number of pregnancies that have been terminated in cases of complex CHDs[4]. Hoffman et al. reported a birth prevalence of ~9 – 10 per 1.000 liveborn infants for all CHDs and of ~6 per 1.000 liveborn infants for moderate and severe forms of CHDs[2].

Reports describing the change in birth prevalence of CHDs over the last decades have been inconsistent, and a decrease as well as an increase has been reported[3,5]. A decrease in birth prevalence might be due to an increased number of pregnancies that have been terminated because of complex CHDs in the fetus. Additionally, the periconceptional use of folate acid supplements, which has been increasingly used since the 90s for the prevention of neural tube defects, has also been reported to lower the birth prevalence of certain types of CHDs[6-7]. In contrast, an increase in birth prevalence might be due to the increased use of echocardiography, as mentioned before. Furthermore, the recurrence risk in offspring of parents with CHDs is ~ 4%[8] and the risk of recurrence of CHDs in siblings of patients with a CHD whose parents are unaffected is higher than in the general population[3]. Combined, this may have lead to an increase in the birth prevalence of CHDs, which will continue in the upcoming years, since the majority of patients with CHDs survive into adulthood nowadays[3,9].

The prevalence of children and adults with CHDs is rising, because survival has increased spectacularly during the last decades since surgical repair became available for the majority of patients with CHDs[3,5,8-11]. However, an increasing number of patients will need lifelong specialized medical care, since late complications will develop in many of these patients.

Etiology

A known cause for the CHD is present in only a small proportion of the patients. Some CHDs are caused by chromosomal abnormalities, which has been reported in 8% – 13% of newborns with CHDs[10]. In contrast, of all children with chromosomal abnormalities, approximately 30% have CHDs, with the incidence varying from that of the general population to nearly 100%[10]. For example, approximately 40% of patients with Down syndrome have a CHD, particularly atrioventricular septal defects[12-13], and approximately 75% of patients with a 22q11 deletion, i.e. DiGeorge syndrome or velocardiofacial syndrome, have CHDs, in particular conotruncal defects including tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch[10,12]. Some CHDs are caused by defects in single genes, as for example in patients with Alagille syndrome or Holt-Oram syndrome[10].

In approximately 85% of the patients with CHDs, the etiology is generally assumed to be multifactorial[5], which implies that the genetic predisposition of the individual interacts with environmental factors to cause CHDs[8,10,12,14]. In the past decades, several CHDs have been found to be associated with mutations in a variety of single genes, or to mutations in more than 1 gene[8,10]. Environmental factors that have been described to increase the chance of having a child with CHDs are maternal illnesses, such as pregestational diabetes and untreated phenylketonuria, maternal infections, such as rubella and febrile illnesses, exposure to specific drugs, such as retinoid acid and anticonvulsant drugs, and exposure to organic solvents[5,7,12,15]. With advancing techniques, it is highly likely that additional gene abnormalities will be defined in the future, which will gain more insight into the etiology of CHDs.

Tetralogy of Fallot

The combination of cardiac abnormalities in tetralogy of Fallot was described by Etienne Fallot in 1888, although it had been recognized long before Fallot's description by Niels Stensen in 1672. Tetralogy of Fallot is characterized by 4 cardiac abnormalities, i.e. 1) (sub)pulmonary stenosis (PS), 2) ventricular septal defect, 3) overriding of the aorta, and 4) right ventricular hypertrophy (Figure 1B). The essential features that causes this phenotype are an antero-cephalad deviation of the (muscular) outlet septum of the RV in combination with hypertrophy of the septoparietal trabeculations[16]. This results in a narrowed muscular orifice to the subpulmonary infundibulum. The degree and extent of the right ventricular outflow tract (RVOT) obstruction can vary considerably between patients. The region of the pulmonary valve, which has only 2 leaflets in the majority of the patients, and the supravalvular region may also be stenotic. Furthermore, the branch pulmonary arteries may also be involved, particularly the left pulmonary artery, at the site of the origin of the ductus arteriosus[16]. The VSD, which is a septal malalignment defect, and the overriding of the aorta are also caused by the deviation of the outlet septum. Right ventricular hypertrophy is a result of the pressure overload to the RV, which is caused by the (sub)pulmonary stenosis.

Tetralogy of Fallot accounts for ~ 4% of all CHDs[2,17]. The birth prevalence of TOF has been reported to be ~ 0.4 per 1.000 liveborn infants[2], with males and females being affected equally[17-

18]. This would mean that approximately 70 children with TOF are born in the Netherlands every year. Tetralogy of Fallot seems to be a polygenic disorder, with a small number of interacting genes[8]. The risk of having a child with a CHD has been reported to be about 3% if one of the parents has TOF[8].

Diagnosis and treatment

Tetralogy of Fallot is frequently diagnosed prenatally using fetal echocardiography. The clinical presentation after birth depends on the severity of the RVOT obstruction. In a normal heart, the pressure in the left ventricle (LV) exceeds the pressure in the RV after birth. However, the pressure in the RV is elevated in patients with unrepaired TOF, due to the RVOT obstruction. This will lead to a right-to-left shunt through the VSD if the RV pressure exceeds the LV pressure. Deoxygenated blood then enters the systemic circulation, which causes cyanosis. The degree of the right-to-left shunt depends on the degree of the RVOT obstruction: the more severe the RVOT obstruction, the larger the right-to-left shunt will be. In patients with severe RVOT obstruction, pulmonary blood flow may be duct-dependent and prostaglandin therapy directly after birth might be necessary to preserve pulmonary blood flow and avoid severe cyanosis. However, most of the TOF patients will have adequate pulmonary blood flow at birth and may be asymptomatic, although increasing cyanosis can develop in the first months of life[17]. Furthermore, a systolic murmur can be detected directly after birth, caused by the RVOT obstruction. In countries with advanced pediatric cardiology units, severe cyanosis, recurrent cyanotic spells, and other consequences of severely obstructed pulmonary blood flow are rare nowadays, because diagnosis is seldom delayed and infants undergo palliative procedures or total intracardiac repair within the first few months of life[17].

Before surgical intervention was possible, about 50% of patients with TOF died within the first few years of life, and it was unusual for a patient to survive longer than 30 years[17]. The first palliative surgical procedure was reported in 1945 by Alfred Blalock and Helen Taussig, who developed a procedure, in which a subclavian artery was used to create an aorta-pulmonary artery connection[19]. This shunt increased blood flow through the lungs, which had a major impact on patients' symptoms. The technique has been modified and is now usually performed using a Goretex tube to create the connection between the subclavian artery and the right or left pulmonary artery (Figure 2A). Although most children nowadays undergo total intracardiac repair initially, the modified Blalock-Taussig shunt is still used on infants with severe RVOT obstruction, who may not be candidates for initial total intracardiac repair.

The first total intracardiac repair was reported by C. Walton Lillehei in 1955[20]. Total intracardiac repair consists of complete VSD closure and relief of the RVOT obstruction (Figure 2B). The VSD is closed with the use of a patch and the RVOT obstruction is relieved by resecting (sub)infundibular muscles bundles, and if necessary pulmonary valvotomy. Furthermore, enlargement of the RVOT is necessary in many patients to obtain adequate pulmonary blood flow. Enlargement of the RVOT requires the use of a patch, often including the area of the pulmonary valve annulus (transannular patch). The consequence of this procedure is that many patients will have a significant amount of pulmonary regurgitation (PR) after surgery.

For a long time, surgical management consisted of initial palliation (if necessary), followed by total intracardiac repair later in childhood. Perioperative mortality was about 20% – 25% in patients operated on in the earliest decades. However, late survival for the patients surviving the first 30 days after surgery, was adequate, with a reported 20-year survival of about 90% – 95%[21-23]. Long-lasting hypoxemia and RV pressure overload are consequences of a delayed total intracardiac repair, and may cause myocardial damage with subsequent fibrosis, increasing the risk for myocardial dysfunction and arrthythmias later in life[17,24-25]. These disadvantages of the staged repair resulted in a rapidly decreasing age of patients undergoing total intracardiac repair. Improvements in surgical techniques, cardiopulmonary bypass techniques, myocardial protection, and postoperative care during the last decades made repair in early childhood possible[25]. Along with a shift in age at intracardiac repair, surgical approach has shifted from a right ventriculotomy to a transatrial-transpulmonary repair. A transatrial-transpulmonary repair aims to maintain RV geometry and avoids RV scarring and dysfunction from right ventriculotomy[26-27]. Long-term survival is excellent in patients operated on in early childhood, with a 20-year survival, including perioperative mortality, of about 94% for patients operated on in 1985[23,28]. The overall long-term survival has therefore improved for the current TOF population due to an impressive decline in perioperative mortality, which has now reported to be < 4%[24-29]. Most patients are nowadays operated on within their first year of life[24-26,29], although results in infants undergoing repair < 3 months of age have been equivocal[25-26,29].

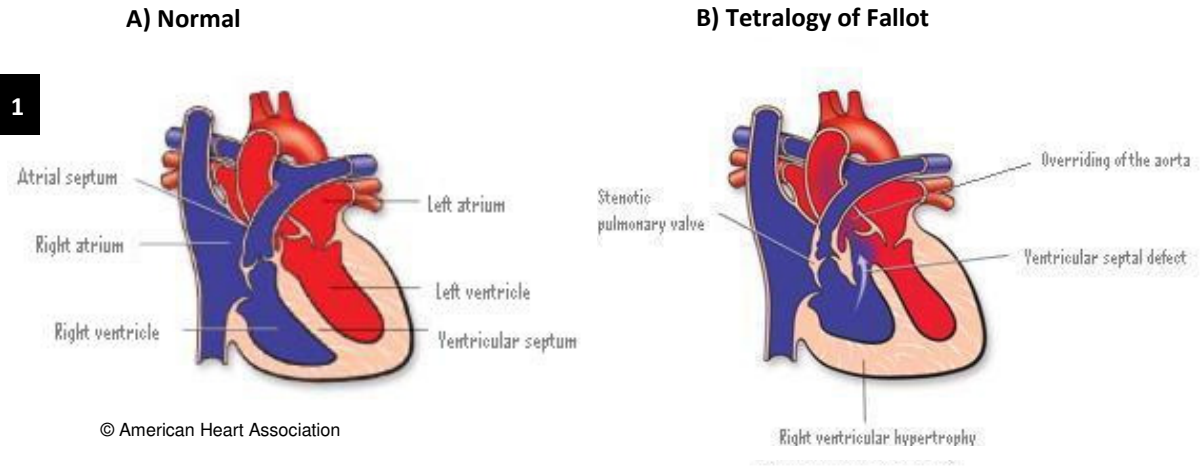


Figure 1: A) Normal anatomy; B) Tetralogy of Fallot anatomy.

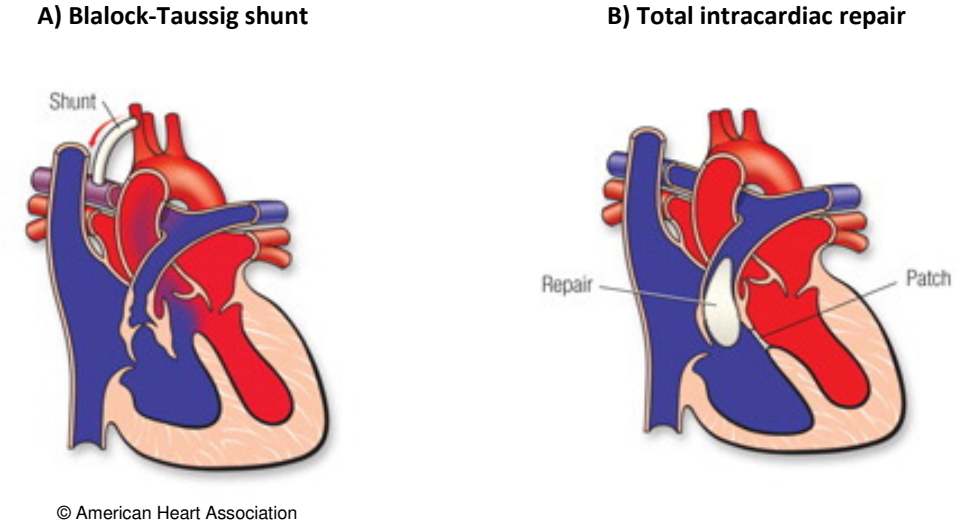


Figure 2: A) Modified Blalock-Taussig shunt; B) Total intracardiac repair with closure of the VSD and relief of the RVOT obstruction with the use of a patch.

Ventricular size and function

Right ventricular anatomy and physiology

In contrast to the ellipsoidal shape of the LV, the RV has a complex geometrical shape, which is triangular or crescent, depending on the orientation of viewing[30-31]. The RV consists of an inlet, an apical trabecular, and an outlet part. The RV inlet part consists of the tricuspid valve, the chordae tendinae, and the papillary muscles. The RV apical part is coarsely trabeculated, in contrast to the LV. A clear cut demarcation between the RV apical trabecular part and RV ouflow part is absent, but the RV outflow part is usually free of muscular trabeculations and contains the pulmonary valve[30-31]. The RV wall is much thinner than that of the LV. In a normal heart, the tremendous hemodynamic changes that occur shortly after birth cause a decline in RV pressure, which result in a thin-walled highly compliant, but less contractile chamber. In contrast, the LV changes into a thick-walled highly contractile chamber after birth[32].

One of the functions of the RV is to pump deoxygenated blood returning from the systemic venous circulation into the pulmonary arteries to be oxygenated before entering the LV and the systemic circulation. Another function of the RV is to provide adequate preload to the LV. Since the RV is connected in series with the LV, it ejects on average the same effective stroke volume as the LV under normal conditions[31,33]. One cardiac cycle consists of a systolic and diastolic phase. The systolic phase starts with an isovolumetric contraction phase, in which the ventricular volumes are maximal and the intraventricular pressures rise after closure of the mitral valve and tricuspid valve. The aortic valve and pulmonary valve open as soon as the ventricular pressures exceed the pressure in the aorta and pulmonary artery. Ventricular ejection takes place until the ventricular pressures drop below the pressure in the aorta and pulmonary artery. The diastolic phase starts with an isovolumetric relaxation phase, in which the ventricular volumes are minimal and the intraventricular pressures decline after closure of the aortic valve and pulmonary valve. The mitral valve and tricuspid valve open when the ventricular pressures drop below atrial pressures. Passive ventricular filling starts, followed by an active ventricular filling phase, which is the active atrial contribution to ventricular filling, also known as the atrial kick. The diastolic phase ends when ventricular pressures exceed atrial pressures again and the mitral valve and tricuspid valve close[31-32,34]. The isovolumetric contraction time is shorter in the RV, since RV pressure rapidly exceeds the pressure in the pulmonary artery[31-32]. The isovolumetric relaxation phase is also shorter in the RV and RV filling starts before and ends after LV filling[31-32].

Ventricular performance depends on several intrinsic and extrinsic factors, like contractility, preload, afterload, heart rate, and ventricular-ventricular interactions[31-32,34]. Contractility is the innate ability of the cardiac muscle to generate force[35], and results from the formation of actin-myosin cross-bridges in the myocyte, which are regulated by intracellular calcium concentration[32,36]. Preload refers to the load which is imposed on the myocardium before contraction, and is often represented by the end-diastolic pressure or end-diastolic volume (EDV)[32,34]. Within physiological limits, an increase in EDV will result in an increase in myocardial contraction, as represented by an increased stroke volume (SV), according to the Frank-Starling mechanism[37]. Afterload represents the load that the ventricle has to overcome in order to enable

ventricular ejection and is reflected by the build up of ventricular pressure until the aortic valve and pulmonary valve open. Afterload depends on several factors including peripheral resistance, ventricular pressure, ventricular size, and wall thickness. Practically, afterload is most often represented by the diastolic pressure in the aorta or pulmonary artery or by end-systolic ventricular pressures[32,34]. Heart rate has an effect on ventricular performance, since cardiac output relates to heart rate and SV (cardiac output = heart rate * stroke volume). In a resting situation, the effect of an increase in heart rate will not have a major effect on cardiac output, since it also shortens the ventricular filling time and therefore results in a smaller SV. However, during exercise, SV increases due to a decline in total peripheral resistance and thereby a decrease in end-systolic volume (ESV), while EDV remains constant. An increase in heart rate will then result in a significant increase in cardiac output[38]. Ventricular-ventricular interactions refer to the concept that the size, shape, and function of 1 ventricle may affect the other ventricle. Factors that contribute to these complex ventricular-ventricular interactions are the common interventricular septum, the shared epicardial myocardial fibers, the common pericardial sac, and series interaction through the pulmonary arterial and systemic vascular bed[31,33,39-41].

Ejection fraction (EF) is the most commonly used parameter of systolic function and although it is not a load-independent parameter, it is easy to assess[35]. Additionally, it has been proven to be a clinically valuable parameter, as it has been related to worse clinical outcome and adverse events in patients with acquired heart disease and congenital heart disease[42-43].

Imaging

Since many patients with repaired TOF develop RV dilatation that requires reintervention, routine evaluation of cardiac function is essential in the follow-up of these patients. Regular imaging of ventricular size, ventricular function, and valvular function will identify patients at risk for ventricular dysfunction, which may be used in clinical decision making and timing of reinterventions.

Although echocardiography is the most commonly used tool for routine assessment of biventricular function, MRI is the current gold standard technique for assessment of biventricular size and function[44-45]. Echocardiography is used extensively in clinical practice since it is widely available, is relatively inexpensive, and is transportable making bedside imaging possible. However, echocardiography has some limitations, like a limited acoustic window, particularly in obese patients. Furthermore, the retrosternal position of the RV makes this ventricle less approachable for echocardiography than the LV. Various echocardiographic imaging planes and techniques can be applied to measure dimensions, areas, volumes, ventricular and valvular functional parameters[46-48]. However, measurements of volumes and EF using two-dimenstional (2D) echocardiography are based on models that assume certain geometries of the ventricles. This is particularly challenging for the complex shaped RV, and despite several attempts to provide an appropriate model, no accurate geometrical model exists for the RV[47]. In patients with surgically repaired TOF, the geometric shape of the RV may be altered due to the abnormal volume loading conditions, which make these geometrical assumptions even less accurate. Ventricular volumes and EF as assessed using 2D echocardiography show important discrepancies compared with MRI derived parameters and

correlations are weak to moderate[49-50]. Because of these limitations in the assessment of RVEF with 2D echocardiography, different parameters of RV function have been introduced, including the tricuspid annular plane systolic excursion (TAPSE) and the fractional area change, but correlation with MRI derived RVEF has been reported to be weak in patients with right-sided CHDs, including TOF patients[51-53]. Of the alternative echocardiographic measurements of RV function, none has achieved the same reference status as RVEF so far[46].

In very recent years, real-time three-dimensional (3D) echocardiography has become available, which allows for assessment of RV size and function without the need for geometrical assumptions. With the currently available software, 3D echocardiography has been shown to improve quantitative assessment of RV size and function as compared with 2D echocardiography in patients with CHDs, including patients after TOF repair. Correlations between 3D echocardiography derived RV volumes and RVEF compared with MRI derived parameters were encouraging, ranging from 0.71 – 0.97. However, RV volumes and RVEF were systematically underestimated using 3D echocardiography as compared with MRI derived parameters[54]. Reproducibility has also been shown to be adequate[53-54]. Therefore, 3D echocardiography is a promising technique and may be used as an additional tool in the follow-up of patients with CHDs.

Computed tomography (CT) may also be used for the assessment of ventricular size and function, but ionizing radiation is an important disadvantage, which makes that it is used mainly in patients in whom MRI is contraindicated or echocardiography is inadequate[55]. Cardiac catheterization and radionuclide studies have been used in the past for assessment of biventricular size and function, but are hardly used anymore since non-invasive and more accurate imaging techniques for assessment of biventricular size and function became available.

As mentioned before, MRI is the current reference technique for assessment of biventricular size and function, as it is an accurate method, which does not rely on geometrical assumptions[44]. Furthermore, velocity-encoded sequences allow for accurate assessment of velocity and volume of flow, which has been proven to be particularly useful in the quantification of aortic and pulmonary regurgitation, as in patients with repaired TOF[56-57]. Echocardiography is unable to quantify regurgitant volumes accurately, and until these velocity-encoded MR sequences became available, the severity of valvular regurgitation had to be graded as mild, moderate, or severe, based on the regurgitant jet on echocardiography. However, echocardiography does allow for quantification of a gradient over a stenotic valve, by using the modified Bernoulli equation. This may be more difficult using velocity-encoded MRI, since accurate assessment of the peak velocity may be hampered when aliasing occurs in areas of high blood-flow velocity, as in stenotic jets. This may lead to underestimation of the peak velocity as assessed with velocity-encoded MRI[55]. Besides accurate assessment of biventricular size and function, and regurgitant volumes and fraction, MRI may also be used for the evaluation of cardiac anatomy, vascular dimensions, and assessment of wall mass and function[55,58]. Contrast-enhanced MR angiography may be used for a detailed overview of cardiac anatomy, including that of the great vessels. Late gadolinium enhanced images may provide information about fibrotic areas in the ventricular wall.

Limitations of MRI are the high costs, the limited availability, the long examination times, and time-consuming post-processing. Furthermore, sedation is required in young children, and older patients need to cooperate to obtain adequate images. Cardiac stents can cause artifacts, which may hamper image quality. Contraindications for performing an MRI include claustrophia, ferromagnetic implants, pacemakers and implantable cardioverter defibrillators (ICD), although MRI compatible devices have been developed in recent years[59].

Since MRI is the imaging method of choice that has been used in this research project, an overview is given of MRI derived parameters of size and function.

Systolic function

To obtain volumetric measurements by MRI, standard scout images have to be made to obtain a four-chamber view of the heart. A short axis set is then acquired, planned on the 4-chamber view, parallel to the atrioventricular valve plane, from the atrioventricular valves down to the apex (Figure 3A-3C). With manual outlining of the endocardial and epicardial borders in the end-diastolic phase and end-systolic phase, EDV and ESV can be calculated, using the disc summation method (Figure 3B-3E). Stroke volume is then calculated by subtracting ESV from EDV. Subsequently, EF can be calculated by dividing SV by EDV and multiplying this by 100%. Ventricular mass is calculated as the difference between the epicardial and endocardial contours multiplied by the slice thickness and a specific gravity of the myocardium of 1.05 g/ml[60].

In recent years, steady-state free precession (SSFP) pulse sequences have become the standard method for assessment of biventricular size and function with MR imaging. In contrast to the older gradient echo sequences, SSFP provides better blood-myocardial contrast, higher image quality, and faster acquisition times[61]. Studies comparing both techniques reported that the better blood-myocardial contrast resulted in a larger EDV, a larger ESV, a lower EF, and a lower mass[62-64]. Furthermore, observer variability seems better with SSFP imaging compared with the older gradient echo sequences[62-64]. Observer variability with SSFP imaging has been tested mainly in healthy controls and patients with acquired heart disease[65-70], but results in patients with CHDs are limited.

Pulmonary regurgitation

To obtain information about pulmonary regurgitant volume and fraction, flow measurements of the pulmonary valve have to be planned perpendicular to flow, using a velocity-encoded MRI sequence. Manual tracing of the pulmonary artery contour in all phases of the cardiac cycle will result in a time-velocity curve (Figure 4A, 4B). This curve represents the forward flow over the pulmonary valve during systole and the backward (regurgitant) flow during diastole. Forward volume and backward volume can be obtained by calculating the areas under the curve. Subsequently, PR fraction can be calculated by dividing the backward flow by the forward flow (= stroke volume) and multiplying this by 100%. Additionally, the effective SV (eff.SV) of the RV can be calculated by subtracting PR volume from RVSV, to obtain a parameter of RV function corrected for the amount of PR.

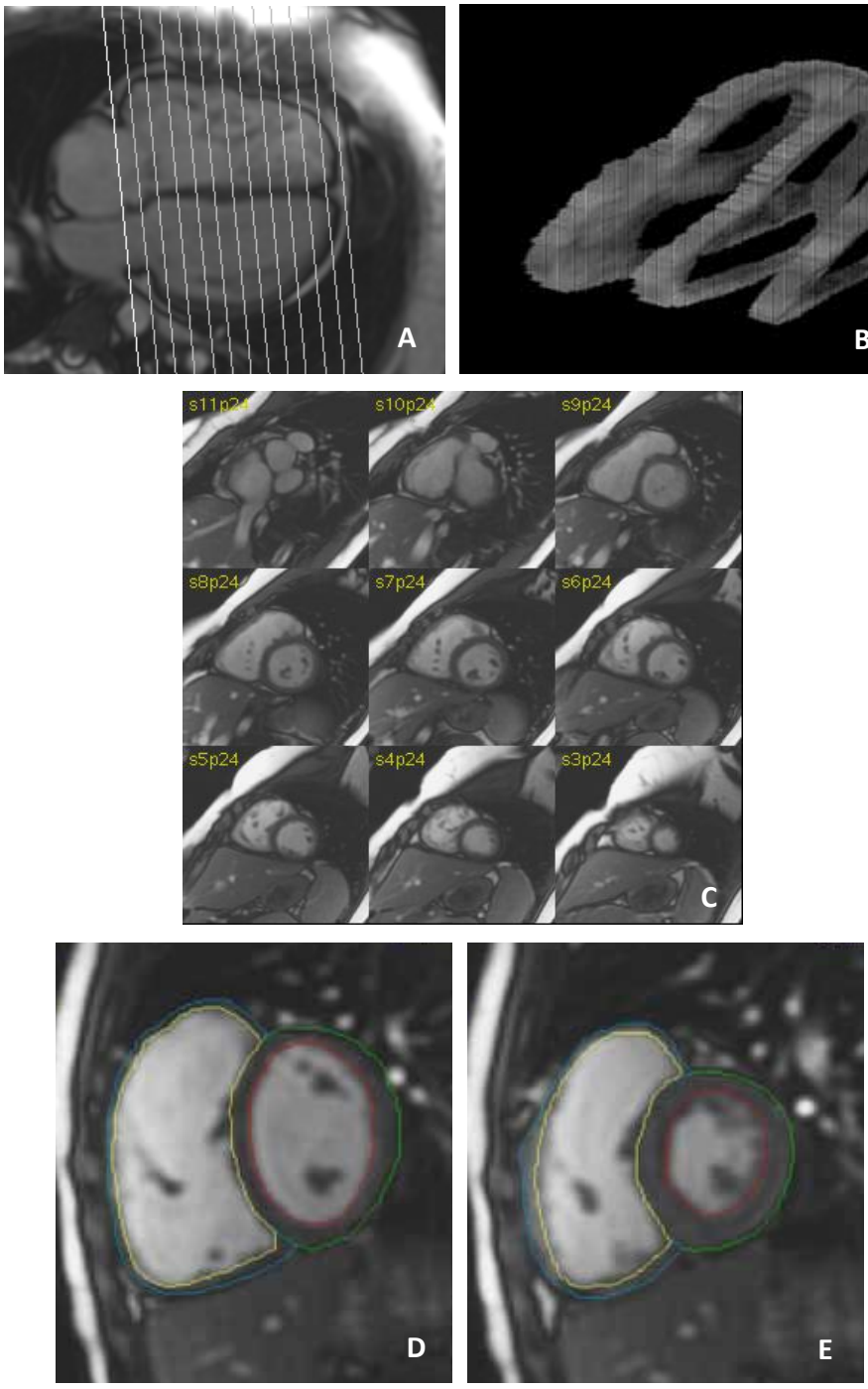
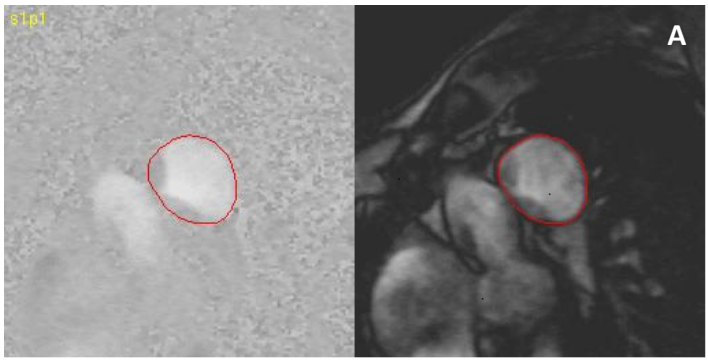


Figure 3: A) Planning of the short axis set parallel to the atrioventricular plane on a 4-chamber view; B) Disc summation method; C) Short axis set; D) Manual contour tracing in the end-diastolic phase; E) Manual contour tracing in the end-systolic phase.



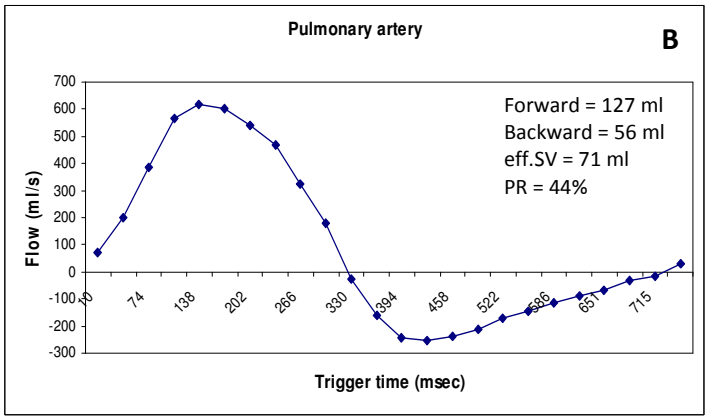


Figure 4: A) Velocity-encoded image of the pulmonary valve; B) Time-velocity curve of the pulmonary artery, showing forward and backward flow over the pulmonary valve.

Diastolic function

Assessment of diastolic function using MRI can be performend in 2 different ways. The diastolic phase refers to the filling phase of the ventricle. In a normal heart without valvular regurgitation, assessment of RV diastolic functional parameters could therefore be achieved by evaluating the inflow pattern over the tricuspid valve using the time-velocity curve of the tricuspid valve, obtained by velocity-encoded MRI. However, some degree of PR is present in the majority of TOF patients. The inflow of this regurgitant volume into the RV during diastole should therefore also be taken into account in these patients when assessing RV diastolic function. Accumulation of the time-velocity curves of the tricuspid valve and pulmonary valve will result in a time-volume change curve, which represents a time-velocity curve of the RV during the entire cardiac cycle (Figure 5A). A RV time-volume curve can then be obtained by integration of the RV time-volume change curve (Figure 5B). From these 2 curves, parameters of RV diastolic function could be calculated[71]. A time-volume curve and time-volume change curve can also be obtained by tracing endocardial contours of the RV in all phases and all slices of the short axis set. A time-volume curve is then obtained by summation

of the volumes of every slice of each phase (Figure 5B). Subsequently, a time-volume change curve can be reconstructed (Figure 5A).

From these curves, the following parameters of diastolic function can be assessed: early filling fraction, defined as ventricular volume increase during the first 1/3 of diastole, expressed as percentage of ventricular SV; early peak filling rate (EPFR), defined as the maximal ventricular volume change in early diastole; deceleration time (Dt), which is the time from EPFR to the extrapolation point of deceleration of flow to the baseline; atrial filling fraction, defined as the increase in ventricular volume after the onset of atrial contraction, expressed as percentage of ventricular SV; atrial peak filling rate (APFR), defined as the maximal ventricular volume change in late diastole; and E/A volume ratio, as the ratio of early filling volume to atrial filling volume. In a normal heart, more blood will enter the RV during early diastole than during late diastole, which will result in an E/A ratio larger than 1 in healthy subjects.

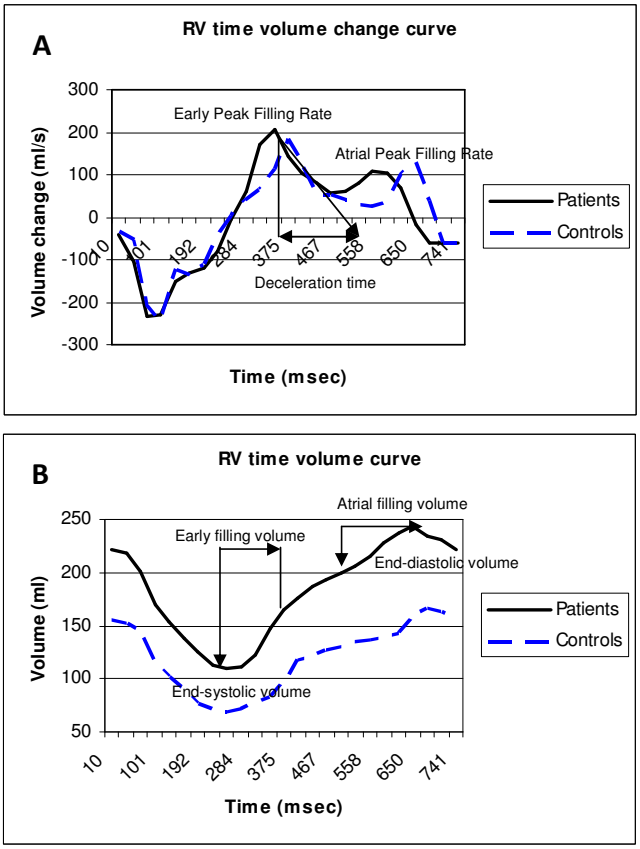


Figure 5: A) Right ventricular time volume change curve; B) Right ventricular time volume curve.

Long-term outcome

Due to a decline in perioperative mortality and the excellent long-term survival, the number of patients with TOF surviving into adulthood is increasing rapidly and we are now facing long-term morbidity and mortality in many of these patients. Pulmonary regurgitation is one of the crucial factors influencing outcome in patients with surgically repaired TOF. For a long time, it was thought that residual PR was unimportant. However, from the 80s onwards, extensive research has shown that PR adversely effects late outcome[17]. Chronic PR causes volume overload to the RV, which leads to RV dilatation. Right ventricular dilatation can lead to RV dysfunction and deterioration of clinical outcome, as represented by deterioration in New York Heart Association (NYHA) class, exercise intolerance, and an increased risk of arrhythmias and sudden cardiac death[42,72-79].

Ventricular function

Several studies have reported on ventricular function long after TOF repair, as assessed with MRI[38,56,72,76,80-83]. Although these studies were different with regard to age at operation, age at study, and surgical approach, RV enlargement and impaired RV function were almost uniformly reported. It has become clear that the amount of PR is positively related to a larger RVEDV and that repair with a transannular patch is a significant predictor of PR severity[76,80]. In the aforementioned reported studies, clinical condition, as represented by NYHA class, was somewhat impaired but adequate in most patients. NYHA class seemed to be better in younger patients who were operated on at a younger age[76]. In multivariate analysis, Geva et al.[72] found that an older age at repair was one of the parameters associated with poor clinical status (defined as NYHA class $\geq$ III), which might explain the reported differences in NYHA class.

It has been reported that diastolic dysfunction may be an important marker preceding systolic dysfunction and it might therefore be important in the early diagnosis of (systolic) RV dysfunction in patients with repaired TOF[84-86]. Furthermore, isolated diastolic dysfunction with preserved systolic function has been reported to be an independent predictor influencing patient outcome in patients with acquired heart disease[87].

Two different patterns of diastolic dysfunction have been recognized. One of them is the pattern of impaired relaxation of the RV: this will result in a smaller contribution of the early filling phase to RV filling and a longer deceleration time. Consequently, atrial filling volume will increase and the E/A ratio will decrease. The other pattern of diastolic dysfunction is that of impaired compliance or restriction to RV filling, which will result in an increased contribution of the early filling phase to RV filling. Consequently, the atrial filling volume will decrease and the E/A ratio will increase. The presence of end-diastolic forward flow (EDFF) in the pulmonary artery, which coincides with atrial contraction, has also been recognized as sign of RV restrictive physiology[71,88]. Both patterns of diastolic dysfunction, impaired relaxation and impaired compliance, have been described in patients after TOF repair at various follow-up durations after surgical repair using echocardiography or MRI[71,88-92]. However, reports have shown equivocal results with regard to the clinical interpretation of several diastolic functional parameters.

Atrial size and function may provide useful information when assessing ventricular diastolic function. The atria play a crucial role in the filling of the ventricle during ventricular diastole. The 3 components of atrial function are: 1) reservoir function, i.e. storing blood when the mitral and tricuspid valves are closed and releasing this stored blood when the atrioventricular valves open; 2) conduit function, i.e. passive blood transfer directly from the superior and inferior caval vein into the RV and from the pulmonary veins into the LV when the atrioventricular valves are open; 3) pump function, i.e. atrial contraction in late diastole to complete ventricular filling[93-94]. Increased atrial volumes usually reflect elevated ventricular filling pressures and atrial size has therefore been suggested to be a reliable indicator of the severity of ventricular diastolic dysfunction[93]. However, limited information is available on atrial size and function measured with MRI, particularly in TOF patients.

Stress imaging

Early diagnosis of RV dysfunction in TOF patients remains a challenge, particularly in asymptomatic patients with severe PR and severe RV dilatation. Magnetic resonance imaging combined with physical or pharmacological stress has been proposed as additional tool to find better predictors of early RV dysfunction. Stress imaging has been proven to have prognostic value in patients with coronary artery disease, since it may be used to identify wall motion abnormalities indicative of myocardial ischemia[95-96], which has been related to an increased risk of experiencing a subsequent cardiac event[95]. In patients with CHD, stress imaging is mostly used to determine ventricular contractile reserve, i.e. the ability to increase EF during stress. Echocardiography and MRI have been the most used imaging modalities. Physical stress imaging has been performed using MR-compatible bicycle ergometers in combination with MRI[38]. Since this technique has practical limitations, pharmacological stressors are now used in the majority of the studies.

Dobutamine is the most commonly used pharmacological stressor. Dobutamine is a catecholamine with positive inotropic and, to a lesser extent, chronotropic effects. In healthy children, positive inotropic effects occur from 1 to 2 µg/kg/min with dose-dependent increases in measures of systolic ventricular function[97], while chronotropic effects are seen from 5 to10 µg/kg/min[98]. Low doses of dobutamine are most frequently used in patients with CHD, with doses ranging from 5 to 20 µg/kg/min[99-102], in contrast to patients with acquired heart disease, in whom higher doses of dobutamine are used.

In healthy subjects, during exercise or dobutamine infusion, EDV does not change, ESV decreases, whereas SV and EF increases[38,99,101,103]. In patients with aortic regurgitation, preserved LV contractile reserve has been related to favourable follow-up results[104]. In patients after TOF repair, stress imaging studies have revealed an abnormal response of the RV to stress, represented by a lack of decrease in ESV and no change in RVEF[38,101]. Tulevski et al. also reported that patients with a combination of RV pressure overload and RV volume overload had a more abnormal response to dobutamine stress than patients with isolated RV pressure overload[101], which emphasizes the negative effect of chronic volume overload on RV function. In a younger TOF population, van den Berg et al. reported a decrease in RVESV and an increase in RVEF with low-dose

dobutamine stress[102]. An explanation for these nearly normal results, which are in contrast to others, may be the younger age at operation and younger age at study of this patient population.

These studies have provided additional insight in the function of the RV during stress, but how these findings relate to clinical outcome requires further study.

Clinical outcome

Exercise capacity is not only influenced by biventricular function, but also by skeletal muscle metabolism, pulmonary function, and heart rate response[76,105-106]. However, a decreased peak oxygen uptake (peak VO_2) during maximal exercise testing has been recognized as an important prognostic factor for survival and outcome in patients with acquired and congenital heart disease[78,105-107]. In recent years, an abnormal ventilatory response to exercise, as assessed by an elevated VE/VCO_2 slope, has also been shown to be a powerful predictor of hospitalization and cardiac-related mortality in patients with CHDs[78,106-107]. An abnormal exercise capacity has been reported in many patients long after TOF repair, although results vary considerably between different patient populations[38,76,78,108-114].

Life-threatening ventricular arrhythmias may be caused by re-entry circuits that can arise in areas of slow conduction, like myocardial scars from surgical procedures, and the RVOT and VSD patch areas[74]. Furthermore, the risk of ventricular arrhythmias also seem to be associated with abnormal mechanoelectrical interactions, i.e. a relation between RV size and function and abnormalities of myocardial depolarization and repolarization[74,115-116]. Abnormal depolarization is present in the majority of patients after TOF repair, which can be identified by prolonged QRS duration and a right bundle branch block on the electrocardiogram (ECG). A prolonged QRS duration has been associated with RV dilatation[72,74,76,117-118], underlining this mechanoelectrical interaction. The risk of sustained ventricular tachycardia and sudden cardiac death has been related to prolonged QRS duration[74,77], particularly a QRS duration on the resting ECG ≥ 180 msec is a sensitive predictor of life-threatening ventricular arrhythmias[74]. Furthermore, the rate of change in QRS duration during follow-up has been shown to be an additional predictor of ventricular tachycardia and sudden cardiac death[73]. Sudden cardiac death is the most common cause of death in surgically repaired TOF patients[22]. It has an overall annual incidence of about 0.15%/year[119-120], and increases 20 years after total intracardiac repair, suggesting a time-dependent risk[119].

Although there is no clear relation between atrial arrythmias and sudden cardiac death, atrial arrhythmias can be an important cause of morbidity in many patients after TOF repair[73,75,77].

Pulmonary valve replacement

Pulmonary regurgitation can be tolerated well for many years, but eventually compensatory mechanisms of the RV will fail as it has been reported that the incidences of arrhythmias, exercise intolerance, heart failure, and cardiac-related death increase with increasing age[21-22,77,119,121]. Patients with severe PR and RV dilatation are often considered to undergo pulmonary valve replacement (PVR), which is mostly done with the use of a pulmonary homograft. Approximately a decade ago, results of clinical and ventricular improvement after PVR were reported in a relatively

large cohort of patients[122]. During the last decade, PVR has been increasingly performed in TOF patients with severe PR, and longer term follow-up results have become available. However, the timing to perform PVR is still subject for debate and should balance between preservation of RV function and the risk for subsequent surgical or interventional procedures later in life. On the one hand, PVR should not be performed "too early", because the lifespan of a homograft is limited, which means that patients often will need subsequent interventions later in life[114,123-126]. On the other hand, PVR should not be performed "too late", because irreversible RV dysfunction might already have occurred, which does not seem to recover completely anymore after PVR[81,83,112,127].

This discussion with regard to timing of PVR relates in particular to asymptomatic patients with severe PR and severe RV dilatation. No uniform guidelines to perform PVR exist for these patients, although several recommendations have been reported in the literature[40,128]. As a consequence, decisions to perform PVR in individual patients are usually made in multidisciplinary teams and may differ between different tertiary referral centers. Several studies have tried to provide thresholds for RV size, above which PVR should be performed, in order to achieve adequate decrease in RV size and to preserve RV function after PVR. This threshold has been reported to be between 150 – 200 ml/m^2 for RVEDV[81-83,112] or between 82 – 85 ml/m^2 for RVESV[81-82], as assessed using cardiac MRI. Therrien et al. concluded that RV volumes did not normalize after PVR if preoperative RVEDV was > 170 ml/m^2 or preoperative RVESV was > 85 ml/m^2[82]. Normal values were considered < 108 ml/m^2 for RVEDV and < 47 ml/m^2 for RVESV. Cut-off values in a study by Oosterhof et al. were < 160 ml/m^2 for RVEDV and < 82 ml/m^2 for RVESV[81]. Valsangiacomo-Buechel and collegues demonstrated prompt RV remodeling after performing PVR if RVEDV exceeded 150 ml/m^2. None of their patients with a preoperative RVEDV > 200 ml/m^2 showed normalization of RV volumes after 6 months. The authors suggest this may be an helpful indicator for defining an upper limit for re-intervention[83].

Biomarkers

Over the past decades, it has been recognized that neurohormonal activation occurs in response to myocardial injury. These neurohormonal systems could adversely affect hemodynamics, as vasoconstriction could occur as well as sodium and water retention, contributing to the progression of heart failure[129-130]. Pharmacological therapies that interfere with these neurohormonal pathways, like angiotensin-converting enzyme inhibitors, are used as standard treatment in patients with heart failure nowadays.

Neurohormones are also used as diagnostic markers and have become useful in the risk stratification of patients with heart failure. The biologically active brain natriuretic peptide or b-type natriuretic peptide (BNP) and the biologically inactive N-terminal prohormone brain natriuretic peptide (NT-proBNP) are derived by cleavage of the prohormone (proBNP). In contrast to neurohormones in the renin-angiotensin system, natriuretic peptides may have a protective role because of the natriuretic, diuretic and vasodilative effects. It is released into peripheral blood by cardiomyocytes in response to increased wall stress. Various reports have shown that the secretion of (NT-pro)BNP increases in proportion to the severity of the LV dysfunction, making them useful as

diagnostic marker[131-133]. Serum levels of (NT-pro)BNP may be affected by age, gender, and renal function. In children and adolescents between 5 – 18 years, mean levels of NT-proBNP have been reported to be between 5 – 15 pmol/l[134] and NT-proBNP levels between 8 – 13 pmol/l have been suggested to be normal for adults[133].

In patients with congenital heart disease, in whom the RV is often the most affected ventricle, (NT-pro)BNP levels have also been reported to be elevated, and have been related to the severity of systemic ventricular dysfunction and clinical condition[135]. More specifically, in patients with repaired TOF, (NT-pro)BNP levels have been reported to be positively associated with RV size and PR fraction, and negatively associated with exercise capacity and RVEF[86,136-138]. However, the prognostic value of (NT-pro)BNP levels with regard to the early diagnosis of RV dysfunction in patients after TOF repair is still undetermined[102,139].

Aims and outline of this thesis

To date, parameters of RV size, biventricular function, clinical tests, and biomarker levels have been studied in patients after TOF repair, in order to predict RV dysfunction at an early stage, i.e. before irreversible RV dysfunction occurs. Various risk factors have been proposed, but results have been inconclusive and no clear guidelines for clinical decision making with regard to PVR have been established. Although TOF patients have been studied extensively, current literature provides limited information on the course of ventricular and functional changes over time in patients who have not undergone PVR already (referred to as "non-PVR patients"). This means that the progression of RV dilatation and the deterioration of RV function over time have not been clarified yet. Serial follow-up studies in non-PVR patients may provide insight in the course of RV enlargement and functional changes over time. This information could be useful in clinical decision making, as in decisions on optimal timing of PVR.

Besides the lack of serial follow-up measurements, biomolecular pathways that are involved in the process of progressive RV dilatation have hardly been studied in TOF patients. These pathways may also play a role in the transition from a state of compensated RV volume overload to RV failure. Knowledge of the pathways involved in these processes may lead to the identification of biomarkers that may be used in risk stratification of TOF patients. It also may provide targets for the development of specific therapies and future research.

Therefore, the aims of this thesis are:

- Assess the progression of RV dilatation and the deterioration of RV function over time, in relation to parameters of clinical condition, in patients after repair of tetralogy of Fallot. Systolic and diastolic ventricular functional parameters will be assessed using cardiac MRI, as well as the ventricular response to dobutamine stress.
- Identify potential biomarkers with the use of high-density protein arrays and enzyme-linked immuno sorbent assays (ELISA), which may be used as diagnostic and prognostic tools. These markers will be assessed in blood samples, obtained from tetralogy of Fallot patients at different stages of the development of RV volume overload.

In **chapter 2**, an overview is given of the role of cardiac MRI in the long-term follow-up of patients with repaired tetralogy of Fallot. We evaluate the ability of MRI to identify patients at risk for adverse outcomes, and its use in clinical decision making and timing of PVR.

In **chapter 3**, the intra-observer and interobserver variability of parameters measured with cardiac MRI, using steady-state free precession pulse sequences, are assessed. Since MRI parameters are increasingly used with regard to clinical decision making and timing of reinterventions in patients with CHDs, including TOF patients, good reproducility is of crucial importance.

In **chapter 4**, results of biventricular function and exercise capacity in TOF patients are compared to a group of patients treated with balloon valvuloplasty for isolated pulmonary valve stenosis. Before corrective treatment, the RV is subjected to pressure overload in both types of

CHDs. In TOF patients, this is combined with hypoxemia caused by a right-to-left shunt through the VSD. Furthermore, treatment options also differ significantly. Al these factors may add to differences in long-term outcome with respect to RV function and clinical status, which is evaluated in this chapter.

In **chapter 5**, the changes in biventricular size and function and clinical parameters over the course of 5 years are studied in non-PVR patients after TOF repair. These results are compared to results in patients who underwent PVR during this follow-up period. Progression rate of RV dilatation in non-PVR patients is reported and risk factors are identified for deterioration of ventricular size and function. Furthermore, results after PVR are described in 2 subgroups to evaluate currently reported guidelines for timing of PVR.

Chapter 6 describes the additional value of the assessment of bi-atrial size and function in relation to biventricular size, systolic and diastolic function, and clinical condition. Right ventricular diastolic function may be complex to assess in patients with important PR. Abnormalities in right atrial size and function may reflect RV diastolic dysfunction, and may therefore be useful to assess in the follow-up of these patients.

In chapter 7 and 8, the use of stress imaging and its clinical and prognostic value is evaluated. In **chapter 7a**, an overview is given of different stress imaging techniques and different stressors used in patients with CHDs. The safety and side-effects of low-dose dobutamine stress imaging are reported in **chapter 7b**, as well as the observer variability of parameters of biventricular size and function assessed using low-dose dobutamine stress imaging. **Chapter 8** describes serial follow-up results of biventricular size and function at rest and during low-dose dobutamine stress in patients with repaired TOF.

In **chapter 9**, biomolecular pathways are studied in TOF patients with different degrees of RV volume overload long after TOF repair. Particularly, the role of transforming growth factor (TGF)-β is evaluated, since the TGF-β pathway has been shown to play an important role in LV remodeling in the setting of LV pressure overload and post-myocardial infarction. Furthermore, various different biomolecules that regulate inflammation, extracellular matrix degradation, fibroblast proliferation, and cardiomyocyte survival were assessed using a protein array analysis.

The results of the aforementioned studies will be evaluated in **chapter 10**.

References

1. Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births. Incidence and natural history. Circulation 1971;43:323-332.
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890-1900.
3. van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJ. The changing epidemiology of congenital heart disease. Nat Rev Cardiol 2011;8:50-60.
4. Bull C. Current and potential impact of fetal diagnosis on prevalence and spectrum of serious congenital heart disease at term in the UK. British Paediatric Cardiac Association. Lancet 1999;354:1242-1247.
5. Botto LD, Correa A. Decreasing the burden of congenital heart anomalies: an epidemiologic evaluation of risk factors and survival. Progress in Pediatric Cardiology 2003;18:111-121.
6. van Beynum IM, Kapusta L, Bakker MK, den Heijer M, Blom HJ, de Walle HE. Protective effect of periconceptional folic acid supplements on the risk of congenital heart defects: a registry-based case-control study in the northern Netherlands. Eur Heart J 2010;31:464-471.
7. Jenkins KJ, Correa A, Feinstein JA, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation 2007;115:2995-3014.
8. Burn J, Brennan P, Little J, et al. Recurrence risks in offspring of adults with major heart defects: results from first cohort of British collaborative study. Lancet 1998;351:311-316.
9. Perloff JK. Congenital heart disease in adults. A new cardiovascular subspecialty. Circulation 1991;84:1881-1890.
10. Pierpont ME, Basson CT, Benson DW, Jr., et al. Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation 2007;115:3015-3038.
11. van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. Eur J Epidemiol 2005;20:549-557.
12. Goldmuntz E. The epidemiology and genetics of congenital heart disease. Clin Perinatol 2001;28:1-10.
13. Vis JC, de Bruin-Bon RH, Bouma BJ, et al. Congenital heart defects are under-recognised in adult patients with Down's syndrome. Heart 2010;96:1480-1484.
14. Nora JJ. Multifactorial inheritance hypothesis for the etiology of congenital heart diseases. The genetic-environmental interaction. Circulation 1968;38:604-617.
15. van Driel LM, de Jonge R, Helbing WA, et al. Maternal global methylation status and risk of congenital heart diseases. Obstet Gynecol 2008;112:277-283.
16. Anderson RH, Weinberg PM. The clinical anatomy of tetralogy of fallot. Cardiol Young 2005;15 Suppl 1:38-47.
17. Apitz C, Webb GD, Redington AN. Tetralogy of Fallot. Lancet 2009;374:1462-1471.
18. Engelfriet P, Mulder BJ. Gender differences in adult congenital heart disease. Neth Heart J 2009;17:414-417.
19. Blalock A, Taussig HB. Landmark article May 19, 1945: The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. By Alfred Blalock and Helen B. Taussig. JAMA 1984;251:2123-2138.
20. Lillehei CW, Cohen M, Warden HE, et al. Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects; report of first ten cases. Ann Surg 1955;142:418-442.
21. Murphy JG, Gersh BJ, Mair DD, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. N Engl J Med 1993;329:593-599.

22. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-Term Survival in Patients With Repair of Tetralogy of Fallot: 36-Year Follow-Up of 490 Survivors of the First Year After Surgical Repair. J Am Coll Cardiol 1997;30:1374-1383.
23. Hickey EJ, Veldtman G, Bradley TJ, et al. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. European Journal of Cardio-Thoracic Surgery 2009;35:156-164.
24. Alexiou C, Mahmoud H, Al-Khaddour A, et al. Outcome after repair of tetralogy of Fallot in the first year of life. The Annals of Thoracic Surgery 2001;71:494-500.
25. Tamesberger MI, Lechner E, Mair R, Hofer A, Sames-Dolzer E, Tulzer G. Early primary repair of tetralogy of fallot in neonates and infants less than four months of age. Ann Thorac Surg 2008;86:1928-1935.
26. Padalino MA, Vida VL, Stellin G. Transatrial-Transpulmonary Repair of Tetralogy of Fallot. Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual 2009;12:48-53.
27. Karl TR, Sano S, Pornviliwan S, Mee RB. Tetralogy of Fallot: favorable outcome of nonneonatal transatrial, transpulmonary repair. Ann Thorac Surg 1992;54:903-907.
28. Park CS, Lee JR, Lim HG, Kim WH, Kim YJ. The long-term result of total repair for tetralogy of Fallot. Eur J Cardiothorac Surg 2010;38:311-317.
29. Van Arsdell GS, Maharaj GS, Tom J, et al. What is the optimal age for repair of tetralogy of Fallot? Circulation 2000;102:III123-129.
30. Ho SY, Nihoyannopoulos P. Anatomy, echocardiography, and normal right ventricular dimensions. Heart 2006;92:i2-i13.
31. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. Circulation 2008;117:1436-1448.
32. Leeuwenburgh B. Chronic pressure overload to the right ventricle. Leiden University Medical Center, 2003:11-60.
33. Lee FA. Hemodynamics of the right ventricle in normal and disease states. Cardiol Clin 1992;10:59-67.
34. Berne RM LM, ed. Physiology. 4th ed: Mosby, 1998:360-378.
35. Carabello BA. Evolution of the study of left ventricular function: everything old is new again. Circulation 2002;105:2701-2703.
36. Hancock WO, Martyn DA, Huntsman LL. Ca2+ and segment length dependence of isometric force kinetics in intact ferret cardiac muscle. Circ Res 1993;73:603-611.
37. Jacob R, Dierberger B, Kissling G. Functional significance of the Frank-Starling mechanism under physiological and pathophysiological conditions. Eur Heart J 1992;13 Suppl E:7-14.
38. Roest AA, Helbing WA, Kunz P, et al. Exercise MR imaging in the assessment of pulmonary regurgitation and biventricular function in patients after tetralogy of fallot repair. Radiology 2002;223:204-211.
39. Brookes C, Ravn H, White P, Moeldrup U, Oldershaw P, Redington A. Acute right ventricular dilatation in response to ischemia significantly impairs left ventricular systolic performance. Circulation 1999;100:761-767.
40. Geva T. Repaired tetralogy of Fallot: the roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. J Cardiovasc Magn Reson 2011;13:9.
41. Tobler D, Crean AM, Redington AN, et al. The left heart after pulmonary valve replacement in adults late after tetralogy of Fallot repair. Int J Cardiol 2012;160(3):165-170.
42. Knauth AL, Gauvreau K, Powell AJ, et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart 2008;94:211-216.
43. Quinones MA, Greenberg BH, Kopelen HA, et al. Echocardiographic predictors of clinical outcome in patients with left ventricular dysfunction enrolled in the SOLVD registry and

trials: significance of left ventricular hypertrophy. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 2000;35:1237-1244.
44. Pennell DJ, Sechtem UP, Higgins CB, et al. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. Eur Heart J 2004;25:1940-1965.
45. Kilner PJ, Geva T, Kaemmerer H, Trindade PT, Schwitter J, Webb GD. Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the European Society of Cardiology. Eur Heart J 2010;31:794-805..
46. Mertens LL, Friedberg MK. Imaging the right ventricle--current state of the art. Nat Rev Cardiol 2010;7:551-563.
47. Jiang L, Levine RA, Weyman AE. Echocardiographic Assessment of Right Ventricular Volume and Function. Echocardiography 1997;14:189-206.
48. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713; quiz 786-788.
49. Helbing WA, Bosch HG, Maliepaard C, et al. Comparison of echocardiographic methods with magnetic resonance imaging for assessment of right ventricular function in children. Am J Cardiol 1995;76:589-594.
50. Lai WW, Gauvreau K, Rivera ES, Saleeb S, Powell AJ, Geva T. Accuracy of guideline recommendations for two-dimensional quantification of the right ventricle by echocardiography. Int J Cardiovasc Imaging 2008;24:691-698.
51. Koestenberger M, Nagel B, Ravekes W, et al. Systolic right ventricular function in pediatric and adolescent patients with tetralogy of Fallot: echocardiography versus magnetic resonance imaging. J Am Soc Echocardiogr 2011;24:45-52.
52. Morcos P, Vick GW, 3rd, Sahn DJ, Jerosch-Herold M, Shurman A, Sheehan FH. Correlation of right ventricular ejection fraction and tricuspid annular plane systolic excursion in tetralogy of Fallot by magnetic resonance imaging. Int J Cardiovasc Imaging 2009;25(3):263-270.
53. van der Zwaan HB, Geleijnse ML, McGhie JS, et al. Right ventricular quantification in clinical practice: two-dimensional vs. three-dimensional echocardiography compared with cardiac magnetic resonance imaging. Eur J Echocardiogr 2011;12:656-664.
54. van der Zwaan HB, Helbing WA, McGhie JS, et al. Clinical value of real-time three-dimensional echocardiography for right ventricular quantification in congenital heart disease: validation with cardiac magnetic resonance imaging. J Am Soc Echocardiogr 2010;23:134-140.
55. Roest AAW, de Roos A. Imaging of patients with congenital heart disease. Nat Rev Cardiol 2012;9:101-115.
56. Helbing WA, Rebergen SA, Maliepaard C, et al. Quantification of right ventricular function with magnetic resonance imaging in children with normal hearts and with congenital heart disease. Am Heart J 1995;130:828-837.
57. Rebergen SA, Chin JG, Ottenkamp J, van der Wall EE, de Roos A. Pulmonary regurgitation in the late postoperative follow-up of tetralogy of Fallot. Volumetric quantitation by nuclear magnetic resonance velocity mapping. Circulation 1993;88:2257-2266.
58. Helbing WA, de Roos A. Clinical applications of cardiac magnetic resonance imaging after repair of tetralogy of Fallot. Pediatr Cardiol 2000;21:70-79.
59. Beinart R, Nazarian S. MRI-Conditional Cardiac Implantable Electronic Devices: What's New and What Can We Expect in the Future? Curr Treat Options Cardiovasc Med 2012;14(5):558-564.
60. Katz J, Milliken MC, Stray-Gundersen J, et al. Estimation of human myocardial mass with MR imaging. Radiology 1988;169:495-498.

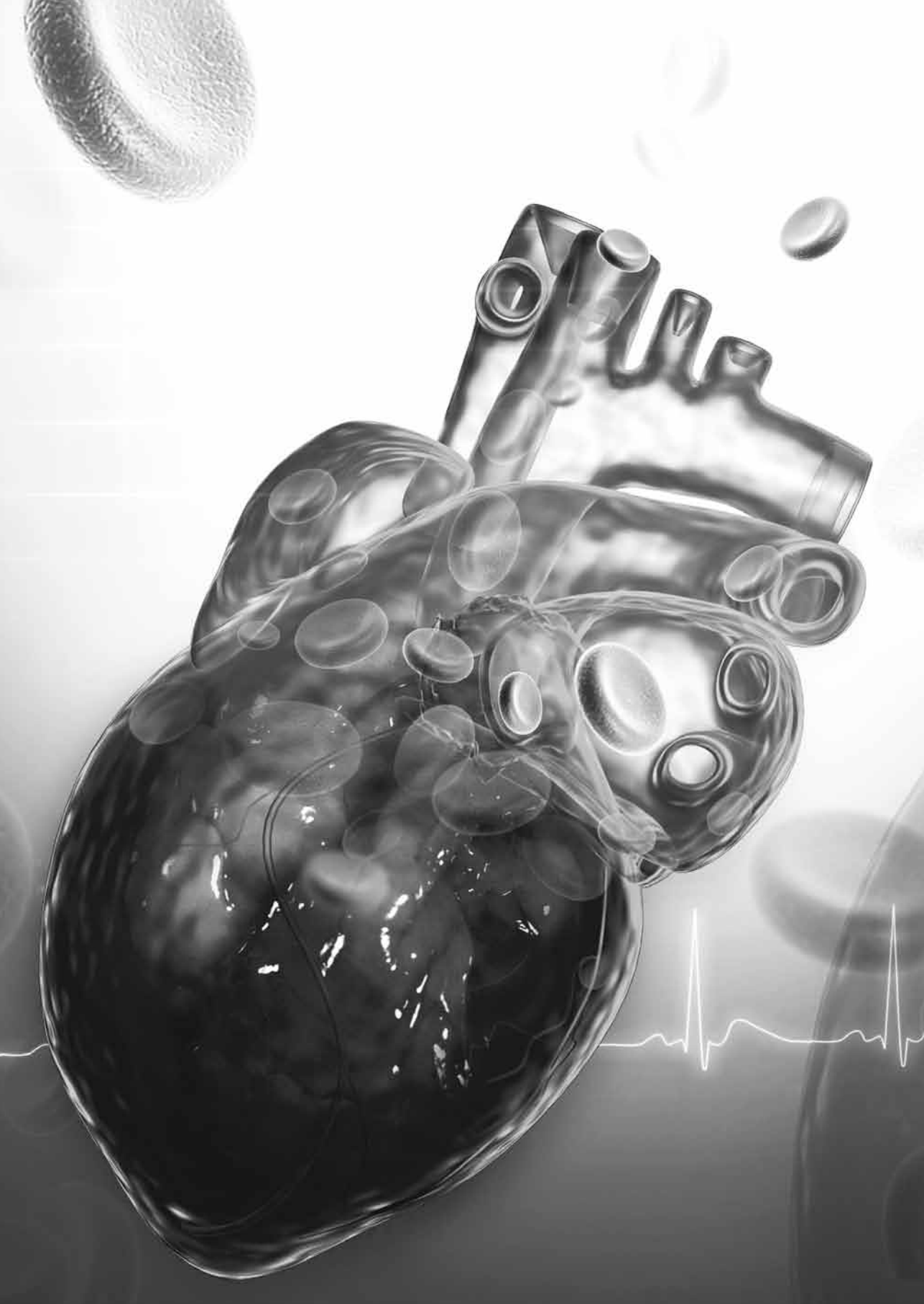
61. Thiele H, Nagel E, Paetsch I, et al. Functional cardiac MR imaging with steady-state free precession (SSFP) significantly improves endocardial border delineation without contrast agents. J Magn Reson Imaging 2001;14:362-367.
62. Alfakih K, Thiele H, Plein S, Bainbridge GJ, Ridgway JP, Sivananthan MU. Comparison of right ventricular volume measurement between segmented k-space gradient-echo and steady-state free precession magnetic resonance imaging. J Magn Reson Imaging 2002;16:253-258.
63. Moon JC, Lorenz CH, Francis JM, Smith GC, Pennell DJ. Breath-hold FLASH and FISP cardiovascular MR imaging: left ventricular volume differences and reproducibility. Radiology 2002;223:789-797.
64. Plein S, Bloomer TN, Ridgway JP, Jones TR, Bainbridge GJ, Sivananthan MU. Steady-state free precession magnetic resonance imaging of the heart: comparison with segmented k-space gradient-echo imaging. J Magn Reson Imaging 2001;14:230-236.
65. Alfakih K, Plein S, Bloomer T, Jones T, Ridgway J, Sivananthan M. Comparison of right ventricular volume measurements between axial and short axis orientation using steady-state free precession magnetic resonance imaging. J Magn Reson Imaging 2003;18:25-32.
66. Catalano O, Antonaci S, Opasich C, et al. Intra-observer and interobserver reproducibility of right ventricle volumes, function and mass by cardiac magnetic resonance. J Cardiovasc Med (Hagerstown) 2007;8:807-814.
67. Clay S, Alfakih K, Messroghli DR, Jones T, Ridgway JP, Sivananthan MU. The reproducibility of left ventricular volume and mass measurements: a comparison between dual-inversion-recovery black-blood sequence and SSFP. Eur Radiol 2006;16:32-37.
68. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. Am Heart J 2004;147:218-223.
69. Hudsmith LE, Petersen SE, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. J Cardiovasc Magn Reson 2005;7:775-782.
70. Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J 2006;27:2879-2888.
71. Helbing WA, Niezen RA, Le Cessie S, van der Geest RJ, Ottenkamp J, de Roos A. Right ventricular diastolic function in children with pulmonary regurgitation after repair of tetralogy of Fallot: volumetric evaluation by magnetic resonance velocity mapping. J Am Coll Cardiol 1996;28:1827-1835.
72. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol 2004;43:1068-1074.
73. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975-981.
74. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation 1995;92:231-237.
75. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation 1995;91:2214-2219.
76. van den Berg J, Hop WC, Strengers JL, et al. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of Fallot. J Thorac Cardiovasc Surg 2007;133:470-477.
77. Khairy P, Aboulhosn J, Gurvitz MZ, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation 2010;122:868-875.

78. Giardini A, Specchia S, Tacy TA, et al. Usefulness of Cardiopulmonary Exercise to Predict Long-Term Prognosis in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2007;99:1462-1467.
79. Carvalho JS, Shinebourne EA, Busst C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. Br Heart J 1992;67:470-473.
80. Davlouros PA, Kilner PJ, Hornung TS, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol 2002;40:2044-2052.
81. Oosterhof T, van Straten A, Vliegen HW, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation 2007;116:545-551.
82. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. Am J of Cardiol 2005;95:779-782.
83. Valsangiacomo Buechel ER, Dave HH, Kellenberger CJ, et al. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. Eur Heart J 2005;26:2721-2727.
84. Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part I. Physiologic and pathophysiologic features. Mayo Clin Proc 1989;64:71-81.
85. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105:1387-1393.
86. Norozi K, Buchhorn R, Bartmus D, et al. Elevated brain natriuretic peptide and reduced exercise capacity in adult patients operated on for tetralogy of fallot is due to biventricular dysfunction as determined by the myocardial performance index. Am J Cardiol 2006;97:1377-1382.
87. Kitahori K, He H, Kawata M, et al. Development of Left Ventricular Diastolic Dysfunction With Preservation of Ejection Fraction During Progression of Infant Right Ventricular Hypertrophy. Circ Heart Fail 2009;2:599-607.
88. Gatzoulis MA, Clark AL, Cullen S, Newman CG, Redington AN. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot. Restrictive physiology predicts superior exercise performance. Circulation 1995;91:1775-1781.
89. Cullen S, Shore D, Redington A. Characterization of Right Ventricular Diastolic Performance After Complete Repair of Tetralogy of Fallot : Restrictive Physiology Predicts Slow Postoperative Recovery. Circulation 1995;91:1782-1789.
90. Lu JC, Cotts TB, Agarwal PP, Attili AK, Dorfman AL. Relation of Right Ventricular Dilation, Age of Repair, and Restrictive Right Ventricular Physiology With Patient-Reported Quality of Life in Adolescents and Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2010;106:1798-1802.
91. Norgard G, Gatzoulis MA, Josen M, Cullen S, Redington AN. Does restrictive right ventricular physiology in the early postoperative period predict subsequent right ventricular restriction after repair of tetralogy of Fallot? Heart 1998;79:481-484.
92. van den Berg J, Wielopolski PA, Meijboom FJ, et al. Diastolic function in repaired tetralogy of Fallot at rest and during stress: assessment with MR imaging. Radiology 2007;243:212-219.
93. Abhayaratna WP, Seward JB, Appleton CP, et al. Left Atrial Size: Physiologic Determinants and Clinical Applications. J Am Coll Cardiol 2006;47:2357-2363.
94. Gaynor SL, Maniar HS, Prasad SM, Steendijk P, Moon MR. Reservoir and conduit function of right atrium: impact on right ventricular filling and cardiac output. Am J Physiol Heart Circ Physiol 2005;288:H2140-2145.

95. Jahnke C, Nagel E, Gebker R, et al. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007;115:1769-1776.
96. Wahl A, Paetsch I, Gollesch A, et al. Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases. Eur Heart J 2004;25:1230-1236.
97. Berg RA, Padbury JF, Donnerstein RL, Klewer SE, Hutter JJ, Jr. Dobutamine pharmacokinetics and pharmacodynamics in normal children and adolescents. J Pharmacol Exp Ther 1993;265:1232-1238.
98. Michelfelder EC, Witt SA, Khoury P, Kimball TR. Moderate-dose dobutamine maximizes left ventricular contractile response during dobutamine stress echocardiography in children. J Am Soc Echocardiogr 2003;16:140-146.
99. Oosterhof T, Tulevski, II, Roest AA, et al. Disparity between dobutamine stress and physical exercise magnetic resonance imaging in patients with an intra-atrial correction for transposition of the great arteries. J Cardiovasc Magn Reson 2005;7:383-389.
100. Robbers-Visser D, Jan ten Harkel D, Kapusta L, et al. Usefulness of Cardiac Magnetic Resonance Imaging Combined With Low-Dose Dobutamine Stress to Detect an Abnormal Ventricular Stress Response in Children and Young Adults After Fontan Operation at Young Age. The American Journal of Cardiology 2008;101:1657-1662.
101. Tulevski, II, Hirsch A, Dodge-Khatami A, Stoker J, van der Wall EE, Mulder BJ. Effect of pulmonary valve regurgitation on right ventricular function in patients with chronic right ventricular pressure overload. Am J Cardiol 2003;92:113-136.
102. van den Berg J, Strengers JLM, Wielopolski PA, et al. Assessment of biventricular functional reserve and NT-proBNP levels in patients with RV volume overload after repair of tetralogy of Fallot at young age. Int J of Cardiol 2009;133:364-370.
103. De Wolf D, Suys B, Verhaaren H, Matthys D, Taeymans Y. Low-Dose Dobutamine Stress Echocardiography in Children and Young Adults. The American Journal of Cardiology 1998;81:895-901.
104. Wahi S, Haluska B, Pasquet A, Case C, Rimmerman CM, Marwick TH. Exercise echocardiography predicts development of left ventricular dysfunction in medically and surgically treated patients with asymptomatic severe aortic regurgitation. Heart 2000;84:606-614.
105. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 2005;112:828-835.
106. Francis DP, Shamim W, Davies LC, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2)slope and peak VO(2). Eur Heart J 2000;21:154-161.
107. Dimopoulos KMD, Okonko DOBM, Diller G-PMD, et al. Abnormal Ventilatory Response to Exercise in Adults With Congenital Heart Disease Relates to Cyanosis and Predicts Survival. Circulation 2006;113:2796-2802.
108. Kipps AK, Graham DA, Harrild DM, Lewis E, Powell AJ, Rhodes J. Longitudinal Exercise Capacity of Patients With Repaired Tetralogy of Fallot. Am J Cardiol 2011;108(1):99-105.
109. Babu-Narayan SV, Uebing A, Davlouros PA, et al. Randomised trial of ramipril in repaired tetralogy of Fallot and pulmonary regurgitation: the APPROPRIATE study (Ace inhibitors for Potential PRevention Of the deleterious effects of Pulmonary Regurgitation In Adults with repaired TEtralogy of Fallot). Int J Cardiol 2012;154:299-305.
110. Wald RM, Haber I, Wald R, Valente AM, Powell AJ, Geva T. Effects of Regional Dysfunction and Late Gadolinium Enhancement on Global Right Ventricular Function and Exercise Capacity in Patients With Repaired Tetralogy of Fallot. Circulation 2009;119(10):1370-1377.
111. Wessel HU, Paul MH. Exercise studies in tetralogy of Fallot: a review. Pediatr Cardiol 1999;20:39-47; discussion 48.

112. Frigiola A, Tsang V, Bull C, et al. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? Circulation 2008;118:S182-190.
113. Gengsakul A, Harris L, Bradley TJ, et al. The impact of pulmonary valve replacement after tetralogy of Fallot repair: a matched comparison. Eur J Cardiothorac Surg 2007;32:462-468.
114. Meijboom FJ, Roos-Hesselink JW, McGhie JS, et al. Consequences of a selective approach toward pulmonary valve replacement in adult patients with tetralogy of Fallot and pulmonary regurgitation. J Thorac Cardiovasc Surg 2008;135:50-55.
115. Tzemos N, Harris L, Carasso S, et al. Adverse Left Ventricular Mechanics in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2009;103:420-425.
116. Redington AN. Physiopathology of right ventricular failure. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2006:3-10.
117. El Rahman MYA, Abdul-Khaliq H, Vogel M, Alexi-Meskishvili V, Gutberlet M, Lange PE. Relation between right ventricular enlargement, QRS duration, and right ventricular function in patients with tetralogy of Fallot and pulmonary regurgitation after surgical repair. Heart 2000;84:416-420.
118. Helbing WA, Roest AA, Niezen RA, et al. ECG predictors of ventricular arrhythmias and biventricular size and wall mass in tetralogy of Fallot with pulmonary regurgitation. Heart 2002;88:515-519.
119. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol 1998;32:245-251.
120. Khairy P, Dore A, Poirier N, et al. Risk stratification in surgically repaired tetralogy of Fallot. Expert Review of Cardiovascular Therapy 2009;7:755-762.
121. Geva T. Indications and Timing of Pulmonary Valve Replacement After Tetralogy of Fallot Repair. Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual 2006;9:11-22.
122. Vliegen HW, van Straten A, de Roos A, et al. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of fallot. Circulation 2002;106:1703-1707.
123. Oosterhof T, Meijboom FJ, Vliegen HW, et al. Long-term follow-up of homograft function after pulmonary valve replacement in patients with tetralogy of Fallot. Eur Heart J 2006;27:1478-1484.
124. van de Woestijne PC, Mokhles MM, de Jong PL, Witsenburg M, Takkenberg JJM, Bogers AJJC. Right Ventricular Outflow Tract Reconstruction With an Allograft Conduit in Patients After Tetralogy of Fallot Correction: Long-Term Follow-Up. The Annals of Thoracic Surgery 2011;92(1):161-166.
125. Brown JW, Ruzmetov M, Rodefeld MD, Vijay P, Turrentine MW. Right Ventricular Outflow Tract Reconstruction With an Allograft Conduit in Non-Ross Patients: Risk Factors for Allograft Dysfunction and Failure. The Annals of Thoracic Surgery 2005;80:655-664.
126. Caldarone CA, McCrindle BW, Van Arsdell GS, et al. Independent factors associated with longevity of prosthetic pulmonary valves and valved conduits. The Journal of Thoracic and Cardiovascular Surgery 2000;120:1022-1031.
127. Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG, Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? Journal of the American College of Cardiology 2000;36:1670-1675.
128. Davlouros PA, Karatza AA, Gatzoulis MA, Shore DF. Timing and type of surgery for severe pulmonary regurgitation after repair of tetralogy of Fallot. Int J Cardiol 2004;97 Suppl 1:91-101.
129. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248-254.

130. Sigurdsson A, Swedberg K. The role of neurohormonal activation in chronic heart failure and postmyocardial infarction. Am Heart J 1996;132:229-234.
131. Yasue H, Yoshimura M, Sumida H, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 1994;90:195-203.
132. O'Donoghue M, Braunwald E. Natriuretic peptides in heart failure: should therapy be guided by BNP levels? Nat Rev Cardiol 2010;7:13-20.
133. Cowie MR, Jourdain P, Maisel A, et al. Clinical applications of B-type natriuretic peptide (BNP) testing. European Heart Journal 2003;24:1710-1718.
134. Smith J, Goetze JP, Andersen CB, Vejlstrup N. Practical application of natriuretic peptides in paediatric cardiology. Cardiol Young 2010:1-11.
135. Bolger AP, Sharma R, Li W, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation 2002;106:92-99.
136. Cheung EW, Lam WW, Chiu CS, Chau AK, Cheung SC, Cheung YF. Plasma brain natriuretic peptide levels, right ventricular volume overload and exercise capacity in adolescents after surgical repair of tetralogy of Fallot. Int J Cardiol 2007;121:155-162.
137. Ishii H, Harada K, Toyono M, Tamura M, Takada G. Usefulness of Exercise-Induced Changes in Plasma Levels of Brain Natriuretic Peptide in Predicting Right Ventricular Contractile Reserve After Repair of Tetralogy of Fallot. The American Journal of Cardiology 2005;95:1338-1343.
138. Oosterhof T, Tulevski, II, Vliegen HW, Spijkerboer AM, Mulder BJ. Effects of volume and/or pressure overload secondary to congenital heart disease (tetralogy of fallot or pulmonary stenosis) on right ventricular function using cardiovascular magnetic resonance and B-type natriuretic peptide levels. Am J Cardiol 2006;97:1051-1055.
139. Apitz C, Sieverding L, Latus H, Uebing A, Schoof S, Hofbeck M. Right Ventricular Dysfunction and B-Type Natriuretic Peptide in Asymptomatic Patients After Repair for Tetralogy of Fallot. Pediatr Cardiol 2009;30(7):898-904.



Chapter 2

Tetralogy of Fallot – Does MR imaging have the answers?

Review

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Abstract

The population of adult survivors with tetralogy of Fallot (TOF) is growing over the last decades due to improvements in perinatal management, intensive care, and surgical techniques. Pulmonary regurgitation (PR) plays a crucial role in the long-term outcome of these patients. Although PR may be tolerated well for many years, eventually it may lead to right ventricular (RV) dilatation, RV dysfunction, exercise intolerance, arrhythmia, and sudden cardiac death. Cardiovascular magnetic resonance (CMR) imaging is an important tool in the follow-up of patients after TOF repair, because biventricular volumes and function, and PR volume and fraction can be measured with great accuracy and reproducibility.

CMR imaging studies have identified risk factors for late adverse outcomes in patients after TOF repair. These include increased RV end-diastolic volume (EDV), reduced left ventricular ejection fraction, and abnormal RV outflow tract function. Other applications of CMR include stress imaging, assessment of diastolic function, and late gadolinium enhancement, which have provided additional insight in the function of the RV.

Timing of pulmonary valve replacement (PVR) is controversial and should balance between the preservation of RV function and the need for subsequent PVR surgery, since the life-span of a homograft is limited. Based on CMR imaging studies, PVR will be considered if the RVEDV reaches a threshold of between 150 and 200 ml/m^2 in the presence of severe PR. However, timing of PVR should be based on multiple factors, other than RV size and PR fraction alone.

Introduction

Tetralogy of Fallot (TOF) is the most common type of cyanotic congenital heart disease (CHD) accounting for approximately 5 – 7% of congenital heart lesions. It has an incidence of approximately 0.4 – 0.5 / 1000 live births[1-2]. The first intracardiac repair was reported by Lillehei in 1954. For a long time, surgical management consisted of initial palliation (if necessary) followed by later repair during childhood. Perioperative death occurred in approximately 20% of patients operated on from the 1950s to the 1970s[3-4]. Twenty-year survival for patients surviving operations in that period is approximately 90%[3-4]. Due to improvements in operative and postoperative management, primary repair in early childhood has become more common during the last decades[5]. Early primary repair is preferred because it shortens the period the patient is exposed to hypoxemia, to right ventricular (RV) pressure overload and subsequent RV hypertrophy[5-6]. It can now be performed with a perioperative mortality rate of < 4%[5-8]. Long-term survival is excellent, with a 20-year survival, including perioperative mortality, up to 98%[7].

The surgical approach has also shifted from a transventricular approach to a transatrial – transpulmonary approach. The latter approach aims to preserve RV integrity, geometry and contractile function in the long term[6] and furthermore to reduce the side effects associated with a ventriculotomy, such as RV myocardial and coronary artery damage[9].

With improved surgical techniques and survival, the population of adult patients with repaired TOF is growing rapidly. However, late morbidity and mortality has been observed in many patients long after total repair. Problems include RV dysfunction, exercise intolerance, atrial- and ventricular arrhythmias, and increased risk of sudden cardiac death (SCD)[9-15]. Pulmonary regurgitation (PR) is a crucial factor in the long-term outcome[1,16-18]. Moderate or severe PR is usually tolerated well in childhood, but eventually causes RV dilatation, which can lead to RV dysfunction, symptoms, and reduced clinical outcome[10,12-13]. Pulmonary valve replacement (PVR) is often considered in these patients as treatment option. Since PVR will introduce problems of its own, timing of this intervention is important.

CMR is the current 'gold standard' for assessment of PR and RV size and function[19-20]. Considering the central role of PR and RV dilatation in the long-term outcome of patients who have been operated for TOF, CMR has become the imaging technique of choice in these patients. In recent years, various studies using MRI have provided detailed information on risk factors for adverse clinical outcome and on the results and timing of PVR. In this review we will provide an overview of these studies. Aim is to address the following questions:

What is the role of CMR imaging:

a) in the identification of patients at risk for adverse clinical outcome
b) in the timing of PVR

a. The role of CMR imaging in the identification of patients at risk for adverse clinical outcome

PR and chronic volume overload of the RV can be tolerated for many years, but morbidity and mortality increases in adult survivors of TOF repair, because compensatory mechanisms of the RV eventually fail[17]. It is known that PR relates to the use of a transannular patch (TAP) during repair[9-10,12,21]. RV loading conditions also influence the severity of PR. The presence of branch pulmonary artery stenosis may result in an increase in PR[22]. The anatomy of the main pulmonary artery and its branches can be accurately visualized with magnetic resonance angiography (MRA)[23].

In recent years, studies by Davlouros et al.[10], Geva et al.[12], and van den Berg et al.[9] reported on long-term outcome after TOF repair, as assessed with CMR imaging (Table 1). Although these studies differed with regard to age at operation, age at study, and surgical technique of the patients included, all studies agreed on increased RV dimensions (RV end diastolic volume (EDV) 116 – 139 ml/m^2) with impaired RV ejection fraction (EF) (49 – 52%) and normal to somewhat impaired LVEF (56 - 65%). The patients in the study of van den Berg et al.[9] were in good clinical condition with 86% of patients in NYHA class I. Clinical condition in both other patient groups was somewhat lower; NYHA class I: 66%[10] and 48%[12]. In multivariate analysis, Geva et al.[12] found that an older age at repair was one of the parameters associated with poor clinical status (defined as NYHA class $\geq$ III). Van den Berg et al.[9] and Davlouros et al.[10] performed univariate and multivariate analysis to determine independent predictors for CMR derived parameters. Not surprisingly, TAP repair was found to be a significant predictor of PR severity[9-10]. PR percentage independently predicted larger RVEDV[9-10]. A longer interval since repair independently predicted larger RVEDV and poorer RVEF[9].

Davlouros and co-workers were the first to show with CMR imaging the independent role of abnormal right ventricular outflow tract (RVOT) motion and aneurysms as a predictor of lower RVEF[10] (Figure 1). This was confirmed by van den Berg et al. in their study population[9]. They also could demonstrate a relationship between abnormal RVOT motion, lower RVEF and relatively poor exercise capacity, even in a group with relatively well preserved exercise performance[9]. Abnormal RVOT motion was not restricted to patients with a TAP[9-10]. A more detailed assessment of regional RV wall motion, including assessment of regional EF and dyskinesia of the RV free wall, demonstrated a direct relationship between RVOT-EF, RVOT (displacement of) dyskinetic area, and late gadolinium enhancement (LGE) score with global RVEF, as reported by Wald et al.[24]. Regional abnormalities in the RVOT also correlated with poor exercise capacity[24]. Since poor exercise capacity is a predictor of poor clinical outcome[25-26]. these findings have direct clinical implications.

Knauth et al.[13] were the first to perform serial follow-up using CMR imaging to determine independent predictors of major adverse clinical outcomes in a cohort of 88 adult TOF patients. Major adverse clinical outcomes were defined as 1) death, 2) sustained ventricular tachycardia lasting > 30 seconds or requiring cardioversion, 3) increase in NYHA to class III or IV. Secondary outcomes included PVR or insertion of an implantable defibrillator, or both. The authors expressed RVEDV as a Z-score to overcome differences between volume measurements by a gradient echo sequence and a steady-state free precession (SSFP) sequence. Multivariate analysis, controlling for length of follow-up from baseline to most recent evaluation, identified RVEDV $Z \geq 7$ (which corresponds in this study to ≥ 172 ml/m^2 in women and ≥ 185 ml/m^2 in men) and LVEF < 55% as independent predictors of major adverse clinical outcomes. Restricting the analysis to RV parameters, the authors found that RVEF < 45% and RVEDV $Z \geq 7$ were independent predictors of major adverse clinical outcomes. Twenty-seven patients (31%) had no clinical worsening during follow-up. The only independent predictor of "no clinical worsening" was age at TOF repair < 3 years. Currently, patients are generally operated within their first year of life, which is expected to contribute to a better long-term outcome.

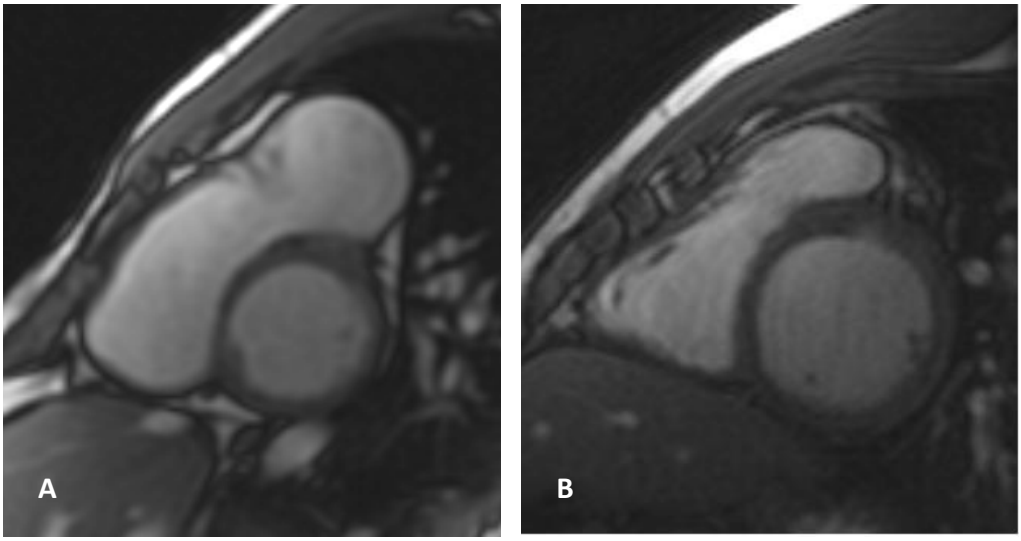


Figure 1. Short axis views of two different 17-year old patients after repair of tetralogy of Fallot (TOF). The first patient underwent TOF repair with a transannular patch (TAP) (**A**), the second patient underwent TOF repair without the use of a TAP (**B**). Note the aneurysmatic right ventricular outflow tract (RVOT) in patient A.

Table 1: Long-term follow-up after TOF repair, CMR imaging studies

		Davlouros[10]	Geva[12]	Van den Berg[9]
N (male)		85 (49)	100	59 (41)
Age at repair (years)		9.0 (0.5 – 50.1)	3.0 (0 – 31.8)	0.8 (0.2 – 2.0)
Shunt (%)		34 (40%)	48 (48%)	3 (5%)
Age at study (years)		33 (± 13)	24 (10 – 57)	15 (6 – 23)
Follow-up (years)		24 (± 8)	21 (10 – 43)	14 (6 – 23)
TAP/RVOT patch (%)		41%	75%	71%
NYHA class		I: 66%	I: 48%	I: 86%
		II: 25%	II: 40%	II: 14%
		III: 9%	III: 12%	
RV	EDV (ml/m^2)	116 (± 34)*	118 #	139 (± 37)*
	ESV (ml/m^2)	56 (± 24)*	62 #	72 (± 26)*
	EF (%)	52 (± 9)*	49 #	49 (± 6)*
	Mass (g/m^2)	51 (± 14)*		24 #
LV	EDV (ml/m^2)	76 (± 21)		81 (± 12)
	ESV (ml/m^2)	28 (± 14)		36 (± 8)*
	EF (%)	65 (± 9)*		56 (± 6)*
	Mass (g/m^2)	66 (± 22)*		53 #
PR (%)		24% (± 16)	32%	35% (0 – 57)

Results are expressed as mean (± standard deviation), as median (range), or as counts (percentages).

* Significantly different ($p < 0.05$) compared to controls.

Data not compared to controls.

Abbreviations: EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricle; M = male; NYHA = New York Heart Association; PR = pulmonary regurgitation; RV = right ventricle; RVOT = right ventricular outflow tract; TAP = transannular patch.

Late gadolinium enhancement

LGE is widely accepted as a marker of fibrosed, scarred, or otherwise abnormal myocardium[27]. Babu-Narayan et al.[27] observed that LGE was frequently seen in TOF patients, especially at locations that most likely reflected surgical procedures, but also in sites remote from surgical instrumentation. Myocardial LGE related to increased age, impaired exercise capacity, ventricular dysfunction, neurohormonal activation, and clinical arrhythmia. Patients with extensive RV LGE were also more likely to have restrictive RV physiology. Oosterhof et al.[28] found that fibrosis in the RVOT was associated with RVOT dilatation, decreased RVEF, and increased RVEDV. LGE showed

moderate correlation with global RV function in the recent study by Wald et al.[24]. They also found that fibrosis often extend beyond the superior aspect of the RVOT, which suggests that more extensive remodeling of the RV might be necessary for optimal functional recovery.

Of these studies, the study of Wald et al. most clearly demonstrates that assessment of RV LGE may contribute to clinical decision making and may have implications for patient management, including RVOT reconstruction at the time of PVR. However, demonstrating LGE may be challenging in the RV, and the role of different LGE patterns awaits further elucidation.

Diastolic function

Diastolic function is an additional important factor in the (long-term) outcome of TOF[29-34]. In TOF, restriction to late diastolic filling of the RV is indicated by end-diastolic forward flow (EDFF) in the main pulmonary artery, coincident with atrial systole[30]. Reports have been inconsistent on how restriction to RV filling affects long-term functional outcome in TOF. Norgard et al.[33] reported that restrictive RV physiology was more common in patients with a TAP repair[33]. Furthermore, they found less QRS prolongation in patients with restrictive RV physiology and concluded that restrictive RV physiology may be associated with fewer long-term complications. This was confirmed by Gatzoulis et al. in an adult patient population[30]. It seems paradoxical that restrictive RV physiology has a negative effect in the early postoperative period[29] and seems to be associated with a favourable long-term outcome[30,33]. It has been questioned if the substrate for this physiology is the same[32]. However, Norgard et al.[32] reported that the strongest predictor for restrictive RV physiology at mid-term follow-up was the presence of restriction in the early postoperative period. The exact nature of the anatomic or hemodynamic substrate that predicts diastolic function remains unknown, but the authors speculate that it is related to an abnormal hypertrophic response in the RV[33].

In these aforementioned studies, diastolic function was assessed by using the Doppler echocardiographic flow pattern across the tricuspid valve[29-30,32-33]. With MRI, optimal RV time-volume curves can be reconstructed either from cine-volumetry data[35] or by combining phase contrast velocity maps of flow through the tricuspid and pulmonary valve[31,34]. The latter technique takes advantage of the relatively good agreements between MR velocity mapping and Doppler echocardiography and between stroke volumes as assessed with MR velocity mapping and MR cine volumetry of the ventricles[31]. Although there is some discussion on the agreement between Doppler echocardiography and MRI with regard to assessment of forward flow in the pulmonary artery, MRI has demonstrated signs of impaired diastolic function in different populations of children with TOF[31,34-35]. Pediatric patients with signs of impaired compliance had more PR and poorer exercise capacity than patients with less abnormalities of RV diastolic function[31,34].

Long-term follow-up studies are necessary to evaluate the effect of restrictive RV physiology on clinical condition and to evaluate the importance of RV diastolic function for the prognosis of these patients and the response to PVR.

Stress imaging

Stress imaging is commonly used in CHD to assess cardiac contractile reserve. Several studies have shown its feasibility and safety[36-39]. Studies have been performed with specific MR-compatible bicycle ergometers in combination with CMR imaging[37]. Since physical exercise is limited by several disadvantages, pharmacological stressors are now used in the majority of the studies. Dobutamine is one of the most frequently used stressors.

In healthy controls, EDV remains unchanged during exercise, end-systolic volume (ESV) decreases, whereas stroke volume (SV) and EF increases[36-38]. Roest et al.[37] studied 15 patients with corrected TOF using a physical exercise – CMR imaging protocol. They found a small decrease of PR fraction with exercise. RV response to exercise in TOF patients was abnormal, as demonstrated by an increase in EDV, a lack of decrease in ESV, and no change in EF. LV response to exercise was normal. They concluded that the abnormal response of RVEF to exercise is mainly the result of the deleterious effects of PR-induced chronic volume overload[37]. Tulevski et al.[38] used low-dose dobutamine stress CMR imaging (dosage 15 µg/kg/min) to assess contractile reserve in 13 patients with RV pressure overload and in 9 patients with combined RV pressure and volume overload. They also found an abnormal RV response to stress in both patient groups, as demonstrated by a decrease in EDV and SV and no change in ESV and EF. They considered the decrease in EDV as a sign of impaired compliance[38]. Furthermore, they found that patients with a combination of RV pressure and volume overload had more severe RV dysfunction than patients with isolated RV pressure overload, which emphasizes the negative effect of chronic volume overload on RV function. Van den Berg et al.[39] also used low-dose dobutamine stress CMR imaging (dosage 7.5 µg/kg/min) to assess contractile reserve in 51 TOF patients. Results in this younger patient population, operated at a younger age, are in contrast to those in earlier studies. The RV response to stress was nearly normal, as ESV decreased and SV and EF increased. However, they did observe a decrease in EDV, which is abnormal and similar to the result of Tulevski et al.[38]. The authors argue that the differences in results most likely reflect differences in populations studied[39].

These studies have demonstrated the feasibility of stress imaging with CMR and have provided additional insight in the function of the RV during stress. How these findings relate to clinical outcome requires further exploration.

b. The role of CMR imaging in the timing of PVR

Considering the central role of PR in morbidity and mortality after repair of TOF, PVR is considered in many of these patients. Timing for PVR must be balanced between the benefits of elimination of RV volume load before irreversible dysfunction occurs and the disadvantages of valve failure and need for reinterventions[17]. There is consensus that severe PR should be included in the indications for PVR[40-45]. PR is generally considered severe if PR percentage is > 40-50%. Recently, Wald et al. have argued that PR volume is a better indicator of RV volume load than PR fraction[46]. Additional to the severity of PR, all studies on PVR have required the presence of RV dilatation to perform PVR. The definition of RV dilatation has varied in different studies (see Table 2), and sometimes a RVEDV $\geq$ 2x LVEDV is used as indication for PVR. Other indications for PVR, besides severe PR and RV dilatation, have included deterioration of clinical state (NYHA class II or worse)[44], the presence of tricuspid regurgitation[41,44], (supra)ventricular arrhythmias[41-42,44-45], QRS duration > 180 msec[41,44], and symptoms of diminished exercise performance[40-42,45]. In asymptomatic patients, reduced parameters in exercise testing have also been part of the indications for PVR[40].

Outcome after PVR – CMR imaging studies:

Several CMR imaging studies have been performed to evaluate the effects of PVR[40-41,43-44,47] (Table 2). It is important to recognize that these studies differed with regard to age at initial repair, since this may have an effect on outcome. In all studies, an improvement in NYHA class and a significant reduction in RV dimensions was observed after PVR. However, a normalization of RV dimensions, defined as EDV $\leq$ 108 ml/m^2 and ESV $\leq$ 47 ml/m^2[41,47], did not occur in all patients. There was a significant reduction in PR fraction in all studies. Frigiola et al.[40] found a significant increase in RVEF from 51% to 54% 1 year after PVR. All other studies did not observe a significant change in RVEF.

Considering the alterations in hemodynamics before and after PVR, several groups have suggested ways to compare pre- and post PVR RV performance corrected for the effects of PR. Vliegen et al.[44] suggested that RV function might better be described by measuring the corrected EF. This is the RVEF corrected for regurgitation of the tricuspid and pulmonary valves and for shunting in case of residual VSD, by dividing the net pulmonary flow by the RVEDV. They observed a significant improvement of the corrected RVEF from 25% before PVR to 43% 7 months after PVR. Van Straten et al.[48] studied the same patient population 19 months after PVR and found sustained improvement of RV function in most patients. This improvement in corrected RVEF was also found in the study of Oosterhof et al.[41]. Recently, Frigiola and co-workers[40] suggested to use effective RV stroke volume (RVSV – PR volume), and found this parameter to improve after PVR. LVEDV significantly increased in the studies who also assessed LV dimensions[40-41,43], but LVEF and effective LVSV only significantly improved in the study of Frigiola et al.[40].

Table 2: Outcome after pulmonary valve replacement, CMR imaging studies

		Vliegen[44]		Therrien[47]		Valsangiacomo - Buechel[43]		Oosterhof [41]		Frigiola[40]	
N (male)		26 (15)		17 (7)		20		71 (42)		71 (39)	
Age at TOF repair (years)		5.0 (0.4 – 21.0)		9.0		1.9 (± 1.1)		5.0 (2.7 – 7.4)		3.3 (± 4.9)	
Age at PVR (years)		29 (17 – 46)		34 (± 12)		14 (± 3)		29 (23 – 37)		22 (± 11)	
Follow-up after PVR (months)		7 (4 – 14)		21 (± 11)		6 (± 0.6)		9 (6 – 15)		12	
Graft		Pulmonary Homograft		Bioprosthetic pulmonary valve		Bovine jugular vein graft		Pulmonary homograft		Pulmonary homograft	
Death (n)		0		0		0		1		0	
		Changes with PVR									
		Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
NYHA class		2.0	1.3*	2.0	1.4*			≥ II: 58%	≥ II: 11%*	2.0	1.0*
RV	EDV (ml/m^2)	167	114*	163	107*	190	109*	171	119*	142	91*
	ESV (ml/m^2)	99	66*	109	69*	102	58*	102	70*	73	43*
	EF (%)	42	42	32	34	47	45	42	43	51	54*
	EFcor. (%)	25	43*					24	41*		
	Eff.SV (ml/m^2)									40	45*
LV	EDV (ml/m^2)					77	84*	85	94*	66	73*
	EF (%)					53	56	52	53	61	64*
PR (%)		46	4*			49	9*	44	5*	41	5*

Results are expressed as mean (± standard deviation), as median (range), or as counts (percentages).

* Significantly different ($p < 0.05$) compared to value pre-PVR.

Abbreviations: EFcor. = corrected ejection fraction; Eff.SV = effective stroke volume; Pre = pre-PVR; Post = post-PVR; PVR = pulmonary valve replacement; TOF = tetralogy of Fallot. Other abbreviations as in Table 1.

Van Straten et al.[49] studied diastolic function before and after PVR in 16 adult TOF patients. The authors found a lack of improvement of diastolic function 8 months after PVR, but observed a recovery at 22 months. They concluded that improvement in diastolic function requires long-term remodeling.

Several studies have tried to provide thresholds above which PVR should be performed, based on CMR imaging parameters[13,40-41,43,47]. Oosterhof et al.[41] found no threshold above which RV volumes did not decrease after PVR. However, for normalization of RVEDV and RVESV, they calculated preoperative cut-off values of 160 ml/m^2 and 82 ml/m^2 respectively. Results from Therrien et al.[47] were quite similar, with no normalization of RV dimensions if preoperative RVEDV > 170 ml/m^2 or preoperative RVESV > 85 ml/m^2. Valsangiacomo-Buechel et al.[43] observed no normalization of RVEDV if preoperative RVEDV was $\geq$ 200 ml/m^2. Prompt remodeling of the RV, with reduction of RV volume and mass, was observed after performing PVR if the RVEDV exceeded 150 ml/m^2. Frigiola et al.[40] concluded that a relatively aggressive PVR policy, performing PVR if RVEDV < 150 ml/m^2, leads to normalization of RV volumes and improvement in biventricular function. Knauth et al.[13] reported that one of the predictors for major adverse clinical outcomes was RVEDV Z $\geq$ 7, corresponding to $\geq$ 172 ml/m^2 in women and $\geq$ 185 ml/m^2 in men in their study. Comparison of these studies is hampered by differences in age at initial repair, age at time of PVR, differences in indications for PVR, and by differences in inclusion criteria for the various studies. Nevertheless, based on the results of these studies, most centers will consider PVR if the RVEDV reaches a threshold of between 150 and 200 ml/m^2. However, we think these threshold values should be interpreted with caution.

In a study using low-dose dobutamine stress CMR, van den Berg et al.[39] studied a group of patients who had undergone TOF repair before the age of 2 years and with few residual lesions. Exercise capacity of these patients was normal, mean RVEDV was 140 ± 38 ml/m^2, mean PR 37% and NT-proBNP was normal (< 35 pmol/l) in 96% of patients. Subgroup analysis based on RVEDV (group I: < 108 ml/m^2; group II: 108 – 170 ml/m^2; group III > 170 ml/m^2) demonstrated normal contractile reserve of the RV and LV in all patients, irrespective of RV size. High-risk levels of NT-proBNP (> 18 pmol/l in females and > 12 pmol/l in males) predicted smaller, but normal RV functional reserve[39].

Since the role of the RV is to maintain pulmonary perfusion and LV preload, it is questionable if RV dilatation in the absence of signs of decreased LV filling or output warrants PVR[16,40]. Exercise testing, assessment of neurohormonal activation, and stress MRI can be used as additional tools in decision making[38-40].

Percutaneous pulmonary valve implantation

Although PVR surgery can be performed with very low mortality[40-41,43-45,47-48], the lifespan of conduits is limited. Recently, overall freedom from homograft dysfunction was shown to be 66% after 5 years and 47% after 10 years[50]. This means that patients will require multiple operations during their lifetime. Over the last years, percutaneous pulmonary valve implantation (PPVI) has become available[51]. This is a promising technique, which can reduce the number of open-heart surgeries in the future. There are some morphological criteria however, which makes that not all TOF

patients are suitable for this technique. Valvar competence of the current device is maintained only up to a diameter of 22 mm. Thus, the dimensions of the RVOT at its narrowest point must not exceed this diameter[51]. CMR imaging is a useful tool in the selection of patients suitable for PPVI, since the diameter of the RVOT can be accurately measured by MRI and / or MRA. Because the RVOT in most patients with a TAP exceeds this upper threshold, devices are now mainly implanted in patients with a RV – PA conduit. Furthermore, long-term results on biventricular volumes and function, clinical condition and valve function are not yet known and are necessary to determine how PPVI should be implemented in the follow-up of TOF patients.

Reproducibility of CMR measurements

Since repeated measurements of biventricular size and function play an important role in timing of re-interventions in patients with TOF, it is of crucial importance that CMR measurements are accurate and highly reproducible. There are several reports on the reproducibility of CMR measurements using a SSFP pulse sequence[43,52-56], but only a few studies measured the reproducibility in patients with CHD[43,54,56]. In 2 studies, patients with TOF were included[43,54]. Interobserver variability for biventricular parameters was good, with the coefficient of variability between < 1 and 13% for all parameters[43,54]. However, it remains an important issue to be taken into consideration when evaluating follow-up data of CMR measurements. Factors to be taken into account are image orientation, strict adherence to ways of endo- and epicardial border tracing, and in- or exclusion of trabeculations and papillary muscles[52,56]. It is therefore important to have clear guidelines for methods of image analysis in routine clinical practice, since different observers may develop slightly different habits.

Conclusions

CMR imaging is an important tool in the follow-up of patients after TOF repair. It allows for adequate measurements of biventricular volumes and function, PR, diastolic function, contractile reserve, and myocardial fibrosis and is increasingly used in the process of decision making.

Risk factors for late deterioration have been identified with the help of studies that have included the use of CMR. Risk factors for late adverse outcome are increased RVEDV and reduced LVEF. Regional RV function is of direct functional importance and can be assessed with MRI. The role of assessment of RV diastolic function, late gadolinium enhancement as a marker of myocardial fibrosis, and stress imaging requires further studies.

Timing for PVR remains controversial, especially in asymptomatic patients, and should be based on multiple factors. CMR studies have provided threshold values for RV size at which we can be reasonably sure that the RV will return to normal dimensions if severe PR is reduced or abolished. However, to many, the problem how to identify patients in whom PVR can no longer be postponed remains.

The introduction of PPVI has provided new treatment options, and poses new questions with regard to indications and follow-up. CMR is a useful technique in many of these patients.

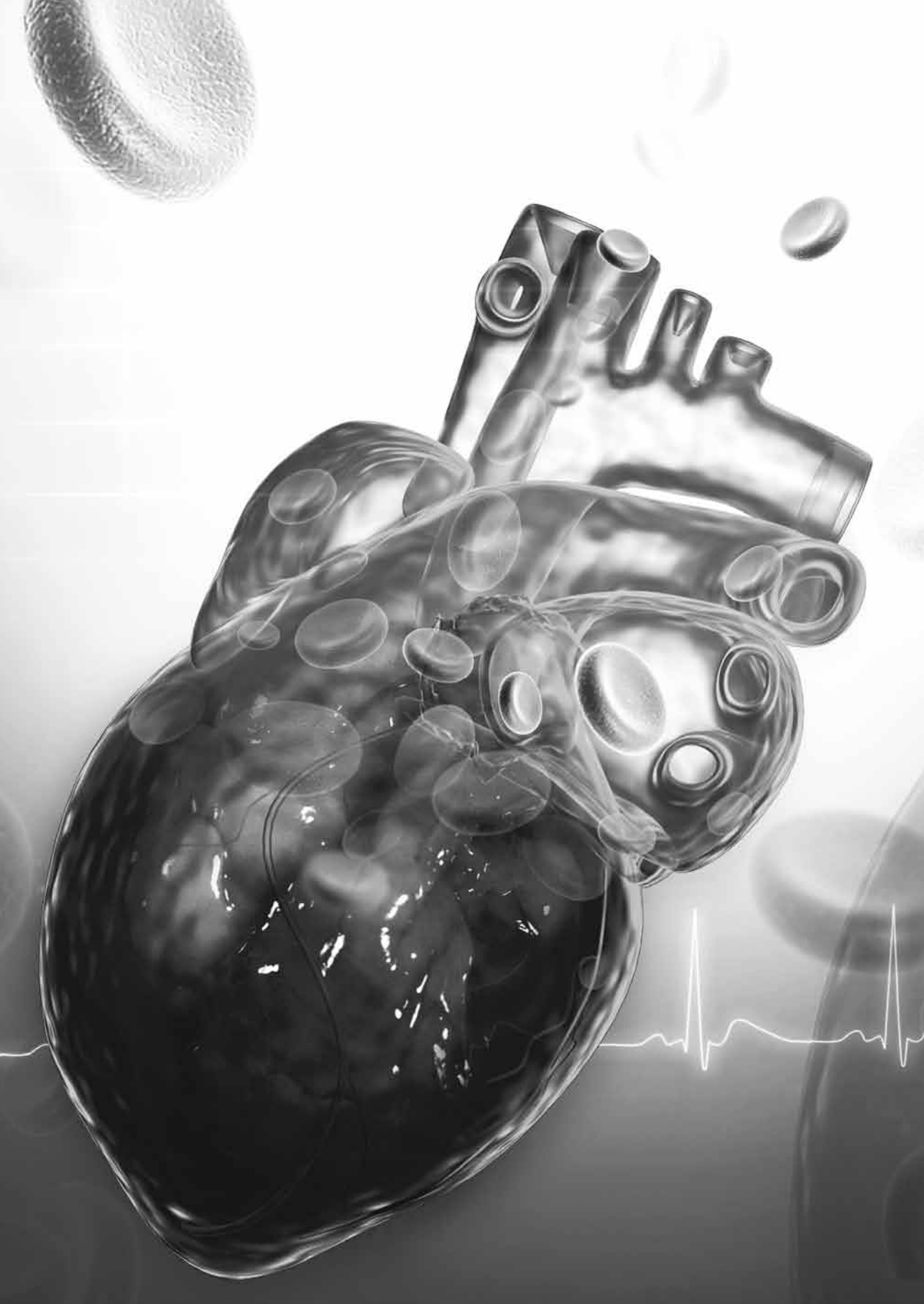
References

1. Davlouros PA, Karatza AA, Gatzoulis MA, Shore DF. Timing and type of surgery for severe pulmonary regurgitation after repair of tetralogy of Fallot. Int J Cardiol 2004;97 Suppl 1:91-101.
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890-1900.
3. Murphy JG, Gersh BJ, Mair DD, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. N Engl J Med 1993;329:593-599.
4. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-Term Survival in Patients With Repair of Tetralogy of Fallot: 36-Year Follow-Up of 490 Survivors of the First Year After Surgical Repair. J Am Coll Cardiol 1997;30:1374-1383.
5. Tamesberger MI, Lechner E, Mair R, Hofer A, Sames-Dolzer E, Tulzer G. Early primary repair of tetralogy of fallot in neonates and infants less than four months of age. Ann Thorac Surg 2008;86:1928-1935.
6. Padalino MA, Vida VL, Stellin G. Transatrial-Transpulmonary Repair of Tetralogy of Fallot. Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual 2009;12:48-53.
7. Alexiou C, Mahmoud H, Al-Khaddour A, et al. Outcome after repair of tetralogy of Fallot in the first year of life. The Annals of Thoracic Surgery 2001;71:494-500.
8. Van Arsdell GS, Maharaj GS, Tom J, et al. What is the optimal age for repair of tetralogy of Fallot? Circulation 2000;102:III123-129.
9. van den Berg J, Hop WC, Strengers JL, et al. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of Fallot. J Thorac Cardiovasc Surg 2007;133:470-477.
10. Davlouros PA, Kilner PJ, Hornung TS, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol 2002;40:2044-2052.
11. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975-981.
12. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol 2004;43:1068-1074.
13. Knauth AL, Gauvreau K, Powell AJ, et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart 2008;94:211-216.
14. Wessel HU, Paul MH. Exercise studies in tetralogy of Fallot: a review. Pediatr Cardiol 1999;20:39-47; discussion 48.
15. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation 1995;91:2214-2219.
16. Frigiola A, Tsang V, Nordmeyer J, et al. Current approaches to pulmonary regurgitation. Eur J Cardiothorac Surg 2008;34:576-80; discussion 581-582.
17. Geva T. Indications and Timing of Pulmonary Valve Replacement After Tetralogy of Fallot Repair. Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual 2006;9:11-22.
18. Kadner A, Tulevski II, Bauersfeld U, Pretre R, Valsangiacomo-Buechel ER, Dodge-Khatami A. Chronic pulmonary valve insufficiency after repaired Tetralogy of Fallot: diagnostics, reoperations and reconstruction possibilities. Expert Review of Cardiovascular Therapy 2007;5:221-230.

19. Pennell DJ, Sechtem UP, Higgins CB, et al. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. Eur Heart J 2004;25:1940-1965.
20. Rebergen SA, Chin JG, Ottenkamp J, van der Wall EE, de Roos A. Pulmonary regurgitation in the late postoperative follow-up of tetralogy of Fallot. Volumetric quantitation by nuclear magnetic resonance velocity mapping. Circulation 1993;88:2257-2266.
21. d'Udekem Y, Ovaert C, Grandjean F, et al. Tetralogy of Fallot : Transannular and Right Ventricular Patching Equally Affect Late Functional Status. Circulation 2000;102:III-116-122.
22. Chaturvedi RR, Kilner PJ, White PA, Bishop A, Szwarc R, Redington AN. Increased airway pressure and simulated branch pulmonary artery stenosis increase pulmonary regurgitation after repair of tetralogy of Fallot. Real-time analysis with a conductance catheter technique. Circulation 1997;95:643-649.
23. Oosterhof T, Mulder BJ, Vliegen HW, de Roos A. Cardiovascular magnetic resonance in the follow-up of patients with corrected tetralogy of Fallot: a review. Am Heart J 2006;151:265-272.
24. Wald RM, Haber I, Wald R, Valente AM, Powell AJ, Geva T. Effects of Regional Dysfunction and Late Gadolinium Enhancement on Global Right Ventricular Function and Exercise Capacity in Patients With Repaired Tetralogy of Fallot. Circulation 2009;119(10):1370-1377.
25. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 2005;112:828-835.
26. Giardini A, Specchia S, Tacy TA, et al. Usefulness of Cardiopulmonary Exercise to Predict Long-Term Prognosis in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2007;99:1462-1467.
27. Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. Circulation 2006;113:405-413.
28. Oosterhof T, Mulder BJM, Vliegen HW, de Roos A. Corrected Tetralogy of Fallot: Delayed Enhancement in Right Ventricular Outflow Tract. Radiology 2005;237:868-871.
29. Cullen S, Shore D, Redington A. Characterization of Right Ventricular Diastolic Performance After Complete Repair of Tetralogy of Fallot : Restrictive Physiology Predicts Slow Postoperative Recovery. Circulation 1995;91:1782-1789.
30. Gatzoulis MA, Clark AL, Cullen S, Newman CG, Redington AN. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot. Restrictive physiology predicts superior exercise performance. Circulation 1995;91:1775-1781.
31. Helbing WA, Niezen RA, Le Cessie S, van der Geest RJ, Ottenkamp J, de Roos A. Right ventricular diastolic function in children with pulmonary regurgitation after repair of tetralogy of Fallot: volumetric evaluation by magnetic resonance velocity mapping. J Am Coll Cardiol 1996;28:1827-1835.
32. Norgard G, Gatzoulis MA, Josen M, Cullen S, Redington AN. Does restrictive right ventricular physiology in the early postoperative period predict subsequent right ventricular restriction after repair of tetralogy of Fallot? Heart 1998;79:481-484.
33. Norgard G, Gatzoulis MA, Moraes F, et al. Relationship between type of outflow tract repair and postoperative right ventricular diastolic physiology in tetralogy of Fallot. Implications for long-term outcome. Circulation 1996;94:3276-3280.
34. van den Berg J, Wielopolski PA, Meijboom FJ, et al. Diastolic function in repaired tetralogy of Fallot at rest and during stress: assessment with MR imaging. Radiology 2007;243:212-219.
35. Singh GK, Greenberg SB, Yap YS, Delany DP, Keeton BR, Monro JL. Right ventricular function and exercise performance late after primary repair of tetralogy of Fallot with the transannular patch in infancy. Am J Cardiol 1998;81:1378-1382.
36. Oosterhof T, Tulevski, II, Roest AA, et al. Disparity between dobutamine stress and physical exercise magnetic resonance imaging in patients with an intra-atrial correction for transposition of the great arteries. J Cardiovasc Magn Reson 2005;7:383-389.

37. Roest AA, Helbing WA, Kunz P, et al. Exercise MR imaging in the assessment of pulmonary regurgitation and biventricular function in patients after tetralogy of fallot repair. Radiology 2002;223:204-211.
38. Tulevski, II, Hirsch A, Dodge-Khatami A, Stoker J, van der Wall EE, Mulder BJ. Effect of pulmonary valve regurgitation on right ventricular function in patients with chronic right ventricular pressure overload. Am J Cardiol 2003;92:113-116.
39. van den Berg J, Strengers JLM, Wielopolski PA, et al. Assessment of biventricular functional reserve and NT-proBNP levels in patients with RV volume overload after repair of tetralogy of Fallot at young age. International Journal of Cardiology 2009;133:364-370.
40. Frigiola A, Tsang V, Bull C, et al. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? Circulation 2008;118:S182-190.
41. Oosterhof T, van Straten A, Vliegen HW, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation 2007;116:545-551.
42. Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG, Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? Journal of the American College of Cardiology 2000;36:1670-1675.
43. Valsangiacomo Buechel ER, Dave HH, Kellenberger CJ, et al. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. Eur Heart J 2005;26:2721-2727.
44. Vliegen HW, van Straten A, de Roos A, et al. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of fallot. Circulation 2002;106:1703-1707.
45. Warner KG, O'Brien PKH, Rhodes J, Kaur A, Robinson DA, Payne DD. Expanding the indications for pulmonary valve replacement after repair of tetralogy of fallot. The Annals of Thoracic Surgery 2003;76:1066-1071.
46. Wald RM, Redington AN, Pereira A, et al. Refining the assessment of pulmonary regurgitation in adults after tetralogy of Fallot repair: should we be measuring regurgitant fraction or regurgitant volume? Eur Heart J 2009;30:356-361.
47. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. The American Journal of Cardiology 2005;95:779-782.
48. van Straten A, Vliegen HW, Hazekamp MG, et al. Right Ventricular Function after Pulmonary Valve Replacement in Patients with Tetralogy of Fallot. Radiology 2004;233:824-829.
49. van Straten A, Vliegen HW, Lamb HJ, et al. Time course of diastolic and systolic function improvement after pulmonary valve replacement in adult patients with tetralogy of Fallot. J Am Coll Cardiol 2005;46:1559-1564.
50. Oosterhof T, Meijboom FJ, Vliegen HW, et al. Long-term follow-up of homograft function after pulmonary valve replacement in patients with tetralogy of Fallot. Eur Heart J 2006;27:1478-1484.
51. Lurz P, Bonhoeffer P. Percutaneous implantation of pulmonary valves for treatment of right ventricular outflow tract dysfunction. Cardiol Young 2008;18:260-267.
52. Alfakih K, Plein S, Bloomer T, Jones T, Ridgway J, Sivananthan M. Comparison of right ventricular volume measurements between axial and short axis orientation using steady-state free precession magnetic resonance imaging. J Magn Reson Imaging 2003;18:25-32.
53. Catalano O, Antonaci S, Opasich C, et al. Intra-observer and interobserver reproducibility of right ventricle volumes, function and mass by cardiac magnetic resonance. J Cardiovasc Med (Hagerstown) 2007;8:807-814.
54. Mooij CF, de Wit CJ, Graham DA, Powell AJ, Geva T. Reproducibility of MRI measurements of right ventricular size and function in patients with normal and dilated ventricles. J Magn Reson Imaging 2008;28:67-73.

55. Robbers-Visser D, Boersma E, Helbing WA. Normal biventricular function, volumes, and mass in children aged 8 to 17 years. J Magn Reson Imaging 2009;29:552-559.
56. Winter MM, Bernink FJ, Groenink M, et al. Evaluating the Systemic Right Ventricle by CMR: the Importance of Consistent and Reproducible Delineation of the Cavity. J Cardiovasc Magn Reson 2008;10:40.



Chapter 3

Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by CMR imaging

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Abstract

Introduction: Cardiovascular magnetic resonance (CMR) imaging provides highly accurate measurements of biventricular volumes and mass and is frequently used in the follow-up of patients with acquired and congenital heart disease (CHD). Data on reproducibility are limited in patients with CHD, while measurements should be reproducible, since CMR imaging has a main contribution to decision making and timing of (re)interventions.

Objective: The aim of this study was to assess intra-observer and interobserver variability of biventricular function, volumes, and mass in a heterogeneous group of patients with CHD using CMR imaging.

Methods: Thirty-five patients with CHD (7 – 62 years) were included in this study. A short axis set was acquired using a steady-state free precession pulse sequence. Intra-observer and interobserver variability was assessed for left ventricular (LV) and right ventricular (RV) volumes, function, and mass by calculating the coefficient of variability.

Results: Intra-observer variability was between 2.9% and 6.8% and interobserver variability was between 3.9% and 10.2%. Overall, variations were smallest for biventricular end-diastolic volume and highest for biventricular end-systolic volume.

Conclusions: Intra-observer and interobserver variability of biventricular parameters assessed by CMR imaging is good for a heterogeneous group of patients with CHD. CMR imaging is an accurate and reproducible method and should allow adequate assessment of changes in ventricular size and global ventricular function.

Introduction

Assessment of ventricular function is important in the follow-up of patients with congenital and acquired heart disease. Cardiovascular magnetic resonance (CMR) imaging is frequently used for the assessment of both left ventricular (LV) and right ventricular (RV) size and function, because it is an accurate and non-invasive method, which has been validated extensively[1].

Reproducibility of CMR measurements plays an important role in establishing the feasibility of CMR imaging in clinical practice. Whether differences in measurements are caused by progression of disease or could be explained by intra- or interobserver variability is of crucial importance, because CMR imaging has a main contribution to decision making and timing of (re)interventions.

There are several reports on the reproducibility of CMR measurements, but most have been done in healthy patients or patients with acquired heart disease[2-11]. Only a few studies measured reproducibility in patients with CHD[12-15]. These studies were performed using gradient echo imaging pulse sequences[12] or only examined a selected group of patients (tetralogy of Fallot (TOF), atrial septal defect (ASD) or systemic RV)[13-15]. Intra-observer and interobserver variability has never been studied in a heterogeneous group of patients with CHD, representative for the total spectrum in a clinical program.

In patients with CHD, the RV is often involved in the disease process. The geometric shape of the RV can be altered by abnormal volume- and/or pressure loading conditions, e.g. caused by pulmonary regurgitation in patients with TOF, or due to extensive trabeculation with hypertrophy, as in patients with intra-atrial correction of transposition of the great arteries (TGA). In theory, the complex geometry of the RV in patients with CHD can potentially lead to higher intra- and interobserver variability, compared to measurements in healthy volunteers.

The objective of this study was to assess intra-observer and interobserver variability of biventricular function, volumes, and mass in a heterogeneous group of patients with CHD using CMR imaging.

Methods

Subjects

Thirty-five patients with CHD (26 males, 9 females; mean age 22 ± 13 years, range 7 – 62 years) were included in this study. The subjects were selected from the total group of patients with CHD in whom CMR imaging was requested in daily clinical practice in 2007.

The characteristics of the study population are displayed in Table 1. The distribution of diagnoses in our study group was representative of the distribution of diagnoses in the total group of subjects with CHD undergoing CMR imaging in 2007.

The study was approved by the institutional review board.

Table 1: Characteristics of the study population

Characteristic	Value
Gender (male / female)	26 / 9
Age (years)	22.2 ± 13.2 (6.8 – 61.6)
Heart rate (beats per minute)	76 ± 11 (62 – 101)
Diagnosis:	n = 35
- Aortic stenosis (repaired / unrepaired)	n = 5 (4 / 1)
- ASD (unrepaired)	n = 1
- ccTGA, PA, VSD (repaired)	n = 1
- DORV, VSD, coarctation (repaired)	n = 1
- Fontan circulation (dominant RV / dominant LV)	n = 10 (3 / 7)
- Intra-atrial correction of TGA	n = 3
- PA, VSD (repaired)	n = 3
- Pulmonary stenosis (repaired)	n = 1
- Tetralogy of Fallot (repaired)	n = 8
- VSD (unrepaired)	n = 2

Results are expressed as mean ± standard deviation (range).

Abbreviations: ASD = atrial septal defect; ccTGA = congenitally corrected transposition of the great arteries; DORV = double outlet right ventricle; LV = left ventricle; PA = pulmonary atresia; RV = right ventricle; TGA = transposition of the great arteries; VSD = ventricular septal defect.

CMR image acquisition

CMR imaging was performed using a Signa 1.5 Tesla whole-body MR imaging system (General Electric, Milwaukee, WI, USA). An 8-channel phased-array cardiac surface coil was placed on top and beneath the chest. All patients were monitored by vector cardiogram gating and respiratory monitoring. Studies were performed by experienced MR-technicians, supervised by one of the four physicians (SEL, DR-V, AM, WAH), or by the physicians themselves. Standard scout images were made to obtain a four chamber view of the heart. A short axis set, using steady-state free precession (SSFP) cine imaging, was acquired from base to apex. An average of 13 contiguous slices were planned on the four chamber image, parallel to the atrioventricular valve plane of the LV in end-diastole. Typical imaging parameters were: repetition time 3.4 msec, echo time 1.5 msec, flip angle 45º, receiver bandwidth 125 kHz, slice thickness 7–10 mm, inter-slice gap 0–1 mm, field of view 380 x 380 mm, phase field of view 0.75, and matrix 164 × 128 mm. All images were obtained during breath-hold in end-expiration.

CMR analysis

The CMR studies were analyzed on a commercially available Advanced Windows workstation (General Electric Medical Systems, Milwaukee, WI, USA), equipped with Q-mass (version 5.2, Medis Medical Imaging Systems, Leiden, the Netherlands).

The ventricular volumetric data set was quantitatively analyzed using manual outlining of endocardial and epicardial borders in end-systole and end-diastole. The following parameters were calculated: biventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), and mass. Criteria for border detection were used as described by Robbers-Visser et al.[11] Specifically: end-diastole and end-systole were visually defined on multiple midventricular slices. In the basal slices, the following criteria were used: 1) when the cavity was only partially surrounded by ventricular myocardium, only the part up to the junction with atrial tissue was included in the ventricular volume; 2) when the pulmonary or aortic valve was visible in the basal slice, contours were drawn up to the junction with the semilunar valves[16]. The interventricular septum was included in the left ventricular mass. Major papillary muscles and trabeculations were excluded from the ventricular volumes and included in the ventricular mass[17].

Ventricular volume was calculated as the sum of the ventricular cavity areas multiplied by the slice thickness. Ventricular mass was calculated as the difference between the epicardial and endocardial contours multiplied by the slice thickness and a specific gravity of the myocardium of 1.05 g/ml.[18]

All data sets were analyzed by one observer (SEL). For intra-observer variability, studies were reanalyzed after an average period of 6 months. For interobserver variability, a second observer (DR-V) analyzed all studies and measured the aforementioned parameters independently and blinded to previous results.

Statistical analysis

Data are expressed as frequencies, or as mean ± standard deviation. Intra- and interobserver variability was assessed using the method of Bland-Altman[19]. The coefficient of variability, i.e. the standard deviation of the difference of the 2 measurements divided by the mean of the 2 measurements, and multiplied by 100%, was calculated to study the percentage of variability of the measurements. A p-value < 0.05 was considered statistically significant.

Results

The intra-observer and interobserver variability data are displayed in Table 2. Intra-observer variability was between 2.9% and 6.8%, with the smallest variation in measurements of LV and RV EDV (2.9% and 3.0% respectively). The highest variation was found in LV ESV (6.8%) and RV mass (5.7%). Interobserver agreement demonstrated more variation for all variables and was between 3.9% and 10.2%. The smallest variation was found in LV EF (3.9%) and RV and LV EDV (4.0% and 4.3% respectively). The highest variation was found in measurements of LV and RV ESV (10.2% and 7.7% respectively) and LV and RV mass (6.0% and 6.2% respectively).

Table 2: Intra-observer and interobserver variability analysis

	LV-EDV	LV-ESV	LV-SV	LV-EF	LV-mass	RV-EDV	RV-ESV	RV-SV	RV-EF	RV-mass
Intra-observer										
Mean difference ± SD	1.6 ± 3.9	1.9 ± 3.4	-0.4 ± 3.4	-0.9 ± 2.3	0.6 ± 4.1	0.9 ± 5.3	3.4 ± 3.4	-2.5 ± 4.4	-1.6 ± 1.9	0.1 ± 4.7
Limits of agreement	-6.3 to 9.4	-4.9 to 8.8	-7.2 to 6.5	-5.6 to 3.7	-7.6 to 8.9	-9.7 to 11.5	-3.3 to 10.2	-11.4 to 6.4	-5.4 to 2.1	-9.3 to 9.5
Mean value ± SD	134.9 ± 42.5	50.3 ± 19.2	84.7 ± 27.8	62.9 ± 6.4	125.2 ± 47.3	179.3 ± 84.8	86.9 ± 51.9	92.3 ± 37.2	53.8 ± 9.5	81.8 ± 44.6
Coefficient of variability	2.9%	6.8%	4.1%	3.7%	3.3%	3.0%	3.9%	4.8%	3.5%	5.7%
Inter-observer										
Mean difference ± SD	0.3 ± 5.8	1.6 ± 5.1	-1.1 ± 4.4	-0.9 ± 2.5	-0.3 ± 7.5	4.0 ± 7.1	6.8 ± 6.4	-2.6 ± 5.2	-2.7 ± 3.0	2.4 ± 5.0
Limits of agreement	-11.2 to 11.9	-8.6 to 11.8	-9.9 to 7.6	-5.9 to 4.1	-15.3 to 14.8	-10.2 to 18.1	-6.1 to 19.6	-13.0 to 7.8	-8.7 to 3.4	-7.5 to 12.4
Mean value ± SD	135.0 ± 41.6	49.7 ± 18.9	85.4 ± 28.0	63.5 ± 6.9	125.3 ± 47.6	177.6 ± 83.7	83.8 ± 50.9	93.9 ± 37.4	55.2 ± 9.8	80.6 ± 45.6
Coefficient of variability	4.3%	10.2%	5.1%	3.9%	6.0%	4.0%	7.7%	5.5%	5.5%	6.2%

Results are expressed as mean ± standard deviation (SD).

Coefficient of variability: expressed as a percentage of the SD of the difference divided by the mean of the 2 measurements.

Volumetric variables in milliliters, mass variables in grams.

Abbreviations: EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricle; SV = stroke volume; RV = right ventricle.

Discussion

In our study, intra-observer and interobserver variability for all variables was good. Overall, the variations were smallest for biventricular EDV and highest for biventricular ESV. Although we expected higher intra- and interobserver variability in the RV, because of its complex shape and heavy trabeculations, we did not find a difference in results for both ventricles. Our results are comparable to those of other studies who reported on reproducibility with SSFP CMR imaging[3-4,6-8,10-11,13,15] (Tables 3 and 4).

Recently, Mooij et al.[13] reported on reproducibility in patients with RV dilation (unrepaired ASD (n = 20); TOF (n = 20)) and in a normal RV group (n = 20). Variability for all patients ranged from 3.6% – 13.0%. Mooij et al. examined a selected group of patients, whereas our study population consisted of a more heterogeneous group of patients with CHD, representative for the total spectrum in a clinical program. Valsangiacomo-Buechel et al.[14] reported that observer variability, in 10 children with TOF, ranged from < 1% to 5% for intra-observer analysis and from < 1% to 13% for interobserver analysis. Although we cannot compare all our reported results to theirs, this seems comparable to our results.

Similar to our results, other authors found the largest amount of intra-observer or interobserver variation in biventricular ESV[4,8,10,13]. One of the possible explanations is the smaller absolute value of ESV. Similar absolute measurement errors will therefore lead to higher observer variation in ESV, compared to for example EDV. Another source of error is the endocardial border detection, which is more difficult in end systole due to more densely packed trabeculations and papillary muscles[15].

Image analysis

A critical review of contours traced revealed that the interobserver variation for both ventricles was mainly caused by different interpretations in the basal slice and in the apical slices. Guidelines for image analysis might be helpful, but are still a subject of debate. Most authors agree on criteria on how to draw contours in the basal slice[4,6,9,16,20]. However, there is less consensus about inclusion or exclusion of papillary muscles and trabeculations[3,6,15-16]. It is important that the used criteria for border detection are described in reports, because inclusion or exclusion of papillary muscles and trabeculations cause differences in measurements of biventricular dimensions and function[15]. To reduce observer variability, it is important to have clear guidelines for methods of delineation in routine clinical practice as well as in research projects, since different observers may develop slightly different habits.

The basal slice will remain an area in which there may be discussion if image acquisition in the short axis plane is used, particularly for the RV. Alternative imaging orientations have been studied, as well as methods to improve image analysis and assessment of volumes and mass. For

Table 3: Reports assessing intra-observer variability of biventricular parameters by SSFP CMR imaging

Study	Population / Diagnosis	M/F	Age (years)	Statistics	LV					RV				
					EDV	ESV	SV	EF	Mass	EDV	ESV	SV	EF	Mass
This study	n = 35	26/9	22 ± 13	CoV										
	CHD		(7 – 62)	n = 35	2.9%	6.8%	4.1%	3.7%	3.3%	3.0%	3.9%	4.8%	3.5%	5.7%
Catalano[3]	n = 45	33/12	49 ± 20	CoV										
	Acquired / Healthy		(8 – 83)	n = 45						7%	9%		10%	12%
Clay[4]	n = 20	14/6	30	CoV										
	Acquired / Healthy			n = 20	5.2%	6.5%		2.9%	4.7%					
Hudsmith[6]	n = 108	63/45	38 ± 12	CoV*										
	Healthy		(21 – 68)	n = 12	5.6%			2.3%	6.1%	9.0%			5.3%	
Maceira[8]	n = 120	60/60	(20 – 80)	CoV										
	Healthy			n = 10						3.6%	6.5%	5.9%	4.0%	5.7%
Plein[10]	n = 41	23/18	53	CoV										
	Acquired / Healthy		(32 – 77)	n = 10	2.8%	10.1%	3.4%	5.2%	3.9%					
Robbers-	n = 60	30/30	(8 – 17)	CoV										
Visser[11]	Healthy			n = 15	2.1%	5.8%	2.6%	0.01%	3.9%	2.1%	6.0%	2.5%	0.08%	6.2%
Winter[15]	n = 29	20/9	35 ± 12	CoV										
	Systemic RV			n = 20						6.1%	6.7%	9.4%	5.8%	

Results are expressed as mean ± standard deviation (range).

* CoV, indexed for body surface area.

Abbreviations: Acquired = acquired heart disease; CHD = congenital heart disease; CoV = coefficient of variability; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; F = female; Healthy = healthy controls; LV = left ventricle; M = male; RV = right ventricle; SV = stroke volume.

Table 4: Reports assessing interobserver variability of biventricular parameters by SSFP CMR imaging

Study	Population / Diagnosis	M/F	Age (years)	Statistics	LV					RV				
					EDV	ESV	SV	EF	Mass	EDV	ESV	SV	EF	Mass
This study	n = 35	26/9	22 ± 13	CoV										
	CHD		(7 – 62)	n = 35	4.3%	10.2%	5.1%	3.9%	6.0%	4.0%	7.7%	5.5%	5.5%	6.2%
Catalano[3]	n = 45	33/12	49 ± 20	CoV										
	Acquired / Healthy		(8 – 83)	n = 45						8%	11%		12%	13%
Clay[4]	n = 20	14/6	30	CoV										
	Acquired / Healthy			n = 20	3.3%	6.8%		4.6%	3.7%					
Hudsmith[6]	n = 108	63/45	38 ± 12	CoV*										
	Healthy		(21 – 68)	n = 12	2.7%			3.3%	5.2%	9.6%			10.7%	
Karamitsos[7]	n = 10	5/5	34 ± 14	CoV										
	Healthy			n = 10	2.6%	6.9%	3.4%	2.9%	5.8%					
Maceira[8]	n = 120	60/60	(20 – 80)	CoV										
	Healthy			n = 10						6.3%	8.6%	7.0%	4.4%	7.8%
Mooij[13]	n = 60	34/26	21 ± 13	CoV*										
	ASD / TOF / Healthy			n = 60	3.6%	10.5%	6.6%	5.8%	5.3%	6.4%	13.0%	11.8%	8.0%	11.3%
Plein[10]	n = 41	23/18	53	CoV										
	Acquired / Healthy		(32 – 77)	n = 41	4.3%	9.4%	9.5%	6.0%	6.0%					
Robbers-Visser[11]	n = 60	30/30	(8 – 17)	CoV										
	Healthy			n = 15	5.3%	13.9%	3.3%	2.3%	6.1%	3.4%	7.6%	4.5%	2.0%	8.9%
Winter[15]	n = 29	20/9	35 ± 12	CoV										
	Systemic RV			n = 20						10.0%	12.7%	12.2%	7.5%	

Results are expressed as mean ± standard deviation (range).

* CoV, indexed for body surface area.

Abbreviations: ASD = atrial septal defect; TOF = tetralogy of Fallot. Other abbreviations as in Table 3.

example, Alfakih et al.[2] found that observer variability for RV measurements in the axial orientation was slightly lower compared to results of the short axis orientation. Strugnell et al.[21] reported on a modified RV short axis orientation, which is aligned to the outflow of the RV. This method demonstrated a closer agreement between the RV and LV stroke volumes compared to the current method. However, observer variability analysis was not performed and should be assessed to establish the real advantage of this new method. Both the axial orientation as well as the modified RV short axis orientation make detection of the atrioventricular valve border easier. However, the major advantage of the use of the short axis orientation is that only one data set is required for both LV and RV measurements. Furthermore, in the axial orientation, the partial volume effect of blood and myocardium on the inferior wall of the RV can make it difficult to identify the blood / myocardial boundary[2].

Kirschbaum et al.[22] have reported that identification of the mitral valve plane and apex on long-axis images in addition to short axis contours reduces the interstudy variability for all parameters in LV functional assessment, when compared with using short axis images alone. This method might be applicable for the RV as well.

Van der Geest et al.[20] suggested that semiautomated contour detection is less hampered by random variabilities. At present, semiautomatic contour detection algorithms are only available for the LV and still require manual correction in a significant number of slices[10,20]. Further analysis and improvement of these algorithms is needed to demonstrate a reduction in observer variation.

Catalano et al[23]. and Corsi et al.[24] reported on a technique for volumetric surface detection (VoSD) and quantification of biventricular volumes without tracing and geometric approximations. The VoSD method showed lower observer variation for all parameters compared to the short axis method. Although limitations clearly exist, this technique might improve reproducibility of biventricular assessments[23-24].

Limitations

The size and variation of our population prevented subgroup analysis. The amount and size of trabeculations and papillary muscles might be a cause of differences in variation between subgroups. In theory, the extensive trabeculations and large papillary muscles in patients with intra-atrial correction of TGA can potentially lead to higher observer variability compared to patients, in whom the shape of the RV is less altered by abnormal loading conditions. In patients after Fontan operation, the interpretation of the basal slice might be more difficult due to the abnormal anatomy, which can potentially lead to higher observer variability too.

Another issue that should be taken into consideration when evaluating follow-up data, is that variation in CMR measurements could also be caused by interoperator variation, introduced during CMR planning, as reported by Danilouchkine et al.[25]. In research protocols it is favourable to have all studies carried out by the same operator, but in routine clinical practice, this is more difficult to achieve. In our center, image acquisition is perfomed according to a standard protocol and studies are carried out by experienced technicians, under direct supervision of an experienced CMR

cardiologist / radiologist, to reduce operator variability.

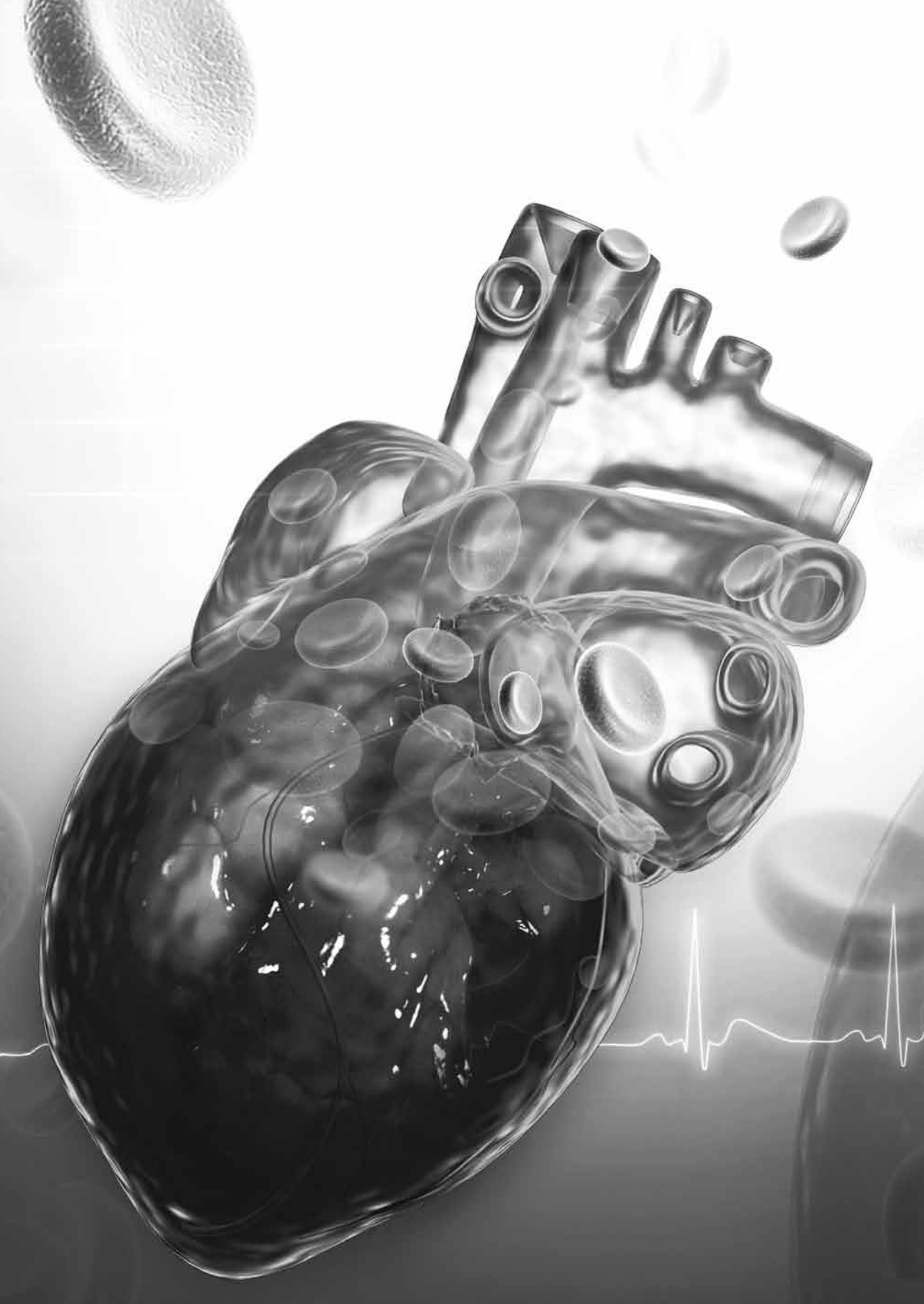
Conclusions

Variations within and between observers and operators will remain an important issue to be taken into consideration when evaluating follow-up data of MRI measurements, especially in patients in whom CMR imaging contributes to decision-making and timing of (re)interventions as in patients with CHD. Our results show that intra-observer and interobserver variability of biventricular parameters assessed by CMR imaging, using SSFP, is good in a heterogeneous group of patients with CHD. CMR imaging is an accurate and reliable method for follow-up of biventricular function and mass and should allow adequate assessment of changes in ventricular size and global ventricular function.

References

1. Pennell DJ, Sechtem UP, Higgins CB, et al. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. Eur Heart J 2004;25:1940-1965.
2. Alfakih K, Plein S, Bloomer T, Jones T, Ridgway J, Sivananthan M. Comparison of right ventricular volume measurements between axial and short axis orientation using steady-state free precession magnetic resonance imaging. J Magn Reson Imaging 2003;18:25-32.
3. Catalano O, Antonaci S, Opasich C, et al. Intra-observer and interobserver reproducibility of right ventricle volumes, function and mass by cardiac magnetic resonance. J Cardiovasc Med (Hagerstown) 2007;8:807-814.
4. Clay S, Alfakih K, Messroghli DR, Jones T, Ridgway JP, Sivananthan MU. The reproducibility of left ventricular volume and mass measurements: a comparison between dual-inversion-recovery black-blood sequence and SSFP. Eur Radiol 2006;16:32-37.
5. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. Am Heart J 2004;147:218-223.
6. Hudsmith LE, Petersen SE, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. J Cardiovasc Magn Reson 2005;7:775-782.
7. Karamitsos TD, Hudsmith LE, Selvanayagam JB, Neubauer S, Francis JM. Operator induced variability in left ventricular measurements with cardiovascular magnetic resonance is improved after training. J Cardiovasc Magn Reson 2007;9:777-783.
8. Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J 2006;27:2879-2888.
9. Moon JC, Lorenz CH, Francis JM, Smith GC, Pennell DJ. Breath-hold FLASH and FISP cardiovascular MR imaging: left ventricular volume differences and reproducibility. Radiology 2002;223:789-797.
10. Plein S, Bloomer TN, Ridgway JP, Jones TR, Bainbridge GJ, Sivananthan MU. Steady-state free precession magnetic resonance imaging of the heart: comparison with segmented k-space gradient-echo imaging. J Magn Reson Imaging 2001;14:230-236.
11. Robbers-Visser D, Boersma E, Helbing WA. Normal biventricular function, volumes, and mass in children aged 8 to 17 years. J Magn Reson Imaging 2009;29:552-559.
12. Helbing WA, Rebergen SA, Maliepaard C, et al. Quantification of right ventricular function with magnetic resonance imaging in children with normal hearts and with congenital heart disease. Am Heart J 1995;130:828-837.
13. Mooij CF, de Wit CJ, Graham DA, Powell AJ, Geva T. Reproducibility of MRI measurements of right ventricular size and function in patients with normal and dilated ventricles. J Magn Reson Imaging 2008;28:67-73.
14. Valsangiacomo Buechel ER, Dave HH, Kellenberger CJ, et al. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. Eur Heart J 2005;26:2721-2727.
15. Winter MM, Bernink FJ, Groenink M, et al. Evaluating the Systemic Right Ventricle by CMR: the Importance of Consistent and Reproducible Delineation of the Cavity. J Cardiovasc Magn Reson 2008;10:40.
16. Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. J Magn Reson Imaging 2003;17:323-329.
17. Lorenz CH, Walker ES, Morgan VL, Klein SS, Graham TP, Jr. Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. J Cardiovasc Magn Reson 1999;1:7-21.

18. Katz J, Milliken MC, Stray-Gundersen J, et al. Estimation of human myocardial mass with MR imaging. Radiology 1988;169:495-498.
19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-310.
20. van der Geest RJ, Buller VG, Jansen E, et al. Comparison between manual and semiautomated analysis of left ventricular volume parameters from short-axis MR images. J Comput Assist Tomogr 1997;21:756-765.
21. Strugnell WE, Slaughter RE, Riley RA, Trotter AJ, Bartlett H. Modified RV short axis series--a new method for cardiac MRI measurement of right ventricular volumes. J Cardiovasc Magn Reson 2005;7:769-774.
22. Kirschbaum SW, Baks T, Gronenschild EH, et al. Addition of the long-axis information to short-axis contours reduces interstudy variability of left-ventricular analysis in cardiac magnetic resonance studies. Invest Radiol 2008;43:1-6.
23. Catalano O, Corsi C, Antonaci S, et al. Improved reproducibility of right ventricular volumes and function estimation from cardiac magnetic resonance images using level-set models. Magn Reson Med 2007;57:600-605.
24. Corsi C, Lamberti C, Catalano O, et al. Improved quantification of left ventricular volumes and mass based on endocardial and epicardial surface detection from cardiac MR images using level set models. J Cardiovasc Magn Reson 2005;7:595-602.
25. Danilouchkine MG, Westenberg JJ, de Roos A, Reiber JH, Lelieveldt BP. Operator induced variability in cardiovascular MR: left ventricular measurements and their reproducibility. J Cardiovasc Magn Reson 2005;7:447-457.



Chapter 4

Exercise capacity and ventricular function in patients treated for isolated pulmonary valve stenosis or tetralogy of Fallot

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Abstract

Introduction: We hypothesized 1.) that long-term ventricular outcome and exercise capacity would be better in patients with isolated pulmonary valve stenosis (PS) treated with balloon pulmonary valvuloplasty (BPV) than in patients operated for tetralogy of Fallot (TOF), and 2.) that ventricular outcome and exercise capacity would not be different in PS patients and healthy controls.

Methods: We included 21 PS patients after BPV (16.2 ± 5.2 years) and 21 patients operated for TOF (16.6 ± 5.6 years), matching them for gender, age at treatment, and age at study. Patients underwent cardiovascular magnetic resonance (CMR) imaging, exercise testing, 12-lead ECG and 24-hour Holter monitoring for assessment of right ventricular (RV) size and function, pulmonary regurgitation (PR), exercise capacity, and electrocardiographic status. Healthy controls for CMR imaging and exercise testing were matched for gender and age at study.

Results: RV volumes and PR percentage were significantly larger in TOF patients than in PS patients; biventricular ejection fraction (EF) was not different. PR was mild in most PS patients. RV end-systolic volume was significantly larger in PS patients than in healthy controls; RVEF was significantly lower. Both patient groups had similar exercise test results. Peak workload and VO_2 max. were significantly lower in PS patients than in healthy controls**.**

Conclusions: Longstanding mild PR in PS patients can lead to an enlarged RV, reduced RV function, and reduced exercise capacity. Despite more PR and larger RV volumes in TOF patients, exercise capacity and biventricular function are similar in both patient groups.

Introduction

Residual pulmonary regurgitation (PR) often occurs after treatment for congenital heart disease (CHD), particularly after repair of tetralogy of Fallot (TOF)[1-4] and isolated pulmonary valve stenosis (PS)[5-8]. The effects of severe PR on right ventricular (RV) function and clinical outcome include RV dilatation, decreased right and left ventricular (LV) function, reduction of exercise capacity, arrhythmias, and increased risk of sudden cardiac death[1-3,9-10]. A pulmonary valve replacement (PVR) is often considered in patients treated for TOF, but the best time for performing a PVR is still uncertain, especially in patients with asymptomatic PR[11-15].

Before corrective treatment, the RV is subjected to pressure overload in both types of CHD. In TOF patients, this is combined with hypoxemia caused by a right-to-left shunt at the ventricular level (ventricular septal defect (VSD)). Treatment options also differ significantly: TOF patients undergo a surgical repair in early childhood, whereas patients with isolated PS are now treated with percutaneous balloon pulmonary valvuloplasty (BPV)[16]. These factors may add to differences in long-term outcome with respect to RV function and clinical status.

Long-term outcome in patients after treatment for isolated PS has been studied less extensively than in patients after repair of TOF and most reports in PS patients focus primarily on results of residual pulmonary valve (PV) peak gradients. Results at long-term follow-up are excellent in the majority of the patients, although mild PR is often reported. While most studies have used echocardiography in their evaluation of long-term outcome in patients treated for isolated PS[5-8], very few have used the current gold standard technique for assessing RV size and function, i.e. cardiovascular magnetic resonance (CMR) imaging[17].

This study was therefore based on two hypotheses: 1) We hypothesized that long-term ventricular function, exercise capacity, and clinical status would be better in patients treated for isolated PS than in patients treated for TOF. 2) We hypothesized that ventricular function, exercise capacity, and clinical status in PS patients would not differ from those in healthy controls.

To test these hypotheses, we compared the long-term outcome in PS patients after BPV with those in a matched group of TOF patients and in a matched group of healthy controls.

Methods

Patients

The study population of the PS patients consisted of patients who underwent balloon pulmonary valvuloplasty for isolated pulmonary valve stenosis at the Erasmus Medical Center between 1990 and 1995. Thirty patients could be identified from the medical records of the Departments of Pediatric Cardiology and Cardiothoracic Surgery; 21 agreed to participate in the current study. They underwent CMR imaging, exercise testing, echocardiography, 12-lead electrocardiography (ECG), and 24-hour Holter monitoring. These PS patients were compared to patients after repair of tetralogy of Fallot. Patients with TOF undergo the aforementioned tests as part of routine clinical care in our center. TOF patients were randomly selected from the clinical database and were matched to the PS

patients for gender, age at treatment, and age at study. Medical records were reviewed for patient characteristics.

Healthy controls, who were matched for gender and age at study, were randomly selected from our databases of healthy volunteers, who had participated in a study to obtain normal values of biventricular function with CMR imaging or in a study to obtain normal values of exercise capacity. Since not all healthy controls had undergone both tests, 2 separate control groups were composed: one for results of CMR imaging and the other for results of exercise testing.

The research study was approved by the local Ethical Committee; all patients, and if required, their parents, gave informed consent.

Echocardiography

Conventional echocardiography was carried out, consisting of transthoracic M-mode and 2-dimensional echocardiography, as well as pulsed-wave and continuous-wave Doppler measurements, using an ultrasound Philips Sonos 5500 (Philips Medical Systems, Best, the Netherlands). The maximum peak gradient across the PV was determined using Doppler measurements and calculated using the modified Bernoulli equation ($\Delta P = 4*(Vmax.^2)$). PR was semiquantitatively classified as none, mild, moderate, or severe, according to the length, the width, and the localization of the regurgitant flow[18].

CMR image acquisition

CMR imaging was performed using a 1.5 Tesla system (General Electric, Milwaukee, WI, USA) and an 8-channel phased-array cardiac surface coil. Standard localizer imaging planes were acquired to plan a short axis set and flow measurements of the pulmonary valve. The short axis set, using steady-state free precession cine imaging, was acquired from base to apex. Typical imaging parameters were: repetition time 3.5 msec, echo time 1.5 msec, flip angle 45º, slice thickness 8 – 9 mm, inter-slice gap 0 – 1 mm, field of view 320 x 240 mm, and matrix 160 $\times$ 128 mm. Flow measurements were performed perpendicular to flow. Typical imaging parameters were: repetition time 4.8 msec, echo time 2.6 msec, flip angle 18º, slice thickness 7 mm, inter-slice gap 0 mm, field of view 290 x 220 mm, and matrix 256 x 128 mm. Velocity encoding was set at 150 cm/sec and was increased whenever phase aliasing occurred. All images were obtained during breath-hold in end-expiration.

CMR analysis

Analysis was performed on a commercially available Advanced Windows workstation (General Electric Medical Systems), equipped with the software packages QMASS (version 5.2) and QFLOW (version 3.2) (Medis Medical Imaging Systems, Leiden, the Netherlands).

The ventricular volumetric data set was quantitatively analyzed using manual outlining of endocardial and epicardial borders in end-systole and end-diastole. Papillary muscles and trabeculations were included in the ventricular cavity. The interventricular septum was included in the left ventricular mass. Ventricular mass was calculated as the difference between the epicardial

and endocardial contours multiplied by the slice thickness and a specific gravity of the myocardium of 1.05 g/ml[19].

The following parameters were calculated: biventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), and mass. Pulmonary regurgitation (in milliliters) was normalized for systolic SV in the main pulmonary artery and was expressed as a percentage. Additionally, RV effective stroke volume (eff.SV) was calculated to correct for PR: RVeff.SV = RVSV – PR volume. Results were indexed for body surface area (BSA). To minimize observer variability, all data sets were analyzed by the same observer (SEL).

Exercise test

Patients performed a maximal bicycle exercise test on a Jaëger Oxycom Champion System (Viasys Healthcare, Hoechberg, Germany). Workload was increased by 15 – 20 Watts per minute. Patients were encouraged to perform until exhaustion. Tests were regarded as maximal when the respiratory quotient (RQ) at peak exercise was ≥ 1.05. The following parameters were recorded: peak heart rate, peak workload, peak oxygen uptake (VO_2 max.), anaerobic threshold (AT), and the ventilatory response to carbon dioxide production (VE/VCO_2). The AT was determined using the V-slope method[20]. The VE/VCO_2 slope was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.

Electrocardiography

A standardised 12-lead ECG was obtained to determine rhythm status, QRS duration and QT interval corrected for heart rate. A 24-hour Holter monitoring was performed in patients on a day with usual activities.

Statistical analysis

Data are expressed as mean (± standard deviation), as median (range), or as counts (percentages). Differences in continuous data between groups of patients were evaluated using the Student t-test, paired t-test, or with nonparametric tests. Differences in categorical data between groups of patients were evaluated with the chi-square or Fisher exact test.
Analysis was performed using the SPSS statistical software package version 15.0 (SPSS, Inc., Chicage, Ill, USA). A p-value < 0.05 was considered to indicate statistical significance.

Results

The patient characteristics are displayed in Table 1. There were no significant differences in height, weight, and BSA between the 2 patient groups, who were matched for gender, age at treatment, and age at study. NYHA class was not significantly different between the PS and TOF patients.

In 7 TOF patients, a palliative shunt had been placed before corrective surgery (33%); 14 TOF patients had corrective surgery with the use of a transannular patch (70%). In 4 patients with TOF, additional surgery had been performed after the initial surgery and before participation in the study. This included closure of a residual VSD in 3 patients and additional relief of pulmonary stenosis in all

4. Three patients with isolated PS had undergone a re-intervention after BPV and before participation in the study. One PS patient first underwent a repeat BPV, but eventually a surgical relief of the repeat pulmonary stenosis was needed twice. One other PS patient underwent closure of a persistent ductus arteriosus; another had surgical repair of moderate tricuspid regurgitation.

The pulmonary valve peak gradient before treatment was significantly higher in PS patients than in TOF patients (83 ± 21 mmHg (PS patients) vs. 63 ± 20 mmHg (TOF patients), p = 0.004) (Table 1). The PV peak gradient significantly decreased immediately after treatment in both patient groups, and decreased even further at long-term follow-up in PS patients. The PV peak gradient immediately after treatment was not significantly different between PS patients and TOF patients. Even so, the PV peak gradient at long-term follow-up was not significantly different between the patient groups.

At long-term follow-up, 20 PS patients (95%) and all TOF patients had pulmonary regurgitation; this was predominantly classified as mild or moderate in PS patients, and as moderate or severe in TOF patients.

Table 1: Characteristics of the study population and results of echocardiography

Characteristic	**PS patients (N = 21)**	**TOF patients (N = 21)**
Male	9 (43%)	9 (43%)
Height (cm)	165 (± 13)	159 (± 13)
Weight (kg)	58 (± 20)	53 (± 14)
BSA (m^2)	1.62 (± 0.33)	1.53 (0.25)
NYHA Class		
- Class I	20 (95%)	16 (76%)
- Class II	1 (5%)	5 (24%)
Age at treatment (years)	3.6 (± 4.2)	3.0 (± 3.2)
Age at study (years)	16.2 (± 5.2)	16.6 (± 5.6)
Interval between treatment and study (years)	12.6 (± 2.1)	13.7 (± 3.1)
Echocardiography		
PV peak gradient before treatment (mmHg)	83 (± 21)*	63 (± 20)
PV peak gradient immediately after treatment (mmHg)	26 (± 10)†	26 (± 15)†
PV peak gradient at long-term follow-up (mmHg)	15 (± 11)‡	20 (± 9)

Results are expressed as mean (± standard deviation), or as counts (percentages).

* Significantly different between PS patients and TOF patients.

† Significantly different between results before treatment and immediately after treatment.

‡ Significantly different between results immediately after treatment and at long-term follow-up.

Abbreviations: BSA = body surface area; NYHA = New York Heart Association; PS = pulmonary stenosis; PV = pulmonary valve; TOF = tetralogy of Fallot.

CMR imaging

PR percentage was significantly higher in TOF patients than in PS patients (PR: 30 ± 13% (TOF patients) vs. 10 ± 10% (PS patients), $p < 0.001$) (Table 2). Right ventricular volumes (EDV, ESV, and SV) and mass were also significantly larger in TOF patients than in PS patients (RVEDV: 131 ± 29 ml/m^2 (TOF patients) vs. 101 ± 20 ml/m^2 (PS patients), $p = 0.001$; RVESV: 66 ± 20 ml/m^2 (TOF patients) vs. 51 ± 15 ml/m^2 (PS patients), $p = 0.009$). RV effective SV, biventricular EF, and LV volumes and mass were not significantly different between the 2 patient groups.

RVESV was significantly larger in PS patients than in healthy controls, and RVEF was significantly lower (RVESV: 51 ± 15 ml/m^2 (PS patients) vs. 41 ± 9 ml/m^2 (healthy controls), $p = 0.02$; RVEF: 50 ± 6% (PS patients) vs. 54 ± 3% (healthy controls), $p = 0.02$). RVEDV was larger in PS patients than in healthy controls, but this was not statistically significant (RVEDV: 101 ± 20 ml/m^2 (PS patients) vs. 90 ± 18 ml/m^2 (healthy controls), $p = 0.09$). All other parameters were not significantly different between PS patients and healthy controls.

Table 2. Results of CMR imaging

Parameter	PS patients (N = 19)	TOF patients (N = 21)	Healthy controls (N = 21)
Age (years)	16.2 (± 5.2)	16.6 (± 5.6)	16.5 (± 5.0)
BSA (m^2)	1.62 (± 0.33)	1.53 (0.25)	1.62 (± 0.23)
PR (%)	10 (± 10)*	30 (± 13)	N/A
Right Ventricle			
EDV (ml/m^2)	101 (± 20)*	131 (± 29)	90 (± 18)
ESV (ml/m^2)	51 (± 15)*†	66 (± 20)	41 (± 9)
SV (ml/m^2)	50 (± 7)*	65 (± 12)	49 (± 11)
eff.SV (ml/m^2)	45 (± 6)	45 (± 6)	49 (± 10)
EF (%)	50 (± 6)†	50 (± 6)	54 (± 3)
Mass (g/m^2)	17 (± 4)*	22 (± 5)	17 (± 3)
Left ventricle			
EDV (ml/m^2)	81 (± 11)	85 (± 14)	85 (± 14)
ESV (ml/m^2)	36 (± 7)	38 (± 10)	36 (± 6)
SV (ml/m^2)	45 (± 6)	47 (± 7)	49 (± 11)
EF (%)	55 (± 4)	55 (± 5)	57 (± 5)
Mass (g/m^2)	53 (± 11)	52 (± 10)	50 (± 11)

Results are expressed as mean (± standard deviation).

* Significantly different between PS patients and TOF patients.

† Significantly different between PS patients and healthy controls.

Abbreviations: CMR = cardiovascular magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; eff.SV = effective stroke volume; ESV = end-systolic volume; N/A = not applicable; PR = pulmonary regurgitation; SV = stroke volume. Other abbreviations as in Table 1.

Exercise test

The exercise test results are given in Table 3. None of the parameters was significantly different between PS patients and TOF patients. Peak heart rate, peak workload, VO_2 max., and the AT were significantly lower in PS patients than in healthy controls (VO_2 max.: 36 ± 10 ml/kg/min (PS patients) vs. 44 ± 7 ml/kg/min (healthy controls), p = 0.004). The VE/VCO_2 slope was not significantly different between PS patients and healthy controls.

Table 3. Results of exercise testing

Parameter	**PS patients (N = 19)**	**TOF patients (N = 19)**	**Healthy controls (N = 21)**
Age (years)	16.2 (± 5.2)	16.6 (± 5.6)	16.2 (± 4.1)
Height (cm)	165 (± 13)	159 (± 13)	166 (± 15)
Peak heart rate (beats/min)	176 (± 15)*	181 (± 12)	185 (± 8)
Peak workload (Watt)	142 (± 40)*	138 (± 34)	186 (± 44)
	(N = 19)	**(N = 15)**	**(N = 21)**
RQ at peak exercise	1.17 (± 0.07)	1.15 (± 0.06)	1.17 (± 0.07)
VO_2 max. (ml/kg/min)	36 (± 10)*	38 (± 7)	44 (± 7)
AT (ml/kg/min)	26 (± 8)*	27 (± 6)	32 (± 6)
VE/VCO_2 slope	29 (± 5)	30 (± 5)	28 (± 5)

Results are expressed as mean (± standard deviation).

* Significantly different between PS patients and healthy controls.

Abbreviations: AT = anaerobic threshold; RQ = respiratory quotient; VE/VCO_2 slope = ventilatory response to carbon dioxide production; VO_2 max. = peak oxygen uptake. Other abbreviations as in Table 1.

Electrocardiography

12-lead ECG data were available for all patients. All patients were in sinus rhythm. The QRS duration was significantly longer in TOF patients than in PS patients (127 ± 23 msec (TOF patients) vs. 95 ± 20 msec (PS patients), p < 0.001). A complete right-bundle branch block (RBBB) was significantly more present in TOF patients than in PS patients (a complete RBBB in 15 TOF patients (71%) vs. 1 PS patient (5%), p < 0,001). The heart rate, PQ time, and QT time corrected for heart rate were not significantly different.

Results of 24-hour Holter recordings were available for all PS patients and 11 TOF patients. There were no significant differences in mean, minimal or maximal heart rate, and total supraventricular premature beats. The median number of total ventricular premature beats (VPB) was higher in TOF patients than in PS patients, although this was not statistically significant (number of VPBs: 2 (0 – 7341) (TOF patients) vs. 1 (0 – 890) (PS patients), p = 0.07). One PS patient had 1 run of ventricular tachycardia (VT), consisting of 5 heart beats. Another PS patient had 2 runs of

supraventricular tachycardia (SVT), consisting of 13 heart beats in total. None of the TOF patients showed runs of VT or SVT.

Discussion

Our results show that adolescent patients with isolated pulmonary valve stenosis and tetralogy of Fallot, whose age at treatment, duration of follow-up, and residual RV outflow gradient were similar, have similar clinical outcomes (NYHA class, and exercise performance). Although clinical condition, as assessed using the NYHA class, was good in the majority of the patients, exercise performance was significantly reduced in both patient groups. Residual PR in the PS group was mild, with a mean PR percentage of 10 ± 10% versus 30 ± 13% in the TOF group. Considering the differences in techniques used to relieve the RV outflow stenosis, it was not unexpected to find more PR after treatment for TOF than for isolated PS. Although RV volumes were significantly larger in TOF patients than in PS patients, LV size, RV effective SV, and biventricular function were not significantly different. Despite the minimal residual RV outflow stenosis and mild PR in the PS group, CMR imaging revealed a larger RVESV and a lower RVEF in the PS group compared with the results in healthy controls.

Relatively few studies have reported on the long-term clinical outcome after BPV for isolated PS. Our study confirms that PR is generally mild in PS patients at follow-up after BPV[5-8]: only 3 PS patients in our study had a PR percentage > 20%. RV enlargement has been considered uncommon in PS patients after BPV. Assessment of RV dimensions in most previous studies, however, has been done using echocardiography[5,7,21]. Recently, Harrild et al. studied PS patients after BPV using CMR imaging and reported that mild PR and mild RV dilatation were often present at long-term follow-up, but that severe PR and severe RV dilatation were very uncommon[17]. Our own results demonstrated that longstanding mild PR in PS patients is associated with an increase in RVESV and a decrease in global RV function. Furthermore, our PS patients had a reduced exercise capacity. These results confirm those of the study by Harrild et al., who also found a reduced VO_2 max. in PS patients.

Although results of exercise testing in patients after repair of TOF are available in the literature, their results differ considerably [10-11,22]. In adults operated on for TOF, VO_2 max. has varied between 58% and 80% of predicted values[10,22]. Age at operation and duration of follow-up are important factors to consider. The good results in our TOF group might be explained by our patients' relatively young age at surgery and young age at study relative to those of the TOF patients described in earlier studies. A younger age at surgery has been recognised to be related to a more favourable clinical outcome[3].

In contrast with our second hypothesis, exercise performance in PS patients was significantly lower than in healthy controls. This might in part be explained by impaired chronotrophy, since the maximal heart rate was significantly lower than in healthy controls. It is striking that the TOF patients in our study had similar results on exercise testing as PS patients, despite significantly higher amounts of PR. A similar result was also found in a study by Yetman et al., who compared a group of pediatric PS patients after surgical valvulotomy with a matched group of TOF patients[23]. Remarkably, exercise capacity was more severely impaired in the PS patients in Yetman's study than it was in the TOF patients. The authors argued that this might result from diastolic RV restriction in

TOF patients, which was suggested to improve exercise capacity, as reported by Gatzoulis et al.[24]. This has however, not been confirmed either in pediatric and adolescent TOF patients who were operated on at a younger age or in a recent study in adult TOF patients[22,25].

In recent years, an abnormal ventilatory response to exercise, as assessed by an elevated VE/VCO_2 slope, has been shown to be a powerful predictor of cardiac-related mortality in patients with CHD[10,26]. Our results were comparable to the results reported by Giardini et al., who found a VE/VCO_2 slope of 31 ± 5 in their total group of TOF patients[10]. In our study however, the VE/VCO_2 slope was not significantly different between PS patients and healthy controls and was also not different between the 2 patient groups.

Our study confirms the adverse effects of longstanding PR. At the same time, exercise performance and ventricular function were comparable between the PS and TOF group, despite important differences in RV dimensions. Based on the fact that exercise capacity was similar in both patient groups, the relatively short hypoxemic period before corrective surgery doesn't seem to have a negative influence on exercise capacity in these TOF patients at the current follow-up duration. It seems therefore that other factors have more impact on exercise capacity, like for example the amount of PR or global RV function. PR percentage was not correlated with peak oxygen uptake or the VE/VCO_2 slope however, although the limited number of patients in the study is a factor to consider. The similar biventricular function in our PS and TOF patients might be an explanation for their similar exercise test results.

A recent functional analysis of 3 components of the RV in adolescent TOF patients by Bodhey et al., demonstrated that the ejection fraction of the apical trabecular component, which provides the major ejectile momentum, is maintained in patients with slight to moderate ventricular dysfunction[27]. In TOF patients operated on at a young age, RV contractile reserve is also well preserved[28]. These findings suggest that RV myocardial performance may be well maintained in TOF patients operated on at a young age, despite enlarged RV size. The RV may therefore be well suited to perform its role of maintaining LV preload in this situation.

It might be speculated that long-term prognosis in TOF patients eventually will be worse than in PS patients, since TOF patients already have a more severe RV dilatation at this follow-up duration. Previous studies have suggested that there is a threshold for the dimension of the RVEDV, above which the RV does not recover completely, even if a PVR is performed[11-12,14-15].

Arrhythmias are an important problem in patients with residual PR, particularly in patients with TOF[9,29]. Significant ventricular arrhythmias in PS patients are uncommon[30], which is in agreement with our results. A QRS duration of > 180 msec and an older age at repair are associated with a higher risk of ventricular tachycardia and sudden death[9]. Dietl et al. reported a significant reduction in ventricular arrhythmias in TOF patients who had had a transatrial repair than in those who had had a transventricular repair[29]. Significant ventricular arrhythmias in our TOF patients were uncommon. This relates to the mild QRS prolongation, young age at repair, and transatrial surgical repair in most of the patients. None of our patients had a QRS duration > 180 msec.

Limitations

No echocardiographic data was available for 10 TOF patients before treatment and for 2 TOF patients immediately after treatment, in all of whom the assessment of RV outflow gradients had been based on results from cardiac catheterizations. Particularly, the significant difference in PV peak gradient before treatment between PS patients and TOF patients should therefore be interpreted with caution.

In some of the older TOF patients, data from exercise testing and 24-hour Holter monitoring were missing. Since exercise capacity might be better preserved at a younger age, this may have resulted in an overestimation of the exercise capacity in the TOF patients.

We studied children, adolescents, and young adults treated at a young age. Our results are therefore representative for patients with a similar age and follow-up-duration.

Since we only had small patient groups, a limited statistical power is a factor to consider.

Future perspectives

Assessment of RV volumes and function with CMR imaging in patients treated with BPV for isolated PS has hardly been done before. We found that PS patients had a larger RV, a lower RV function, and a lower exercise capacity than healthy controls, although their clinical condition was excellent. Since we only had a small PS patient group, results should be confirmed in larger studies. Serial follow-up studies in PS patients are necessary to evaluate the degree of progression of their PR and RV dilatation and to see how this influences their clinical condition and exercise capacity later in life.

Serial follow-up data might also be useful to evaluate whether certain parameters, like PR percentage and RV dilatation, might be more progressive in the TOF group and to see how this would then influence biventricular function and exercise capacity at longer term follow-up.

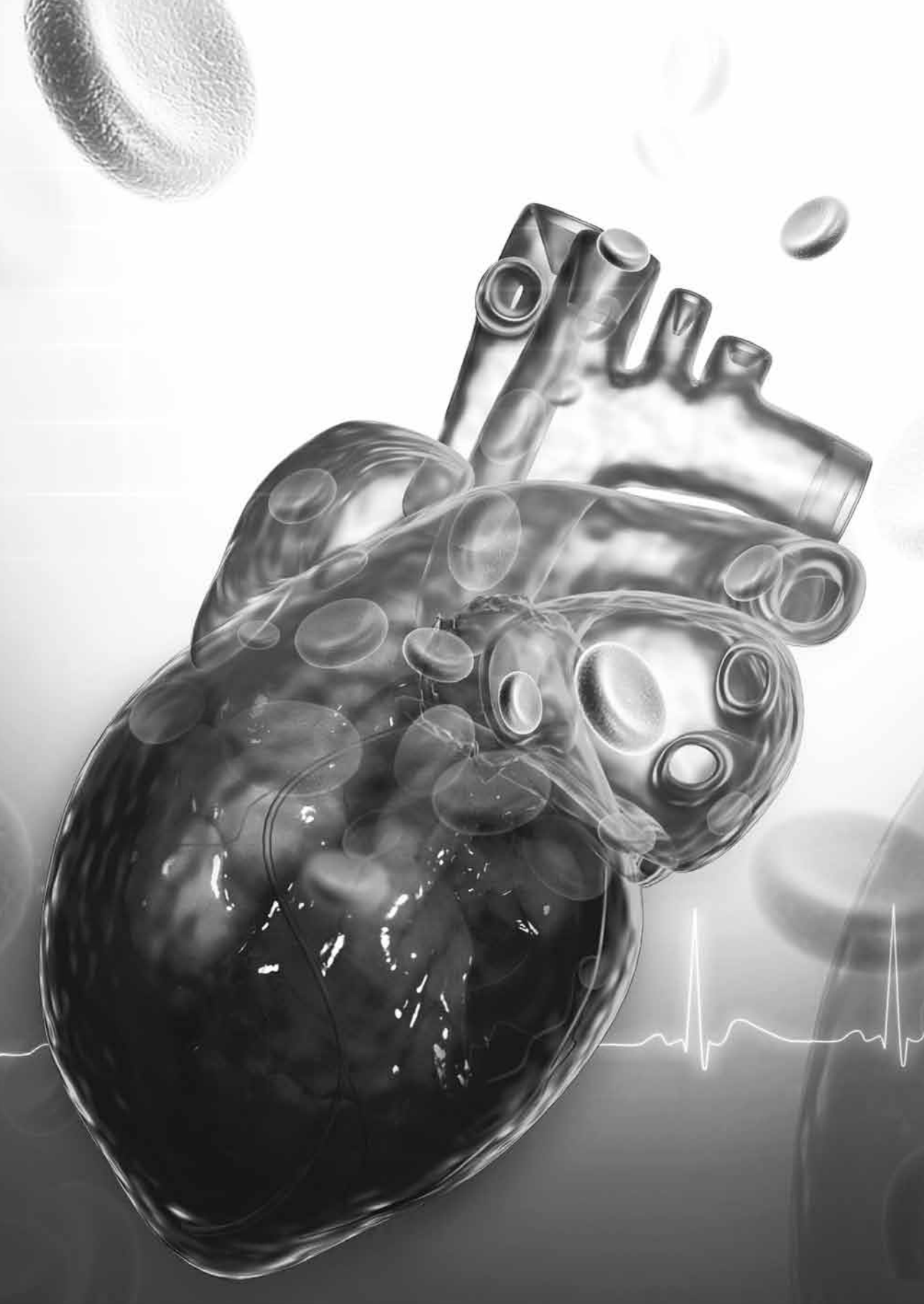
Conclusions

In contrast to our hypothesis, pediatric and adolescent patients with isolated pulmonary valve stenosis have a lower exercise capacity, a larger right ventricle, and a lower RV function than healthy controls, although their clinical condition is excellent. However, exercise performance and biventricular function are similar to those in patients with tetralogy of Fallot, despite more severe pulmonary regurgitation and larger RV volumes in Fallot patients.

References

1. Davlouros PA, Kilner PJ, Hornung TS, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol 2002;40:2044-2052.
2. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol 2004;43:1068-1074.
3. Knauth AL, Gauvreau K, Powell AJ, et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart 2008;94:211-216.
4. van den Berg J, Hop WC, Strengers JL, et al. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of Fallot. J Thorac Cardiovasc Surg 2007;133:470-477.
5. Gupta D, Saxena A, Kothari SS, Juneja R. Factors influencing late course of residual valvular and infundibular gradients following pulmonary valve balloon dilatation. International Journal of Cardiology 2001;79:143-149.
6. McCrindle BW. Independent predictors of long-term results after balloon pulmonary valvuloplasty. Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry Investigators. Circulation 1994;89:1751-1759.
7. Rao PS. Percutaneous balloon pulmonary valvuloplasty: State of the art. Catheterization and Cardiovascular Interventions 2007;69:747-763.
8. Witsenburg M, Talsma M, Rohmer J, Hess J. Balloon valvuloplasty for valvular pulmonary stenosis in children over 6 months of age: initial results and long-term follow-up. Eur Heart J 1993;14:1657-1660.
9. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975-981.
10. Giardini A, Specchia S, Tacy TA, et al. Usefulness of Cardiopulmonary Exercise to Predict Long-Term Prognosis in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2007;99:1462-1467.
11. Frigiola A, Tsang V, Bull C, et al. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? Circulation 2008;118:S182-190.
12. Oosterhof T, van Straten A, Vliegen HW, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation 2007;116:545-551.
13. Vliegen HW, van Straten A, de Roos A, et al. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of fallot. Circulation 2002;106:1703-1707.
14. Valsangiacomo Buechel ER, Dave HH, Kellenberger CJ, et al. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. Eur Heart J 2005;26:2721-2727.
15. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. Am J of Cardiol 2005;95:779-782.
16. Kan JS, White RI, Jr., Mitchell SE, Gardner TJ. Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary-valve stenosis. N Engl J Med 1982;307:540-542.
17. Harrild DM, Powell AJ, Tran TX, et al. Long-term pulmonary regurgitation following balloon valvuloplasty for pulmonary stenosis risk factors and relationship to exercise capacity and ventricular volume and function. J Am Coll Cardiol 2010;55:1041-1047.

18. Grothoff M, Spors B, Abdul-Khaliq H, Gutberlet M. Evaluation of postoperative pulmonary regurgitation after surgical repair of tetralogy of Fallot: comparison between Doppler echocardiography and MR velocity mapping. Pediatric Radiology 2008;38:186-191.
19. Katz J, Milliken MC, Stray-Gundersen J, et al. Estimation of human myocardial mass with MR imaging. Radiology 1988;169:495-498.
20. Wasserman K, Beaver WL, Whipp BJ. Gas exchange theory and the lactic acidosis (anaerobic) threshold. Circulation 1990;81:II14-30.
21. Fawzy ME, Hassan W, Fadel BM, et al. Long-term results (up to 17 years) of pulmonary balloon valvuloplasty in adults and its effects on concomitant severe infundibular stenosis and tricuspid regurgitation. American Heart Journal 2007;153:433-438.
22. Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. Circulation 2006;113:405-413.
23. Yetman AT, King S, Bornemeier RA, Fasules J. Comparison of exercise performance in patients after pulmonary valvulotomy for pulmonary stenosis and tetralogy of Fallot. The American Journal of Cardiology 2002;90:1412-1414.
24. Gatzoulis MA, Clark AL, Cullen S, Newman CG, Redington AN. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot. Restrictive physiology predicts superior exercise performance. Circulation 1995;91:1775-1781.
25. van den Berg J, Wielopolski PA, Meijboom FJ, et al. Diastolic function in repaired tetralogy of Fallot at rest and during stress: assessment with MR imaging. Radiology 2007;243:212-219.
26. Dimopoulos KMD, Okonko DOBM, Diller G-PMD, et al. Abnormal Ventilatory Response to Exercise in Adults With Congenital Heart Disease Relates to Cyanosis and Predicts Survival. Circulation 2006;113:2796-2802.
27. Bodhey NK, Beerbaum P, Sarikouch S, et al. Functional Analysis of the Components of the Right Ventricle in the Setting of Tetralogy of Fallot. Circ Cardiovasc Imaging 2008;1:141-147.
28. van den Berg J, Strengers JLM, Wielopolski PA, et al. Assessment of biventricular functional reserve and NT-proBNP levels in patients with RV volume overload after repair of tetralogy of Fallot at young age. Int J of Cardiol 2009;133:364-370.
29. Dietl CA, Cazzaniga ME, Dubner SJ, Perez-Balino NA, Torres AR, Favaloro RG. Life-Threatening Arrhythmias and RV Dysfunction After Surgical Repair of Tetralogy of Fallot: Comparison Between Transventricular and Transatrial Approaches. Circulation 1994;90:7-12.
30. Roos-Hesselink JW, Meijboom FJ, Spitaels SEC, et al. Long-term outcome after surgery for pulmonary stenosis (a longitudinal study of 22-33 years). Eur Heart J 2006;27:482-488.



Chapter 5

Serial follow-up of clinical condition and ventricular function in patients with and without pulmonary valve replacement after repair of tetralogy of Fallot

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Abstract

Objective: To study the course of biventricular size and function, and clinical parameters in repaired tetralogy of Fallot (TOF) patients who did not undergo pulmonary valve replacement (PVR) versus patients who did.

Methods: We prospectively included 78 non-PVR patients (20 (6 – 60) years at baseline). Patients underwent magnetic resonance imaging, exercise testing, electrocardiography (ECG), and biomarker assessment. Biventricular size and function, peak oxygen uptake (peak VO_2), ECG characteristics, and N-terminal prohormone brain natriuretic peptide (NT-proBNP) were assessed at baseline and after 5 years. Results were compared to 52 PVR patients (23 (7 – 46) years) before and after PVR.

Results: In non-PVR patients, pulmonary regurgitation (PR), right ventricular (RV) volumes (end-diastolic volume (EDV) 130 ± 30 ml/m^2 → 138 ± 34 ml/m^2), and QRS duration increased during follow-up; peak VO_2 decreased (96 ± 19% → 91 ± 17%). RV ejection fraction (EF), RV effective stroke volume (eff.SV), and NT-proBNP levels remained unchanged. RVEDV slope was 1.6 ± 3.0 ml/m^2/year, and was dependent on RVeff.SV, but not RVEDV at baseline. After PVR, PR and RV volumes decreased; RVeff.SV (45 ± 9 ml/m^2 → 51 ± 8 ml/m^2) and LV filling increased, and QRS duration remained stable. Biventricular EF remained unchanged after PVR.

Conclusions: In non-PVR TOF patients with moderate RV dilatation, RVEDV increased by 1.6 ± 3.0 ml/m^2/year, irrespective of RV size at baseline. Despite limited progression in RV size, unfavourable changes occurred. PVR performed at the upper level of current recommendations had favourable effects, but RV volumes were still abnormal after PVR in patients with RVEDV at baseline ≥ 170 ml/m^2. This data suggests a less conservative approach towards PVR may be required.

Introduction

Residual pulmonary regurgitation (PR) plays an important role in the long-term morbidity of patients after repair of tetralogy of Fallot (TOF). Although usually well tolerated in childhood, longstanding PR leads to right ventricular (RV) dilatation, impairment of RV function, deterioration of exercise capacity, arrhythmias, and an increased risk of sudden cardiac death[1-5].

Pulmonary valve replacement (PVR) is often considered as a treatment option, but the optimal timing to perform PVR remains controversial, especially in asymptomatic patients. Preoperative thresholds have been established, above which the RV does not seem to recover completely, even if PVR is performed. Threshold values of RV end-diastolic volume (EDV) have been reported to be between approximately 142 – 200 ml/m^2[6-9], as assessed using magnetic resonance imaging (MRI).

Current literature provides limited information on the course of ventricular and functional changes in patients who have not undergone PVR (referred to as “non-PVR patients”)[10-11]. Serial follow-up studies in non-PVR patients may provide insight in the course of RV size and functional changes over time after the initial surgery, which could provide information useful to determine follow-up strategies and in decisions on optimal timing of PVR.

We aimed to prospectively study the course of biventricular size and function over time in patients with repaired tetralogy of Fallot, in relation to clinical parameters, and to identify independent predictors for deterioration of ventricular size and function and clinical outcome.

Methods

Patients

This prospective serial follow-up study was performed in 3 tertiary referral centers in the Netherlands. Inclusion criteria were: 1) surgical repair of tetralogy of Fallot without associated cardiac lesions, 2) no PVR, and 3) the availability of an MRI study at least 3 years earlier. One-hundred and twenty-five of such patients were identified; 78 agreed to participate and were included between September 2007 and February 2010. These patients underwent an MRI study, exercise testing, 12-lead electrocardiography (ECG), and N-terminal prohormone brain natriuretic peptide (NT-proBNP) assessment. Results of the baseline study have been reported previously for 36 of these 78 patients[12].

Results of the non-PVR patients were compared to results of TOF patients who had undergone PVR. Inclusion criteria for these PVR patients were: 1) surgical repair of tetralogy of Fallot without associated cardiac lesions, 2) PVR after initial correction, 3) the availability of an MRI study before and after PVR within the same time period as the studies for the non-PVR patients, and 4) an interval between the 2 MRI studies of ≥ 3 years. Patients with a homograft used for initial correction were excluded. Fifty-two PVR patients were included and the medical records of these patients were reviewed. Data was collected retrospectively and included patient characteristics, details about surgical procedures, and results of clinical studies. Results of exercise tests, ECGs, and NT-proBNP

levels were used only when performed within 1 year of the MRI study. The decision to replace the pulmonary valve was based on local guidelines of the participating centers.

Results of MRI parameters were compared to a group of 30 healthy controls (15 male, 31 ± 7 years) within our center. Healthy controls were volunteers without cardiac symptoms.

The study protocol was approved by the local Ethical Committee of each participating center; participants, and if required, their parents, gave written informed consent.

Magnetic Resonance Imaging

Cardiac MRI was performed on locally available 1.5 Tesla MRI systems (General Electric, Milwaukee, WI, USA; Philips Medical Systems, Best, the Netherlands; Siemens Medical System, Erlangen, Germany). MRI studies were performed with the use of local imaging protocols. A multi-slice, multi-phase data set was acquired using steady-state free precession cine imaging in short axis or axial orientation. Flow measurements of the pulmonary valve were performed perpendicular to flow.

Analysis was performed on a commercially available Advanced Windows workstation (General Electric Medical Systems), equipped with the software packages MASS and FLOW (Medis Medical Imaging Systems, the Netherlands). From the volumetric data set, EDV, end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), and mass were assessed using manual outlining of endocardial and epicardial borders in end-systole and end-diastole. Papillary muscles and trabeculations were included in the ventricular cavity. The interventricular septum was included in the left ventricular (LV) mass. When the pulmonary valve was visible in the basal slice, contours were drawn up to the junction with the pulmonary valve. All data sets were analyzed by the same observer (SL), with 4 years of experience in cardiac contour tracing.

Pulmonary regurgitation was expressed as a percentage of systolic SV in the main pulmonary artery. Additionally, RV effective stroke volume (eff.SV) was calculated to correct for PR: RVeff.SV = RVSV – PR volume.

Clinical parameters

Patients performed a maximal bicycle exercise test on a Jaëger Oxycom Champion System (Viasys Healthcare, Germany). Workload was increased by 10 – 20 Watts per minute. Peak workload and peak oxygen uptake (peak VO_2) were recorded and expressed as percentages of predicted values[13-14]. The ventilatory response to carbon dioxide production (VE/VCO_2 slope) was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.

Blood samples were drawn from a peripheral vein after 30 minutes rest in supine position. Plasma and serum were separated immediately after sample collection and stored at -80ºC. NT-proBNP was measured using the commercially available Elecsys kit electrochemiluminescence immunoassay (Roche Diagnostics, Germany).

A standardised 12-lead ECG was obtained to determine QRS duration and QT interval corrected for heart rate (QTc).

Statistical analysis

Continuous data were tested for normality with the Kolmogorov-Smirnov test. Normally distributed data are expressed as mean (± standard deviation); non-normally distributed data as median (range). Differences between groups of patients were evaluated using Student t-test, paired t-test or with nonparametric tests, as appropriate. Categorical data are expressed as counts (percentages); differences between groups of patients were evaluated with chi-square test, Fisher exact test, or McNemar test, as appropriate. Analysis of covariance was used for multiple group comparisons with correction for multiple testing by Bonferroni's method. Multivariate linear regression analyses were used to determine independent predictors for continuous outcome variables and multivariate bivariate logistic regression analyses for dichotomous outcome variables. Backward stepwise regression method was used in multivariate analyses.

Analysis was performed using the SPSS statistical software package version 17.0 (SPSS, Inc., Chicage, Ill, USA). A p-value < 0.05 was considered to indicate statistical significance.

Results

Characteristics of the patients are displayed in Table 1.

MRI parameters

In non-PVR patients, PR percentage and RV volumes increased, and RV mass/EDV ratio decreased during 5-year follow-up (Table 2). Left ventricular volumes (EDV and ESV) increased during follow-up; LVEF decreased.

After PVR, PR percentage and RV volumes decreased; RVeff.SV and RV mass/EDV ratio increased (Table 2). Left ventricular volumes increased after PVR. After PVR, RVeff.SV and LVSV were higher in PVR patients than in non-PVR patients at follow-up.

Table 1: Characteristics of the study population

Characteristic	Non-PVR patients (N = 78)		PVR patients (N = 52)	
Male	48 (62%)		31 (60%)	
Palliative shunt before corrective surgery	21 (27%)		13 (25%)	
Age at corrective surgery (years)	1.1 (0.1 – 32.8)		2.5 (0.2 – 16.6)	
Transannular patch	43 (55%)		40 (77%) †	
Interval baseline and follow-up study (years)	5.2 (± 1.0)		5.5 (± 1.7)	
Interval PVR and follow-up study (years)	N/A		4.2 (± 2.0)	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
Age at study (years)	20 (6 – 60)	25 (10 – 66) *	23 (7 – 46)	28 (13 – 51) *
BSA (m^2)	1.65 (± 0.37)	1.81 (± 0.25) *	1.79 (± 0.27) †	1.88 (± 0.24) *
NYHA class	I: 66 (85%)	I: 60 (77%)	I: 28 (54%) †	I: 46 (88%) *
	II: 12 (15%)	II: 17 (22%)	II: 23 (44%)	II: 5 (10%)
	III: 0 (0%)	III: 1 (1%)	III: 1 (2%)	III: 1 (2%)

Results are expressed as mean (± standard deviation), as median (range), or as counts (percentages).

* Significantly different between baseline and follow-up.

† Significantly different between non-PVR patients and PVR patients.

Abbreviations: BSA = body surface area; N/A = not applicable; NYHA = New York Heart Association; PVR = pulmonary valve replacement.

Table 2: Results of MRI parameters

Parameter		Non-PVR patients (N = 78)		PVR patients (N = 52)		Healthy controls (N = 30)
		Baseline	Follow-up	Baseline	Follow-up	
HR (beats / min)		74 (± 12)	72 (± 12)	68 (± 11) †	68 (± 11)	72 (± 12)
PR (%)		26 (± 16)	29 (± 17) *	44 (± 9) †	6 (± 9) *†	N/A
RV	EDV (ml/m^2)	130 (± 30) $	138 (± 34) *$	183 (± 39) †$	122 (± 28) *†$	94 (± 17)
	ESV (ml/m^2)	67 (± 19) $	71 (± 22) *$	102 (± 31) †$	68 (± 26) *$	42 (± 11)
	SV (ml/m^2)	64 (± 14) $	67 (± 15) *$	81 (± 14) †$	54 (± 7) *†	52 (± 8)
	Eff. SV (ml/m^2)	46 (± 8) $	46 (± 7) $	45 (± 9) $	51 (± 8) *†	52 (± 8)
	EF (%)	49 (± 5) $	49 (± 5) $	45 (± 7) †$	46 (± 7) †$	56 (± 6)
	Mass (g/m^2)	25 (± 6) $	25 (± 6) $	33 (± 7) †$	26 (± 7) *$	16 (± 4)
	Mass / EDV ratio (g/ml)	0.20 (± 0.04) $	0.19 (± 0.04) *	0.18 (± 0.04)	0.21 (± 0.04) *†$	0.17 (± 0.02)
LV	EDV (ml/m^2)	84 (± 13)	88 (± 13) *	85 (± 14)	94 (± 15) *†	88 (± 12)
	ESV (ml/m^2)	37 (± 8)	40 (± 9) *	39 (± 8)	43 (± 10) *$	36 (± 7)
	SV (ml/m^2)	46 (± 7) $	48 (± 6)	46 (± 8) $	51 (± 7) *†	51 (± 8)
	EF (%)	56 (± 5) $	55 (± 5) *$	54 (± 5) $	55 (± 5) $	58 (± 4)
	Mass (g/m^2)	53 (± 10)	54 (± 10)	55 (± 11)	54 (± 10) *	51 (± 11)
	Mass / EDV ratio (g/ml)	0.64 (± 0.11)	0.62 (± 0.09) *	0.66 (± 0.15) $	0.58 (± 0.10) *†	0.59 (± 0.08)

Results are expressed as mean (± standard deviation).

* Significantly different between baseline and follow-up.

† Significantly different between non-PVR patients and PVR patients.

$ Significantly different with healthy controls (ANOVA, Bonferroni).

Abbreviations: HR = heart rate; EDV = end-diastolic volume; EF = ejection fraction; Eff.SV = effective stroke volume; ESV = end-systolic volume; LV = left ventricle; MRI = magnetic resonance imaging; N/A = not applicable; PR = pulmonary regurgitation; PVR = pulmonary valve replacement; RV= right ventricle; SV = stroke volume.

Clinical parameters

At baseline, peak workload was higher in non-PVR than in PVR patients; at follow-up, the difference in peak workload was not significant (p = 0.081) (Table 3). In non-PVR patients, peak VO_2 decreased during follow-up. In PVR patients, peak VO_2 tended to decrease during follow-up, but this was not significant (p = 0.17).

There were no differences in NT-proBNP levels at baseline or at follow-up between non-PVR and PVR patients, nor did NT-proBNP levels change during follow-up in non-PVR or PVR patients (Table 3).

At baseline and at follow-up, QRS duration was shorter in non-PVR patients than in PVR patients (Table 3). In non-PVR patients, QRS duration and QTc interval increased during follow-up, whereas these parameters remained unchanged in PVR patients after PVR.

Table 3: Results of clinical parameters

Parameter	**Non-PVR patients**		**PVR patients**	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
	(N = 46)	**(N = 66)**	**(N = 33)**	**(N = 21)**
Peak workload (%)	92 (± 15)	91 (± 17)	85 (± 16) †	84 (± 10)
	(N = 37)	**(N = 50)**	**(N = 20)**	**(N = 9)**
RQ	1.19 (± 0.07)	1.16 (± 0.07) *	1.17 (± 0.08)	1.13 (± 0.04) *
Peak VO_2 (%)	96 (± 19)	91 (± 17) *	92 (± 17)	87 (± 9)
VE/VCO_2 slope	31 (± 4)	30 (± 5)	29 (± 5)	30 (± 6)
	(N = 36)	**(N = 71)**	**(N = 12)**	**(N = 17)**
NT-proBNP (pmol/l)	17 (± 12)	18 (± 24)	13 (± 9)	23 (± 35)
	(N = 78)	**(N = 78)**	**(N = 52)**	**(N = 52)**
QRS duration (msec)	132 (± 27)	139 (± 27) *	149 (± 26) †	148 (± 26) †
QTc interval (msec)	429 (± 30)	440 (± 36) *	435 (± 25)	437 (± 32)

Results are expressed as mean (± standard deviation).

* Significantly different between baseline and follow-up.

† Significantly different between non-PVR patients and PVR patients.

Abbreviations: NT-proBNP = N-terminal prohormone brain natriuretic peptide; peak VO_2 = peak oxygen uptake; PVR = pulmonary valve replacement; QTc = QT interval, corrected for heart rate; RQ = respiratory quotient; VE/VCO_2 slope = ventilatory response to carbon dioxide production.

Subgroups

In order to evaluate if patients who underwent PVR at a smaller RV size would show a more normal post-PVR course, we divided the PVR patients into 2 subgroups: 1) patients with RVEDV at baseline < 170 ml/m^2 (N = 24); 2) patients with RVEDV at baseline ≥ 170 ml/m^2 (N = 28)[8]. Patients with RVEDV at baseline < 170 ml/m^2 showed normalization of RV volumes and an increase in RVeff.SV after PVR, whereas RV volumes decreased but remained enlarged, and RVeff.SV did not increase after PVR in patients with RVEDV at baseline ≥ 170 ml/m^2 (supplementary Tables 1 and 2).

We also divided our non-PVR patients into 2 subgroups, to evaluate if the increase in RV size would be different between patients with smaller versus larger right ventricles at baseline. Because of the differences that we found in our PVR patient subgroups, we decided to use RVEDV at baseline 142 ml/m^2 as cutoff point in our non-PVR patients, based on a recently reported study[6]. The increase in RV volumes during follow-up was not different between our subgroups, but the increase in PR was higher in patients with RVEDV at baseline ≥ 142 ml/m^2 than in patients with RVEDV at baseline < 142 ml/m^2 (supplementary Tables 3 and 4). Furthermore, in patients with RVEDV at baseline ≥ 142 ml/m^2 NYHA class decreased during follow-up, whereas it remained unchanged in patients with smaller right ventricles.

Changes over time in non-PVR patients

Slopes were calculated as the difference between 2 measurements divided by the time-interval between the 2 measurements, to indicate changes over time. In non-PVR patients, the RVEDV slope was 1.6 ± 3.0 ml/m^2/year; the peak VO_2 slope was -1.4 ± 2.9 %/year and the QRS slope was 1.1 ± 1.8 msec/year.

Regression analyses

According to Knauth et al., LVEF < 55% and RVEF < 45% were independent predictors for major adverse clinical events after TOF repair[4]. These parameters were used as outcome parameters in multivariate analyses, as were the RVEDV slope and peak VO_2 slope.

Patient characteristics, baseline MRI and clinical parameters were tested in univariate analyses to identify predictors for outcome parameters. Variables with significant correlations in univariate analysis were included in a multivariate model. Variables with strong mutual correlations were not all included in the multivariate model.

A palliative shunt before corrective surgery, a lower LVEF at baseline, and a higher LVEDV at baseline were independent predictors for LVEF < 55% at follow-up (Table 4). A lower RVEF at baseline was the only independent predictor for RVEF < 45% at follow-up.

A lower BSA and a lower RVeff.SV at baseline were the best predictors for a higher RVEDV slope in non-PVR patients; RVEDV at baseline was not (Table 5).

Discussion

This serial prospective follow-up study demonstrated that in patients who had undergone repair of tetralogy of Fallot without subsequent PVR, there was a steady, but limited, increase in pulmonary regurgitant fraction and RV size during 5-year follow-up. RV effective SV and RV ejection fraction remained stable in this period, but were subnormal. Concomitantly, peak VO_2 decreased and QRS duration increased during follow-up. There was also a trend towards decrease in NYHA class, but this was not significant. Combined, these changes may be interpreted as unfavourable. The clinical impact of these unfavourable changes was limited however, considering that exercise capacity was still adequate, NT-proBNP levels were stable, and only 3 of 78 patients had an QRS duration ≥ 180 msec, a known risk factor for sudden cardiac death[2].

Table 4: Predictors for outcome parameters in all patients (N = 130)

Parameter		Univariate analysis		Multivariate analysis	
Outcome variable	**Predictors**	**Regression coefficient ± SE**	**p-value**	**Regression coefficient ± SE**	**p-value**
LVEF at follow-up < 55%	Constant			9.95 ± 3.59	
	Palliative shunt before corrective surgery (yes)	1.19 ± 0.44	0.007	1.13 ± 0.50	0.024
Area under ROC curve = 0.81	LVEDV baseline (ml/m^2)	0.05 ± 0.02	0.002	0.03 ± 0.02	0.047
Hosmer and Lemeshow: p = 0.66	LVEF baseline (%)	-0.26 ± 0.05	< 0.001	-0.23 ± 0.06	< 0.001
	Sexe (0 = male / 1 = female)	-0.93 ± 0.37	0.012		ns
	RVEF baseline (%)	-0.08 ± 0.03	0.009		ns
RVEF at follow-up < 45%	Constant			15.27 ± 3.35	
	RVEF baseline (%)	-0.36 ± 0.07	< 0.001	-0.36 ± 0.07	< 0.001
Area under ROC curve = 0.87	Palliative shunt before corrective surgery (yes)	0.98 ± 0.43	0.023		ns
Hosmer and Lemeshow: p = 0.066	RVEDV baseline (ml/m^2)	0.02 ± 0.01	< 0.001		ns
	RV Mass baseline (g/m^2)	0.08 ± 0.03	0.005		ns
	LVEF baseline (%)	-0.11 ± 0.01	0.014		ns
	QRS duration baseline (msec)	0.03 ± 0.01	0.001		ns
	Peak VO_2 baseline (%)	-0.08 ± 0.03	0.007		ns

Abbreviations: ns = not significant; ROC = receiver operating characteristic; SE = standard error. Other abbreviations as in Tables 2 and 3.

Table 5: Predictors for changes over time in non-PVR patients (N = 78)

Parameter		Univariate analysis			Multivariate analysis	
Outcome variable	**Predictors**	**Regression coefficient ± SE**	**r**	**p-value**	**Regression coefficient ± SE**	**p-value**
RVEDV slope (ml/m^2/year)	Constant				12.38 ± 2.20	
	BSA baseline (m^2)	-2.69 ± 0.87	-0.33	0.003	-2.66 ± 0.82	0.002
R^2 = 0.25	RVeff.SV baseline (ml/m^2)	-0.15 ± 0.04	-0.38	0.001	-0.14 ± 0.04	0.001
	Interval surgery and baseline study (years)	-0.09 ± 0.04	-0.26	0.020		ns
	LVEDV at baseline (ml/m^2)	-0.06 ± 0.03	-0.25	0.028		ns
	PR baseline (%)	0.05 ± 0.02	0.27	0.016		ns
Peak VO_2 slope (%/year)	Constant				7.35 ± 2.06	
	Peak VO_2 baseline (%)	-0.09 ± 0.02	-0.63	< 0.001	-0.09 ± 0.02	< 0.001
R^2 = 0.39	RVEF baseline (%)	-0.28 ± 0.08	-0.53	0.002		ns
	LVEF baseline (%)	-0.23 ± 0.10	-0.39	0.028		ns

Abbreviations: ns = not significant; r = Pearsson's correlation coefficient; SE = standard error. Other abbreviations as in Tables 1, 2, and 3.

Reduction plasty of the right ventricular outflow tract had been performed in almost half of the PVR patients at the time of PVR, and contributed to the decrease in RV size after PVR. The expected decrease of PR and RV size after PVR[6-9,15] was accompanied by an increase in NYHA class, RV effective SV and LV volumes, and stabilization of QRS duration. There was a trend however towards decrease in peak VO_2 after PVR, but this was not significant, and should be interpreted with caution, since this data was available only in a limited number of patients.

The discussion with regard to timing of PVR centres around the assumption that irreversible impairment of RV contractility may occur if PVR is performed too late[7-8]. Our subgroup analysis in PVR patients showed that RV volumes indeed did not normalize after PVR in patients with RVEDV at baseline ≥ 170 ml/m^2. Furthermore, these patients also did not show a significant increase in RVeff.SV after PVR, which was observed in patients who underwent PVR at RVEDV < 170 ml/m^2. Although NYHA class improved and QRS duration stabilized after PVR in both subgroups, it may be questioned if current recommendations for PVR are valid[16]. On the basis of our current data it may be argued that earlier intervention is warranted, as has been suggested by Frigiola and co-workers[6]. A recent study on outcome after PVR in 126 TOF patients reported that freedom from valve replacement was 83% after 10 years and 70% after 15 years[17], which is more encouraging than reported in earlier studies[18]. Combined with the successful introduction of percutaneous pulmonary valve implantation[19], this may contribute to improved outlook for earlier intervention.

Serial follow-up data in non-PVR patients is required to improve criteria for PVR, but serial follow-up studies are limited[4,10]. In one of the few serial follow-up studies, it has been reported that the only predictor of no clinical worsening during serial follow-up was age at TOF repair < 3 years[4], which is current practice in many institutions nowadays. None of our non-PVR patients operated < 3 years reached any of the endpoints used in the study by Knauth and co-workers [4]. Furthermore, we found a limited decrease in peak VO_2 over time (-1.4 ± 2.9 %/year), which is comparable to the results reported by Kipps et al.[20]. The results in our patients underline the fact that patients operated according to current surgical strategies may perform remarkably well despite important PR and RV dilatation.

Surprisingly, subgroup analysis in our non-PVR patients did not reveal differences in the increase in RV size over time between patients with smaller versus larger right ventricles at baseline. This was confirmed by the fact that RVEDV at baseline was not associated with the RVEDV slope ($r = 0.04$, $p = 0.72$).

It might be speculated that patients with a more rapid increase in RV size may have already undergone PVR during this 5-year follow-up period. Unfortunately, serial MRI measurements before PVR were lacking in our PVR patients. Future serial follow-up studies are needed to evaluate if the RVEDV slope is larger in this subgroup of patients. In contrast to RVEDV, we found that RVeff.SV at baseline was an independent predictor of progression of RV remodeling, as a lower RVeff.SV was associated with a larger RVEDV slope. Since this parameter may be useful in the follow-up of TOF patients, measuring RVeff.SV should therefore be incorporated in clinical practice.

In our PVR patients, LVEDV increased after PVR, which is in agreement with results of several others studies[6-7,9], and seems to be a reflection of better LV filling, resulting from an increased RV

effective output. However, in our non-PVR patients, we also found a small increase in LV size, and we found an independent relationship between a higher LVEDV at baseline and a lower LVEF at follow-up. This is in agreement with results of Tobler et al.[21], but the exact mechanisms for increased LV size in patients with longstanding PR and RV dilatation have not been fully elucidated. It might be speculated that this relates to adverse ventricular-ventricular interactions. Close relationships have been demonstrated between RV and LV function in TOF patients based on studies using MRI, or echocardiographic measurements of strain and twist[1,3,22-23], underlining the importance of ventricular-ventricular interactions.

Limitations

The main limitation of this study is the lack of hard end-points. Detailed evaluation of clinical status, MRI measurements, exercise testing, electrocardiography, and neurohormonal markers provided a set of surrogate markers[24], but real hard end-points are sparse in this relatively young patient population.

When interpreting the results of the non-PVR patients, the possibility of selection bias should be taken into account. The older TOF patients in the non-PVR group could be considered as patients with a favourable clinical outcome. A good comparison between non-PVR and PVR patients remained difficult, because of different baseline results.

Data from exercise testing and NT-proBNP levels are incomplete, particularly for the PVR patients. This may have limited the statistical power.

Inclusion or exclusion of papillary muscles and trabeculations cause differences in biventricular dimensions[25]. We included papillary muscles and trabeculations in the ventricular cavity, since this has been reported to provide more reproducible measurements[25].

Conclusions

In non-PVR patients with adequate clinical condition and moderate RV dilatation, RVEDV increased by 1.6 ± 3.0 ml/m^2/year, irrespective of RV size at baseline. This limited progression in RV size was accompanied by some unfavourable changes during 5-year follow-up. PVR performed at the upper level of current recommendations had several favourable effects, but RV volumes were far from normal, particularly in patients who underwent PVR at RVEDV ≥ 170 ml/m^2. This data may point towards the need for a less conservative approach towards PVR.

References

1. Davlouros PA, Kilner PJ, Hornung TS, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol 2002;40:2044-2052.
2. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975-981.
3. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol 2004;43:1068-1074.
4. Knauth AL, Gauvreau K, Powell AJ, et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart 2008;94:211-216.
5. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation 1995;91:2214-2219.
6. Frigiola A, Tsang V, Bull C, et al. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? Circulation 2008;118:S182-190.
7. Oosterhof T, van Straten A, Vliegen HW, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation 2007;116:545-551.
8. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. Am J of Cardiol 2005;95:779-782.
9. Valsangiacomo Buechel ER, Dave HH, Kellenberger CJ, et al. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. Eur Heart J 2005;26:2721-2727.
10. Grothoff M, Hoffmann J, Lehmkuhl L, et al. Time course of right ventricular functional parameters after surgical correction of tetralogy of Fallot determined by cardiac magnetic resonance. Clin Res Cardiol 2011;100(4):343-350.
11. Gengsakul A, Harris L, Bradley TJ, et al. The impact of pulmonary valve replacement after tetralogy of Fallot repair: a matched comparison. Eur J Cardiothorac Surg 2007;32:462-468.
12. van den Berg J, Hop WC, Strengers JL, et al. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of Fallot. J Thorac Cardiovasc Surg 2007;133:470-477.
13. Wasserman K HJ, Sue DY, Stringer WW, Whipp BJ, ed. Principles of exercise testing and interpretation. 4th ed: Philadelphia: Lippincott Williams & Wilkins, 2005:160-182.
14. Godfrey S, Davies CT, Wozniak E, Barnes CA. Cardio-respiratory response to exercise in normal children. Clin Sci 1971;40:419-431.
15. Vliegen HW, van Straten A, de Roos A, et al. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of fallot. Circulation 2002;106:1703-1707.
16. Harrild DM, Berul CI, Cecchin F, et al. Pulmonary valve replacement in tetralogy of Fallot: impact on survival and ventricular tachycardia. Circulation 2009;119:445-451.
17. van de Woestijne PC, Mokhles MM, de Jong PL, Witsenburg M, Takkenberg JJM, Bogers AJJC. Right Ventricular Outflow Tract Reconstruction With an Allograft Conduit in Patients After Tetralogy of Fallot Correction: Long-Term Follow-Up. The Annals of Thoracic Surgery 2011;92(1):161-166.

18. Stark J, Bull C, Stajevic M, Jothi M, Elliott M, de Leval M. Fate of subpulmonary homograft conduits: determinants of late homograft failure. J Thorac Cardiovasc Surg 1998;115:506-14; discussion 514-516.
19. Lurz P, Bonhoeffer P. Percutaneous implantation of pulmonary valves for treatment of right ventricular outflow tract dysfunction. Cardiol Young 2008;18:260-267.
20. Kipps AK, Graham DA, Harrild DM, Lewis E, Powell AJ, Rhodes J. Longitudinal Exercise Capacity of Patients With Repaired Tetralogy of Fallot. Am J Cardiol 2011;108(1):99-105.
21. Tobler D, Crean AM, Redington AN, et al. The left heart after pulmonary valve replacement in adults late after tetralogy of Fallot repair. Int J Cardiol 2012;160(3):165-170.
22. Tzemos N, Harris L, Carasso S, et al. Adverse Left Ventricular Mechanics in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2009;103:420-425.
23. van der Hulst AE, Delgado V, Holman ER, et al. Relation of Left Ventricular Twist and Global Strain with Right Ventricular Dysfunction in Patients After Operative "Correction" of Tetralogy of Fallot. Am J Cardiol 2010;106:723-729.
24. Mahony L, Sleeper LA, Anderson PA, et al. The Pediatric Heart Network: a primer for the conduct of multicenter studies in children with congenital and acquired heart disease. Pediatr Cardiol 2006;27:191-198.
25. Winter MM, Bernink FJ, Groenink M, et al. Evaluating the Systemic Right Ventricle by CMR: the Importance of Consistent and Reproducible Delineation of the Cavity. J Cardiovasc Magn Reson 2008;10:40.

Supplementary Table 1: Results of MRI parameters in PVR subgroups

Parameter		PVR patients: RVEDV baseline < 170 ml/m^2 (N = 24)			PVR patients: RVEDV baseline ≥ 170 ml/m^2 (N = 28)		
		Baseline	**Follow-up**	**Change at follow-up**	**Baseline**	**Follow-up**	**Change at follow-up**
HR (beats / min)		71 (± 10)	68 (± 10)	-3 (± 12)	67 (± 12)	68 (± 11)	1 (± 12)
PR (%)		42 (± 9)	4 (± 7) *	-38 (± 11)	46 (± 10)	8 (± 10) *	-38 (± 13)
RV	EDV (ml/m^2)	150 (± 16)	107 (± 13) *	-42 (± 17)	211 (± 28) #	135 (± 32) *#	-76 (± 35) #
	ESV (ml/m^2)	76 (± 12)	53 (± 10) *	-22 (± 9)	124 (± 24) #	80 (± 29) *#	-44 (± 26) #
	SV (ml/m^2)	74 (± 9)	54 (± 6) *	-20 (± 10)	87 (± 15) #	55 (± 8) *	-33 (± 16) #
	Eff. SV (ml/m^2)	43 (± 8)	52 (± 7) *	9 (± 9)	47 (± 10)	50 (± 9)	3 (± 11)
	EF (%)	50 (± 5)	51 (± 5)	1 (± 3)	42 (± 6) #	42 (± 7) #	0 (± 6)
	Mass (g/m^2)	30 (± 6)	24 (± 5) *	-6 (± 5)	35 (± 7) #	27 (± 8) *	-8 (± 8)
	Mass/EDV ratio (g/ml)	0.20 (± 0.04)	0.22 (± 0.04) *	0.02 (± 0.03)	0.17 (± 0.03) #	0.20 (± 0.05) *	0.03 (± 0.05)
LV	EDV (ml/m^2)	80 (± 10)	92 (± 13) *	12 (± 13)	90 (± 16) #	95 (± 17)	5 (± 18)
	ESV (ml/m^2)	36 (± 7)	41 (± 8) *	4 (± 6)	41 (± 9) #	44 (± 11)	3 (± 11)
	SV (ml/m^2)	43 (± 6)	51 (± 7) *	8 (± 8)	48 (± 9) #	51 (± 8)	3 (± 10)
	EF (%)	55 (± 5)	56 (± 4)	1 (± 4)	54 (± 5)	54 (± 5)	0 (± 5)
	Mass (g/m^2)	50 (± 9)	49 (± 10)	-1 (± 6)	60 (± 11) #	58 (± 8) *#	-2 (± 6)
	Mass/EDV ratio (g/ml)	0.64 (± 0.17)	0.53 (± 0.10) *	-0.11 (± 0.15)	0.68 (± 0.14)	0.62 (± 0.10) *#	-0.07 (± 0.14)

Results are expressed as mean (± standard deviation).

* Significantly different between baseline and follow-up.

Significantly different between PVR patients with RVEDV baseline < and ≥ 170 ml/m^2.

Abbreviations: EDV = end-diastolic volume; EF = ejection fraction; Eff.SV = effective stroke volume; ESV = end-systolic volume; HR = heart rate; LV = left ventricle; MRI = magnetic resonance imaging; PR = pulmonary regurgitation; PVR = pulmonary valve replacement; RV= right ventricle; SV = stroke volume.

Supplementary Table 2: Results of clinical parameters in PVR subgroups

Parameter	PVR patients: RVEDV baseline < 170 ml/m^2 (N = 24)			PVR patients: RVEDV baseline ≥ 170 ml/m^2 (N = 28)		
Male	12 (50%)			19 (68%)		
Palliative shunt before corrective surgery	4 (17%)			9 (32%)		
Age at corrective surgery (years)	2.6 (0.2 – 11.4)			2.4 (0.2 – 16.6)		
Transannular patch	16 (67%)			24 (86%)		
Interval PVR and follow-up study (years)	4.3 (± 2.0)			4.2 (± 2.0)		
	Baseline	**Follow-up**	**Change at follow-up**	**Baseline**	**Follow-up**	**Change at follow-up**
Age at study (years)	25 (± 9)	30 (± 9) *	6 (± 2)	26 (± 9)	32 (± 9) *	5 (± 2)
NYHA class	I: 9 (38%) II: 15 (62%)	I: 22 (92%) * II: 2 (8%)	N/A	I: 19 (68%) # II: 8 (29%) III: 1 (3%)	I: 24 (86%) II: 3 (11%) III: 1 (3%)	N/A
QRS duration (msec)	141 (± 23)	140 (± 24)	-1 (± 10)	155 (± 26) #	155 (± 26) #	0 (± 11)
QTc interval (msec)	440 (± 21)	433 (± 26)	-7 (± 31)	431 (± 27)	440 (± 37)	9 (± 29)
	(N = 14)	**(N = 8)**	**(N = 6)**	**(N = 19)**	**(N = 13)**	**(N = 11)**
Peak workload (%)	88 (± 17)	86 (± 10)	-3 (± 19)	84 (± 15)	83 (± 11)	-6 (± 10)
	(N = 9)	**(N = 3)**	**(N = 1)**	**(N = 11)**	**(N = 6)**	**(N = 4)**
RQ	1.15 (± 0.07)	1.12 (± 0.02)		1.18 (± 0.08)	1.14 (± 0.05)	
Peak VO_2 (%)	95 (± 22)	94 (± 6)		89 (± 10)	83 (± 9)	
VE/VCO_2 slope	29 (± 6)	29 (± 9)		29 (± 5)	30 (± 4)	
	(N = 5)	**(N = 7)**	**(N = 4)**	**(N = 7)**	**(N = 10)**	**(N = 5)**
NT-proBNP (pmol/l)	18 (± 7)	17 (± 11)		10 (± 9)	27 (± 45)	

Results are expressed as mean (± standard deviation), as median (range), or as counts (percentages).

* Significantly different between baseline and follow-up.

Significantly different between PVR patients with RVEDV baseline < and ≥ 170 ml/m^2.

Abbreviations: N/A = not applicable; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; peak VO_2 = peak oxygen uptake; PVR = pulmonary valve replacement; QTc = QT interval, corrected for heart rate; RQ = respiratory quotient; RVEDV = right ventricular end-diastolic volume; VE/VCO_2 slope = ventilatory response to carbon dioxide production.

Supplementary Table 3: Results of MRI parameters in non-PVR subgroups

Parameter		Non-PVR patients: RVEDV baseline < 142 ml/m^2 (N = 54)			Non-PVR patients: RVEDV baseline ≥ 142 ml/m^2 (N = 24)		
		Baseline	**Follow-up**	**Change at follow-up**	**Baseline**	**Follow-up**	**Change at follow-up**
HR (beats / min)		74 (± 12)	72 (± 11)	-2 (± 10)	73 (± 12)	73 (± 14)	-1 (± 13)
PR (%)		21 (± 16)	23 (± 16) *	2 (± 5)	37 (± 11) #	42 (± 9) *#	5 (± 7) #
RV	EDV (ml/m^2)	114 (± 17)	121 (± 22) *	7 (± 14)	167 (± 16) #	176 (± 25) *#	9 (± 17)
	ESV (ml/m^2)	57 (± 11)	61 (± 14) *	4 (± 9)	89 (± 12) #	94 (± 19) *#	5 (± 12)
	SV (ml/m^2)	57 (± 9)	60 (± 11) *	3 (± 8)	78 (± 11) #	82 (± 10) *#	4 (± 8)
	Eff. SV (ml/m^2)	44 (± 7)	46 (± 7)	1 (± 6)	49 (± 8) #	47 (± 7)	-2 (± 6)
	EF (%)	50 (± 5)	50 (± 6)	-1 (± 4)	47 (± 5) #	47 (± 5) #	0 (± 3)
	Mass (g/m^2)	24 (± 5)	23 (± 5)	0 (± 3)	29 (± 5) #	28 (± 7) #	0 (± 4)
	Mass/EDV ratio (g/ml)	0.21 (± 0.04)	0.20 (± 0.04) *	-0.01 (± 0.03)	0.17 (± 0.03) #	0.16 (± 0.03) *#	-0.01 (± 0.02)
LV	EDV (ml/m^2)	82 (± 13)	87 (± 13) *	5 (± 11)	88 (± 11) #	90 (± 12)	2 (± 8)
	ESV (ml/m^2)	37 (± 9)	40 (± 9) *	3 (± 7)	39 (± 7)	41 (± 9)	2 (± 5)
	SV (ml/m^2)	45 (± 7)	47 (± 6) *	2 (± 6)	50 (± 7) #	50 (± 6)	0 (± 7)
	EF (%)	56 (± 5)	54 (± 5) *	-1 (± 4)	56 (± 5)	55 (± 5)	-1 (± 4)
	Mass (g/m^2)	52 (± 9)	53 (± 10)	1 (± 6)	57 (± 10) #	57 (± 9) #	0 (± 6)
	Mass/EDV ratio (g/ml)	0.64 (± 0.11)	0.61 (± 0.09) *	-0.04 (± 0.08)	0.66 (± 0.11)	0.64 (± 0.08)	-0.02 (± 0.09)

Results are expressed as mean (± standard deviation).

* Significantly different between baseline and follow-up.

Significantly different between non-PVR patients with RVEDV baseline < and ≥ 142 ml/m^2.

Abbreviations: EDV = end-diastolic volume; EF = ejection fraction; Eff.SV = effective stroke volume; ESV = end-systolic volume; HR = heart rate; LV = left ventricle; MRI = magnetic resonance imaging; PR = pulmonary regurgitation; PVR = pulmonary valve replacement; RV= right ventricle; SV = stroke volume.

Supplementary Table 4: Results of clinical parameters in non-PVR subgroups

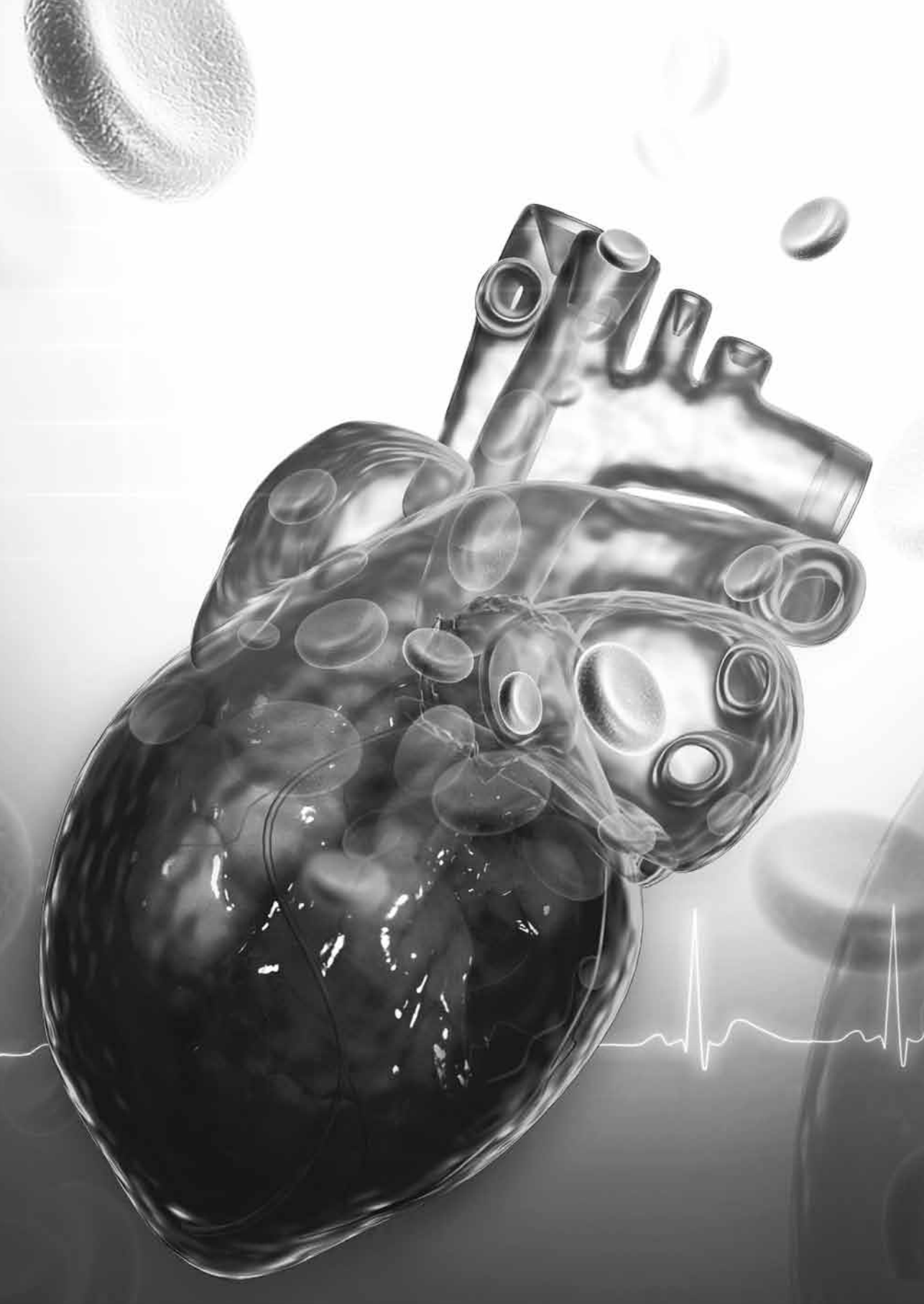
Parameter	Non-PVR patients: RVEDV baseline < 142 ml/m^2 (N = 54)			Non-PVR patients: RVEDV baseline ≥ 142 ml/m^2 (N = 24)		
Male	33 (61%)			15 (63%)		
Palliative shunt before corrective surgery	16 (30%)			5 (21%)		
Age at corrective surgery (years)	1.5 (0.1 – 32.8)			0.9 (0.2 – 17.5)		
Transannular patch	21 (39%)			22 (92%) #		
	Baseline	**Follow-up**	**Change at follow-up**	**Baseline**	**Follow-up**	**Change at follow-up**
Age at study (years)	24 (± 15)	29 (± 15) *	5 (± 1)	22 (± 12)	28 (± 12) *	5 (± 1)
NYHA class	I: 44 (81%) II: 10 (19%)	I: 44 (81%) II: 9 (17%) III: 1 (2%)	N/A	I: 22 (92%) II: 2 (8%)	I: 16 (67%) * II: 8 (33%)	N/A
QRS duration (msec)	131 (± 26)	138 (± 25) *	7 (± 9)	134 (± 28)	140 (± 46)	5 (± 12)
QTc interval (msec)	429 (± 24)	441 (± 32) *	11 (± 31)	429 (± 42)	438 (± 46)	8 (± 31)
	(N = 27)	**(N = 45)**	**(N = 27)**	**(N = 19)**	**(N = 21)**	**(N = 19)**
Peak workload (%)	94 (± 12)	92 (± 17)	-3 (± 17)	90 (± 18)	89 (± 17)	0 (± 9)
	(N = 22)	**(N = 32)**	**(N = 18)**	**(N = 15)**	**(N = 18)**	**(N = 13)**
RQ	1.18 (± 0.07)	1.14 (± 0.06) *	-0.05 (± 0.07)	1.20 (± 0.07)	1.19 (± 0.08) #	-0.04 (± 0.08)
Peak VO_2 (%)	95 (± 20)	92 (± 18)	-8 (± 16)	97 (± 18)	89 (± 17)	-5 (± 12)
VE/VCO_2 slope	31 (± 4)	29 (± 5)	0 (± 5)	31 (± 3)	32 (± 3) *	2 (± 2)
	(N = 21)	**(N = 50)**	**(N = 19)**	**(N = 15)**	**(N = 21)**	**(N = 14)**
NT-proBNP (pmol/l)	16 (± 14)	18 (± 27)	-1 (± 11)	18 (± 11)	17 (± 12)	-2 (± 12)

Results are expressed as mean (± standard deviation), as median (range), or as counts (percentages).

* Significantly different between baseline and follow-up.

Significantly different between non-PVR patients with RVEDV baseline < and ≥ 142 ml/m^2.

Abbreviations: N/A = not applicable; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; peak VO_2 = peak oxygen uptake; PVR = pulmonary valve replacement; QTc = QT interval, corrected for heart rate; RQ = respiratory quotient; RVEDV = right ventricular end-diastolic volume; VE/VCO_2 slope = ventilatory response to carbon dioxide production.



Chapter 6

Abnormal right atrial and right ventricular diastolic function relate to impaired clinical condition in patients operated for tetralogy of Fallot

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Abstract

Introduction: Atrial enlargement may reflect ventricular diastolic dysfunction. Although patients with tetralogy of Fallot (TOF) have been studied extensively, little is known about atrial size and function. We assessed bi-atrial size and function in patients after TOF repair, and related them to biventricular systolic and diastolic function, and clinical parameters.

Methods: 51 patients (21 ± 8 years) and 30 healthy controls (31 ± 7 years) were included and underwent magnetic resonance imaging to assess bi-atrial and biventricular size, systolic and diastolic function. Patients also underwent exercise testing, and N-terminal prohormone brain natriuretic peptide (NT-proBNP) assessment.

Results: In patients, right atrial (RA) minimal volume (34 ± 8 ml/m^2 vs. 28 ± 8 ml/m^2, p = 0.001) and late emptying fraction were increased; RA early emptying fraction was decreased. Patients had longer right ventricular (RV) deceleration time (0.24 ± 0.10 vs. 0.13 ± 0.04, p < 0.001), reflecting impaired RV relaxation, and larger RV volumes. Patients with end-diastolic forward flow (EDFF) had larger RA and RV size, abnormal RA emptying, higher NT-proBNP levels, higher VE/VCO_2 slope (ventilatory response to carbon dioxide production), and the most abnormal LV diastolic function (impaired compliance). Patients with abnormal RA emptying (reservoir function < 30% and pump function > 24%) had higher NT-proBNP levels and worse exercise capacity. RA minimal volume was associated with RV end-diastolic volume (r = 0.35, p = 0.013).

Conclusions: In TOF patients with moderate RV dilatation, abnormal bi-atrial function and biventricular diastolic dysfunction is common. Abnormal RA emptying was associated with signs of impaired clinical condition, as was the presence of EDFF. These parameters, together with RA enlargement, could serve as useful markers for clinically relevant RV diastolic dysfunction.

Introduction

Chronic pulmonary regurgitation (PR) with subsequent right ventricular (RV) dilatation is an important cause of late morbidity and mortality in patients long after surgical repair of tetralogy of Fallot (TOF)[1-4]. Up to now, it remains difficult to predict the course of RV dilatation and deterioration in TOF patients, and the precise indications and optimal timing to perform a pulmonary valve replacement (PVR) have therefore not been fully clarified.

Biventricular size and systolic functional parameters have been studied extensively in TOF patients, but little information is available on atrial size and function. The atria play a crucial role in the filling of the ventricle during ventricular diastole. It has been reported that left atrial (LA) enlargement reflects the burden of left ventricular (LV) diastolic dysfunction and that LA volumes increase with the severity of diastolic dysfunction[5]. This emphasizes the need for measurement of atrial size and function if diastolic function is assessed.

Diastolic dysfunction may be important as a marker preceding systolic dysfunction[6-7], but isolated diastolic dysfunction with preserved ejection fraction (EF) may also be an independent parameter influencing patient outcome[8]. The relationship between RV diastolic function and clinical parameters has been debated in TOF patients[9-13], but relatively little is known on the effects of right sided abnormalities on LV diastolic function.

Magnetic resonance imaging (MRI) is the gold standard technique for the assessment of biventricular size and function[14], and it has also been demonstrated to be an accurate tool for the analysis of atrial size and function[15].

The aim of our study was to assess bi-atrial size and function in patients after repair of tetralogy of Fallot and to evaluate the clinical value of these parameters by relating them to biventricular systolic and diastolic function, exercise capacity, electrocardiographic (ECG) parameters, and N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels.

Methods

Patients

This study is part of a larger, prospective serial follow-up study, for which the inclusion criteria were: 1) surgical repair of tetralogy of Fallot without associated cardiac lesions, 2) the availability of an MRI study at least 3 years before the current study. Patients with more than mild tricuspid regurgitation or evidence of a residual ventricular septal defect were excluded.

Fifty-four patients were included in the current cross-sectional study between September 2007 and February 2010. Patients underwent an MRI study with imaging of the atria, 12-lead ECG, 24-hour Holter monitoring, NT-proBNP assessment, and exercise testing, all on the same day.

Results of MRI parameters were compared to a group of 30 healthy controls (15 male, 31 ± 7 years), within our center. Healthy controls were volunteers without cardiac symptoms.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Our study protocol was approved by the local Ethical Committee; all participants, and if required parents, gave written informed consent.

Magnetic Resonance Imaging

Cardiac MRI was performed at a Signa 1.5 Tesla system (General Electric, Milwaukee, WI, USA) and an 8-channel phased-array cardiac surface coil. All patients were monitored by vector cardiogram gating and respiratory monitoring. All images were obtained during breath-hold in end-expiration. A multi-slice, multi-phase data set was acquired using steady-state free precession cine imaging in a short axis direction, covering the whole heart, including the atria. Typical imaging parameters were: repetition time 3.4 msec, echo time 1.4 msec, flip angle 45º, slice thickness 8–10 mm, inter-slice gap 1 mm, field of view 380 x 380 mm, and matrix 160 × 128 mm. Flow measurements of the pulmonary valve were performed perpendicular to flow, using a velocity-encoded MRI sequence. Typical imaging parameters were: repetition time 4.5 msec, echo time 2.4 msec, flip angle 18º, slice thickness 7 mm, field of view 290 x 220 mm, and matrix 256 x 128 mm. Velocity encoding was set at 150 cm/sec and was increased whenever phase aliasing occurred.

Analysis was performed on a commercially available Advanced Windows workstation (General Electric Medical Systems), equipped with the software packages MASS and FLOW (Medis Medical Imaging Systems, Leiden, the Netherlands). Endocardial and epicardial borders of both ventricles were manually traced in end-systole and end-diastole. Endocardial borders of the right atrium (RA), LA, RV, and LV were subsequently defined in all phases and all slices of the short axis set using a previously described semi-automated full cardiac cycle contour detection method[16]. Contours were manually corrected if necessary. The atrial appendages were included in the atrial volumes. The superior and inferior caval veins, coronary sinus, and pulmonary veins were excluded at their junction to the atrium. Papillary muscles and trabeculations were included in the ventricular cavity. The interventricular septum was included in the LV mass. When the pulmonary valve was visible in the basal slice, contours were drawn up to the junction with the pulmonary valve. All atrial data-sets were analyzed by 1 observer (RP) and supervised by another observer (SL), who also analyzed all ventricular data-sets and had 4 years of experience in cardiac contour tracing. Figure 1 shows bi-atrial and biventricular endocardial contour tracing.

MRI parameters

Time volume curves for the RA, LA, RV, and LV were acquired by summation of the volumes of every slice of each phase. Additionally, time volume change curves were reconstructed (Figure 2). The terms systole and diastole always refer to ventricular systole and ventricular diastole.

<u>RA and LA function</u>

The following parameters were assessed for RA and LA function (Figure 2A, 2B), as described by Riessenkampf and colleagues[17]: 1) maximal volume (max.vol); 2) minimal volume (min.vol); 3) cyclic volume change, defined as the difference between maximal and minimal atrial volume; 4) cyclic volume change function, which is the cyclic volume change, expressed as percentage of maximal atrial volume; 5) reservoir function, calculated by subtracting the minimal atrial volume at middiastole from the maximal atrial volume, expressed as percentage of ventricular effective stroke

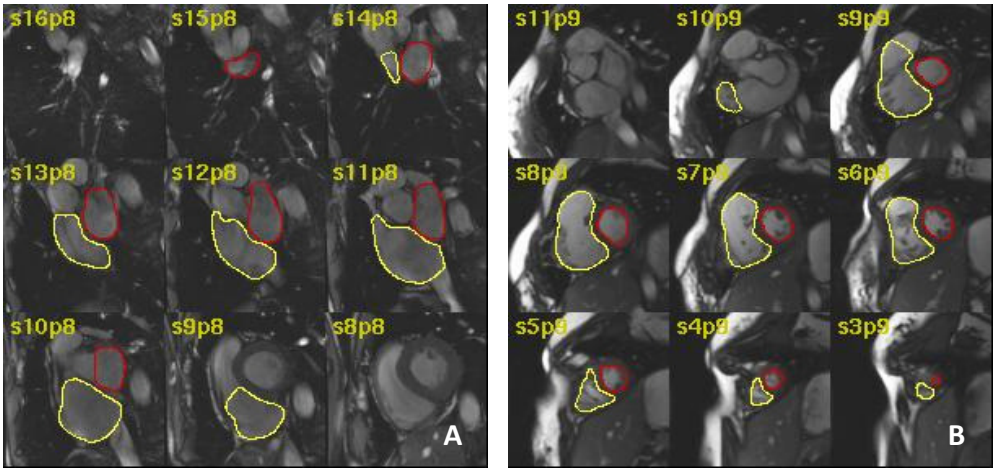


Figure 1. Contour tracing of atrial and ventricular borders in short axis orientation. A) Right atrial and left atrial contours; B) Right ventricular and left ventricular contours.

volume (SV); 6) pump function, calculated by subtracting the minimal atrial volume from the maximal atrial volume at middiastole, expressed as percentage of ventricular effective SV; 7) conduit function, calculated by subtraction of the sum of reservoir and pump volume from the effective SV of the ventricle, expressed as percentage of ventricular effective SV; 8) early emptying fraction, defined as atrial volume decrease during the first 1/3 of ventricular diastole, expressed as percentage of the cyclic volume change; 9) early peak emptying rate (EPER), defined as the maximal atrial volume change in early ventricular diastole; 10) late emptying fraction, defined as the decrease in atrial volume after the onset of atrial contraction, expressed as percentage of the cyclic volume change; 11) late peak emptying rate (LPER), defined as the maximal atrial volume change in late ventricular diastole; and 12) E/A volume ratio, as the ratio of early emptying volume to late emptying volume. Volumetric parameters were indexed for body surface area (BSA); EPER and LPER were indexed for cyclic volume change.

RV and LV function

The following parameters were assessed for RV and LV systolic and diastolic function (Figure 2C, 2D): 1) biventricular end-diastolic volume (EDV); 2) end-systolic volume (ESV); 3) SV; 4) EF; 5) mass; 6) early filling fraction, defined as ventricular volume increase during the first 1/3 of diastole, expressed as percentage of ventricular SV; 7) early peak filling rate (EPFR), defined as the maximal ventricular volume change in early diastole; 8) deceleration time (Dt), which is the time from EPFR to the extrapolation point of deceleration of flow to the baseline; 9) atrial filling fraction, defined as the increase in ventricular volume after the onset of atrial contraction, expressed as percentage of ventricular SV; 10) atrial peak filling rate (APFR), defined as the maximal ventricular volume change in late diastole; and 11) E/A volume ratio, as the ratio of early filling volume to atrial filling volume. Pulmonary regurgitation was expressed as percentage of systolic SV in the main pulmonary artery.

Additionally, RV effective stroke volume (eff.SV) was calculated to correct for PR: RVeff.SV = RVSV – PR volume. End-diastolic forward flow (EDFF) was defined as the presence of late diastolic forward flow in the pulmonary artery.

Volumes and mass were indexed for BSA; Dt for the RR-interval, and EPFR and APFR were indexed for SV.

Clinical parameters

A standardised 12-lead ECG was obtained to determine QRS duration and QT interval corrected for heart rate (QTc). A 24-hour Holter monitoring was performed on a day with usual activities.

Blood samples were drawn from a peripheral vein after 30 minutes rest in supine position. Plasma and serum were separated immediately after sample collection and stored at -80ºC. NT-proBNP was measured using the following commercially available Elecsys kit: electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany).

Patients performed a maximal bicycle exercise test on a Jaëger Oxycom Champion System (Viasys Healthcare, Hoechberg, Germany). Workload was increased by 20 Watts per minute. Peak workload and peak oxygen uptake (peak VO_2) were recorded and expressed as percentages of predicted values[18-19]. The ventilatory response to carbon dioxide production (VE/VCO_2 slope) was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.

Statistical analysis

Continuous data were tested for normality with the Kolmogorov-Smirnov test. Normally distributed data are expressed as mean (± standard deviation) and non-normally distributed data as median (range). Differences between groups of patients were evaluated using Student t-test or nonparametric tests, as appropriate. Categorical data are expressed as counts (percentages) and differences between groups of patients were evaluated with chi-square or Fisher exact test. To test the potential clinical value of parameters of bi-atrial size and function on relevant outcome parameters, correlations were assessed in all patients using linear regression analysis.

Analyses were performed using the SPSS statistical software package version 17.0 (SPSS, Inc., USA). A p-value < 0.05 was considered to indicate statistical significance.

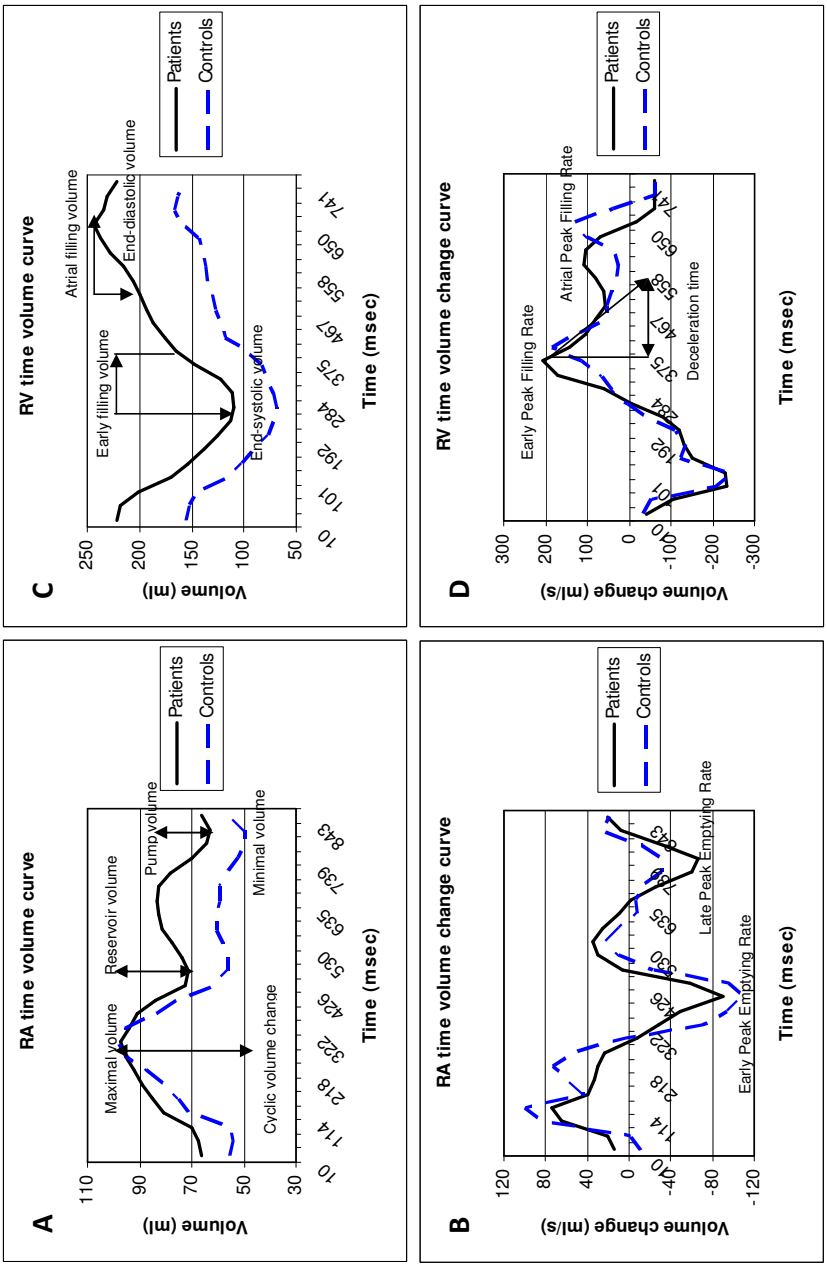


Figure 2. Time volume curves and time volume changes curves for RA parameters and RV parameters. A) RA time volume curve; B) RA time volume change curve; C) RV time volume curve; D) RV time volume change curve.

Abbreviations: RA = right atrium; RV = right ventricle.

Results

Fifty-four patients were included in our study. Three patients were excluded because of incomplete MRI data. Characteristics of the remaining 51 patients, and results of 12-lead ECG, 24-hour Holter monitoring, NT-proBNP assessment, and exercise testing are displayed in Table 1.

Table 1: Characteristics of the study population and results of ECG parameters, NT-proBNP, and exercise capacity

Parameter	All patients (N = 51)
Palliative shunt before corrective surgery	6 (12%)
Age at corrective surgery (years)	0.8 (0.1 – 9.4)
Transannular patch	41 (80%)
Age at study (years)	21 (± 8)
Male (%)	32 (63%)
PVR patients	10 (20%)
BSA (m^2)	1.79 (± 0.25)
NYHA class	I: 42 (82%)
	II: 9 (18%)
Heart rate (beats / minute)	75 (± 13)
QRS duration (msec)	137 (± 26)
QTc interval (msec)	434 (± 36)
VT run (number of patients)	1 (2%)
SVT run (number of patients)	2 (4%)
NT-proBNP (pmol/l)	14 (± 10)
Peak workload (%)	87 (± 12)
Peak VO_2 (%)	89 (± 14)
VE/VCO_2 slope	31 (± 5)

Results are expressed as mean (± standard deviation), as median (range), or as counts (percentages).
Abbreviations: BSA = body surface area; ECG = electrocardiography; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; PVR = pulmonary valve replacement; QTc = QT interval, corrected for heart rate; SVT = supraventricular tachycardia; VE/VCO_2 = ventilatory response to carbon dioxide production; peak VO_2 = peak oxygen uptake; VT = ventricular tachycardia.

Patients vs. Controls

Results of bi-atrial functional parameters are displayed in Table 2. Compared to healthy controls, patients had a larger RA minimal volume, a lower RA reservoir function, RA early emptying fraction, and E/A volume ratio; the RA pump function and RA late emptying fraction were higher. Patients had a lower LA maximal volume, LA reservoir function, LA early emptying fraction, and LA pump function than controls. Bi-atrial cyclic volume change function was lower in patients than in controls.

Results of biventricular functional parameters are displayed in Table 3. Patients had larger RV volumes than controls; RVeff.SV and LVSV were smaller, and biventricular EF was lower than in controls. Compared to healthy controls, patients had a lower RV EPFR, LV early filling fraction, LV atrial filling fraction, and LV APFR; the LV E/A volume ratio was higher. Biventricular Dt was longer in patients than in controls.

Table 2: Results of bi-atrial functional parameters

	RA			LA		
Parameter	**Controls (N = 30)**	**All patients (N = 51)**	**p-value (*)**	**Controls (N = 30)**	**All patients (N = 51)**	**p-value (*)**
Maximal volume (ml/m^2)	57 (± 11)	55 (± 10)	ns	41 (± 6)	33 (± 6) *	< 0.001
Minimal volume (ml/m^2)	28 (± 8)	34 (± 8) *	0.001	16 (± 3)	15 (± 4)	ns
Cyclic volume change (ml/m^2)	30 (± 7)	21 (± 4) *	< 0.001	26 (± 5)	18 (± 4) *	< 0.001
Cyclic volume change function (%)	52 (± 8)	39 (± 7) *	< 0.001	62 (± 5)	56 (± 6) *	< 0.001
Reservoir function (%)	41 (± 10)	30 (± 9) *	< 0.001	35 (± 5)	26 (± 6) *	< 0.001
Pump function (%)	21 (± 5)	24 (± 9) *	0.046	20 (± 6)	16 (± 6) *	0.002
Conduit function (%)	38 (± 10)	46 (± 12) *	0.003	46 (± 6)	58 (± 9) *	< 0.001
Early emptying fraction (%)	62 (± 15)	52 (± 17) *	0.008	64 (± 12)	56 (± 17) *	0.017
Late emptying fraction (%)	36 (± 9)	51 (± 16) *	< 0.001	40 (± 10)	39 (± 11)	ns
E/A volume ratio	1.9 (± 0.9)	1.1 (± 0.5) *	< 0.001	1.7 (± 0.6)	1.6 (± 0.8)	ns
EPER / cyclic volume change (/sec)	2.0 (± 0.5)	1.8 (± 0.5)	ns	2.2 (± 0.5)	2.3 (± 0.6)	ns
LPER / cyclic volume change (/sec)	1.3 (± 0.5)	1.7 (± 0.5) *	< 0.001	1.5 (± 0.6)	1.4 (± 0.5)	ns

Results are expressed as mean (± standard deviation).

* Significantly different between patients and controls.

Abbreviations: E/A volume ratio = ratio of early emptying volume to late emptying volume; EPER = early peak emptying rate; LA = left atrium; LPER = late peak emptying rate; ns = not significant; RA = right atrium.

Table 3: Results of biventricular functional parameters

	RV			LV		
Parameter	**Controls (N = 30)**	**All patients (N = 51)**	**p-value (*)**	**Controls (N = 30)**	**All patients (N = 51)**	**p-value (*)**
PR (%)	N/A	28 (± 18) *	< 0.001	N/A	N/A	
EDV (ml/m^2)	94 (± 17)	138 (± 34) *	< 0.001	88 (± 12)	86 (± 13)	ns
ESV(ml/m^2)	42 (± 11)	72 (± 22) *	< 0.001	36 (± 7)	38 (± 9)	ns
SV (ml/m^2)	52 (± 8)	66 (± 15) *	< 0.001	51 (± 8)	47 (± 7) *	0.014
Effective SV (ml/m^2)	52 (± 8)	46 (± 7) *	0.003	51 (± 8)	47 (± 7) *	0.014
EF (%)	56 (± 6)	48 (± 5) *	< 0.001	58 (± 4)	55 (± 5) *	0.008
Mass (g/m^2)	16 (± 4)	25 (± 7) *	< 0.001	51 (± 11)	54 (± 9)	ns
Mass/EDV ratio	0.17 (± 0.02)	0.18 (± 0.04)	ns	0.59 (± 0.08)	0.63 (± 0.09) *	0.021
Early filling fraction (%)	38 (± 12)	37 (± 10)	ns	54 (± 17)	46 (± 18) *	0.046
Atrial filling fraction (%)	31 (± 10)	33 (± 14)	ns	23 (± 8)	17 (± 10) *	0.006
E/A volume ratio	1.3 (± 0.7)	1.6 (± 1.3)	ns	2.7 (± 1.3)	4.2 (± 3.7) *	0.008
EPFR / SV (/sec)	1.6 (± 0.4)	1.3 (± 0.3) *	0.003	1.9 (± 0.3)	1.9 (± 0.3)	ns
Dt / RR interval ratio	0.13 (± 0.04)	0.24 (± 0.10) *	< 0.001	0.14 (± 0.03)	0.16 (± 0.04) *	0.012
APFR / SV (/sec)	1.2 (± 0.4)	1.0 (± 0.4)	ns	0.9 (± 0.4)	0.6 (± 0.3) *	< 0.001

Results are expressed as mean (± standard deviation).

* Significantly different between patients and controls.

Abbreviations: APFR = atrial peak filling rate; Dt = deceleration time; E/A volume ratio = ratio of early filling volume to atrial filling volume; EDV = end-

Patients with EDFF vs. patients without EDFF

Results for patients with EDFF vs. patients without EDFF are displayed in Table 4: only significant results are shown. RA maximal volume and minimal volume were larger, and RA pump function and RA late emptying fraction were higher in patients with EDFF than in patients without EDFF. Patients with EDFF had more PR and larger RV volumes than patients without EDFF. The LV E/A volume ratio, the NT-proBNP level, and the VE/VCO_2 slope were higher in patients with EDFF than in patients without EDFF.

Table 4: Results for patients with and without end-diastolic forward flow

Characteristic	Patients with EDFF (N = 31)	Patients without EDFF (N = 20)	p-value (#)
PVR patients	2 (6%) #	8 (40%)	0.008
RA maximal volume (ml/m^2)	58 (± 10) #	52 (± 9)	0.047
RA minimal volume (ml/m^2)	36 (± 9) #	31 (± 6)	0.047
RA pump function (%)	27 (± 8) #	20 (± 7)	0.003
RA conduit function (%)	43 (± 13) #	51 (± 9)	0.014
RA late emptying fraction (%)	54 (± 15) #	45 (± 15)	0.039
LA cyclic volume change (ml/m^2)	20 (± 4) #	16 (± 4)	0.004
LA cyclic volume change function (%)	58 (± 6) #	52 (± 5)	0.001
LA reservoir function (%)	28 (± 6) #	24 (± 6)	0.023
LA pump function (%)	17 (± 6) #	13 (± 4)	0.013
LA conduit function (%)	55 (± 9) #	63 (± 6)	< 0.001
PR (%)	36 (± 13) #	15 (± 17)	< 0.001
RVEDV (ml/m^2)	151 (± 33) #	120 (± 27)	0.001
RVESV(ml/m^2)	79 (± 22) #	63 (± 19)	0.010
RVSV (ml/m^2)	72 (± 14) #	57 (± 12)	< 0.001
RV mass/EDV ratio	0.17 (± 0.04) #	0.19 (± 0.03)	0.045
LV E/A volume ratio	5.0 (± 4.1) #	2.9 (± 2.5)	0.032
NT-proBNP (pmol/l)	16 (± 10) #	9 (± 9)	0.015
VE/VCO_2 slope	32 (± 4) #	28 (± 6)	0.014

Results are expressed as mean (± standard deviation), or as counts (percentages).

Significantly different between patients with and without EDFF.

Abbreviations: EDFF = end-diastolic forward flow; other abbreviations as in Tables 1 – 3.

Patients with "normal" RA emptying vs. patients with "abnormal" RA emptying

Since results of bi-atrial parameters showed that RA emptying was abnormal in patients (lower RA reservoir function and RA early emptying fraction; higher RA pump function and RA late emptying fraction), we subdivided our 51 patients into 2 groups to evaluate the clinical consequences of abnormal RA emptying: 1) patients with RA reservoir function > 30% and RA pump function < 24%

("normal" RA emptying) (N = 15); and 2) patients with RA reservoir function < 30% and RA pump function > 24% ("abnormal" RA emptying) (N = 36). These cut-off values for RA reservoir function and RA pump function were based on the mean values of all patients. Results are displayed in Table 5.

EDFF in the pulmonary artery was more present in patients with "abnormal" RA emptying than in patients with "normal" RA emptying. RV mass tended to be larger in patients with "abnormal" RA emptying, but this was not significant. Patients with "abnormal" RA emptying had higher NT-proBNP levels, and a lower peak workload than patients with "normal" RA emptying.

Table 5: Results for patients with "normal" and "abnormal" RA emptying

Characteristic	**"Normal" RA emptying (N = 15)**	**"Abnormal" RA emptying (N = 36)**	**p-value ($)**
EDFF	6 (40%)	25 (69%)	0.050
RA reservoir function (%)	37 (± 5)	27 (± 9) $	< 0.001
RA pump function (%)	17 (± 4)	27 (± 8) $	< 0.001
RA late emptying fraction (%)	35 (± 11)	58 (± 12) $	< 0.001
RA E/A volume ratio	1.6 (± 0.6)	0.9 (± 0.4) $	0.001
RA EPER / cyclic volume change (/sec)	2.3 (± 0.4)	1.7 (± 0.4) $	< 0.001
RA LPER / cyclic volume change (/sec)	1.3 (± 0.3)	1.9 (± 0.4) $	< 0.001
RVEDV (ml/m^2)	132 (± 32)	141 (± 35)	ns (p = 0.40)
RV mass (g/m^2)	22 (± 4)	26 (± 8)	ns (p = 0.074)
LV E/A volume ratio	3.1 (± 2.7)	4.7 (± 4.0)	ns (p = 0.19)
NT-proBNP (pmol/l)	7 (± 7)	16 (± 10) $	0.002
Peak workload (%)	95 (± 15)	84 (± 9) $	0.017
Peak VO_2 (%)	94 (± 16)	87 (± 12)	ns (p = 0.099)

Results are expressed as mean (± standard deviation), as median (range), or as counts (percentages).
$ Significantly different between patients with "normal" and "abnormal" RA emptying.
Abbreviations: as in Tables 1 – 4.

Correlations

Relevant associations between RA parameters and parameters of clinical condition and RV size are displayed in Figure 3. RA minimal volume was positively associated with RVEDV (Figure 3A); RA cyclic volume change function was negatively associated with RVEDV (Figure 3B). A higher RA late emptying fraction was correlated with a higher RVEDV and a higher NT-proBNP level (Figure 3C, 3E). A lower RA early emptying fraction was associated with a longer QRS duration (Figure 3D); a higher RA E/A volume ratio was associated with a higher peak VO_2 (Figure 3F).

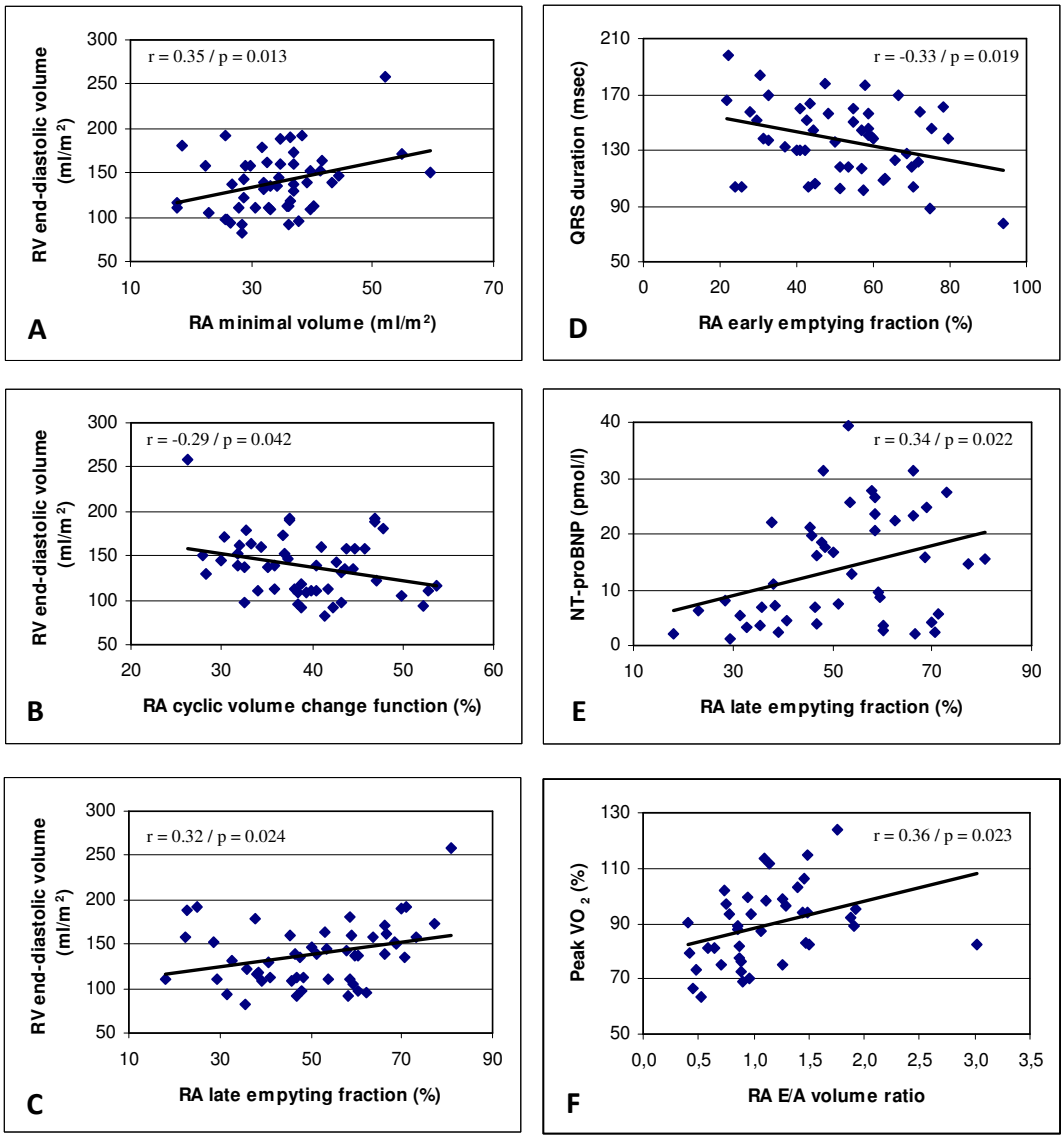


Figure 3. Correlations between RA parameters and parameters of clinical condition and RV size.
Correlation between: A) RA minimal volume and RVEDV; B) RA cyclic volume change function and RVEDV; C) RA late emptying fraction and RVEDV; D) RA early emptying fraction and QRS duration; E) RA late empyting fraction and NT-proBNP level; F) RA E/A volume ratio and peak VO_2.
Abbreviations: E/A volume ratio = ratio of early emptying volume to late emptying volume; NT-proBNP = N-terminal prohormone brain natriuretic peptide; RA = right atrium; RVEDV = right ventricular end-diastolic volume; peak VO_2 = peak oxygen uptake.

Discussion

This cross-sectional study in patients after surgical repair of tetralogy of Fallot demonstrated that in patients with adequate clinical condition, moderately dilated right ventricles and mildly impaired biventricular systolic function, bi-atrial size and function are clearly abnormal. The RA showed a larger minimal volume as well as reduced early emptying and increased late emptying, while the LA showed diminished filling and decreased emptying. The RV showed signs of impaired relaxation, while the LV showed signs of impaired compliance, particularly in patients with EDFF and in patients with “abnormal” RA emptying. “Abnormal” RA emptying was related to signs of impaired clinical condition, as was the presence of EDFF. Furthermore, larger RA size was associated with larger RV size.

In our patients, RA reservoir function and RA early emptying were diminished, which is in agreement with results of a recent study by Riessenkampf et al.[17]. We argue that RA early emptying is in competition with simultaneous inflow in the RV of pulmonary regurgitant backflow. This might also explain the normal filling of the RV in early diastole, despite signs of abnormal RV relaxation. These limitations to early RA emptying explain the observation that RA reservoir function and RA early emptying fraction are decreased and RA pump function and RA late emptying fraction are increased. “Abnormal” RA emptying was related to signs of impaired clinical condition, since patients with “abnormal” RA emptying had a higher NT-proBNP level, a lower exercise capacity, and showed a trend towards larger RV volumes than patients with “normal” RA emptying (Table 5, Figure 3C-3F).

In our patients with an important amount of PR, the marked RV dilatation and mildly decreased RV systolic function was not unexpected. Except for the signs of impaired RV relaxation in our patients, i.e. prolonged RV deceleration time and lower RV EPFR, RV diastolic functional parameters were comparable between our patients and healthy controls. Surprisingly, no major differences in RV diastolic functional parameters could be observed between patients with EDFF and patients without EDFF. Whether these observations represent true normal diastolic function or a pseudonormal state[7] cannot be directly determined from our data. Increased RA size has been related to increased RV end-diastolic pressure[20]. We speculate that the higher RA maximal and minimal volume, and the higher RV volumes that we found in our patients with EDFF relate to increased RV end-diastolic pressure. This would point towards abnormal RV diastolic function in these patients, which is compatible to the abnormal finding of EDFF. We have previously demonstrated that with dobutamine stress testing, impaired RV diastolic function is a common finding even in TOF patients with few signs of abnormal RV diastolic function at rest[21]. Assessment of RA size and function may be helpful in clinical practice to identify abnormal RV diastolic function.

End-diastolic forward flow has been recognized as sign of restriction to RV filling, but reports have been equivocal about the effects of EDFF on clinical outcome. Some studies have shown beneficial effects with regard to RV size and clinical condition in patients with EDFF[9,22], but other studies have reported that EDFF should be interpreted as a negative sign[10-11,13]. The latter is in agreement with our results, as we found that patients with EDFF had more PR, more RV dilatation, higher NT-proBNP levels, and a higher VE/VCO_2 slope than patients without EDFF. Lu et al. argued that the differences in effects of EDFF can be explained by the era of treatment of the different

patient populations[11]. In the patients who are operated at a younger age, according to current strategies, the presence of EDFF might reflect an overdistended ventricle due to poor compliance from excessive RV dilatation, rather than the traditional definition of RV restriction that represents restricted filling and a decreased RV volume[11].

In our patients, LA maximal volume was lower than in healthy controls. We assume that this reduced LA size is caused by the lower RV effective SV, and subsequently reduced LA filling. Left atrial emptying was also lower than in healthy controls, which presumably relates to the LV diastolic functional abnormalities that we found.

The LV showed signs of impaired relaxation (prolonged deceleration time), and of impaired compliance, as the LV E/A ratio was significantly higher in patients than in healthy controls. Left ventricular diastolic dysfunction is present in up to 25% of adult patients with repaired TOF[23]. The presence of reduced LV compliance might relate to the finding that LV mass/EDV ratio was increased. This might represent chronic underfilling of the LV, but LV volumetric data in our patients do not support this hypothesis. More likely, reduced LV compliance relates to LV fibrosis[24], LV dyssynchrony[25], and abnormal RV – LV diastolic interaction through the interventricular septum[25-28]. The presence of adverse right-to-left interactions is supported by our observation that patients with a large RA and large RV size showed the most abnormal LV diastolic function. Furthermore, it has been reported that RV pressure overload causes reduced LV compliance through mechanical and molecular effects on the septum and LV myocardium[8]. Our data suggest a relation between RV volume overload and reduced LV compliance as well, since reduced LV compliance was particularly seen in our patients with EDFF, who had a more volume overloaded RV than patients without EDFF. This points towards the clinical relevance of EDFF, a marker that can be easily obtained with different imaging techniques[10].

Supraventricular and ventricular arrhythmias are common after TOF repair[23,29]. The risk of arrhythmias, particularly of intraatrial reentrant tachycardia, increases with larger RA size[23]. Left atrial size, among other factors, has been related to increased risk for atrial fibrillation in an adult TOF population[23,29]. Left ventricular diastolic function and PR are some of the factors increasing the risk for ventricular arrhythmias[2,23]. Despite the presence of several of these factors in our patients, tachyarrhythmias were uncommon. An older age at repair and increasing age have been associated with a higher risk of atrial and ventricular arrhythmias, [2,23,29], which might explain the lower prevalence of arrhythmias in our relatively young patient population operated at young age..

Limitations

Information about invasive pressure measurements is lacking since our study was noninvasive. Invasive pressure measurements could have given more insight into biventricular diastolic functional parameters and its implications.

Our study has been performed in adolescents and young adults operated on according to current surgical strategies. Our results may therefore be not representative for older TOF patients.

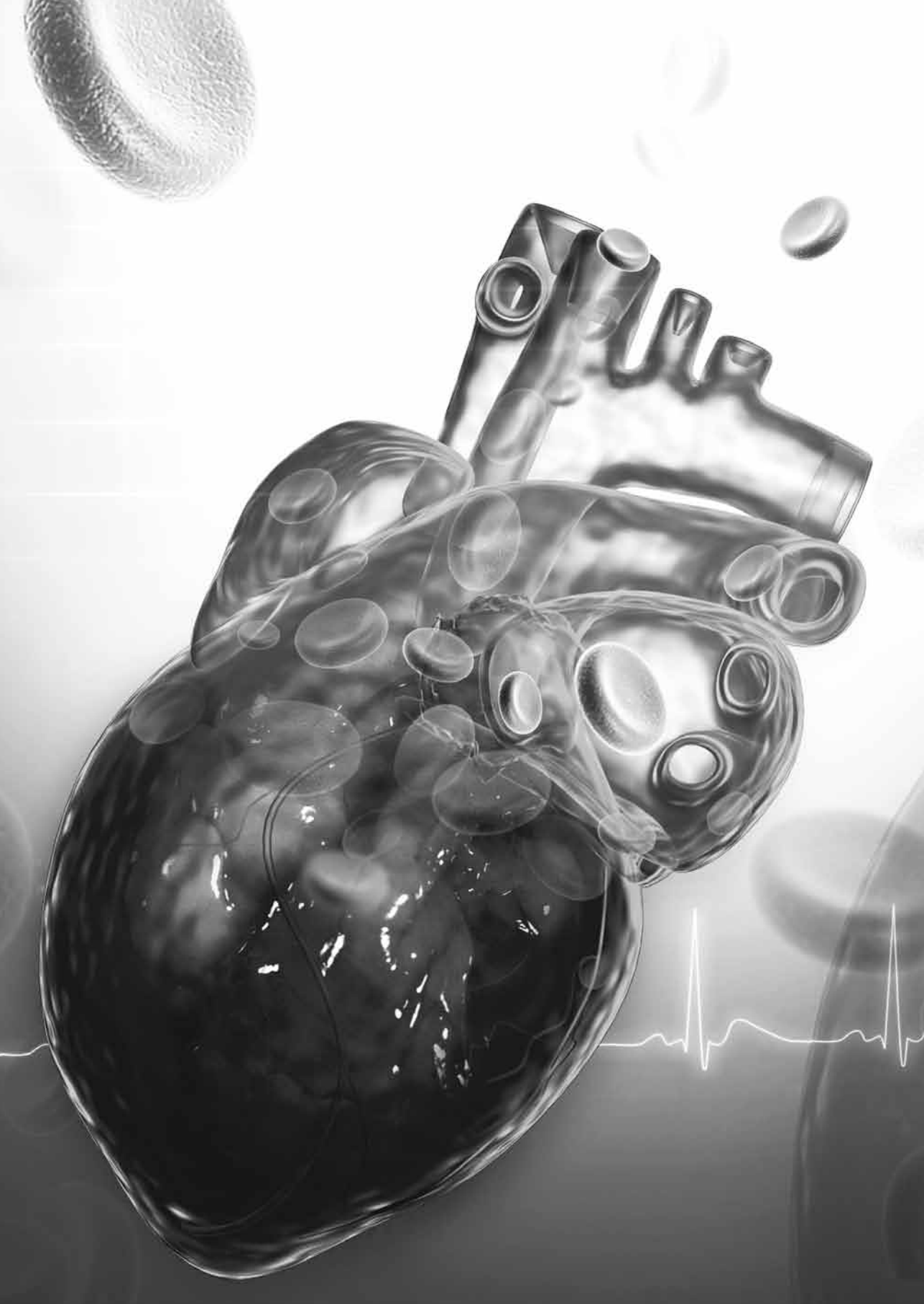
Conclusions

In TOF patients with moderately dilated right ventricles and mildly impaired biventricular systolic function, bi-atrial function is clearly impaired and abnormal biventricular diastolic function is common. Right atrial enlargement, impaired RA early emptying and increased RA late emptying were related to signs of impaired clinical condition, as was the presence of EDFF. Assessment of RV diastolic dysfunction in the presence of PR is complex: the presence of EDFF, RA enlargement, and abnormal RA emptying may serve as useful markers for clinically relevant RV diastolic dysfunction in TOF patients, which emphasizes the need for routine assessment of these parameters.

References

1. Davlouros PA, Kilner PJ, Hornung TS, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol 2002;40:2044-2052.
2. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975-981.
3. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol 2004;43:1068-1074.
4. Knauth AL, Gauvreau K, Powell AJ, et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart 2008;94:211-216.
5. Abhayaratna WP, Seward JB, Appleton CP, et al. Left Atrial Size: Physiologic Determinants and Clinical Applications. J Am Coll Cardiol 2006;47:2357-2363.
6. Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part I. Physiologic and pathophysiologic features. Mayo Clin Proc 1989;64:71-81.
7. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105:1387-1393.
8. Kitahori K, He H, Kawata M, et al. Development of Left Ventricular Diastolic Dysfunction With Preservation of Ejection Fraction During Progression of Infant Right Ventricular Hypertrophy. Circ Heart Fail 2009;2:599-607.
9. Gatzoulis MA, Clark AL, Cullen S, Newman CG, Redington AN. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot. Restrictive physiology predicts superior exercise performance. Circulation 1995;91:1775-1781.
10. Helbing WA, Niezen RA, Le Cessie S, van der Geest RJ, Ottenkamp J, de Roos A. Right ventricular diastolic function in children with pulmonary regurgitation after repair of tetralogy of Fallot: volumetric evaluation by magnetic resonance velocity mapping. J Am Coll Cardiol 1996;28:1827-1835.
11. Lu JC, Cotts TB, Agarwal PP, Attili AK, Dorfman AL. Relation of Right Ventricular Dilation, Age of Repair, and Restrictive Right Ventricular Physiology With Patient-Reported Quality of Life in Adolescents and Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2010;106:1798-1802.
12. Norgard G, Gatzoulis MA, Josen M, Cullen S, Redington AN. Does restrictive right ventricular physiology in the early postoperative period predict subsequent right ventricular restriction after repair of tetralogy of Fallot? Heart 1998;79:481-484.
13. Cardoso SM, Miyague NI. Right ventricular diastolic dysfunction in the postoperative period of tetralogy of Fallot. Arq Bras Cardiol 2003;80:198-201, 194-197.
14. Kilner PJ, Geva T, Kaemmerer H, Trindade PT, Schwitter J, Webb GD. Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the European Society of Cardiology. Eur Heart J 2010;31:794-805.
15. Sarikouch S, Koerperich H, Boethig D, et al. Reference values for atrial size and function in children and young adults by cardiac MR: A study of the german competence network congenital heart defects. J Magn Reson Imaging 2011;33:1028-1039.
16. Uzumcu M, van der Geest RJ, Swingen C, Reiber JH, Lelieveldt BP. Time continuous tracking and segmentation of cardiovascular magnetic resonance images using multidimensional dynamic programming. Invest Radiol 2006;41:52-62.

17. Riesenkampff E, Mengelkamp L, Mueller M, et al. Integrated analysis of atrio-ventricular interaction in tetralogy of Fallot. Am J Physiol Heart Circ Physiol 2010;299:H364-H371.
18. Wasserman K HJ, Sue DY, Stringer WW, Whipp BJ, ed. Principles of exercise testing and interpretation. 4th ed: Philadelphia: Lippincott Williams & Wilkins, 2005:160-182.
19. Godfrey S, Davies CT, Wozniak E, Barnes CA. Cardio-respiratory response to exercise in normal children. Clin Sci 1971;40:419-431.
20. Do DH, Therrien J, Marelli A, Martucci G, Afilalo J, Sebag IA. Right atrial size relates to right ventricular end-diastolic pressure in an adult population with congenital heart disease. Echocardiography 2011;28:109-116.
21. van den Berg J, Wielopolski PA, Meijboom FJ, et al. Diastolic function in repaired tetralogy of Fallot at rest and during stress: assessment with MR imaging. Radiology 2007;243:212-219.
22. Norgard G, Gatzoulis MA, Moraes F, et al. Relationship between type of outflow tract repair and postoperative right ventricular diastolic physiology in tetralogy of Fallot. Implications for long-term outcome. Circulation 1996;94:3276-3280.
23. Khairy P, Aboulhosn J, Gurvitz MZ, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation 2010;122:868-875.
24. Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. Circulation 2006;113:405-413.
25. Tzemos N, Harris L, Carasso S, et al. Adverse Left Ventricular Mechanics in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2009;103:420-425.
26. Kondo C, Nakazawa M, Kusakabe K, Momma K. Left ventricular dysfunction on exercise long-term after total repair of tetralogy of Fallot. Circulation 1995;92:II250-255.
27. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. Circulation 2008;117:1436-1448.
28. Geva T. Repaired tetralogy of Fallot: the roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. J Cardiovasc Magn Reson 2011;13:9.
29. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation 1995;91:2214-2219.



Chapter 7a

Stress imaging in congenital heart disease

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Abstract

In patients with coronary artery disease, stress imaging is able to demonstrate abnormalities in the motion of the ventricular walls, and abnormalities in coronary arterial perfusion not apparent at rest. It can also provide information on prognostic factors. In patients with congenitally malformed hearts, stress imaging is used to determine contractile reserve, abnormalities of mural motion, and global systolic function, but also to assess diastolic and vascular function. In most of these patients, stress is usually induced using pharmacological agents, mainly dobutamine given in varying doses. The clinical usefulness of abnormal responses to the stress induced in such patients has to be addressed in follow-up studies. The abnormal stress might serve as surrogate endpoints, predicting primary endpoints at an early stage, which are useful for stratification of risk in this population of growing patients. We review here the stress imaging studies performed to date in patients with congenitally malformed hearts, with a special emphasis on echocardiography and cardiac magnetic resonance imaging.

Introduction

In 1979, exercise-induced abnormalities of ventricular mural motion were identified using cross-sectional echocardiography in patients with ischemic heart disease[1]. From then on, assessment of ventricular function with stress imaging has been widely applied in patients with coronary artery disease[2]. In these patients, stress imaging is able to demonstrate abnormalities of ventricular mural motion and coronary arterial perfusion not apparent at rest, and can provide information on risk factors and prognostic factors[2-4]. The use of stress imaging has subsequently been extended to patients with dilated or hypertrophic cardiomyopathy, valvular heart disease, and those with congenitally malformed hearts. In patients with dilated or hypertrophic cardiomyopathy, this form of imaging is used to assess, in addition to abnormalities of mural motion, gradients across the outflow tracts, and the contractile reserve, that is the change in ventricular ejection fraction induced by stress[5]. In patients with congenitally malformed hearts, stress imaging is used to determine all these factors, but also to assess diastolic and vascular function. In this review, we will discuss the use, limitations, and future applications of stress imaging in patients with congenitally malformed hearts, placing our emphasis on echocardiography and cardiovascular magnetic resonance imaging.

Stressors

Physical exercise

Physical exercise is the ideal stressor. It results in the combined activation of cardiac, pulmonary, vascular, neurohormonal, muscular, and metabolic systems involved in the adaptations to stress. Common tools to perform physical exercise during imaging procedures are the treadmill, bicycle ergometer, or handgrip. Specific magnetic resonance-compatible supine or upright bicycle ergometers have been used for exercise testing in combination with magnetic resonance imaging. In this respect, the posture of the patient is important, since this has a significant effect on central hemodynamics, with lower cardiac output, higher stroke volumes, and lower heart rates in those tested in supine as opposed to upright positions[6].

Different protocols have been described for study of patients with congenitally malformed hearts, including:1) exercise to a certain percentage of their maximal exercise capacity or oxygen consumption[7-9]; 2) symptom-limited exercise[10-12]; 3) exercise at 0.5 and 2.5 W/kg[13-16]. Physical exercise has several limitations. Maximal physical stress is dependent on the motivation and cooperation of the patient, and cannot be attained in patients with certain co-existing neurologic or orthopedic diseases. Hyperventilation during physical exercise hinders breath-holding during the acquisition of images. In combination with echocardiography, it is difficult to acquire images during physical exercise. Hence, images are usually obtained directly after exercise. This is also applicable to magnetic resonance imaging[8-9,16-18], although with real-time

imaging this limitation has been overcome, and scanning during rapid breathing is feasible, even in patients with complex lesions[13-14].

Pharmacological stress

During the 1980s pharmacological agents were introduced as stressors to overcome the limitations of physical exercise[19-20]. Use of these agents has extended the use of stress imaging to patients with constraints that preclude adequate exercise. The most commonly used drugs are adenosine, dipyridamole, and dobutamine.

Adenosine and dipyridamole are coronary vasodilators that generate a reduced supply of oxygen in myocardial areas supplied by stenotic coronary arteries, and are used for coronary perfusion imaging. Adenosine is a naturally occurring substance in the body that causes coronary vasodilatation through activation of A2-receptors. This results in increased flow in normal coronary arteries compared to stenotic ones, a steal phenomenon which results in a perfusion mismatch. It does not necessarily cause ischemia. Adenosine has a very short half life of only 2 seconds, and therefore needs to be administered through continuous intravenous infusion. The dose used for stress-testing is 0.14 mg/kg/min over 6 minutes, or until the patient suffers significant discomfort, whichever comes first. Common side effects are flushing, dyspnea, chest pain, gastro-intestinal discomfort, headache, and light-headedness. Most side effects disappear shortly after discontinuation of administration of the agent, and do not require medical treatment. Adenosine is contra-indicated in patients with active restrictive airway disease, 2nd or 3rd degree atrioventricular block, and in patients taking dipyridamole. Since theophylline and caffeine are adenosine receptor antagonists, abstention of these substances is required for 1 to 2 days before stress testing with adenosine or dipyridamole. In patients with congenitally malformed hearts, adenosine has been rarely used for stress imaging, since coronary artery abnormalities are not common.

Dipyridamole inhibits reuptake of adenosine by vascular endothelial cells, and indirectly causes coronary vasodilatation. It has a considerably longer half-life than adenosine, and its hemodynamic effects can persist up to 30 minutes. The agent is administered in a rate of 0.56 mg/kg over 4 minutes. Side effects and contraindications for the use of dipyridamole are similar to those of adenosine.

Dobutamine increases the myocardial demand for oxygen similar to physical exercise, and is used to study contractile reserve and abnormalities of ventricular mural motion. It is a synthetic catecholamine with positive inotropic and, to a lesser extent, chronotropic effects. In healthy children, positive inotropic effects occur from 1 to 2 µg/kg/min, with dose-dependent increases in measures of systolic ventricular function[21], while chronotropic effects are seen from 5 to10 µg/kg/min[22]. The agent is also known to enhance diastolic function, and to decrease preload and afterload[23]. In normal subjects, during its infusion, stroke volume increases, end-diastolic

volume does not change, end-systolic volume decreases, and ejection fraction increases[24]. The half-life is only 2 minutes, and therefore it should be given through continuous intravenous infusion. In patients with congenitally malformed hearts, different dosages are used to answer different research questions. When used at low or moderate doses, dobutamine is used to assess cardiac contractile reserve. The infusion is started at 2.5 or 5 μg/kg/min, and increased every 3 to 5 minutes with 2.5 or 5 μg/kg/min to 5 to 20 μg/kg/min. At high doses, dobutamine is used to detect mural abnormalities in patients with coronary arterial abnormalities, as in patients after Kawasaki disease or after arterial switch operation. Infusion usually starts at 10 μg/kg/min, and the rate is increased every 3 to 5 minutes with 10 μg/kg/min, until the heart rate is 85% of the maximal predicted heart rate for age, or to 40 μg/kg/min maximum. If 85% of the maximal predicted heart rate for age is not reached at 40 μg/kg/min, atropine can be administered in conjunction with dobutamine to reach the target heart rate. Heart rate, blood pressure, and cardiac rhythm if possible, are continuously monitored during dobutamine stress-testing. Common minor side effects, such as headache, nausea, hypertension, hypotension, and hemodynamically insignificant arrhythmias, can occur in up to one-fifth of children[25]. Major side effects have not been reported in patients with congenitally malformed hearts. Side effects of atropine are dry mouth, tachycardia, and hallucinations. Side effects of both dobutamine and atropine can be treated with β-blockers or calcium antagonists, albeit the latter preferably not in children, and these agents should be readily available during stress-testing. Administration of dobutamine is contra-indicated in patients with a mechanical obstruction of systemic ventricular filling or ejection, in patients with 2nd or 3rd degree atrioventricular block, and in patients with a history of sustained ventricular tachycardia.

The majority of stress imaging studies in patients with congenitally malformed hearts has been performed with pharmacological stress, almost exclusively using dobutamine. Only one study reported on the safety and feasibility of adenosine-stress cardiovascular magnetic resonance imaging in children with congenital aortic stenosis or after arterial switch operation[26]. Stress imaging has only been performed in a limited number of studies using high doses[27-30]. In studies performing stress imaging at low doses, the doses have ranged from 5.0 to 20 μg/kg/min. In our experience, a dosage of 7.5 μg/kg/min is safe, with a low incidence of only minor adverse effects. Furthermore, it is sufficiently high to elicit a significant cardiovascular stress response[31-34]. Arrhythmias are side effects of special concern in this group of patients. Although the incidence of arrhythmias is low in the studies performed so far, most occurred with a dobutamine dosage of at least 10 μg/kg/min[35-38]. In patients who had undergone a Fontan operation for functionally univentricular hearts, administration at 7.5 μg/kg/min provoked an increase in heart rate of more than 150% from baseline in 10 of 37 patients[32]. This was well tolerated, and lowering the dosage to 5 μg/kg/min was sufficient to decrease the heart rate and successfully complete the study protocol, producing images adequate for analysis.

Imaging modalities

Radionuclide myocardial perfusion imaging

Positron emission tomography and single-photon emission computed tomography allow evaluation of myocardial perfusion and the effects of myocardial hypoperfusion on metabolic activity and myocardial contractility[39]. Positron emission tomography and single-photon emission computed tomography cameras capture the photons emitted by radiopharmaceuticals, such as nitrogen-13 labeled ammonia, and technetium-99m tetrophosmin or sestamibi, and translate the information into digital data representing the magnitude and location of the emission in the heart. Positron emission tomography has a better performance on spatial and temporal resolution, with less attenuation of the emitted signal than single-photon emission computed tomography. In children and patients with congenitally malformed hearts, positron emission tomography and single-photon emission computed tomography are rarely used, predominantly in patients with coronary arterial disease[40-45]. These studies assessed myocardial perfusion and coronary flow reserve at rest and during adenosine or dipyridamole infusion. Although showing signs of coronary arterial damage or decreased coronary vasoreactivity, use of these imaging modalities is limited because of concerns on radiation exposure in young children. Furthermore, coronary arterial abnormalities can also be assessed with radiation-free imaging modalities, such as echocardiography and cardiovascular magnetic resonance imaging.

Echocardiography

Conventional echocardiography, M-mode, Doppler and tissue Doppler imaging have all been performed in combination with stress in patients with various forms of congenitally malformed hearts[7,10-12,15,27-29,35,37]. Although the first report on stress imaging in these patients involved echocardiography, its implementation has been largely hampered by the limitations of the acoustic window. Suboptimal acquisition of images, producing images of suboptimal image, is common in patients with complex cardiac anatomy. Combined with an abnormal orientation of the heart and great vessels in the chest, and the problems encountered in imaging the functionally univentricular arrangements as well as the morphologically right ventricle[46-47]. this has led to limited use of stress echocardiography in the setting of congenital heart disease.

Magnetic resonance imaging

In patients with coronary arterial disease, echocardiography was the modality of choice for stress imaging up until the early 1990s. In 1992, the use of dobutamine stress cardiovascular magnetic resonance imaging was introduced[48] and has proven to be a valuable tool to detect ischemia in patients with known or suspected coronary arterial disease[3,49]. Dobutamine stress

cardiovascular magnetic resonance imaging can assess abnormalities of mural motion, contractile reserve, abnormalities of diastolic function, and vascular function. It has a sensitivity and specificity comparable to dobutamine stress echocardiography for identifying coronary arterial disease[49]. The technique overcomes the limitations of echocardiography in selected patients with congenitally malformed hearts[50]. A few groups have reported on the use of this modality to evaluate the reaction of the cardiovascular system in such patients when stressed[8-9,13-14,16,18,26,30-34,36,38,50-54]. These studies have shown abnormal systolic, and diastolic function, and abnormal vascular responses which help elucidate the pathophysiological processes. An important advantage of dobutamine stress cardiovascular magnetic resonance imaging is that all these parameters can be obtained in one single study. Disadvantages are the exclusion of patients with claustrophobia, severe obesity, and magnetic resonance-incompatible devices, and the need for sedation or general anaesthesia in young children, usually those under the age of 5 to 6 years.

Stress imaging in children and patients with congenital cardiac disease

Stress echocardiography

The first report of stress-testing by supine exercise combined with echocardiography in children with left-sided cardiac disease was published in 1980[7]. Thereafter, stress echocardiography combined with dobutamine was used to assess contractile reserve in children with thalassemia major, children after Kawasaki disease, those having chemotherapy for childhood cancer, and those with transplanted hearts[24-25,55-58]. These studies showed that the technique could provide impotant information on subclinical global ventricular dysfunction or coronary arterial disease.

There are, however, relatively few studies reported on use of stress echocardiography in patients with congenital heart disease, albeit that the technique has been used in patients with complex lesions, such as patients after atrial or arterial corrections for transposition, those with the Fontan circulation, and patients with tetralogy of Fallot[10-12,15,27-29,35,37]. The results of these studies are summarized in Table 1. Half of these studies have been performed in combination with physical exercise. The other half has been performed using dobutamine stress-testing, with dosages ranging from 20 to 40 µg/kg/min. With infusions of at least 20 µg/kg/min, no major side effects have been reported, albeit that one study reported hypertension in two-thirds of the studied patients[37]. The definition of hypertension used by these investigators, however, was an increase in systolic blood pressure of greater than 30% from baseline, while others defined hypertension as an increase in systolic blood pressure of greater than half from baseline[24].

Outcomes of these studies cannot be easily compared. There is a wide variety in the age and diagnoses of the patients, the type of measurements with echocardiography, and the type of stressor. All studies demonstrated abnormal ventricular and/or vascular responses with stress-

testing. Some studies identified these abnormal responses as predictors of exercise capacity[12,29]. In general, the clinical relevance of these abnormal findings with stress-testing is unknown. Standardized studies using identical stressors and identical methods of measurement are needed to determine their clinical relevance. Furthermore, the combination of new techniques, such as 3-dimensional echocardiography, with its capability for assessment of ventricular volumes and dyssynchronicity, and of tissue Doppler and speckle tracking techniques with stress imaging need further exploration.

Stress cardiovascular magnetic resonance imaging

Only a few groups have performed stress cardiovascular magnetic resonance imaging in patients with congenital heart disease (Table 2). In more than 200 patients, these studies showed the feasibility and safety of the technique. Unfortunately, as for those using stress echocardiography, differences in diagnoses, ages, measurements, and protocols preclude direct comparison of the reported outcomes.

Studies have been performed predominantly in: 1) patients with a pressure overloaded right ventricle, such as in congenitally corrected transposition, pulmonary arterial stenosis, or the Eisenmenger syndrome[9,36,38,50-54]; 2) patients with a volume overloaded right ventricle, as aftercorrection for tetralogy of Fallot[8,33-34,53]; and 3) patients with a potentially impaired ventricular preload as a result of atrial baffle reconstruction after creation of the Fontan circulation or atrial correction for transposition[13-14,16,31-32,38,50,52,54].

In patients with a pressure overloaded right ventricle, the technique demonstrated abnormal responses of the systemic right ventricle. In patients with congenitally corrected transposition, different responses of the systemic right ventricle have been reported, according to the type of repair. Some[38,51] reported that stroke volume did not increase, with the latter study reporting a normal response to stress, with an increase in stroke volume, in patients with congenitally corrected transposition who had not undergone repair compared to patients after physiologic repair. Others[36] also demonstrated an increase in stroke volume with dobutamine stress cardiovascular magnetic resonance imaging in unoperated patients with congenitally corrected transposition. The first group suggested that unoperated patients, with a favorable anatomy, may never require an operation, and that dobutamine stress cardiovascular magnetic resonance imaging might be helpful in identifying the patients who will need anatomic correction[51]. In patients with pulmonary arterial stenosis, and in those with Eisenmenger syndrome, end-diastolic volume was significantly larger compared to controls, but ejection fraction was normal at rest. With stress-testing, end-diastolic volume, end-systolic volume, and stroke volume all decreased, and ejection fraction did not change, clearly demonstrating the highly abnormal response of these morphologically right ventricles to stress[38].

Several investigators have reported on the biventricular stress response in patients with a volume overloaded right ventricle. In one study[8] supine bicycle exercise demonstrated a decrease in pulmonary regurgitation with stress-testing, and a normal left ventricular stress response in patients with tetralogy of Fallot. Others reported on the use of low-dose dobutamine stress cardiovascular magnetic resonance imaging in patients after contemporary repair of tetralogy of Fallot[33-34]. They showed well preserved functional reserve in all patients despite important pulmonary regurgitation and right ventricular dilatation, as well as an abnormal relaxation with stress-testing in patients with end-diastolic forward flow, which was not appreciated at rest. Many of these patients with normal contractile reserve had right ventricular volumes that would have made them candidates for replacement of the pulmonary valve according to criteria based on right ventricular volumes[33,59]. This demonstrates the potential added value of stress imaging in clinical decision making.

In patients with an impaired ventricular preload as a result of atrial baffle reconstruction, several groups have performed various stress cardiovascular magnetic resonance studies, studying the systemic venous return, pulmonary arterial circulation, and systemic ventricular function[13-14,16,31-32]. Measurements were made by some in both pulmonary arteries, along with flow in the caval veins, immediately after exercise or during exercise using real-time cardiovascular magnetic resonance imaging[13-14,16]. All the children, with mean ages between 9 and 12 years, were able to perform and complete the protocol. They demonstrated that an increase in cardiac output with exercise is predominantly caused by an increase in heart rate, and that the influence of inspiration on systemic venous return is less pronounced during exercise.

Table 1: Stress echocardiography in congenital heart disease

Study	Stressor	Patients	Age	Adverse effects	Measurements	Outcome
Alpert[7]	Supine bicycle exercise	19 patients with LV pressure and/or LV volume overload 1 patient with cardiomyopathy; 1 patient s.p. LVOTO resection	8-19 years	None	M-mode echocardiography combined with cardiac catheterization: mean Vcf, peak meridional wall stress	Feasibility and safety of the technique. With exercise the change in Vcf and peak wall stress discriminated between different patient groups and indicate functional reserve.
Oyen[15]	Supine bicycle exercise	35 patients with AS, or AVR, or coarctation, or VSD, or AR, or HOCM	6-14 years	None	LV end-diastolic and end-systolic diameter, fractional shortening, and Vcf	Frequency corrected Vcf indicated a disproportion in heart rate increase and LV contraction and could discriminate LV reaction between patients and controls.
Cyran[10]	Upright treadmill exercise	24 patients after coarctation repair	5-19 years	None	Ascending and descending aortic systolic velocities	Identification of descending aortic systolic velocity abnormalities as a determinant of systolic blood pressure.
Kaplan[12]	Supine bicycle exercise	27 patients with TOF, or ASD, or VSD, or TGA, or ccTGA, or Ebstein's anomaly	17-63 years	None	Biventricular systolic function, peak velocity of tricuspid regurgitation jet, pulmonary valve gradients	Poor exercise tolerance associated with 1) abnormal responses of PA pressure during exercise; 2) abnormal LV systolic function.
Hauser[11]	Maximal exercise	21 patients after ASO for TGA 9 patients after Ross procedure	12 (2) years 19 (8) years	None	Conventional, Doppler, and M-mode echocardiography, analysis of WMA	Stress-induced dyskinetic areas in 2 patients after ASO.
Li[29]	Dobutamine stress, 40 µg/kg/min max	27 patients after atrial switch for TGA	29 (7) years	Shortness of breath (n = 1) Lightheadedness (n = 1)	Biventricular function applied to the long axis of the heart with conventional echocardiography, Doppler, M-mode and TDI	Depressed RV ventricular long-axis function with stress. Excursion of the RV free wall (at rest or during stress) predicts exercise capacity.

Table 1, continued.

Study	Stressor	Patients	Age	Adverse effects	Measurements	Outcome
Hui[37]	Dobutamine stress, 20 µg/kg/min max	31 patients after ASO for TGA	7-14 years	Hypertension (n = 23) , arrhyth-mia (n = 7), tachycardia (n = 6), chestpain (n = 3), hypotension (n = 1), headache (n = 1)	2D echocardiography: apical 2 and 4 chamber, parasternal long and short axis for analysis of WMA	Stress induced WMA in 23 patients.
Apostolopulou[27]	Dobutamine stress, 40 µg/kg/min max	25 patients after TOF repair	6-27 years	None	RVOT pulsed Doppler, tricuspid valve continuous Doppler, TDI at the lateral corner of the tricuspid valve annulus	Decreased TDI indices at rest, with a significant gradual increase during dobutamine. TDI indices correlate with functional RV parameters.
Brili[28]	Dobutamine stress, 40 µg/kg/min max	10 patients after Fontan operation	28 (5) years	None	2D and Doppler echocardiography: LVOT diameter and VTI, LVEDV, LVESV, LVEF, LVSV, CO, WMA	Feasibility and safety of the technique for assessment of global hemodynamics, propensity to arrhythmia and cardiac reserve.
Brili[35]	Dobutamine stress, 20 µg/kg/min max	21 patients after TOF repair	19-48 years	Non-sustained monomorphic VT of 15 beats at 20 µg/kg/min (n = 1)	TDI of the tricuspid valve annulus	Lower TDI indices at baseline and during dobutamine. TDI predicts RV contractile reserve at rest.

Ages are given as ranges, or mean (standard deviation).

Abbreviations: AR = aortic regurgitation; AS = aortic stenosis; ASD = atrial septal defect; ASO = arterial switch operation; AVR = aortic valve replacement; ccTGA = congenitally corrected transposition of the great arteries; CO = cardiac output; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HOCM = hypertrophic obstructive cardiomyopathy; LV = left ventricle; LVOT = left ventricular outflow tract; LVOTO = LVOT obstruction; PA = pulmonary artery; RV = right ventricle; RVOT = right ventricular outflow tract; SV = stroke volume; TDI = tissue Doppler imaging; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect; VT = ventricular tachycardia; VTI = velocity time integral; WMA = wall motion abnormalities.

Table 2: Stress cardiovascular magnetic resonance imaging in congenital heart disease

Study	Stressor	Patients	Age	Adverse effects	Measurements	Outcome
Tulevski[50]	Dobutamine, 15 µg/kg/min max	12 patients after atrial switch for TGA	18-28 years	None	Biventricular volumes, function	No increase in RVSV and decrease in LVSV with stress-testing.
Roest[9]	Supine bicycle exercise	10 patients after atrial switch for TGA	17-31 years	None	Biventricular volumes, function Ascending aorta flow	Prolonged SV recovery after supine bicycle exercise in patients after atrial switch for TGA.
Dodge-Khatami[51]	Dobutamine, 15 µg/kg/min max	13 patients with ccTGA	28 (12) years	None	Biventricular volumes, function	No increase in RVSV with DCMR. Five asymptomatic, unoperated patients had near normal volumes and adequate response to stress-testing.
Roest[8]	Supine bicycle exercise	15 patients after TOF repair	14-24 years	None	Pulmonary regurgitation Biventricular volumes, function	Decrease in pulmonary regurgitation with supine bicycle exercise. Abnormal RV response, normal LV response to exercise.
Tulevski[38]	Dobutamine, 15 µg/kg/min max	47 patients with RV pressure overload	26 (5) years	Dizziness, nausea (n = 3). Arrhythmia (n = 1)	Biventricular volumes, function	Clear heterogeneity in response to DCMR between different groups with chronic pressure overloaded RV.
Pedersen[16]	Supine bicycle exercise	11 patients after Fontan operation	11 (5)	None	Branch pulmonary artery and caval vein flow	During exercise: Unchanged flow distribution to the branch pulmonary arteries Increase in cardiac output predominantly by increase in heart rate.
Hjortdal[14]	Supine bicycle exercise	11 patients after Fontan operation	12 (5)	None	Real-time aorta and IVC and SVC flow	Feasibility of the technique. Aortic and IVC flow increase with supine leg exercise. Inspiration facilitates IVC flow at rest, less during exercise.
Tulevski[53]	Dobutamine, 5 µg/kg/min	13 patients with RV pressure overload 9 patients with RV pressure + volume overload	27 (7) years	None	RV volumes, function	During DCMR: significant decrease in RVEDV and RVSV, no increase in EF. Impaired RV filling during stress in asymptomatic or minimally symptomatic patients.

Table 2, continued.

Study	Stressor	Patients	Age	Adverse effects	Measurements	Outcome
Van der Zedde[54]	Dobutamine, 15 µg/kg/min max	13 patients with ccTGA 17 patients after atrial switch for TGA	17-65 years	None	Segmental and global ventricular function and volumes	At rest: TGA-patients have diminished segmental and global ventricular function. During stress: ccTGA-patients no increase in segmental and global ventricular function.
Oosterhof[52]	Dobutamine, 15 µg/kg/min max Supine bicycle exercise	39 patients after atrial switch for TGA:	25 (4) years	None	Segmental and global ventricular function and volumes	Dobutamine stress and physical exercise not interchangeably for assessment of systolic and diastolic function in patients with after atrial switch for TGA.
Taylor[26]	Adenosine, 0.14 mg/kg/min	15 patients with congenital AS 2 patients after ASO for TGA	9-17 years	None	Biventricular volumes, function	Feasibility of adenosine stress-testing for assessment of biventricular function during single breath-hold cine CMR.
Van den Berg[34]	Dobutamine, 7.5 µg/kg/min max	36 patients after TOF repair	7-23 years	Bigeminy (n = 1)	Biventricular volumes, function Pulmonary artery, tricuspid, and IVC flow	Abnormal relaxation with stress-testing in patients with end-diastolic forward flow.
Van den Berg[33]	Dobutamine, 7.5 µg/kg/min max	51 patients after TOF repair	7-26 years	None	Biventricular volumes, function Pulmonary artery and tricuspid flow	Biventricular functional reserve preserved in TOF repaired at young age, irrespective of RV volume.
Hjortdal[13]	Supine bicycle exercise	14 Fontan patients	9 (5) years	None	Aortic and caval vein flow	A similar increase in flow rates in Fontan patients as in healthy controls.
Fratz[36]	Dobutamine, 10 µg/kg/min max	12 patients after atrial switch for TGA 11 patients with ccTGA	15-28 years	Arrhythmias (n = 3)	Biventricular function, mass Aortic flow	Non increase in SV during dobutamine stress in patients after atrial switch for TGA. Increased SV in patients with ccTGA.
Robbers-Visser [31]	Dobutamine, 7.5 µg/kg/min max	32 patients after Fontan operation	8-22 years	Minor headache (n = 1)	Systemic ventricular volumes, function. Aortic and IVC flow	Abnormal decrease in EDV with stress-testing, adequate decrease in ESV and increase in EF.

Table 2, continued.

Study	Stressor	Patients	Age	Adverse effects	Measurements	Outcome
Robbers-Visser[32]	Dobutamine, 7.5 µg/kg/min max	14 patients after Fontan operation	8-20 years	None	Branch pulmonary artery flow	Flow variables, distensibility, and wall shear stress lower compared to controls; abnormal reaction to stress.
Strigl[30]	Dobutamine, atropine 40 µg/kg/min max	28 patients with (suspected) coronary artery abnormalities	0.8-22 years	None	Wall motion abnormalities	Feasibility of the technique with high observer agreement for test positivity (κ 1.0) and wall motion analysis (κ 0.72).

Ages are given as ranges, or mean (standard deviation).

Abbreviations: AS = aortic stenosis; ASO = arterial switch operation; CMR = cardiovascular magnetic resonance; ccTGA = congenitally corrected transposition of the great arteries; DCMR = dobutamine CMR; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; IVC = inferior caval vein; LV = left ventricle; RV = right ventricle; SV = stroke volume; SVC = superior caval vein; TGA = transposition of the great arteries; TOF = tetralogy of Fallot.

Using pharmacological stress with dobutamine at 7.5 μg/kg/min, we[32] demonstrated an abnormal decrease in end-diastolic volumes and no increase in stroke volumes with stress-testing in patients having conversion to the Fontan circulation at a young age. We also showed abnormal reactions of flow variables, distensibility, and wall shear stress with stress-testing in the pulmonary arteries[31]. These results demonstrate that low-dose dobutamine stress cardiovascular magnetic resonance imaging revealed abnormal findings that were not apparent at rest, and helped in understanding the pathophysiology of this group of patients, notably the progression of dysfunction during their follow-up.

In patients after atrial switch operation stroke volume did not increase with pharmacological stress-testing[36,38,50,52]. A smaller increase in stroke volume was noted in patients after the atrial switch when compared to healthy subjects, and a prolonged stroke volume recovery using supine bicycle exercise testing[9]. In patients after intra-atrial correction for transposition, heart rate increase is significantly higher when compared to patients with congenitally corrected transposition, or healthy subjects, probably as a compensatory mechanism for the lack of increase in stroke volume with stress-testing[36,38].

Recently, data has been published on the feasibility of high-dose dobutamine stress cardiovascular magnetic resonance imaging in children and young adults with suspected coronary arterial abnormalities by examination of abnormalities of mural motion[30]. No major adverse effects were found, and high-quality imaging was obtained in all ventricular mural segments in patients from less than 1 year of age. In only 1 patient was there an inducible abnormality, with the group recommending further exploration of high-dose dobutamine stress cardiovascular magnetic resonance in children.

The type of stressor should be taken into account when comparing the results of stress studies. One group[60] showed a different response in healthy volunteers to physical exercise and to dobutamine stress. Global and regional ejection fraction increased more with dobutamine than with physical exercise. Another group[52] demonstrated a discrepancy in response to physical exercise and low-dose dobutamine stress in patients after intra-atrial correction for transposition, whilst in controls the response to both stressors was comparable. They suggested that this disagreement was the result of differences in preload and afterload. Both dobutamine and physical exercise, however, increase contractility, and decrease preload and afterload[22,61]. There are also some differences in acquisition between the studies depending on dobutamine as opposed to physical exercise studies that might explain the discrepancies. Additional studies are needed to clarify this phenomenon.

Although the studies cited this far showed pathophysiologically relevant observations in patients with various types of congenital cardiac disease, the clinical significance of these abnormal responses still has to be assessed. In congenital cardiology, surrogate endpoints for clinical trials are necessary. Primary endpoints, such as death and major complications, are rare, requiring large study populations or prolonged study length to acquire adequate statistical power, while the population is relatively small[62]. Surrogate endpoints are expected to predict a primary endpoint, and have a higher incidence in the population under investigation. Thus, surrogate endpoints facilitate clinical trials in congenital cardiology by reducing the numbers of subjects needed and by reducing the

length of the study. The abnormal stress responses found in patients with congenital cardiac disease are potential surrogate endpoints for this purpose and their clinical usefulness has to be addressed in follow-up studies.

Future applications

As for echocardiography, standardized dobutamine stress cardiovascular magnetic resonance studies using identical stressors and identical methods of measurement are needed to determine the clinical relevance of the abnormal stress responses in patients with congenital cardiac disease. Such future applications might involve the assessment of pressure-volume loops. Pressure-volume loops give information on myocardial contractility, ventricular pump function, and ventriculo-arterial coupling, which might help explain the pathophysiological processes in cardiac function in patients with congenital cardiac disease[63]. The feasibility of magnetic resonance-derived pressure volume loops in the right ventricle of patients with chronic pressure overload has already been demonstrated[64].

Magnetic resonance tissue-tagging with radiofrequency signals destroys the spins in a selected plane, resulting in a line or grid of signal void on the image[65]. These lines or grids deform with ventricular contraction and relaxation and this allows quantification of strain, that is the deformation of an object normalized to its original shape, as a measure of regional myocardial function. In combination with stress-testing, this technique could reveal important regional functional information in patients with complex lesions. In patients with coronary arterial disease, the response of systolic strain to low-dose dobutamine has a significant promise in discriminating between viable and non-viable myocardium[66].

Lastly, in pathways with complex patterns of flow, such as the Fontan circulation, or intra-atrial baffles, 3-directional flow measurements can give important additional information on shear stress and energy dissipation and the influence of increased flow during stress on these variables.

Conclusions

Stress imaging is a tool that has been used in limited fashion in patients with congenitally malformed hearts when compared to its implementation in patients with coronary arterial disease. Several studies, nonetheless, have shown its feasibility and safety. Stress imaging is able to assess systolic, diastolic, and vascular responses in patients with various types of complex lesions. At present, magnetic resonance imaging has been used more often for this purpose than echocardiography. The clinical relevance of these findings needs to be investigated in standardized protocols. The abnormal stress responses can potentially be used for risk assessment in the follow-up of patients with congenital cardiac disease.

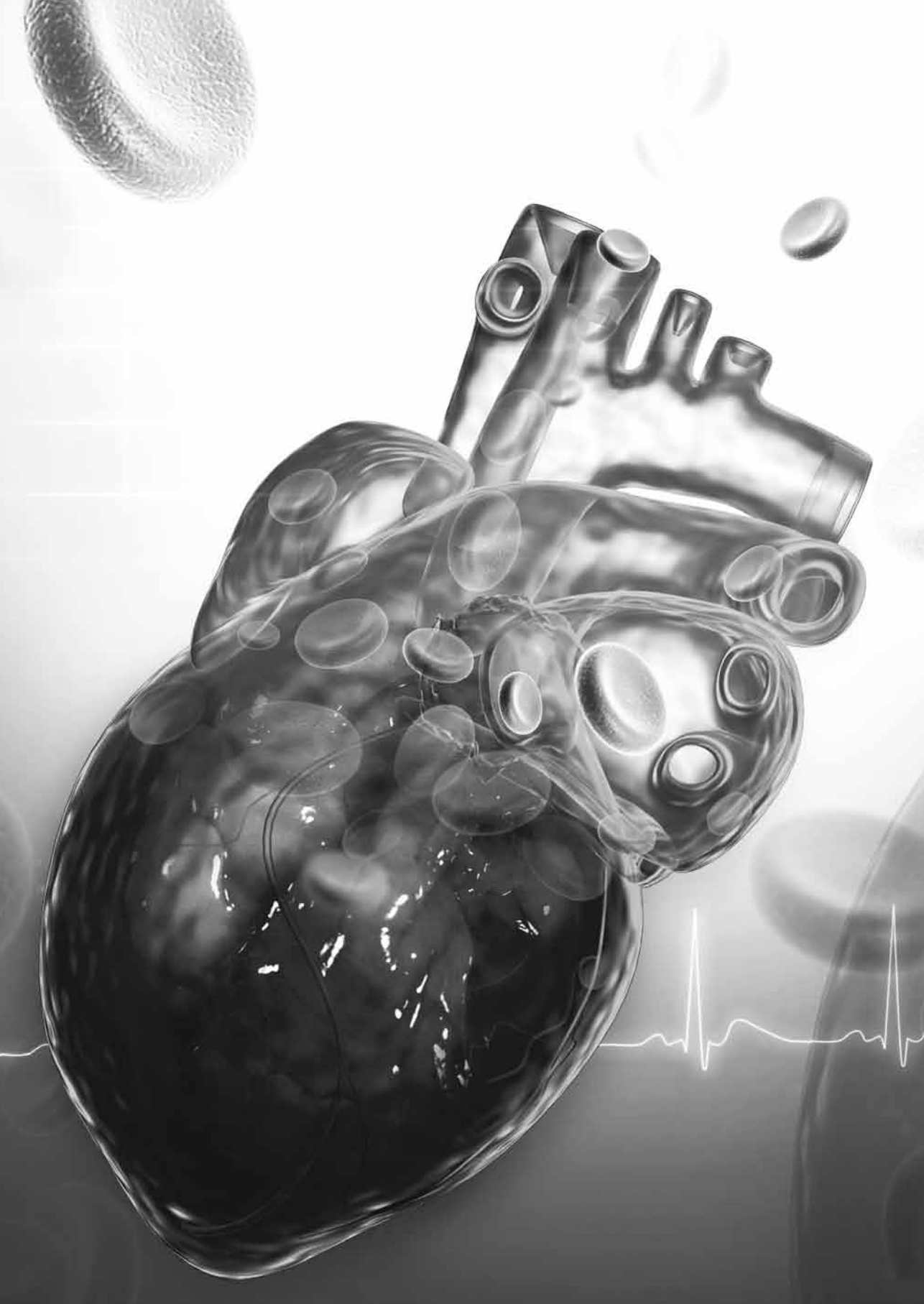
References

1. Wann LS, Faris JV, Childress RH, Dillon JC, Weyman AE, Feigenbaum H. Exercise cross-sectional echocardiography in ischemic heart disease. Circulation 1979;60:1300-1308.
2. Wahl A, Paetsch I, Gollesch A, et al. Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases. Eur Heart J 2004;25:1230-1236.
3. Jahnke C, Nagel E, Gebker R, et al. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007;115:1769-1776.
4. Kuijpers D, van Dijkman PR, Janssen CH, Vliegenthart R, Zijlstra F, Oudkerk M. Dobutamine stress MRI. Part II. Risk stratification with dobutamine cardiovascular magnetic resonance in patients suspected of myocardial ischemia. Eur Radiol 2004;14:2046-2052.
5. Wu WC, Bhavsar JH, Aziz GF, Sadaniantz A. An overview of stress echocardiography in the study of patients with dilated or hypertrophic cardiomyopathy. Echocardiography 2004;21:467-475.
6. Cheng CP, Herfkens RJ, Lightner AL, Taylor CA, Feinstein JA. Blood flow conditions in the proximal pulmonary arteries and vena cavae: healthy children during upright cycling exercise. Am J Physiol Heart Circ Physiol 2004;287:H921-926.
7. Alpert BS, Bloom KR, Olley PM. Assessment of left ventricular contractility during supine exercise in children with left-sided cardiac disease. Br Heart J 1980;44:703-710.
8. Roest AA, Helbing WA, Kunz P, et al. Exercise MR imaging in the assessment of pulmonary regurgitation and biventricular function in patients after tetralogy of fallot repair. Radiology 2002;223:204-211.
9. Roest AA, Kunz P, Helbing WA, et al. Prolonged cardiac recovery from exercise in asymptomatic adults late after atrial correction of transposition of the great arteries: evaluation with magnetic resonance flow mapping. Am J Cardiol 2001;88:1011-1017.
10. Cyran SE, Grzeszczak M, Kaufman K, et al. Aortic "recoarctation" at rest versus at exercise in children as evaluated by stress Doppler echocardiography after a "good" operative result. Am J Cardiol 1993;71:963-970.
11. Hauser M, Bengel FM, Kuhn A, et al. Myocardial blood flow and flow reserve after coronary reimplantation in patients after arterial switch and ross operation. Circulation 2001;103:1875-1880.
12. Kaplan JD, Foster E, Redberg RF, Schiller NB. Exercise Doppler echocardiography identifies abnormal hemodynamics in adults with congenital heart disease. Am Heart J 1994;127:1572-1580.
13. Hjortdal VE, Christensen TD, Larsen SH, Emmertsen K, Pedersen EM. Caval blood flow during supine exercise in normal and Fontan patients. Ann Thorac Surg 2008;85:599-603.
14. Hjortdal VE, Emmertsen K, Stenbog E, et al. Effects of exercise and respiration on blood flow in total cavopulmonary connection: a real-time magnetic resonance flow study. Circulation 2003;108:1227-1231.
15. Oyen EM, Ingerfeld G, Ignatzy K, Brode PE. Dynamic exercise echocardiography in children with congenital heart disease affecting the left heart. Int J Cardiol 1987;17:315-325.
16. Pedersen EM, Stenbog EV, Frund T, et al. Flow during exercise in the total cavopulmonary connection measured by magnetic resonance velocity mapping. Heart 2002;87:554-558.
17. Pedersen EM, Kozerke S, Ringgaard S, Scheidegger MB, Boesiger P. Quantitative abdominal aortic flow measurements at controlled levels of ergometer exercise. Magn Reson Imaging 1999;17:489-494.
18. Roest AA, Kunz P, Lamb HJ, Helbing WA, van der Wall EE, de Roos A. Biventricular response to supine physical exercise in young adults assessed with ultrafast magnetic resonance imaging. Am J Cardiol 2001;87:601-605.

19. Berthe C, Pierard LA, Hiernaux M, et al. Predicting the extent and location of coronary artery disease in acute myocardial infarction by echocardiography during dobutamine infusion. Am J Cardiol 1986;58:1167-1172.
20. Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A. High dose dipyridamole echocardiography test in effort angina pectoris. J Am Coll Cardiol 1986;8:848-854.
21. Berg RA, Padbury JF, Donnerstein RL, Klewer SE, Hutter JJ, Jr. Dobutamine pharmacokinetics and pharmacodynamics in normal children and adolescents. J Pharmacol Exp Ther 1993;265:1232-1238.
22. Michelfelder EC, Witt SA, Khoury P, Kimball TR. Moderate-dose dobutamine maximizes left ventricular contractile response during dobutamine stress echocardiography in children. J Am Soc Echocardiogr 2003;16:140-146.
23. Harada K, Tamura M, Ito T, Suzuki T, Takada G. Effects of low-dose dobutamine on left ventricular diastolic filling in children. Pediatr Cardiol 1996;17:220-225.
24. De Wolf D, Suys B, Verhaaren H, Matthys D, Taeymans Y. Low-Dose Dobutamine Stress Echocardiography in Children and Young Adults. The American Journal of Cardiology 1998;81:895-901.
25. Noto N, Ayusawa M, Karasawa K, et al. Dobutamine stress echocardiography for detection of coronary artery stenosis in children with Kawasaki disease. J Am Coll Cardiol 1996;27:1251-1256.
26. Taylor AM, Dymarkowski S, De Meerleer K, et al. Validation and application of single breath-hold cine cardiac MR for ventricular function assessment in children with congenital heart disease at rest and during adenosine stress. J Cardiovasc Magn Reson 2005;7:743-751.
27. Apostolopoulou S, Laskari C, Tsoutsinos A, Rammos S. Doppler Tissue Imaging Evaluation of Right Ventricular Function at Rest and During Dobutamine Infusion in Patients After Repair of Tetralogy of Fallot. The International Journal of Cardiovascular Imaging (formerly Cardiac Imaging) 2007;23:25-31.
28. Brili SV, Alexopoulos NA, Barberis VI, et al. Dobutamine stress echocardiography for the evaluation of cardiac reserve late after Fontan operation. Hellenic J Cardiol 2007;48:252-257.
29. Li W, Hornung TS, Francis DP, et al. Relation of biventricular function quantified by stress echocardiography to cardiopulmonary exercise capacity in adults with Mustard (atrial switch) procedure for transposition of the great arteries. Circulation 2004;110:1380-1386.
30. Strigl S, Beroukhim R, Valente AM, et al. Feasibility of dobutamine stress cardiovascular magnetic resonance imaging in children. J Magn Reson Imaging 2009;29:313-319.
31. Robbers-Visser D, Helderman F, Strengers JL, et al. Pulmonary artery size and function after Fontan operation at a young age. J Magn Reson Imaging 2008;28:1101-1107.
32. Robbers-Visser D, Jan ten Harkel D, Kapusta L, et al. Usefulness of Cardiac Magnetic Resonance Imaging Combined With Low-Dose Dobutamine Stress to Detect an Abnormal Ventricular Stress Response in Children and Young Adults After Fontan Operation at Young Age. The American Journal of Cardiology 2008;101:1657-1662.
33. van den Berg J, Strengers JLM, Wielopolski PA, et al. Assessment of biventricular functional reserve and NT-proBNP levels in patients with RV volume overload after repair of tetralogy of Fallot at young age. Int J of Cardiol 2009;133:364-370.
34. van den Berg J, Wielopolski PA, Meijboom FJ, et al. Diastolic function in repaired tetralogy of Fallot at rest and during stress: assessment with MR imaging. Radiology 2007;243:212-219.
35. Brili S, Stamatopoulos I, Barbetseas J, et al. Usefulness of dobutamine stress echocardiography with Tissue Doppler imaging for the evaluation and follow-up of patients with repaired tetralogy of Fallot. J Am Soc Echocardiogr 2008;21:1093-1098.
36. Fratz S, Hager A, Busch R, et al. Patients after atrial switch operation for transposition of the great arteries can not increase stroke volume under dobutamine stress as opposed to patients with congenitally corrected transposition. Circ J 2008;72:1130-1135.

37. Hui L, Chau AK, Leung MP, Chiu CS, Cheung YF. Assessment of left ventricular function long term after arterial switch operation for transposition of the great arteries by dobutamine stress echocardiography. Heart 2005;91:68-72.
38. Tulevski, II, van der Wall EE, Groenink M, et al. Usefulness of magnetic resonance imaging dobutamine stress in asymptomatic and minimally symptomatic patients with decreased cardiac reserve from congenital heart disease (complete and corrected transposition of the great arteries and subpulmonic obstruction). Am J Cardiol 2002;89:1077-1081.
39. Vesely MR, Dilsizian V. Nuclear cardiac stress testing in the era of molecular medicine. J Nucl Med 2008;49:399-413.
40. Bengel FM, Hauser M, Duvernoy CS, et al. Myocardial blood flow and coronary flow reserve late after anatomical correction of transposition of the great arteries. J Am Coll Cardiol 1998;32:1955-1961.
41. Donnelly JP, Raffel DM, Shulkin BL, et al. Resting coronary flow and coronary flow reserve in human infants after repair or palliation of congenital heart defects as measured by positron emission tomography. J Thorac Cardiovasc Surg 1998;115:103-110.
42. Fukuda T, Ishibashi M, Shinohara T, Miyake T, Kudoh T, Saga T. Follow-up assessment of the collateral circulation in patients with Kawasaki disease who underwent dipyridamole stress technetium-99m tetrofosmin scintigraphy. Pediatr Cardiol 2005;26:558-564.
43. Hauser M, Bengel F, Kuehn A, et al. Myocardial blood flow and coronary flow reserve in children with "normal" epicardial coronary arteries after the onset of Kawasaki disease assessed by positron emission tomography. Pediatr Cardiol 2004;25:108-112.
44. Hauser M, Bengel FM, Kuhn A, et al. Myocardial perfusion and coronary flow reserve assessed by positron emission tomography in patients after Fontan-like operations. Pediatr Cardiol 2003;24:386-392.
45. Karasawa K, Miyashita M, Taniguchi K, et al. Detection of myocardial contractile reserve by low-dose dobutamine quantitative gated single-photon emission computed tomography in patients with Kawasaki disease and severe coronary artery lesions. Am J Cardiol 2003;92:865-868.
46. Helbing WA, Bosch HG, Maliepaard C, et al. Comparison of echocardiographic methods with magnetic resonance imaging for assessment of right ventricular function in children. Am J Cardiol 1995;76:589-594.
47. Hirsch R, Kilner PJ, Connelly MS, Redington AN, St John Sutton MG, Somerville J. Diagnosis in adolescents and adults with congenital heart disease. Prospective assessment of individual and combined roles of magnetic resonance imaging and transesophageal echocardiography. Circulation 1994;90:2937-2951.
48. Pennell DJ, Underwood SR, Manzara CC, et al. Magnetic resonance imaging during dobutamine stress in coronary artery disease. Am J Cardiol 1992;70:34-40.
49. Paetsch I, Jahnke C, Wahl A, et al. Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance perfusion. Circulation 2004;110:835-842.
50. Tulevski, II, Lee PL, Groenink M, et al. Dobutamine-induced increase of right ventricular contractility without increased stroke volume in adolescent patients with transposition of the great arteries: evaluation with magnetic resonance imaging. Int J Card Imaging 2000;16:471-478.
51. Dodge-Khatami A, Tulevski II, Bennink GBWE, et al. Comparable systemic ventricular function in healthy adults and patients with unoperated congenitally corrected transposition using MRI dobutamine stress testing. The Annals of Thoracic Surgery 2002;73:1759-1764.
52. Oosterhof T, Tulevski, II, Roest AA, et al. Disparity between dobutamine stress and physical exercise magnetic resonance imaging in patients with an intra-atrial correction for transposition of the great arteries. J Cardiovasc Magn Reson 2005;7:383-389.

53. Tulevski, II, Hirsch A, Dodge-Khatami A, Stoker J, van der Wall EE, Mulder BJ. Effect of pulmonary valve regurgitation on right ventricular function in patients with chronic right ventricular pressure overload. Am J Cardiol 2003;92:113-116.
54. van der Zedde J, Oosterhof T, Tulevski, II, Vliegen HW, Mulder BJ. Comparison of segmental and global systemic ventricular function at rest and during dobutamine stress between patients with transposition and congenitally corrected transposition. Cardiol Young 2005;15:148-153.
55. Donofrio MT, Kakavand B, Moskowitz WB. Evaluation of regional wall motion and quantitative measures of ventricular function during dobutamine stress echocardiography in pediatric cardiac transplantation patients. J Am Soc Echocardiogr 2000;13:932-940.
56. Hui L, Leung MP, Ha SY, Chau AK, Cheung YF. Early detection of left ventricular dysfunction in patients with beta thalassaemia major by dobutamine stress echocardiography. Heart 2003;89:669-670.
57. Lanzarini L, Bossi G, Laudisa ML, Klersy C, Arico M. Lack of clinically significant cardiac dysfunction during intermediate dobutamine doses in long-term childhood cancer survivors exposed to anthracyclines. Am Heart J 2000;140:315-323.
58. Larsen RL, Applegate PM, Dyar DA, et al. Dobutamine stress echocardiography for assessing coronary artery disease after transplantation in children. J Am Coll Cardiol 1998;32:515-520.
59. Valsangiacomo Buechel ER, Dave HH, Kellenberger CJ, et al. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. Eur Heart J 2005;26:2721-2727.
60. Coma-Canella I, Garcia Velloso MJ, Maceira A, et al. [Isotopic ventriculography in healthy young volunteers. Their response to different types of stress]. Ventriculografia isotopica en voluntarios jovenes sanos. Respuesta a diferentes tipos de estres. Rev Esp Cardiol 1997;50:709-714.
61. Kimball TR, Mays WA, Khoury PR, Mallie R, Claytor RP. Echocardiographic determination of left ventricular preload, afterload, and contractility during and after exercise. J Pediatr 1993;122:S89-94.
62. Mahony L, Sleeper LA, Anderson PA, et al. The Pediatric Heart Network: a primer for the conduct of multicenter studies in children with congenital and acquired heart disease. Pediatr Cardiol 2006;27:191-198.
63. Derrick GP, Narang I, White PA, et al. Failure of stroke volume augmentation during exercise and dobutamine stress is unrelated to load-independent indexes of right ventricular performance after the Mustard operation. Circulation 2000;102:III154-159.
64. Kuehne T, Yilmaz S, Steendijk P, et al. Magnetic resonance imaging analysis of right ventricular pressure-volume loops: in vivo validation and clinical application in patients with pulmonary hypertension. Circulation 2004;110:2010-2016.
65. Fogel MA. Assessment of cardiac function by magnetic resonance imaging. Pediatr Cardiol 2000;21:59-69.
66. Bree D, Wollmuth JR, Cupps BP, et al. Low-dose dobutamine tissue-tagged magnetic resonance imaging with 3-dimensional strain analysis allows assessment of myocardial viability in patients with ischemic cardiomyopathy. Circulation 2006;114:I33-I36.



Chapter 7b

Safety and observer variability of cardiac magnetic resonance imaging combined with low-dose dobutamine stress-testing in patients with complex congenital heart disease

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Abstract

Introduction: In patients with complex congenital heart disease (CHD), abnormal ventricular stress responses have been reported with dobutamine stress cardiovascular magnetic resonance (DCMR). These abnormal stress responses are potential indicators of long-term outcome. However, safety and reproducibility of this technique has not been reported in a larger study. The aim of this study was to report our experiences regarding safety and intra-observer and interobserver variability of low-dose DCMR in complex CHD.

Methods: In 91 patients, 110 low-dose DCMR studies were performed with acquisition of a short axis set at rest, and during dobutamine administration (7.5 µg/kg/min maximum). We assessed biventricular end-diastolic volumes, end-systolic volumes, stroke volumes, ejection fraction and ventricular mass. Intra- and interobserver variability for all variables was assessed by calculating the coefficient of variation (%), i.e. the standard deviation of the difference divided by the mean of 2 measurements multiplied by 100%.

Results: In 3 patients minor side effects occurred (vertigo, headache, and bigeminy). Ten patients experienced an increase in heart rate of >150% from baseline, although well tolerated. For all variables, intra-observer variability was < 10% at rest and during stress. At rest, interobserver variability was 10.5% maximal. With stress-testing, only the variability of biventricular end-systolic volumes (ESV) exceeded 10%.

Conclusions: In patients with complex CHD, low-dose DCMR is feasible, and safe. Intra-observer variability is low for rest and stress measurements. Interobserver variability of biventricular ESV is high with stress-testing. Whether this limits the potential usefulness of DCMR for risk assessment during follow-up has to be assessed.

Introduction

Assessment of ventricular function with stress-testing is safe and widely applied in adult patients with coronary artery disease[1]. It is used to study wall motion abnormalities under stress conditions. Stress-testing is able to reveal symptoms not apparent at rest, and can give information on prognostic factors[1-3]. Dobutamine stress echocardiography has been widely used for this purpose, and its use has been extended to pediatric patients with coronary artery abnormalities, e.g. patients after Kawasaki disease or after arterial switch operation for transposition of the great arteries[4-5]. Stress echocardiography has several limitations, such as poor acoustic windowing, high interobserver variability, and high interoperator variability[6]. Cardiovascular magnetic resonance (CMR) imaging combined with dobutamine stress (DCMR) can overcome these limitations and has a higher sensitivity and specificity for identifying coronary artery disease as compared to dobutamine stress echocardiography[7].

In patients with complex congenital heart disease (CHD), several groups have studied the stress response of the heart, predominantly looking at the change in ventricular volumes and ejection fraction during stress-testing. Wall motion analysis is of lesser importance in this patient group with few coronary artery abnormalities. In several small studies abnormal stress responses of ventricular and vascular function have been reported[8-18]. These abnormal stress responses are of special interest since they are potential surrogate markers related to primary endpoints relevant for assessment of long-term outcome, such as death or functional impairment.

Although the clinical usefulness of the abnormal stress responses in patients with complex CHD with DCMR imaging still has to be assessed in follow-up studies, it is important to know the reliability of the measurements and the safety of the technique. The intra-observer and interobserver variability of CMR measurements of biventricular function, volumes, and mass have been assessed in patients and controls at rest and multiple studies have shown a good reproducibility of these measurements[19-20]. Reproducibility of these measurements obtained during stress-testing in patients with complex CHD has only been assessed in one study[12]. The objective of this study was to assess the intra-observer and interobserver variability, and, in addition, to report on the adverse effects of low-dose DCMR imaging in pediatric and adult patients with complex CHD.

Materials and Methods

Patients

We included 91 patients who had undergone 110 low-dose DCMR studies between September 2002 and August 2008. Most of these studies were performed in research protocols and the results of ventricular and vascular responses have been previously published[11-12,16-17]. Low-

dose DCMR studies that were performed for research purposes conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a *priori* approval by the Dutch Central Committee on Research involving Human Subjects and the institutional review board. All subjects and/or their parents (if required) gave written informed consent. The study group included 54 patients after repair of tetralogy of Fallot, and 37 patients with a functionally univentricular heart after Fontan operation[11-12,16-17]. Characteristics of the study population are displayed in Tables 1 and 2. Median age at study was 14.2 (6.8 – 25.5) years. We obtained patient demographics, diagnosis, maximal dobutamine dosage, and occurrence of adverse effects.

Table 1: Patient and study characteristics

Characteristic	**Patients**
Number (male)	91 (63)
Tetralogy of Fallot / Fontan (n)	54 / 37
Age at 1st study (years)	14.2 (6.8 – 25.5)
Follow-up since repair / palliation (years)	12.5 (5.1)
Repeat studies (n)	19
Interval 1st and 2nd study (years)	5.0 (0.3)
Systolic blood pressure rest (mm Hg)	115 (9)
Systolic blood pressure stress (mm Hg)	133 (14)
Heart rate rest (beats per minute)	75 (13)
Heart rate stress (beats per minute)	91 (17)
Adverse effects (n)	3
Vertigo (n)	1
Bigeminy (n)	1
Minor headache (n)	1
Studies discontinued (n)	2
Dobutamine lowered to 5 µg/kg/min (n)	10

Results are expressed as frequencies, median (range), or mean (standard deviation) as appropriate.

Table 2: Diagnoses in patients after Fontan operation

Diagnosis	Number
Tricuspid atresia	10
Pulmonary atresia / intact ventricular septum	3
Double inlet left ventricle	6
Double outlet right ventricle	7
Hypoplastic left heart syndrome	5
Other complex CHD	6

CMR study

The study protocol and image analysis have been previously reported[11-12,16-17]. In summary, all patients underwent CMR imaging at a Signa 1.5 Tesla whole-body MR imaging system (General Electric, Milwaukee, WI, USA). A multi-phase, multi-slice volumetric data-set was acquired using a fast 2D cine scan employing steady-state free precession. Contiguous slices were planned starting at and parallel to the atrioventricular valve plane of the systemic ventricle to cover the heart from base to apex. Imaging parameters: slice thickness 7 to 10 mm, inter-slice gap 0 mm, field of view 280 – 370 mm, phase field of view 0.75, matrix 160 x 128 mm, repetition time 3.5 msec, echo time 1.5 msec, 12 views/segment, flip angle 45°, mean in-plane resolution 2 mm^2, range of temporal resolution 22 – 37 msec. When the study protocol had been completed at rest, dobutamine-hydrochloride (Centrafarm Services, Etten-Leur, the Netherlands) was administered by continuous infusion into a large antecubital vein at 7.5 μg/kg/min. In healthy children important changes in systolic function, diastolic function, and afterload occur from 5 μg/kg/min, and the incidence rate of adverse symptoms increases significantly from 10 μg/kg/min[21-22]. Therefore, a dobutamine dosage of 7.5 μg/kg/min was considered safe and effective. When heart rate and blood pressure were at steady state, a second short-axis stack was acquired. Dobutamine infusion was lowered to 5 μg/kg/min whenever heart rate, systolic blood pressure, or diastolic blood pressure increased to more than 150% from baseline or decreased to less than 80% from baseline. The test was discontinued in the event of arrhythmias or significant patient discomfort. Dobutamine was administered for 10 minutes to reach a new steady-state and another 10 minutes for image acquisition.

Image analysis

From the short-axis set, biventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), and mass were assessed with manual contour detection. Criteria for border detection have been previously described[23]. For intra-observer

variability, 25 randomly selected studies (15 tetralogy of Fallot, 10 Fontan studies) were reanalyzed after a mean period of 11 months (SD 11, range 1 – 38 months). For interobserver variability, a second experienced observer analyzed these 25 studies and measured the aforementioned parameters independently and blinded to previous results. The 2 observers who were involved in these analyses (DR-V and SEL) have 3.5 years and 1.5 years CMR experience in patients with complex CHD respectively.

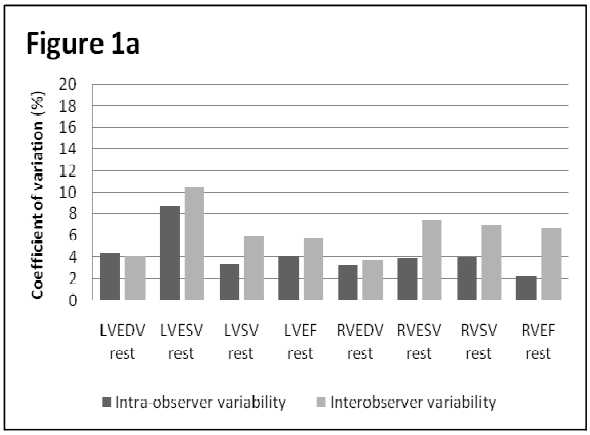
Statistical analysis

Data with a normal distribution are expressed as mean value ± one standard deviation, whereas the median (range) is shown for data with a non-normal distribution. Dichotomous data are presented as counts and percentages. Intra- and interobserver variability were assessed using the method of Bland-Altman[24]. The coefficient of variation, i.e. the standard deviation of the difference of the 2 measurements divided by the mean of the 2 measurements, and multiplied by 100%, was calculated to study the percentage of variability of the measurements. A p-value < 0.05 was considered to indicate statistical significance.

Results

Minor side effects occurred in 3 patients. In one patient with vertigo, the CMR study was discontinued subsequently. Another patient with bigeminy completed the first study. Due to inadequate triggering during the bigeminy, images were of insufficient quality for analysis. She experienced the same side effect during a repeat study 5 years later and the study was discontinued for this reason. One patient with minor headache completed the whole study. All side effects disappeared shortly after discontinuation of dobutamine administration. In 10 Fontan patients, dobutamine was lowered to 5 μg/kg/min because of an increase in heart rate of more than 150% from baseline, although this was well tolerated. In conclusion, of 110 studies 2 studies were discontinued because of minor side effects, only 1 study was of insufficient image quality.

Tables 3 and 4 show the intra-observer and interobserver variability for the rest and stress measurements. At rest, intra-observer variability was good with the coefficient of variation between 2.3% and 8.7% (Figure 1a). During stress-testing, intra-observer variability was between 3.0% and 7.0%. The highest variation was found in biventricular ESV and mass. At rest, interobserver variability was between 3.6% and 10.5% and again, the highest variation in biventricular ESV and mass. With stress-testing, the coefficient of variation of all variables stayed < 10%, except for biventricular ESV. The latter increased to ≥ 14.9%, which was significantly higher compared to the rest measurements ($p = 0.04$ for intra-observer variability, $p = 0.004$ for interobserver variability) (Figure 1b).



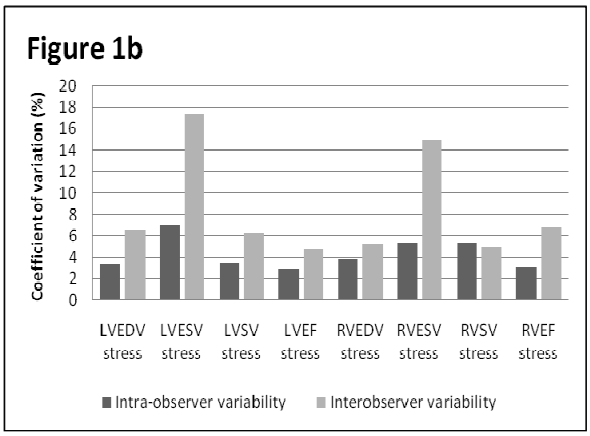


Figure 1: Bar charts of the coefficients of variation for rest (1a) and stress (1b) measurements.

Table 3: Intra- and interobserver variability analysis of rest measurements

	LV-EDV	LV-ESV	LV-SV	LV-EF	LV-mass	RV-EDV	RV-ESV	RV-SV	RV-EF	RV-mass
Intraobserver variability										
Mean value	87 (25)	37 (13)	51 (14)	58 (7)	69 (20)	133 (28)	65 (17)	69 (15)	52 (6)	25 (6)
Mean difference	1.2 (3.4)	1.2 (3.0)	-0.1 (1.6)	-0.7 (2.4)	-0.5 (5.2)	-1.2 (4.2)	0.9 (2.8)	-2.1 (2.2)	-1.2 (1.2)	0.5 (1.9)
Limits of agreement	-5.6 to 8.0	-4.8 to 7.2	-3.3 to 3.1	-5.5 to 4.1	-10.9 to 9.9	-9.6 to 7.2	-4.7 to 6.5	-6.5 to 2.3	-3.6 to 1.2	-3.3 to 4.3
Coefficient of variation	4.3%	8.7%	3.3%	4.1%	6.6%	3.2%	3.9%	4.0%	2.3%	7.3%
Inter-observer variability										
Mean difference	-0.4 (3.8)	0.5 (3.4)	-1.0 (2.7)	-0.8 (3.3)	0.9 (6.1)	3.7 (4.7)	3.7 (4.1)	-0.09 (4.1)	-2.0 (3.5)	0.6 (2.2)
Limits of agreement	-10.8 to 10.4	-10.2 to 12.6	-10.2 to 7.4	-7.4 to 6.6	-20.3 to 20.9	-8.8 to 22.4	-8.4 to 22.4	-15.3 to 14.7	-9.0 to 5.0	-6.1 to 8.7
Coefficient of variation	4.1%	10.5%	5.9%	5.7%	10.5%	3.6%	7.3%	6.9%	6.7%	9.0%

Results are expressed as mean (standard deviation).

Volumetric variables in ml/m^2, mass in g/m^2.

Abbreviations: LV = left ventricular; RV = right ventricular.

Table 4: Intra- and interobserver variability analysis of stress measurements

	LV-EDV	LV-ESV	LV-SV	LV-EF	RV-EDV	RV-ESV	RV-SV	RV-EF
Intraobserver variability								
Mean value	78 (26)	23 (10)	55 (19)	71 (7)	121 (27)	44 (13)	76 (18)	64 (6)
Mean difference	0.8 (2.4)	0.6 (1.3)	0.2 (1.9)	-0.8 (2.1)	-0.5 (4.6)	-0.2 (2.4)	-0.4 (4.2)	-0.2 (2.0)
Limits of agreement	-4.0 to 5.6	-2.0 to 3.2	-3.7 to 4.0	-5.0 to 3.4	-9.7 to 8.7	-5.0 to 4.6	-8.8 to 8.0	-4.2 to 3.8
Coefficient of variation	3.4%	7.0%	3.6%	3.0%	3.8%	5.4%	5.4%	3.1%
Inter-observer variability								
Mean difference	-0.7 (5.2)	-0.4 (4.1)	-0.2 (2.9)	0.06 (3.4)	-0.5 (5.4)	-0.3 (5.6)	-0.2 (3.2)	-0.3 (4.4)
Limits of agreement	-11.1 to 9.7	-8.6 to 7.8	-6.0 to 5.6	-6.8 to 6.8	-11.3 to 10.3	-11.5 to 10.9	-6.6 to 6.2	-9.1 to 8.5
Coefficient of variation	6.6%	17.4%	6.3%	4.8%	5.3%	14.9%	5.0%	6.9%

Results are expressed as mean (standard deviation).

Volumetric variables in ml/m^2, mass in g/m^2.

Abbreviations: LV = left ventricular; RV = right ventricular.

Discussion

Although the first report on stress imaging in patients with CHD involved echocardiography[25], its implementation has been largely hampered by the limitations of the acoustic window that occur in this patient group. Suboptimal image acquisition and suboptimal image quality are common in patients with complex cardiac anatomy. Combined with an abnormal orientation of the heart and great vessels in the chest, and the problems encountered in imaging the single and right ventricle[26-27], this has led to limited use of stress echocardiography in CHD. CMR imaging overcomes these limitations in this patient group. In this report, we demonstrated the feasibility of low-dose DCMR imaging in selected pediatric and adult patients with complex CHD. Intra-observer and interobserver variability for biventricular function, volumes, and mass were good. In addition, low-dose DCMR imaging was safe, with a low incidence of minor adverse effects.

In this study, the incidence of adverse effects was 4%. The reported effects (bigeminy, headache, and vertigo) were not severe, and all disappeared shortly after discontinuation of dobutamine administration. Major side effects, such as ventricular arrhythmias or even death, have been described in adult patients with coronary artery disease, receiving high doses of dobutamine of up to 40 μg/kg/min[1,3]. High-dose dobutamine stress imaging is rarely used in children and patients with CHD[13,28-30]. It is usually performed to induce wall motion abnormalities in patients with coronary artery abnormalities[5,13]. In both echocardiographic and CMR studies, no major side effects have been reported in pediatric patients using high-dose dobutamine. However, minor side effects, such as headache and nausea, have been reported in up to 20%[5]. DCMR imaging has been combined with low-dose dobutamine stress-testing in patients with complex CHD in most studies[8-12,14-18].

In other studies performing low-dose dobutamine stress imaging in patients with CHD, the reported incidence of arrhythmias is low. Of these, all occurred with a dobutamine dosage of ≥ 10 μg/kg/min, as has been demonstrated in healthy children[9,15,28]. In the study by Fratz et al. 3 of 23 patients experienced arrhythmias at 10 μg/kg/min, that disappeared at 5 μg/kg/min[9]. In another study, the reported arrhythmia occurred at a dobutamine dosage of 15 μg/kg/min necessitating termination of that particular DCMR study[15]. At a dobutamine dosage of 20 μg/kg/min, 1 of 21 patients with tetralogy of Fallot had a monomorphic non-sustained ventricular tachycardia of 15 beats[28].

Different dobutamine dosages are used in other studies performing low-dose DCMR imaging in patients with CHD, ranging from 5 to 15 μg/kg/min[8-10,14-15,18]. In our experience, a dobutamine dosage of 7.5 μg/kg/min is safe, with a low incidence of only minor adverse effects. It is high enough to elicit a significant cardiovascular response and to demonstrate abnormal stress responses in patients with CHD[11-12,16-17]. Although in 27% of Fontan patients dobutamine was lowered to 5 μg/kg/min because of an increase in heart rate of > 150% from baseline, we do not think this is a contra-indication for this dosage in these patients since it was well tolerated without patient discomfort. Standardization of low-dose dobutamine stress protocols will facilitate comparison of different stress responses in different types of CHD.

Intra-observer and interobserver variability of biventricular function, volumes, and mass with CMR imaging at rest have been reported in healthy subjects and in patients with tetralogy of Fallot[19-20,23]. The results of these studies are comparable to our results in Table 3. When comparing intra-observer variability of rest and stress measurements, in general, the variability of LV measurements was lower during stress-testing, and the variability of RV measurements was somewhat higher during stress-testing, but still <10%. Interobserver variability of biventricular SV and EF improved with stress-testing or was comparable to the rest measurements. Interobserver variability of biventricular EDV and ESV was higher with stress-testing, with the highest increase in the variability for biventricular ESV (Figure 1, Tables 3 and 4). This was an unexpected finding as we observed a better blood-myocardial contrast in end-systole during stress-testing when compared to rest. This could be explained by the fact that with increased heart rates during stress-testing, there is a faster inflow of unsaturated blood into the region of interest which will yield more signal during acquisition. However, during stress-testing, biventricular ESV decreased significantly, so that small differences in consecutive measurements (with a comparable standard deviation of the difference for LVESV at rest and during stress), result in an increase in the coefficient of variation. For clinical evaluation, EDV and EF are important parameters to study cardiac functional status with MRI in patients with CHD[31-32]. Therefore, with the current experiences, we do not think the higher variability of biventricular ESV during stress-testing limits the potential clinical usefulness of low-dose DCMR imaging. However, as stated before, the clinical usefulness of the abnormal stress responses in patients with complex CHD with DCMR imaging still has to be assessed and it might be possible that the stress response of RVESV or LVESV turns out to be an interesting parameter. The use of reliable automatic contour detection, that is not available for complex CHD up until now, will be an important improvement in diminishing observer variability.

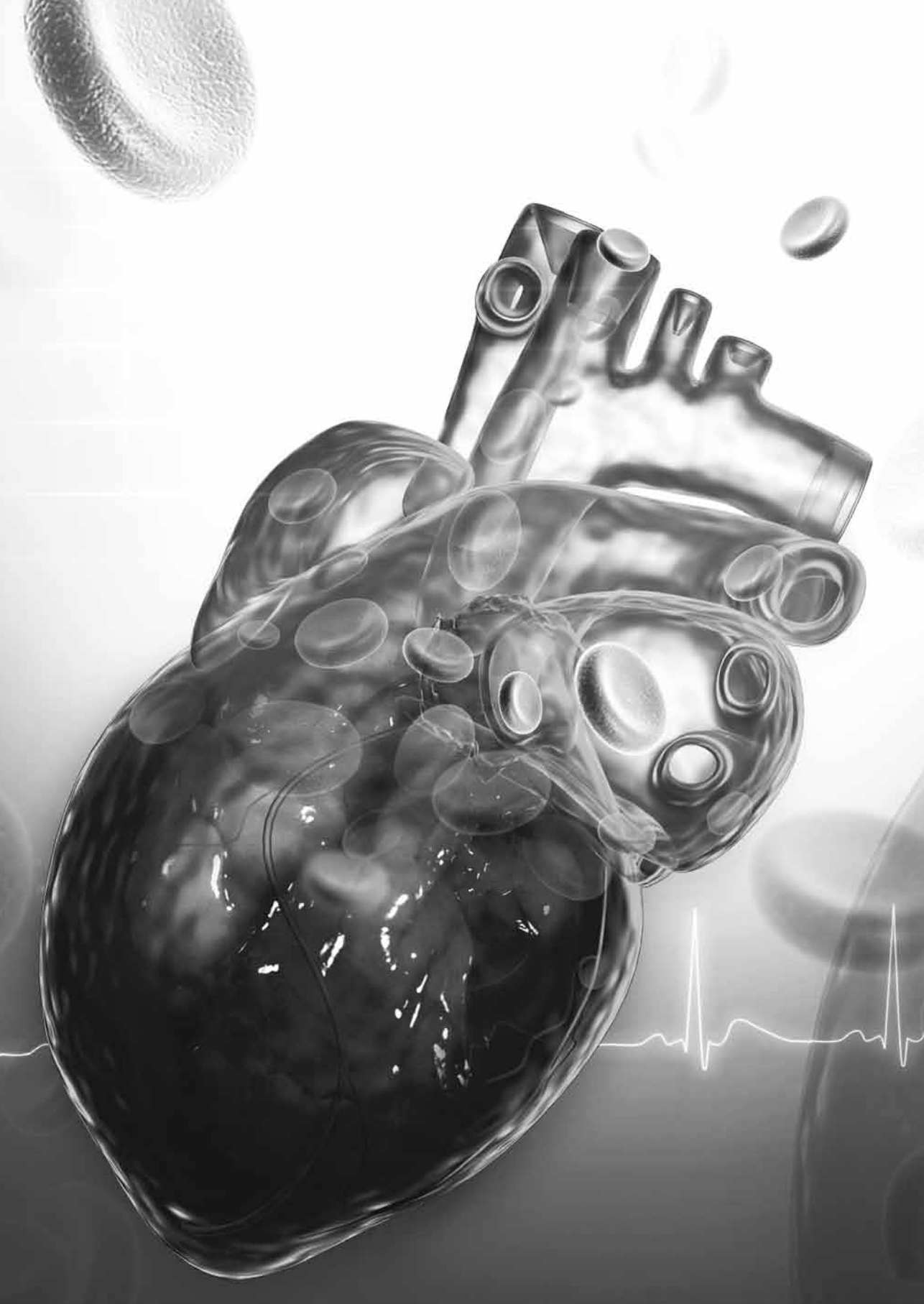
Conclusions

In patients with complex CHD, CMR imaging combined with low-dose dobutamine stress-testing is feasible, safe, and can be performed in selected pediatric and adult patients. Intra-observer variability is low for both rest and stress measurements. With stress-testing, interobserver variability of biventricular ESV increases significantly. Whether this limits the potential usefulness of DCMR imaging for risk assessment during follow-up has to be assessed.

References

1. Wahl A, Paetsch I, Gollesch A, et al. Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases. Eur Heart J 2004;25:1230-1236.
2. Jahnke C, Nagel E, Gebker R, et al. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007;115:1769-1776.
3. Kuijpers D, van Dijkman PR, Janssen CH, Vliegenthart R, Zijlstra F, Oudkerk M. Dobutamine stress MRI. Part II. Risk stratification with dobutamine cardiovascular magnetic resonance in patients suspected of myocardial ischemia. Eur Radiol 2004;14:2046-2052.
4. Hauser M, Bengel FM, Kuhn A, et al. Myocardial blood flow and flow reserve after coronary reimplantation in patients after arterial switch and ross operation. Circulation 2001;103:1875-1880.
5. Noto N, Ayusawa M, Karasawa K, et al. Dobutamine stress echocardiography for detection of coronary artery stenosis in children with Kawasaki disease. J Am Coll Cardiol 1996;27:1251-1256.
6. Mandapaka S, Hundley WG. Dobutamine cardiovascular magnetic resonance: a review. J Magn Reson Imaging 2006;24:499-512.
7. Nagel E, Lehmkuhl HB, Bocksch W, et al. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. Circulation 1999;99:763-770.
8. Dodge-Khatami A, Tulevski II, Bennink GBWE, et al. Comparable systemic ventricular function in healthy adults and patients with unoperated congenitally corrected transposition using MRI dobutamine stress testing. The Annals of Thoracic Surgery 2002;73:1759-1764.
9. Fratz S, Hager A, Busch R, et al. Patients after atrial switch operation for transposition of the great arteries can not increase stroke volume under dobutamine stress as opposed to patients with congenitally corrected transposition. Circ J 2008;72:1130-1135.
10. Oosterhof T, Tulevski, II, Roest AA, et al. Disparity between dobutamine stress and physical exercise magnetic resonance imaging in patients with an intra-atrial correction for transposition of the great arteries. J Cardiovasc Magn Reson 2005;7:383-389.
11. Robbers-Visser D, Helderman F, Strengers JL, et al. Pulmonary artery size and function after Fontan operation at a young age. J Magn Reson Imaging 2008;28:1101-1107.
12. Robbers-Visser D, Jan ten Harkel D, Kapusta L, et al. Usefulness of Cardiac Magnetic Resonance Imaging Combined With Low-Dose Dobutamine Stress to Detect an Abnormal Ventricular Stress Response in Children and Young Adults After Fontan Operation at Young Age. The American Journal of Cardiology 2008;101:1657-1662.
13. Strigl S, Beroukhim R, Valente AM, et al. Feasibility of dobutamine stress cardiovascular magnetic resonance imaging in children. J Magn Reson Imaging 2009;29:313-319.
14. Tulevski, II, Lee PL, Groenink M, et al. Dobutamine-induced increase of right ventricular contractility without increased stroke volume in adolescent patients with transposition of the great arteries: evaluation with magnetic resonance imaging. Int J Card Imaging 2000;16:471-478.
15. Tulevski, II, van der Wall EE, Groenink M, et al. Usefulness of magnetic resonance imaging dobutamine stress in asymptomatic and minimally symptomatic patients with decreased cardiac reserve from congenital heart disease (complete and corrected transposition of the great arteries and subpulmonic obstruction). Am J Cardiol 2002;89:1077-1081.
16. van den Berg J, Strengers JLM, Wielopolski PA, et al. Assessment of biventricular functional reserve and NT-proBNP levels in patients with RV volume overload after repair of tetralogy of Fallot at young age. Int J of Cardiol 2009;133:364-370.
17. van den Berg J, Wielopolski PA, Meijboom FJ, et al. Diastolic function in repaired tetralogy of Fallot at rest and during stress: assessment with MR imaging. Radiology 2007;243:212-219.

18. van der Zedde J, Oosterhof T, Tulevski, II, Vliegen HW, Mulder BJ. Comparison of segmental and global systemic ventricular function at rest and during dobutamine stress between patients with transposition and congenitally corrected transposition. Cardiol Young 2005;15:148-153.
19. Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. J Magn Reson Imaging 2003;17:323-329.
20. Valsangiacomo Buechel ER, Dave HH, Kellenberger CJ, et al. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. Eur Heart J 2005;26:2721-2727.
21. De Wolf D, Suys B, Verhaaren H, Matthys D, Taeymans Y. Low-Dose Dobutamine Stress Echocardiography in Children and Young Adults. The American Journal of Cardiology 1998;81:895-901.
22. Klewer SE, Goldberg SJ, Donnerstein RL, Berg RA, Hutter JJ, Jr. Dobutamine stress echocardiography: a sensitive indicator of diminished myocardial function in asymptomatic doxorubicin-treated long-term survivors of childhood cancer. J Am Coll Cardiol 1992;19:394-401.
23. Robbers-Visser D, Boersma E, Helbing WA. Normal biventricular function, volumes, and mass in children aged 8 to 17 years. J Magn Reson Imaging 2009;29:552-559.
24. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-310.
25. Alpert BS, Bloom KR, Olley PM. Assessment of left ventricular contractility during supine exercise in children with left-sided cardiac disease. Br Heart J 1980;44:703-710.
26. Helbing WA, Bosch HG, Maliepaard C, et al. Comparison of echocardiographic methods with magnetic resonance imaging for assessment of right ventricular function in children. Am J Cardiol 1995;76:589-594.
27. Hirsch R, Kilner PJ, Connelly MS, Redington AN, St John Sutton MG, Somerville J. Diagnosis in adolescents and adults with congenital heart disease. Prospective assessment of individual and combined roles of magnetic resonance imaging and transesophageal echocardiography. Circulation 1994;90:2937-2951.
28. Brili S, Stamatopoulos I, Barbetseas J, et al. Usefulness of dobutamine stress echocardiography with Tissue Doppler imaging for the evaluation and follow-up of patients with repaired tetralogy of Fallot. J Am Soc Echocardiogr 2008;21:1093-1098.
29. Brili SV, Alexopoulos NA, Barberis VI, et al. Dobutamine stress echocardiography for the evaluation of cardiac reserve late after Fontan operation. Hellenic J Cardiol 2007;48:252-257.
30. Li W, Hornung TS, Francis DP, et al. Relation of biventricular function quantified by stress echocardiography to cardiopulmonary exercise capacity in adults with Mustard (atrial switch) procedure for transposition of the great arteries. Circulation 2004;110:1380-1386.
31. Broberg CS, Ujita M, Prasad S, et al. Pulmonary arterial thrombosis in eisenmenger syndrome is associated with biventricular dysfunction and decreased pulmonary flow velocity. J Am Coll Cardiol 2007;50:634-642.
32. Oosterhof T, van Straten A, Vliegen HW, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation 2007;116:545-551.



Chapter 8

Ventricular response to dobutamine stress relates to the change in peak oxygen uptake during 5-year follow-up in patients with repaired tetralogy of Fallot

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Abstract

Objective: To evaluate the additional value of dobutamine stress testing in patients with repaired tetralogy of Fallot (TOF) by relating stress imaging parameters at baseline to relevant parameters of clinical condition and right ventricular (RV) size during serial follow-up.

Methods: We prospectively included 27 patients (14 ± 4 years at baseline), who were studied twice with a 5-year interval. Patients underwent magnetic resonance imaging to assess RV systolic and diastolic function at rest and during dobutamine stress. Normal response to dobutamine was defined as decrease in RV end-systolic volume (ESV), and increase in RV ejection fraction (EF) during stress. Exercise testing and electrocardiography were performed to determine peak oxygen uptake (peak VO_2), QRS duration, and QTc interval.

Results: RV volumes, QRS duration, and QTc interval increased significantly from baseline to follow-up; peak VO_2 tended to decrease (95 ± 20% to 89 ± 14%, p = 0.086). Response to dobutamine was normal in 26 of 27 patients and remained stable during follow-up (relative increase in RVEF during stress: +25 ± 9% (baseline) vs. +27 ± 10% (follow-up)). A smaller relative increase in RVEF during stress at baseline related to a larger decrease in peak VO_2 during follow-up (r = 0.59, p = 0.004). No significant associations were found with the relative increase in QRS duration, QTc interval, or RV end-diastolic volume during 5-year follow-up.

Conclusions: In a young TOF population, response to dobutamine stress was normal and remained stable during 5-year follow-up. A smaller increase in RVEF during stress at baseline was predictive for a larger decrease in peak VO_2 during 5-year follow-up.

Introduction

Residual pulmonary regurgitation (PR) is an important cause of long-term morbidity in patients after repair of tetralogy of Fallot (TOF)[1-5]. Patients with severe PR are often treated with pulmonary valve replacement (PVR), but the optimal timing to perform a PVR remains subject for debate. Preoperative thresholds for magnetic resonance imaging (MRI) parameters have been established[6-9] and clinical predictors for adverse outcomes have been recognized[2,5,10-13]. Since many of these factors interact, it remains difficult to predict the course of right ventricular (RV) deterioration and clinical condition over time in asymptomatic TOF patients.

Magnetic resonance imaging during physical or pharmacological stress has been proposed as additional tool in the early diagnosis of RV dysfunction, since its prognostic value has been proven in patients with coronary artery disease[14-15]. Furthermore, in patients with a systemic RV, the inability to decrease RV end-systolic volume (ESV) or increase RV ejection fraction (EF) during stress was predictive for future cardiac events[16]. Various studies have revealed abnormal responses to stress in TOF patients[17-20], but the prognostic value in these patients is yet undetermined.

Our aim was to evaluate the additional value of dobutamine stress testing in patients with repaired tetralogy of Fallot by relating stress imaging parameters at baseline to relevant parameters of clinical condition and RV size during serial follow-up.

Methods

Patients

We conducted a prospective serial follow-up study, for which the inclusion criteria were: 1) surgical repair of tetralogy of Fallot without associated cardiac lesions, 2) corrective surgery at an age of 24 months or younger, and 3) transatrial-transpulmonary approach to repair. Patients with a residual ventricular septal defect or significant residual pulmonary valve stenosis (echo-Doppler mean gradient > 30 mmHg) were excluded, as were patients with a homograft. Fifty-one patients participated in the baseline study between September 2002 and June 2004[21]. Thirty-nine patients agreed to participate in the follow-up study between September 2007 and March 2010. At both time points, patients underwent cardiac MRI at rest and during low-dose dobutamine stress, cardiopulmonary exercise testing, 12-lead electrocardiography (ECG), and N-terminal prohormone brain natriuretic peptide (NT-proBNP) assessment.

MRI parameters and NT-proBNP levels were compared to groups of healthy controls within our center: controls-MRI (N = 20): 11 male (55%), 27.0 ± 3.3 years; controls-NT-proBNP (N = 27): 19 male (70%), 19.3 ± 4.3 years. Controls were healthy volunteers without cardiac symptoms.

The study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments. Our study protocol was approved by the local Ethical Committee; all participants, and if required their parents, gave written informed consent before inclusion in the study.

Magnetic Resonance Imaging

Cardiac MRI was performed using a 1.5 Tesla system (General Electric, Milwaukee, WI, USA). All patients were monitored by vector cardiogram gating and respiratory monitoring. All images were obtained during breath-hold in end-expiration. A multi-slice, multi-phase data set was acquired using steady-state free precession cine imaging in a short axis orientation. Flow measurements at the level of the pulmonary valve were performed perpendicular to flow, using a velocity-encoded MRI sequence. All scans were repeated during continuous infusion of dobutamine-hydrochloride at 7.5 µg/kg/min, as described previously[21]. Dobutamine infusion was decreased to 5.0 µg/kg/min if any of the following events occurred: an increase of > 50% or a decrease of > 20% in heart rate or systolic blood pressure, or diastolic blood pressure. The test was discontinued if serious rhythm disturbances were seen, or if the patient experienced significant discomfort.

Analysis was performed on an Advanced Windows workstation (General Electric Medical Systems), equipped with the software packages MASS and FLOW (Medis Medical Imaging Systems, Leiden, the Netherlands). Endocardial borders of both ventricles were manually traced in end-diastole and end-systole. Endocardial borders of the RV were defined in all phases and all slices of the short axis set using a previously described semi-automated full cardiac cycle contour detection method[22]. Contours were manually corrected if necessary. Papillary muscles and trabeculations were included in the ventricular cavity. When the pulmonary valve was visible in the basal slice, contours were drawn up to the junction with the pulmonary valve. Time volume curves for the RV were acquired by summation of the volumes of every slice of each phase; additionally, RV time volume change curves were reconstructed. All RV data-sets were analyzed by a single observer (SM) and supervised by another observer (SL), who also analyzed all LV data-sets and had 4 years of experience in cardiac contour tracing.

The following parameters were assessed, as has been reported previously: 1) end-diastolic volume (EDV); 2) ESV; 3) stroke volume (SV); 4) EF; 5) early filling fraction, defined as ventricular volume increase during the first 1/3 of diastole, expressed as percentage of ventricular SV; 6) deceleration time (Dt), which is the time from the early peak filling rate to the extrapolation point of deceleration of flow to the baseline; 7) atrial filling fraction, defined as the increase in ventricular volume after the onset of atrial contraction, expressed as percentage of ventricular SV; 8) and early-to-atrial filling (E/A) volume ratio. RV effective SV (eff.SV) was

calculated to correct for PR: RVeff.SV = RVSV – PR volume. Volumes were indexed (i) for body surface area, and deceleration time for the RR-interval.

A normal stress response was defined as the ability to decrease RVESVi during stress and to increase RVEF during stress. The decrease in RVESVi and increase in RVEF during stress were expressed as relative changes compared with the value at rest: relative change in RVESVi = $((RVESVi_{stress} – RVESVi_{rest})/RVESVi_{rest}) * 100\%$, and the relative change in RVEF = $((RVEF_{stress} – RVEF_{rest})/RVEF_{rest}) * 100\%$.

Clinical parameters

A standardized 12-lead ECG was obtained to determine QRS duration and QT interval corrected for heart rate (QTc).

Blood samples were drawn from a peripheral vein after 30 minutes rest in supine position. Plasma and serum were separated immediately after sample collection and stored at -80ºC. NT-proBNP was measured using a Cobas E411 immunoanalyzer (Roche Diagnostics, Mannheim, Germany): coefficient of variation < 2.55%.

Patients performed a maximal bicycle exercise test on a Jaëger Oxycom Champion System (Viasys Healthcare, Hoechberg, Germany). Workload was increased by 10 – 20 Watts per minute. Tests were regarded as maximal when the respiratory quotient at peak exercise was ≥ 1.05. Peak workload and peak oxygen uptake (peak VO_2) were recorded and expressed as percentages of the predicted values[23-24]. The ventilatory response to carbon dioxide production (VE/VCO_2 slope) was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.

Statistical analysis

Continuous data were tested for normality with the Kolmogorov-Smirnov test. Normally distributed data are expressed as mean (± standard deviation) and non-normally distributed data as median (range). Differences between groups of patients were evaluated using Student t-test, paired t-test or with nonparametric tests, as appropriate. Categorical data are expressed as counts (percentages); differences between groups of patients were evaluated with chi-square test, Fisher-exact test, or McNemar test. To test the potential additional value of stress imaging parameters on relevant outcome parameters, correlations were assessed using linear regression analysis. The relative change in RVESVi during stress and the relative change in RVEF during stress were defined as independent variables. The change in parameters of clinical condition and RV size during 5-year follow-up were defined as dependent variables.

Analysis was performed using the SPSS statistical software package version 17.0 (SPSS, Inc., Chicago, Ill, USA). A p-value < 0.05 was considered to indicate statistical significance.

Results

Stress imaging data was incomplete in 3 of 39 patients and 9 other patients had undergone PVR during the 5-year follow-up period. They were excluded from our serial follow-up analysis and results are therefore given for the remaining 27 patients. In 3 patients (11%), dobutamine infusion had been decreased to 5.0 µg/kg/min, because of an increase in heart rate of > 50%. This was well tolerated and the study protocol was completed with a dobutamine dosage of 5.0 µg/kg/min. No serious adverse effects to dobutamine were observed. Characteristics of the patients are displayed in Table 1.

Table 1: Characteristics of the study population and results of clinical tests

Parameter	**Patients (N = 27)**	
Male	19 (70%)	
Palliative shunt before surgery	1 (4%)	
Age at corrective surgery (years)	0.8 (± 0.4)	
Transannular patch	21 (78%)	
	BASELINE	**FOLLOW-UP**
Age at study (years)	14.1 (± 4.4)	19.4 (± 4.3) *
BSA (m^2)	1.49 (± 0.40)	1.80 (± 0.26) *
NYHA class	I: 24 (89%)	I: 21 (78%)
	II: 3 (11%)	II: 6 (22%)
QRS duration (msec)	130 (± 24)	139 (± 27) *
QTc interval (msec)	425 (± 30)	443 (± 39) **
NT-proBNP (pmol/l)	14 (± 10)	13 (± 10)
Peak Workload (% of predicted)	90 (± 13)	90 (± 13)
	(N = 22)	
Peak VO_2 (ml/kg/min)	40 (± 8)	37 (± 9)
Peak VO_2 (% of predicted)	95 (± 20)	89 (± 14)
VE/VCO_2 slope	30 (± 3)	31 (± 4)

Results are expressed as mean (± standard deviation), or as counts (percentages).

* / ** Significantly different between baseline and follow-up: * $p < 0.01$ / ** $p < 0.05$.

Abbreviations: BSA = body surface area; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; QTc = QT interval, corrected for heart rate; peak VO_2 = peak oxygen uptake; VE/VCO_2 slope = ventilatory response to carbon dioxide production.

Magnetic Resonance Imaging

Response to dobutamine

For the parameters of systolic function, the response to dobutamine stress was similar at both time points: a decrease in biventricular EDVi and biventricular ESVi was observed during dobutamine stress, as well as an increase in heart rate, biventricular SVi, RVeff.SVi, and biventricular EF (Table 2). No major changes were observed in RV diastolic functional parameters during dobutamine stress, except for an increase in RV deceleration time.

At baseline, all patients were able to increase RVEF and to decrease RVESVi during dobutamine stress. At follow-up, only 1 patient was unable to increase RVEF and to decrease RVESVi during dobutamine stress.

Follow-up period

The relative increase in RVEF during dobutamine stress and the relative decrease in RVESVi during dobutamine stress remained unchanged during 5-year follow-up: relative increase in RVEF during stress: +25 ± 9% (baseline) vs. +27 ± 10% (follow-up), not significant; relative decrease in RVESVi during stress: -30 ± 10% (baseline) vs. -32 ± 10% (follow-up), not significant.

RV volumes and PR fraction increased significantly during 5-year follow-up; resting RVEF remained unchanged (Table 2).

Clinical parameters

QRS duration and the QTc interval increased significantly during 5-year follow-up (Table 1). Exercise capacity was adequate at both time points, but peak VO_2 tended to decrease during follow-up (peak VO_2: 40 ± 8 ml/kg/min (baseline) to 37 ± 9 ml/kg/min (follow-up), p = 0.051; or 95 ± 20% (baseline) to 89 ± 14% (follow-up), p = 0.086). NT-proBNP levels remained unchanged during follow-up, but were higher than in healthy controls (NT-proBNP: 13 ± 10 pmol/l (patients at follow-up) vs. 4 ± 2 pmol/l (controls), p < 0.001).

Table 2: Results of MRI parameters at rest and during dobutamine stress for patients and healthy controls

		Controls (N = 20)	Patients (N = 27)			
Parameter			**BASELINE**		**FOLLOW-UP**	
		Rest	**Rest**	**Stress**	**Rest**	**Stress**
HR (beats / minute)		69 (± 11)	78 (± 12) ‡	89 (± 16) §	78 (± 14) ‡‡	92 (± 16) §
PR (%)		N/A	30 (± 16)	29 (± 16)	33 (± 18) **	29 (± 17) §
RV	EDV (ml/m^2)	97 (± 18)	136 (± 34) ‡	126 (± 34) §	147 (± 41) *‡	133 (± 38) §**
	ESV (ml/m^2)	45 (± 11)	69 (± 21) ‡	49 (± 19) §	76 (± 26) *‡	52 (± 22) §
	SV (ml/m^2)	52 (± 9)	67 (± 15) ‡	77 (± 16) §	71 (± 17) **‡	81 (± 19) §
	Eff. SV (ml/m^2)	52 (± 9)	46 (± 7) ‡‡	52 (± 9) §	45 (± 6) ‡	55 (± 9) §
	EF (%)	54 (± 5)	50 (± 6) ‡	62 (± 6) §	49 (± 5) ‡	62 (± 7) §
LV	EDV (ml/m^2)	90 (± 14)	81 (± 10) ‡‡	78 (± 11) §§	85 (± 11) **	80 (± 13) §
	ESV (ml/m^2)	38 (± 7)	35 (± 6)	23 (± 5) §	37 (± 7)	23 (± 6) §
	SV (ml/m^2)	52 (± 9)	47 (± 6) ‡‡	55 (± 7) §	47 (± 6) ‡‡	57 (± 9) §
	EF (%)	58 (± 4)	57 (± 4)	71 (± 4) §	56 (± 4)	71 (± 4) §
RV	Early filling fraction (%)	42 (± 11)	38 (± 11)	41 (± 10)	39 (± 9)	37 (± 10) **
	Atrial filling fraction (%)	28 (± 9)	33 (± 12)	30 (± 13)	31 (± 14)	35 (± 13)
	E/A volume ratio	1.6 (± 0.6)	1.5 (± 1.2)	1.9 (± 1.5)	1.7 (± 1.1)	1.3 (± 0.9)
	Dt/RR interval ratio	0.14 (± 0.05)	0.23 (± 0.09) ‡	0.28 (± 0.11)	0.24 (± 0.09) ‡	0.30 (± 0.11) §§

Results are expressed as mean (± standard deviation).

* / ** Significantly different between baseline and follow-up: * $p < 0.01$ / ** $p < 0.05$.

§ / §§ Significantly different between rest and dobutamine stress: § $p < 0.001$ / §§ $p < 0.05$.

‡ / ‡‡ Significantly different between rest measurements of patients and healthy controls: ‡ $p < 0.01$ / ‡‡ $p < 0.05$.

Abbreviations: Dt = deceleration time; E/A volume ratio = ratio of early filling volume to atrial filling volume; EDV = end-diastolic volume; EF = ejection fraction; Eff.SV = effective stroke volume; ESV = end-systolic volume; HR = heart rate; LV = left ventricle; MRI = magnetic resonance imaging; N/A = not applicable; PR = pulmonary regurgitation; RV= right ventricle; SV = stroke volume.

Correlations

At both time points, a larger decrease in RVESVi during stress related to a larger increase in RVEF during stress (Figure 1a) (both time points: r = -0.72, p < 0.001). Both parameters were used as independent variables to test associations with changes in clinical parameters and RV size during 5-year follow-up.

A smaller relative increase in RVEF during stress at baseline was significantly associated with a larger decrease in peak VO_2 during 5-year follow-up (relative change in peak VO_2 = ((peak $VO_{2follow-up}$ – peak $VO_{2baseline}$)/peak $VO_{2baseline}$) * 100%) (Figure 1b). There were no significant associations however between the relative increase in RVEF during stress at baseline and the relative increase in QRS duration or QTc interval during 5-year follow-up, nor were there significant associations between the relative decrease in RVESVi during stress at baseline and the relative increase in QRS duration or QTc interval during 5-year follow-up. There were also no significant relations between the relative increase in RVEF during stress at baseline and the relative increase in resting RVEDVi during 5-year follow-up (r = -0.22, p = 0.28), or between the relative decrease in RVESVi during stress at baseline and the increase in resting RVEDVi during follow-up (r = 0.26, p = 0.20).

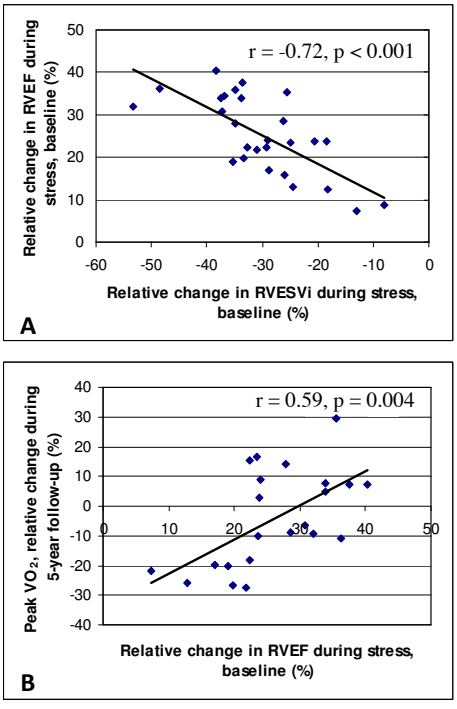


Figure 1a: Correlation between relative change in RVESVi during stress at baseline and the relative increase in RVEF during stress at baseline. **Figure 1b**: Correlation between the relative increase in RVEF during stress at baseline and the relative change in peak VO_2 during 5-year follow-up.
Abbreviations: EF = ejection fraction; ESV = end-systolic volume; i = indexed for body surface area; RV = right ventricle; peak VO_2 = peak oxygen uptake.

Discussion

This serial prospective follow-up study demonstrated that in a young population of patients with repaired tetralogy of Fallot, response to dobutamine stress was good and remained stable during 5-year follow-up. A smaller increase in RVEF during dobutamine stress at baseline was predictive for a larger decrease in peak VO_2 during 5-year follow-up. Since several studies have established the prognostic value of peak VO_2 with regard to adverse outcomes and mortality in patients with congenital heart disease[4,25], this finding is of additional value in the follow-up of TOF patients. Clinical condition was adequate in these patients at both time points, despite a limited, but statistically significant, increase in RV size, QRS duration, and QTc interval during the follow-up period. Furthermore, peak VO_2 tended to decrease during these 5 years. NT-proBNP levels were higher than in healthy controls, and remained stable during follow-up.

Early diagnosis of RV dysfunction in asymptomatic patients after TOF repair remains a challenge and new parameters have been studied to improve decision making with regard to timing of PVR. Stress imaging might be useful in this process, as its prognostic value has been proven in patients with other types of congenital heart disease[16,26]. In aortic regurgitation, a lesion that bears analogy to PR, preserved LV contractile reserve has been related to favourable follow-up results[26]. In patients with a systemic RV, the inability to decrease RVESV or increase RVEF during stress, was predictive for adverse cardiac events (e.g. hospitalization for heart failure, cardiac surgery, aborted cardiac arrest, or death)[16]. In our study, only 1 patient showed no decrease in RVESVi and no increase in RVEF during dobutamine stress at follow-up. Response to dobutamine stress was normal in all other patients, with regard to decreasing RVESV and increasing RVEF during stress. An exception was the prolongation of the RV deceleration time during dobutamine stress. It might be speculated that this is an initial sign of deterioration[27]. One of the explanations for the different results in our study compared to those of Winter et al. might be the different populations studied. It may be speculated that RV dysfunction and thus an abnormal stress response will occur earlier in patients with a systemic RV than in our TOF patients, operated on according to current surgical strategies. Our results illustrate the generally excellent midterm outcome in currently treated young TOF patients, which most likely relates to the young age at surgery[5].

In contrast to the adequate response to dobutamine in our TOF patients, Roest et al. observed an abnormal response to physical exercise in a comparable TOF population, as RVESVi did not decrease and RVEF did not increase during stress in their patients[17]. An explanation for these different results might be the different methods used: Roest and collegues used physical exercise to assess the stress response, whereas we used pharmacological stress. Oosterhof et al. have demonstrated differences in response to dobutamine or physical exercise in patients with a systemic RV[28], which may also apply to TOF patients.

The normal response to dobutamine stress in our TOF patients is in agreement with recently reported results of Parish et al., who demonstrated a decrease in RVESVi and an increase in RVEF with a dobutamine dosage of 10 µg/kg/min in their TOF patients[29]. In a small number of their TOF population, an increase to a dobutamine dosage of 20 µg/kg/min resulted in either lack of further reduction or even increase in RVESVi, and a significant worsening of the increase in RVEF during

stress[29]. A limitation to their study is the lack of clinical outcome parameters. Further research is warranted to determine the optimal dobutamine dosage in TOF patients.

Since no major events as death or heart failure occurred in our young TOF population during the follow-up period, we evaluated the additional value of stress testing by assessing relevant relations between stress imaging parameters and parameters that have been shown to have prognostic relevance in the TOF population[1-5,12-13,25]. These included parameters of RV size, exercise test results, ECG parameters, and NT-proBNP levels. At both time points, we found several significant relations between the relative increase in RVEF during stress or the relative decrease in RVESVi during stress, and parameters of RV size and clinical condition (e.g. RVEDVi, QRS duration, QTc interval, and NT-proBNP level) (data not shown). However, we were unable to find a significant correlation between the relative increase in RVEF during stress at baseline and the relative increase in resting RVEDVi during 5-year follow-up ($r = -0.22$, $p = 0.28$), or between the relative decrease in RVESVi during stress at baseline and the relative increase in resting RVEDVi during follow-up ($r = 0.26$, $p = 0.20$). The small number of patients may have limited statistical power and further studies are needed to establish if this relation is present.

Limitations

The main limitation of this study is the lack of hard end-points. Detailed evaluation of clinical status, MRI measurements, exercise testing, ECGs, and NT-proBNP levels provided a set of surrogate markers.

Our study has been performed in young TOF patients operated on according to current surgical strategies. Our results may therefore not be representative for older TOF patients.

Our patient population is most likely biased towards patients with a more favourable outcome, since patients who underwent PVR during follow-up were excluded. This may have influenced our results. Additional analyses in the 9 excluded patients who underwent PVR after the baseline study demonstrated a significantly smaller decrease in RVESVi during dobutamine stress at baseline than in our 27 non-PVR patients (relative decrease in RVESVi at baseline: -20 ± 11% (pre-PVR patients) vs. -30 ± 10% (non-PVR patients), $p = 0.016$) (data not shown). This may indicate that stress imaging may be of additional value in the decision making regarding PVR. This should be confirmed in larger studies.

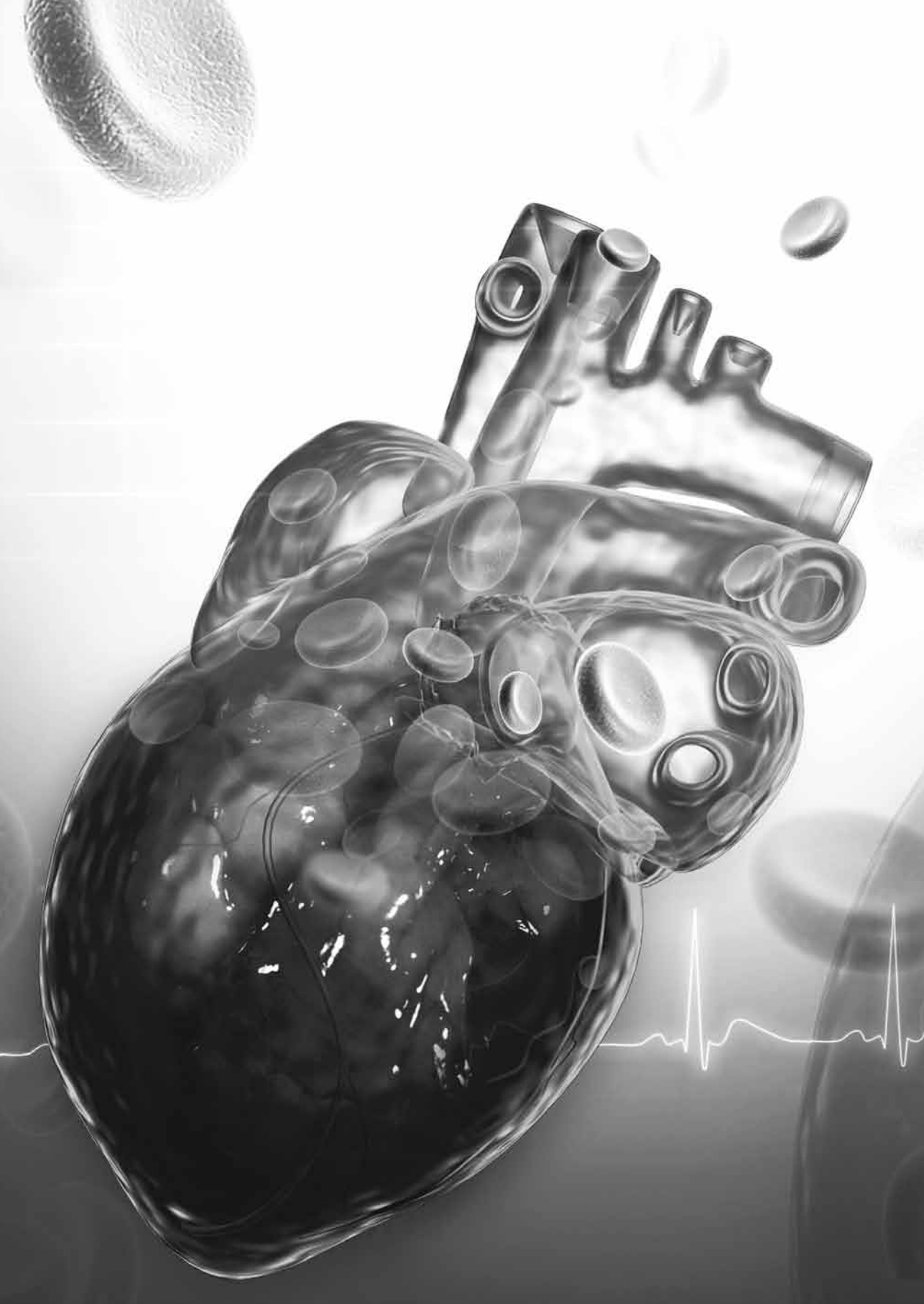
Conclusions

In a young TOF population, operated on according to current surgical strategies, the response to dobutamine stress is normal and remained normal during 5-year follow-up in the majority of the patients. A smaller increase in RVEF during dobutamine stress at baseline was predictive for a larger decrease in peak VO_2 during 5-year follow-up. This indicates the potential additional value of dobutamine stress imaging in the follow-up of TOF patients.

References

1. Davlouros PA, Kilner PJ, Hornung TS, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol 2002;40:2044-2052.
2. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975-981.
3. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol 2004;43:1068-1074.
4. Giardini A, Specchia S, Tacy TA, et al. Usefulness of Cardiopulmonary Exercise to Predict Long-Term Prognosis in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2007;99:1462-1467.
5. Knauth AL, Gauvreau K, Powell AJ, et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart 2008;94:211-216.
6. Frigiola A, Tsang V, Bull C, et al. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? Circulation 2008;118:S182-190.
7. Oosterhof T, van Straten A, Vliegen HW, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation 2007;116:545-551.
8. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. Am J of Cardiol 2005;95:779-782.
9. Valsangiacomo Buechel ER, Dave HH, Kellenberger CJ, et al. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. Eur Heart J 2005;26:2721-2727.
10. Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. Circulation 2006;113:405-413.
11. Giardini A, Specchia S, Coutsoumbas G, et al. Impact of pulmonary regurgitation and right ventricular dysfunction on oxygen uptake recovery kinetics in repaired tetralogy of Fallot. Eur J Heart Fail 2006;8:736-743.
12. Bolger AP, Sharma R, Li W, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation 2002;106:92-99.
13. Oosterhof T, Tulevski, II, Vliegen HW, Spijkerboer AM, Mulder BJ. Effects of volume and/or pressure overload secondary to congenital heart disease (tetralogy of fallot or pulmonary stenosis) on right ventricular function using cardiovascular magnetic resonance and B-type natriuretic peptide levels. Am J Cardiol 2006;97:1051-1055.
14. Jahnke C, Nagel E, Gebker R, et al. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007;115:1769-1776.
15. Wahl A, Paetsch I, Gollesch A, et al. Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases. Eur Heart J 2004;25:1230-1236.
16. Winter MM, Scherptong RW, Kumar S, et al. Ventricular response to stress predicts outcome in adult patients with a systemic right ventricle. Am Heart J 2010;160:870-876.
17. Roest AA, Helbing WA, Kunz P, et al. Exercise MR imaging in the assessment of pulmonary regurgitation and biventricular function in patients after tetralogy of fallot repair. Radiology 2002;223:204-211.

18. Tulevski, II, Hirsch A, Dodge-Khatami A, Stoker J, van der Wall EE, Mulder BJ. Effect of pulmonary valve regurgitation on right ventricular function in patients with chronic right ventricular pressure overload. Am J Cardiol 2003;92:113-116.
19. Uebing A, Fischer G, Schlangen J, Apitz C, Steendijk P, Kramer HH. Can we use the end systolic volume index to monitor intrinsic right ventricular function after repair of tetralogy of Fallot? Int J Cardiol 2011;147:52-57.
20. van den Berg J, Wielopolski PA, Meijboom FJ, et al. Diastolic function in repaired tetralogy of Fallot at rest and during stress: assessment with MR imaging. Radiology 2007;243:212-219.
21. van den Berg J, Strengers JLM, Wielopolski PA, et al. Assessment of biventricular functional reserve and NT-proBNP levels in patients with RV volume overload after repair of tetralogy of Fallot at young age. Int J of Cardiol 2009;133:364-370.
22. Uzumcu M, van der Geest RJ, Swingen C, Reiber JH, Lelieveldt BP. Time continuous tracking and segmentation of cardiovascular magnetic resonance images using multidimensional dynamic programming. Invest Radiol 2006;41:52-62.
23. Wasserman K HJ, Sue DY, Stringer WW, Whipp BJ, ed. Principles of exercise testing and interpretation. 4th ed: Philadelphia: Lippincott Williams & Wilkins, 2005:160-182.
24. Godfrey S, Davies CT, Wozniak E, Barnes CA. Cardio-respiratory response to exercise in normal children. Clin Sci 1971;40:419-431.
25. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation 2012;125:250-259.
26. Wahi S, Haluska B, Pasquet A, Case C, Rimmerman CM, Marwick TH. Exercise echocardiography predicts development of left ventricular dysfunction in medically and surgically treated patients with asymptomatic severe aortic regurgitation. Heart 2000;84:606-614.
27. Luijnenburg SE, Peters RE, van der Geest RJ, et al. Abnormal right atrial and right ventricular diastolic function relate to impaired clinical condition in patients operated for tetralogy of Fallot. Int J Cardiol 2012;Mar 3 [Epub ahead of print].
28. Oosterhof T, Tulevski, II, Roest AA, et al. Disparity between dobutamine stress and physical exercise magnetic resonance imaging in patients with an intra-atrial correction for transposition of the great arteries. J Cardiovasc Magn Reson 2005;7:383-389.
29. Parish V, Valverde I, Kutty S, et al. Dobutamine stress MRI in repaired tetralogy of Fallot with chronic pulmonary regurgitation A comparison with healthy volunteers. Int J Cardiol 2011;Dec 8 [Epub ahead of print].



Chapter 9

Diminished TGF-β levels in patients with right ventricular dilatation after repair of tetralogy of Fallot

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Abstract

Objective: Our aim was to investigate the role and the use of transforming growth factor (TGF)-β as a plasma biomarker in patients with right ventricular (RV) volume overload and progressive RV enlargement after tetralogy of Fallot (TOF) repair.

Methods: 96 patients (22 (7 – 66) years) were included and underwent magnetic resonance imaging to assess RV size and function. Serum levels of TGF-β were assessed using ELISA kits; inflammatory factors (e.g. tumor necrosis factor-α and interferon-γ), cardiomyocyte growth and survival factors (e.g. epidermal growth factor and endocrine gland-derived vascular endothelial growth factor) were measured using a protein array analysis. In 36 patients, serial follow-up measurements were available with a 5-year interval (14 ± 5 years at baseline). Results were compared to 70 healthy controls (21 (12 – 64) years).

Results: TGF-β tended to be lower in patients with a large RV (TGF-β: 3.8 ± 3.3 ng/ml (RV end-diastolic volume (EDV) 171 ± 22 ml/m^2) vs. 6.3 ± 5.7 ng/ml (small RV: RVEDV 102 ± 12 ml/m^2), p = 0.10). During 5-year serial follow-up, RVEDV increased (137 ± 33 ml/m^2 to 148 ± 38 ml/m^2, p = 0.001) while TGF-β decreased (4.6 ± 2.6 ng/ml to 3.0 ± 1.9 ng/ml, p = 0.005). In controls, TGF-β remained unchanged with increasing age. Contrary to results in patients with a small RV and controls, inflammatory factors increased with increasing follow-up duration in patients with a large RV, while cardiomyocyte growth and survival factors decreased.

Conclusions: We have linked the process of progressive RV dilatation with declining serum levels of TGF-β in patients after TOF repair. Lower TGF-β levels coincided with immune activation and loss of cardiac protection, rendering this subgroup of patients more susceptible to adverse RV remodeling.

Introduction

The number of patients with repaired tetralogy of Fallot (TOF) surviving into adulthood has grown rapidly over the last decades, because long-term survival is excellent[1]. However, in many patients residual pulmonary regurgitation (PR) may result in right ventricular (RV) dilatation. Untreated, this may lead to RV dysfunction and RV failure. Ventricular function and clinical parameters have been studied extensively[2-6], and neurohormonal activation has been related to biventricular dysfunction and impaired clinical condition in patients after TOF repair[7-9]. However, on the basis of available literature, it remains difficult to determine parameters that predict RV failure at an early stage. More insight in the biomolecules that are involved in the process of progressive RV dilatation might aid in the identification of biomarkers that may be used in the early detection of RV dysfunction.

A recent study by Villar et al. has identified transforming growth factor (TGF)-β as a new biomarker of left ventricular (LV) remodeling in aortic stenosis[10]. TGF-β is a cytokine with pleiotropic function with high expression levels in the heart region. During adult life, TGF-β can be activated after injury to aid in wound healing[11]. Indeed, TGF-β levels are significantly increased in infarcted myocardium, and multiple studies have proven that this cytokine plays a central role in the subsequent processes of infarct healing, cardiac repair, and remodeling[12-14]. A significant correlation between plasma levels of TGF-β and LV remodeling has been demonstrated in patients operated for aortic stenosis and in an animal model of transverse aortic arch constriction[10]. In addition, TGF-β levels were positively correlated with the myocardial expression of genes that encode for extracellular matrix (ECM) components, including many regulatory targets of TGF-β. Involvement of TGF-β in RV remodeling in patients with repaired TOF in a similar regulatory mechanism as in patients with aortic stenosis seems plausible.

Here we investigated the role and the use of TGF-β as a plasma biomarker in patients with RV volume overload and progressive RV enlargement after tetralogy of Fallot repair.

Methods

Patients

This research is part of a larger, prospective serial follow-up study in 3 referral centers in the Netherlands, for which the inclusion criteria were: 1) surgical repair of tetralogy of Fallot without associated cardiac lesions, 2) no pulmonary valve replacement (PVR), and 3) the availability of a magnetic resonance imaging (MRI) study at least 3 years before the current study. Ninety-six patients (median age 22 (7 – 66) years) were included in the current cross-sectional study between September 2007 and February 2010 and underwent an MRI study, blood sample withdrawal, cardiopulmonary exercise testing, and 12-lead electrocardiography (ECG).

In 36 of these 96 patients, serial follow-up measurements were available, since the aforementioned tests had also been performed 5 years earlier in this subgroup of patients (mean age at baseline 14 ± 5years)[15].

Healthy controls were recruited for comparison of biomarker results (N = 118, median age 22 (12 – 64) years). Controls were healthy volunteers without cardiac symptoms.

This study conforms with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the local Ethical Committees of all participating centers; all patients and healthy controls, and if required, their parents, gave written informed consent.

Magnetic Resonance Imaging

Cardiac MRI was performed on locally available 1.5 Tesla MRI systems (General Electric, Milwaukee, WI, USA; Philips Medical Systems, Best, the Netherlands; Siemens Medical Systems, Erlangen, Germany). All patients were monitored by vector cardiogram gating and respiratory monitoring. MRI studies were performed with the use of local imaging protocols. A multi-slice, multi-phase data set was acquired using steady-state free precession cine imaging in a short axis or axial orientation. In the serial follow-up group (N = 36), all multi-slice, multi-phase data-sets were acquired in a short axis orientation at the same MRI scanner at both time points. Flow measurements of the pulmonary valve were performed perpendicular to flow, using a velocity-encoded MRI sequence. Velocity encoding was set at 150 cm/sec and was increased whenever phase aliasing occurred.

All analyses were performed on a commercially available Advanced Windows workstation (General Electric Medical Systems), equipped with the software packages MASS and FLOW (Medis Medical Imaging Systems, Leiden, the Netherlands). With manual detection of endocardial and epicardial borders in end-systole and end-diastole, the following parameters were calculated: biventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), and mass. Volumes and mass were indexed for body surface area. Papillary muscles and trabeculations were included in the ventricular cavity. The interventricular septum was included in the LV mass. When the pulmonary valve was visible in the basal slice, contours were drawn up to the junction with the pulmonary valve. Pulmonary regurgitation was expressed as percentage of systolic SV in the main pulmonary artery. Additionally, RV effective stroke volume (eff.SV) was calculated to correct for PR: RVeff.SV = RVSV – PR volume.

All MRI data-sets were analyzed by a single observer (SL) to limit observer variability[16].

Patient subgroups

In the cross-sectional group of 96 patients, 4 subgroups were composed, based on the lowest and highest tertiles of RVEDV and follow-up (FU) duration after corrective surgery. The following subgroups were composed: (1) subgroup A (N = 14): patients with a small RV (RVEDV < 119 ml/m^2), at short follow-up (FU-duration < 17 years); (2) subgroup B (N = 12): patients with a large RV (RVEDV > 153 ml/m^2), at long follow-up (FU-duration > 24 years); (3) subgroup C (N = 12): patients with a small RV (RVEDV < 119 ml/m^2), at long follow-up (FU-duration > 24 years); (4) subgroup D (N = 11): patients with a large RV (RVEDV > 153 ml/m^2), at short follow-up (FU-duration < 17 years).

Additionally, 4 subgroups of healthy controls were composed, in the same age-range as the cross-sectional and serial follow-up patients: (1) controlgroup 1 (N = 10): age 13 ± 1 years, 7 male; (2) controlgroup 2 (N = 20): age 16 ± 3 years, 15 male; (3) controlgroup 3 (N = 20): age 23 ± 3 years, 13 male; (4) controlgroup 4 (N = 20): age 41 ± 13 years, 11 male.

Protein array analysis

To study the potential mechanism by which TGF-β could affect the process of progressive RV dilatation, we conducted a protein array analysis to assess serum levels of biomolecules that regulate inflammation, ECM degradation, fibroblast proliferation, and cardiomyocyte survival. Serum samples were analyzed for protein levels using a glass-slide based protein array spotted with antibodies directed against the aforementioned different biomolecules, following the protocol provided by the manufacturer (nr: AAH-CYT-G4000, RayBiotech, Norcross, GA, USA). Protein array analysis was performed in the 4 cross-sectional patient-subgroups and the 4 healthy control-subgroups; serum samples were pooled per group. The samples of the individual patients were not analyzed separately.

The biomolecules of interest are described below. Transforming growth factor (TGF)-β plays a critical role in suppressing the initial inflammatory reaction that is responsible for adverse dilatation of the ventricular wall. In this process, the pro-inflammatory cytokines interferon (IFN)-γ and tumor necrosis factor (TNF)-α are the main molecular conductors that determine the extent of the immune response. In addition to IFN-γ and TNF-α, serum levels of the inflammatory cytokines interleukin 18 binding protein (IL18BP), E-Selectin, tumor necrosis factor receptor superfamily member 21 (TNFRSF21), interleukin 8 (IL8), chemokine (C-X-C motif) ligand 3 (CXCL3), chemokine (C-C motif) ligand 26 (CCL26), chemokine (C-X-C motif) ligand 12 (CXCL12), L-Selectin, interferon-γ induced protein 10 (IP10), interleukin 9 (IL9), and interleukin 2 receptor (IL2R) were evaluated.

TGF-β protects against adverse ventricular dilatation, not only by suppression of immune activation, but also by promoting cardiomyocyte survival and by promoting scar tissue formation by inducing proliferation of resident fibroblast cells. Serum levels of epidermal growth factor receptor (EGFR), epidermal growth factor (EGF), and endocrine gland-derived vascular endothelial growth factor (EGVEGF) were evaluated. Furthermore, TGF-β activation of fibroblasts is known to stimulate tissue inhibitors of metalloproteinases (TIMPs). The function of TIMPs include maintaining the stability of the extracellular matrix by protecting it against degradation by metalloproteinase activity. Therefore, serum levels of TIMP2 were evaluated. Finally, cardiotrophin 1 (CTF1), a secreted cytokine that is known to trigger cardiac myocyte hypertrophy, was evaluated.

ELISAs

Serum samples of the individual patients were measured for levels of TGF-β, IFN-γ, and TNF-α using commercially available ELISA arrays, following the protocols recommended by the manufacturer (R&D systems, Abingdon, UK): TGF-β (nr. DY240); IFN-γ (DIF50); TNF-α (nr. HSTA00D). A standard dilution series of a positive serum sample was included per ELISA experiment and a conversion factor was calculated and used to correct the read out of patient samples for interassay variations. Serum levels of TGF-β, IFN-γ, and TNF-α were assessed in all individual patients and in 32 individual controls (8 controls per controlgroup).

Biomarkers

Blood samples were drawn from a peripheral vein after 30 minutes rest in supine position. Plasma and serum were separated immediately after sample collection and stored at -80ºC.

High-sensitivity C-reactive protein (hsCRP) was measured using a nephelometric assay and N-terminal prohormone brain natriuretic peptide (NT-proBNP) on a Cobas E411 immunoanalyzer (Roche Diagnostics, Mannheim, Germany).

Clinical parameters

Patients performed a maximal bicycle exercise test on a Jaëger Oxycom Champion System (Viasys Healthcare, Hoechberg, Germany). Peak oxygen uptake (peak VO_2) was recorded and expressed as percentage of the predicted value[17]. The ventilatory response to carbon dioxide production (VE/VCO_2 slope) was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.

A standardised 12-lead ECG was obtained to determine QRS duration.

Statistical analysis

Continuous data were tested for normality with the Kolmogorov-Smirnov test. Data are expressed as mean (± standard deviation) or as median (range). Differences between groups of patients were evaluated using Student t-test, paired t-test, or with nonparametric tests, as appropriate. Categorical data are expressed as counts (percentages); differences between groups of patients were evaluated with chi-square test, Fisher exact test, or McNemar test, as appropriate. Analysis of covariance was used for multiple group comparisons with correction for multiple testing by Bonferroni's method. Analysis was performed using the SPSS statistical software package version 17.0 (SPSS, Inc., Chicage, Ill, USA). A p-value < 0.05 was considered to indicate statistical significance.

Results

Diminished TGF-β serum levels are associated with RV dilatation in patients with repaired tetralogy of Fallot.

Cross-sectional group: Results of all 96 cross-sectional patients and subgroups are displayed in Table 1. In patients with the smallest right ventricles, TGF-β did not change with increasing follow-up duration, nor did TGF-β levels change in patients with the largest right ventricles (Small RV: TGF-β: 5.6 ± 6.7 ng/ml (subgroup A) vs. 7.4 ± 3.7 ng/ml (subgroup C), p = 0.49; Large RV: TGF-β: 3.6 ± 3.6 ng/ml (subgroup D) vs. 4.0 ± 3.2 ng/ml (subgroup B), p = 0.80).

TGF-β levels tended to be lower in patients with a large RV than in patients with a small RV (TGF-β: 3.8 ± 3.3 ng/ml (subgroups B and D) vs. 6.3 ± 5.7 ng/ml (subgroups A and C), p = 0.10).

Serial follow-up group: In the serial follow-up group, RVEDV increased in 5 years time from 137 ± 33 ml/m^2 at baseline to 148 ± 38 ml/m^2 at follow-up (p = 0.001), while TGF-β levels decreased during this period from 4.6 ± 2.6 ng/ml to 3.0 ± 1.9 ng/ml (p = 0.005) (Table 2).

Healthy controls: TGF-β did not change significantly with increasing age in healthy controls (Table 3).

Table 1: Results of the cross-sectional study

Parameter	All patients (N = 96)	SubA (N = 14) (Small RV / Short FU)	SubC (N = 12) (Small RV / Long FU)	SubA + SubC (N = 26) (Small RV)	SubD (N = 11) (Large RV / Short FU)	SubB (N = 12) (Large RV / LongFU)	SubB + SubD (N = 23) (Large RV)	p-value (*)
Male	64 (67%)	12 (86%)	7 (58%)	19 (73%)	7 (64%)	7 (58%)	14 (61%)	ns
Age at corrective surgery (years)	1.0 (0.1 – 32.8)	0.9 (0.2 – 1.8)	7.0 (0.7 – 22.9) †	1.2 (0.2 – 22.9)	0.6 (0.3 – 5.7)	1.6 (0.3 – 17.5)	0.9 (0.3 – 17.5)	ns
Transannular patch	55 (57%)	4 (29%)	0 (0%)	4 (15%)	11 (100%)	10 (83%)	21 (91%) *	< 0.001
Age at study (years)	22 (7 – 66)	15 (7 – 18)	45 (25 – 59) †	18 (7 – 59)	14 (10 – 21)	30 (24 – 64) ‡	24 (10 – 64)	ns
NYHA class	I/II/III: 79/16/1	I/II: 13/1	I/II: 11/1	I/II: 24/2	I/II: 10/1	I/II: 9/3	I/II: 19/4	ns
TGF-β (ng/ml)	4.9 (± 4.6)	5.6 (± 6.7)	7.4 (± 3.7)	6.3 (± 5.7)	3.6 (± 3.6)	4.0 (± 3.2)	3.8 (± 3.3)	ns
NT-proBNP (pmol/l)	16 (± 21)	10 (± 8)	20 (± 24)	14 (± 18)	15 (± 12)	22 (± 13)	19 (± 13)	ns
hsCRP (mg/l)	1.1 (0.2 – 20.5)	0.9 (0.2 – 2.8)	1.3 (0.3 – 13.8)	1.1 (0.2 – 13.8)	0.8 (0.2 – 8.8)	2.9 (0.5 – 20.5)	1.6 (0.2 – 20.5)	ns
PR (%)	30 (± 17)	13 (± 11)	8 (± 9)	11 (± 11)	46 (± 7)	40 (± 8)	43 (± 8) *	< 0.001
RVEDV (ml/m^2)	140 (± 37)	105 (± 10)	99 (± 14)	102 (± 12)	171 (± 28)	170 (± 16)	171 (± 22) *	< 0.001
RVEF (%)	49 (± 6)	54 (± 5)	50 (± 7)	52 (± 6)	47 (± 4)	46 (± 5)	46 (± 5) *	< 0.001
RV Mass/EDV ratio	0.18 (± 0.04)	0.19 (± 0.04)	0.21 (± 0.03)	0.20 (± 0.04)	0.17 (± 0.03)	0.16 (± 0.03)	0.17 (± 0.03) *	0.001
LVEDV (ml/m^2)	87 (± 13)	86 (± 16)	86 (± 12)	86 (± 14)	89 (± 11)	91 (± 16)	90 (± 13)	ns
LVEF (%)	55 (± 5)	59 (± 5)	54 (± 4) †	57 (± 5)	54 (± 5)	54 (± 5)	54 (± 5)	ns
QRS duration (msec)	136 (± 26)	123 (± 24)	142 (± 22) †	132 (± 24)	129 (± 30)	140 (± 31)	135 (± 31)	ns
Peak VO_2 (%)	93 (± 17)	98 (± 16)	107 (± 20)	101 (± 18)	99 (± 16)	89 (± 18)	93 (± 18)	ns
VE/VCO_2 slope	30 (± 5)	28 (± 3)	27 (± 2)	27 (± 3)	30 (± 6)	32 (± 3)	31 (± 4) *	0.003

Results are expressed as mean (± standard deviation), median (range), or as counts (percentages).

* Significantly different between subgroups A and C (small RV) and subgroups B and D (large RV).

† Significantly different between subgroup A and subgroup C.

‡ Significantly different between subgroup B and subgroup D.

Abbreviations: EDV = end-diastolic volume; EF = ejection fraction; FU = follow-up duration after corrective surgery; hsCRP = high-sensitivity C-reactive protein; LV = left ventricle; ns = not significant; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; PR = pulmonary regurgitation; RV = right ventricle; subA = subgroup A; subB = subgroup B; subC = subgroup C; subD = subgroup D; TGF-β = transforming growth factor-β; VE/VCO_2 = ventilatory response to carbon dioxide production; peak VO_2 = peak oxygen uptake.

Table 2: Results of the serial follow-up study

Parameter	**Patients (N = 36)**		
Male	23 (64%)		
Age at corrective surgery (years)	0.8 (± 0.5)		
Transannular patch	28 (78%)		
	Baseline	**Follow-up**	**p-value (*)**
Age at study (years)	14 (± 5)	19 (± 5) *	< 0.001
NYHA class	I/II: 31/5	I/II: 28/8	ns
TGF-β (ng/ml)	4.6 (± 2.6)	3.0 (± 1.9) *	0.005
NT-proBNP (pmol/l)	16 (± 11)	14 (± 10)	ns
hsCRP (mg/l)	0.5 (0.2 – 17.5)	1.0 (0.2 – 20.5)	ns
PR (%)	31 (± 15)	33 (± 17) *	0.013
RVEDV (ml/m^2)	137 (± 33)	148 (± 38) *	0.001
RVEF (%)	50 (± 5)	49 (± 5)	ns
RV Mass/EDV ratio	0.18 (± 0.03)	0.17 (± 0.03)	ns (p = 0.075)
LVEDV (ml/m^2)	82 (± 11)	86 (± 12) *	0.011
LVEF (%)	57 (± 5)	56 (± 5)	ns
QRS duration (msec)	126 (± 27)	135 (± 28) *	< 0.001
Peak VO_2 (%)	94 (± 19)	88 (± 15)	ns (p = 0.055)
VE/VCO_2 slope	30 (± 4)	31 (± 4)	ns

Results are expressed as mean (± standard deviation SD), median (range), or as counts (percentages).

* Significantly different between baseline and follow-up.

Abbreviations: as in Table 1.

Multi-protein array analysis shows augmented immune reactivity in patients with repaired tetralogy of Fallot with severe RV dilatation.

In TOF patients with a small RV, serum levels of IFN-γ and TNF-α decreased with increasing follow-up duration. In healthy controls, these levels decreased with increasing age (Figure 1). In contrast, in TOF patients with severe RV dilatation, little decline (IFN-γ) or a small increase (TNF-α) in serum levels was observed with increasing follow-up duration.

Low TGF-β levels and consistently elevated serum levels of TNF-α and INF-γ often point towards a heightened inflammatory state. Indeed, in TOF patients with severe RV dilatation, serum levels of known inflammatory regulators IL18BP, E-Selectin, TNFRSF21, IL8, CXCL3, CCL26, CXCL12, L-Selectin, IP10, IL9, and IL2R all increased with increasing follow-up duration (Figure 2), in contrast to results in patients with a small RV or healthy controls. This observation indicates that immune activation in TOF patients with severe RV dilatation is persistently heightened and does not diminish with increasing follow-up duration, as in healthy controls or in TOF patients with a small RV.

Table 3: Results of healthy controls

Parameter	Controls (N = 32)	Controlgroup 1 (N = 8)	Controlgroup 2 (N = 8)	Controlgroup 3 (N = 8)	Controlgroup 4 (N = 8)
Male	18 (60%)	5 (63%)	8 (100%)	4 (50%)	3 (38%)
Age at study (years)	23 (± 13)	13 (± 1) ‡	16 (± 3) ‡	22 (± 3) ‡	38 (± 15)
TGF-β (ng/ml)	4.6 (± 2.6)	4.5 (± 1.4)	5.7 (± 3.4)	4.3 (± 1.7)	3.9 (± 3.4)
NT-proBNP (pmol/l)	5 (± 5)	4 (± 2)	4 (± 2)	7 (± 8)	4 (± 3)
hsCRP (mg/l)	0.6 (0.2 – 27.1)	0.3 (0.2 – 1.5)	0.5 (0.2 – 1.9)	1.5 (0.4 – 27.1)	2.7 (0.2 – 6.4)

Results are expressed as mean (± standard deviation), median (range), or as counts (percentages).

‡ Significantly different with controlgroup 4 (ANOVA, Bonferroni).

Abbreviations: as in Table 1.

Serum levels of the proliferation and cardiomyocyte survival factors EGFR, EGF, and EGVEGF and serum levels of protective TIMP2 decreased with increasing follow-up duration in TOF patients with severe RV dilatation (Figure 3), in contrast to results in patients with a small RV or healthy controls. Finally, CTF1 increased with increasing follow-up duration in patients with severe RV dilatation, whereas CTF1 levels decreased in patients with a small RV or healthy controls (Figure 3).

Figure 1 – 3: Results of multi-protein array analysis in cross-sectional patient-subgroups and healthy control-subgroups. Results show changes in serum levels of different proteins with increasing follow-up duration in TOF patients with severe RV dilatation (large RV: subgroup B vs. subgroup D) and in TOF patients without severe RV dilatation (small RV: subgroup C vs. subgroup A). In healthy controls, the results are changes in serum levels of different proteins with increasing age (controlgroup 4 vs. subgroup 1).
Results are %change in absolute values obtained from pooled serum samples per group.

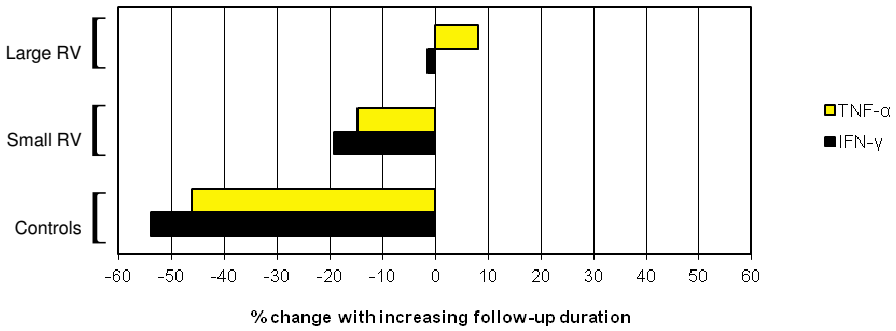


Figure 1: Increase of IFN-γ and TNF-α serum levels point towards a heightened inflammatory state in repaired TOF patients with severe RV dilatation. Results show changes in serum levels of IFN-γ and TNF-α.

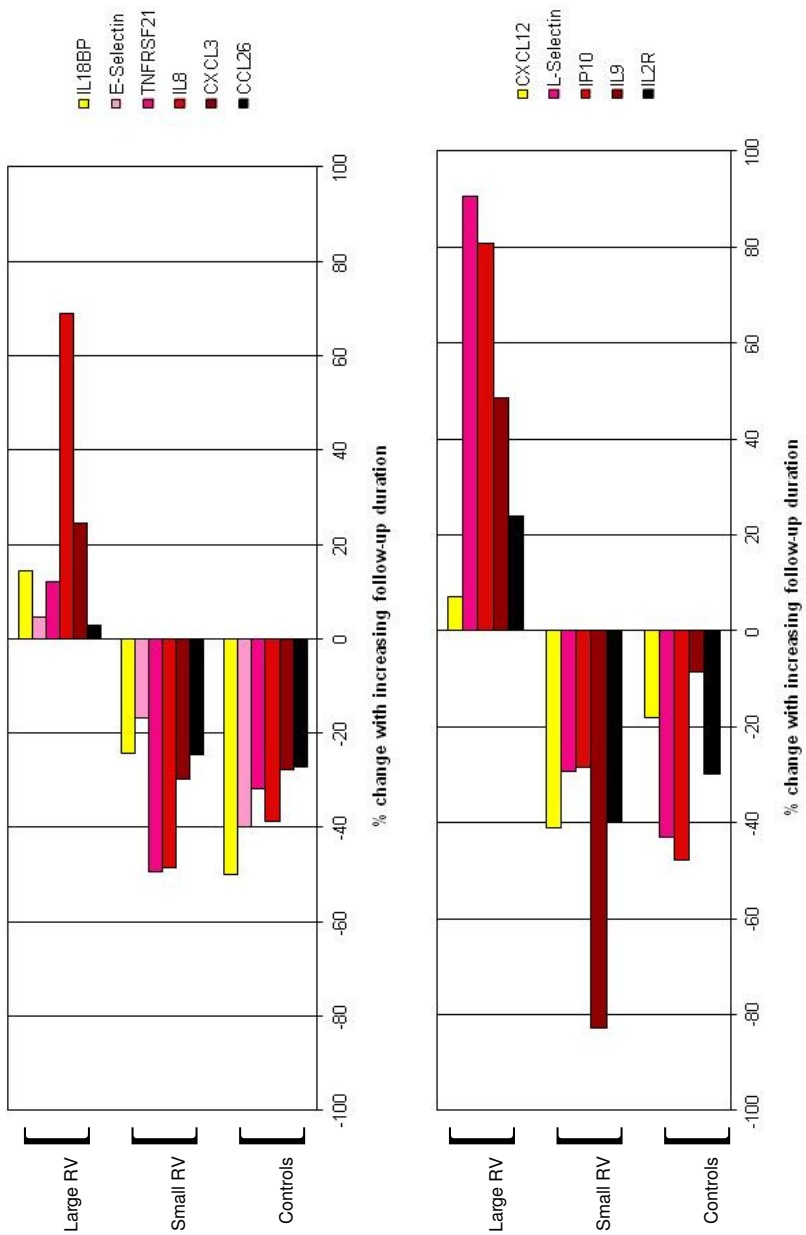


Figure 2: Rise in serum levels of inflammatory biomolecules in repaired TOF patients with severe RV dilatation. Results show changes in serum levels of IL18BP, E-Selectin, TNFRSF21, IL8, CXCL3, CCL26, CXCL12, L-Selectin, IP10, IL9, and IL2R.

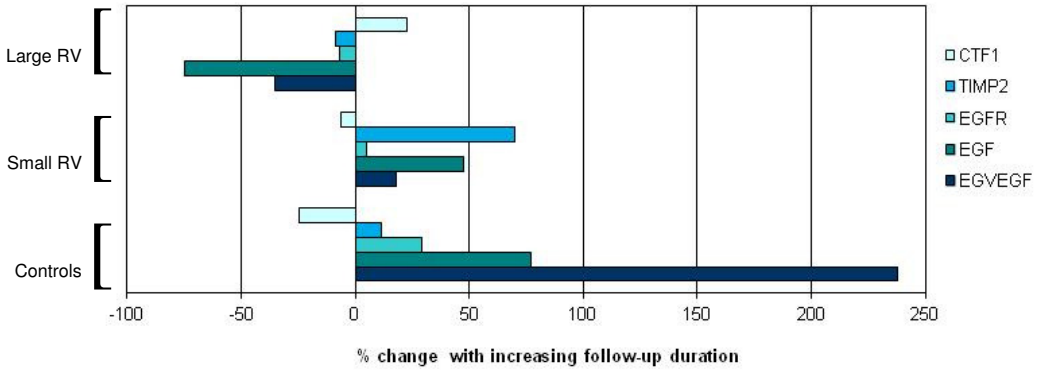


Figure 3: Decline in serum levels of cardioprotective biomolecules in repaired TOF patients with severe RV dilatation. Results show changes in serum levels of EGFR, EGF, EGVEGF, TIMP2 and CTF1.

Discussion

In this study we demonstrated that: (1) repaired TOF patients with progressive RV enlargement were characterized by a decline in serum levels of protective TGF-β over time; (2) patients with severe RV dilatation were characterized by a trend towards lower TGF-β levels; (3) this coincided with an increase in a significant number of immune regulatory factors that indicate an augmented inflammatory state; (4) IFN-γ and TNF-α levels were augmented with increasing follow-up duration in TOF patients with severe RV dilatation, indicating that TGF-β suppression of these 2 key cytokines is diminished; (5) in addition, TOF patients with severe RV dilatation lost their long-term cardiac protection due to a decline in growth and survival factors and metalloproteinase inhibitors with increasing follow-up duration, while levels of hypertrophy inducers increased.

From previous studies we know that RV volume overload from pulmonary regurgitation can be tolerated well for many years. However, eventually compensatory mechanisms will fail, as it has been reported that the incidences of arrhythmias, exercise intolerance, heart failure, and death increase significantly with increasing age[1,5,18]. Up till now, the mechanisms involved in the transition from the initial state of compensated RV volume overload to RV failure have not been elucidated. In previous studies, NT-proBNP has been proposed as marker of RV dysfunction in TOF patients[7-8]. In our study, NT-proBNP levels were higher in patients than in healthy controls, but were not discriminative between subgroups of patients. In our serial follow-up study, we found a decrease in TGF-β levels over the course of 5 years, coinciding with an increase in RV size and QRS duration, and a trend towards a decrease in RV mass/volume ratio and peak VO_2. This indicates that TGF-β may be involved in the process of progressive RV dilatation and decline of RV function.

Multiple studies have indicated an important function for TGF-β in the processes of infarct healing, cardiac repair and LV remodeling[12-14]. It is known that myocardial infarction initially triggers an inflammatory response[11]. Although immune activation is required for the following steps including fibroblast activation and scar tissue formation, lack of timely suppression of the immune response inhibits progression of the healing process. TGF-β has been shown to act as a

potent immuno-suppressor by deactivating macrophages and inhibiting synthesis of pro-inflammatory cytokines and chemokines[19]. In line with these observations, we found that TGF-β levels decreased over time in TOF patients who showed an increase in RV size over time. In our cross-sectional study, TGF-β levels tended to be lower in patients with severe RV dilatation than in patients with limited RV dilatation. This coincided with an increase in a significant number of pro-inflammatory factors, whereas the same biomolecules were declining with longer follow-up duration in TOF patients with limited RV dilatation and in healthy controls of similar age.

TGF-β is a potent inhibitor of TNF-α and IFN-γ synthesis and activation[20-21]. Previous studies have shown the importance of TNF-α and IFN-γ in the onset of cardiomyopathy[22-23]. Inhibition of TNF-α in volume-overloaded rats attenuated ventricular dilatation and improved cardiac function[22]. IFN-γ transgenic mice induced synthesis of pro-inflammatory cytokines in the heart region and subsequent chronically active myocarditis with LV dilatation and reduced heart function[23]. In our study, we found little decline or an increase in TNF-α and IFN-γ levels with increasing follow-up duration in TOF patients with severe RV dilatation. These findings imply that this subpopulation of TOF patients suffer from a chronic heightened state of immune activity as a result of a lack of TGF-β mediated immune suppression. However, it has to be noted that we could not validate the data for TNF-α and IFN-γ using commercially available ELISA assays, which was partly due to the low sensitivity of the method.

TGF-β also plays a role in scar tissue formation: it recruits fibroblasts to the damaged region and promotes differentiation of these cells into myofibroblasts[11-12]. It also promotes the synthesis of ECM components and controls ECM preservation by inducing the production of TIMPs[11]. Therefore, diminished TGF-β availability could significantly affect the cardiac healing process. Indeed, experiments in transgenic mice have shown that interruption of the TGF-β mechanism attenuated ECM deposition and proliferation of interstitial fibroblasts, while ventricular dilatation was promoted[12]. In line with these findings, we observed a decline in proliferation and cardiomyocyte survival factors in TOF patients with severe RV dilatation, while TIMP2 levels were reduced. These data suggest a role for TGF-β in the setting of longstanding RV volume overload, indicating that diminished TGF-β signaling disrupts the complex process of cardiac healing, leading to progressive RV dilatation.

Previous experimental studies have evaluated the effects of angiotensin converting enzyme (ACE)-inhibitors, angiotensin II type-1 (AT_1) receptor blockers, β-blockers, and spironolactone on various biomolecules involved in the process of heart failure[11,24-27]. TGF-β seems to act downstream of angiotensin-II and treatment with ACE inhibitors or AT_1-receptor blockers have been reported to decrease TGF-β levels in hypertrophied and infarcted hearts of rats[28-29]. In our TOF patients with progressive RV dilatation, TGF-β levels decreased over time, which suggests that ACE inhibitors would not be beneficial in these patients. In a clinical trial, Babu-Narayan et al. demonstrated that the increase in RV size over 6 months time was not different between TOF patients treated with ramipril and a placebo group[30]. Furthermore, the change in RV ejection fraction was also not significantly different between the 2 groups, but echocardiographic long-axis shortening improved after ramipril treatment[30]. Further experimental and clinical studies are

required to evaluate the effects of these drugs on TGF-β levels in the setting of chronic RV volume overload and to evaluate whether these drugs might be or might not be useful in the treatment of patients after TOF repair.

Limitations

Limitations of our study include the lack of confirmation of the biomolecular changes noted in the serum of our patients in myocardium. Furthermore, late gadolinium enhancement MRI may have given more insight in the importance of current observations. Although late gadolinium enhancement MRI can be used to demonstrate areas of RV myocardial fibrosis[6], it does not provide information on the time of occurrence of fibrosis. Prospective tissue characterization in relation to assessment of serum and myocardial changes in relevant biomarker levels is required to further elucidate the myocardial mechanisms related to adaptation to chronic RV volume overload.

The cytokines assessed with the protein array analysis were not analyzed in the individual patients, but were measured in pooled serum samples per subgroup. Results were not available for the patients in the serial follow-up study. Since we only had small subgroups, a limited statistical power is a factor to consider.

Conclusions

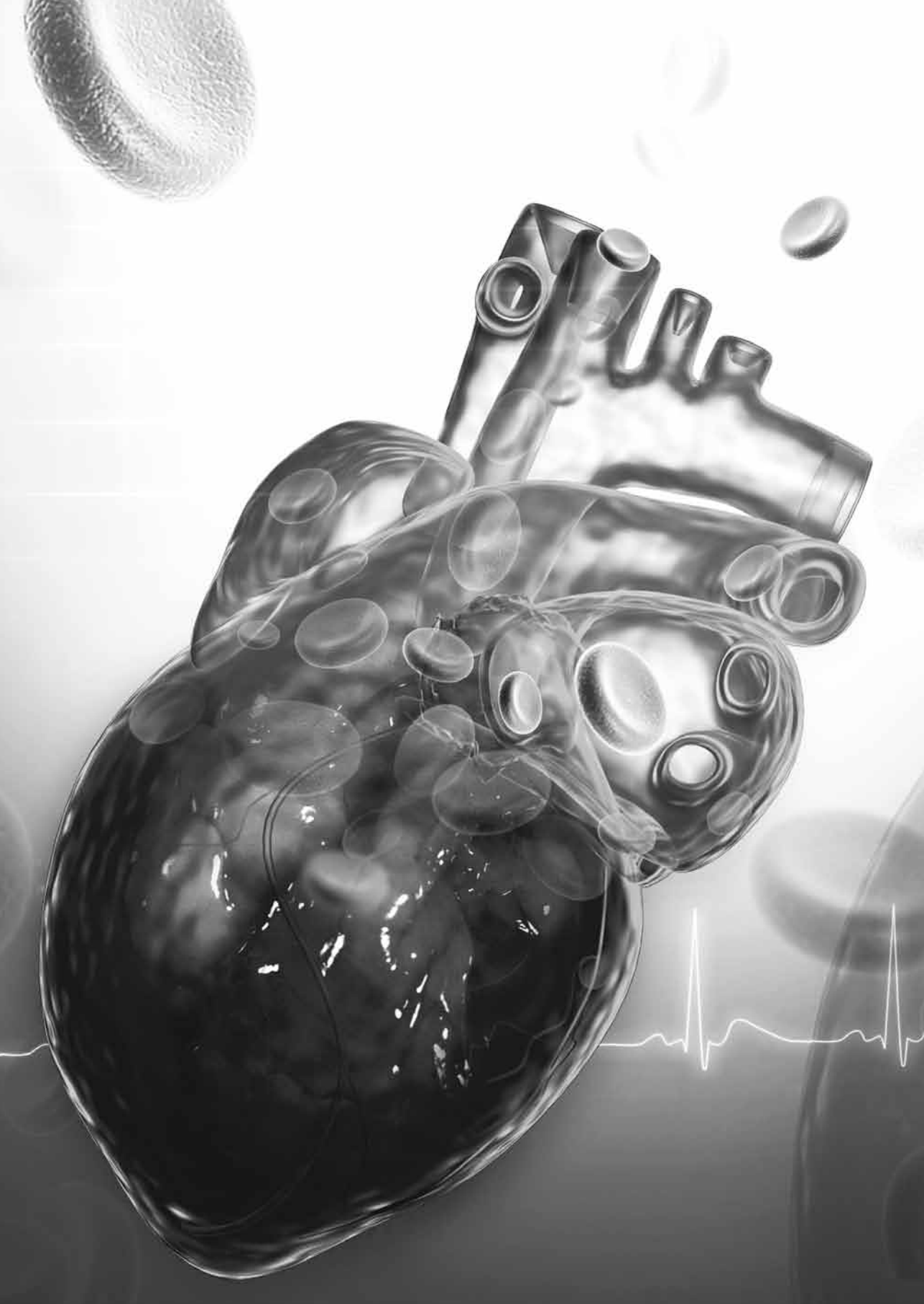
Here we have linked, for the first time to our knowledge, the process of progressive RV dilatation with declining serum levels of TGF-β in patients after tetralogy of Fallot repair. Diminished serum levels of TGF-β coincided with increased markers of immune activation, and reduced markers of cardiac protection, rendering this subgroup of patients more susceptible to adverse RV remodeling and eventually RV failure.

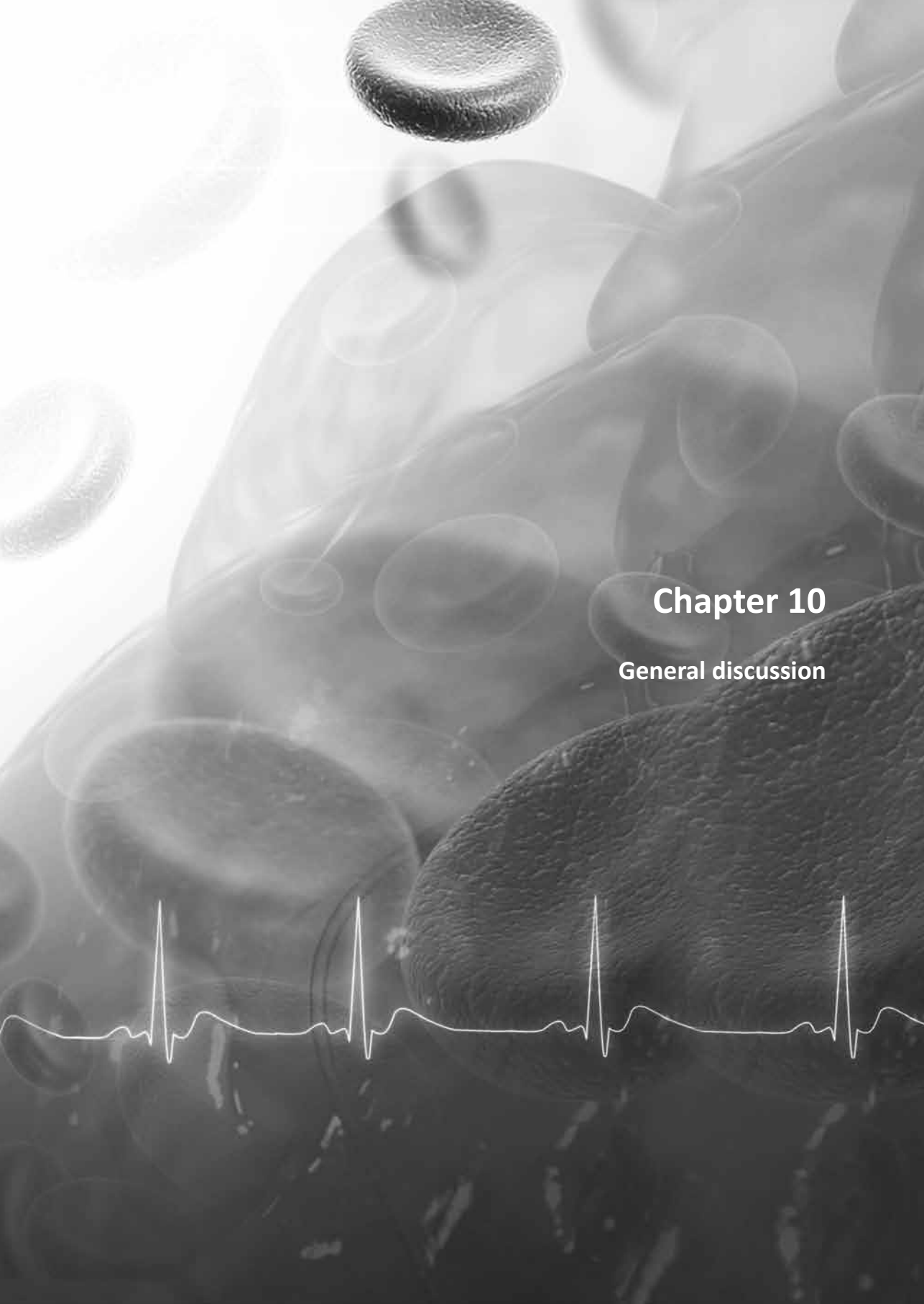
A better understanding of the molecular biology that governs this process might aid in earlier recognition of patients at risk for heart failure and better treatment options. Future research is warranted to evaluate if biocomponents in the TGF-β pathway may be used as biomarkers for predicting the progression of the disease by long-term monitoring, and if specific TGF-β based therapy could be developed.

References

1. Hickey EJ, Veldtman G, Bradley TJ, et al. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. European Journal of Cardio-Thoracic Surgery 2009;35:156-164.
2. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975-981.
3. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol 2004;43:1068-1074.
4. Giardini A, Specchia S, Tacy TA, et al. Usefulness of Cardiopulmonary Exercise to Predict Long-Term Prognosis in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2007;99:1462-1467.
5. Khairy P, Aboulhosn J, Gurvitz MZ, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation 2010;122:868-875.
6. Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. Circulation 2006;113:405-413.
7. Bolger AP, Sharma R, Li W, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation 2002;106:92-99.
8. Norozi K, Buchhorn R, Bartmus D, et al. Elevated brain natriuretic peptide and reduced exercise capacity in adult patients operated on for tetralogy of fallot is due to biventricular dysfunction as determined by the myocardial performance index. Am J Cardiol 2006;97:1377-1382.
9. Oosterhof T, Tulevski, II, Vliegen HW, Spijkerboer AM, Mulder BJ. Effects of volume and/or pressure overload secondary to congenital heart disease (tetralogy of fallot or pulmonary stenosis) on right ventricular function using cardiovascular magnetic resonance and B-type natriuretic peptide levels. Am J Cardiol 2006;97:1051-1055.
10. Villar AV, Cobo M, Llano M, et al. Plasma levels of transforming growth factor-beta1 reflect left ventricular remodeling in aortic stenosis. PLoS One 2009;4:e8476.
11. Bujak M, Frangogiannis NG. The role of TGF-β signaling in myocardial infarction and cardiac remodeling. Cardiovascular Research 2007;74:184-195.
12. Lucas JA, Zhang Y, Li P, et al. Inhibition of transforming growth factor-beta signaling induces left ventricular dilation and dysfunction in the pressure-overloaded heart. Am J Physiol Heart Circ Physiol 2010;298:H424-H432.
13. Li P, Wang D, Lucas J, et al. Atrial natriuretic peptide inhibits transforming growth factor beta-induced Smad signaling and myofibroblast transformation in mouse cardiac fibroblasts. Circ Res 2008;102:185-192.
14. Sakata Y, Chancey AL, Divakaran VG, Sekiguchi K, Sivasubramanian N, Mann DL. Transforming growth factor-beta receptor antagonism attenuates myocardial fibrosis in mice with cardiac-restricted overexpression of tumor necrosis factor. Basic Res Cardiol 2008;103:60-68.
15. van den Berg J, Strengers JLM, Wielopolski PA, et al. Assessment of biventricular functional reserve and NT-proBNP levels in patients with RV volume overload after repair of tetralogy of Fallot at young age. Int J of Cardiol 2009;133:364-370.
16. Luijnenburg SE, Robbers-Visser D, Moelker A, Vliegen HW, Mulder BJ, Helbing WA. Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by CMR imaging. Int J Cardiovasc Imaging 2010;26:57-64.
17. Wasserman K HJ, Sue DY, Stringer WW, Whipp BJ, ed. Principles of exercise testing and interpretation. 4th ed: Philadelphia: Lippincott Williams & Wilkins, 2005:160-182.

18. Geva T. Repaired tetralogy of Fallot: the roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. J Cardiovasc Magn Reson 2011;13:9.
19. Werner F, Jain MK, Feinberg MW, et al. Transforming growth factor-beta 1 inhibition of macrophage activation is mediated via Smad3. J Biol Chem 2000;275:36653-36658.
20. Lebastchi AH, Khan SF, Qin L, et al. Transforming growth factor beta expression by human vascular cells inhibits interferon gamma production and arterial media injury by alloreactive memory T cells. Am J Transplant 2011;11:2332-2341.
21. Sumiyoshi K, Nakao A, Setoguchi Y, Tsuboi R, Okumura K, Ogawa H. TGF-beta/Smad signaling inhibits IFN-gamma and TNF-alpha-induced TARC (CCL17) production in HaCaT cells. J Dermatol Sci 2003;31:53-58.
22. Jobe LJ, Melendez GC, Levick SP, Du Y, Brower GL, Janicki JS. TNF-alpha inhibition attenuates adverse myocardial remodeling in a rat model of volume overload. Am J Physiol Heart Circ Physiol 2009;297:H1462-H1468.
23. Reifenberg K, Lehr HA, Torzewski M, et al. Interferon-gamma induces chronic active myocarditis and cardiomyopathy in transgenic mice. Am J Pathol 2007;171:463-472.
24. Brower GL, Levick SP, Janicki JS. Inhibition of matrix metalloproteinase activity by ACE inhibitors prevents left ventricular remodeling in a rat model of heart failure. Am J Physiol Heart Circ Physiol 2007;292:H3057-H3064.
25. Flesch M, Hoper A, Dell'Italia L, et al. Activation and functional significance of the renin-angiotensin system in mice with cardiac restricted overexpression of tumor necrosis factor. Circulation 2003;108:598-604.
26. Yu CM, Sanderson JE, Chan S, Yeung L, Hung YT, Woo KS. Right ventricular diastolic dysfunction in heart failure. Circulation 1996;93:1509-1514.
27. Seeland U, Schaffer A, Selejan S, et al. Effects of AT1- and beta-adrenergic receptor antagonists on TGF-beta1-induced fibrosis in transgenic mice. Eur J Clin Invest 2009;39:851-859.
28. Kim S, Ohta K, Hamaguchi A, Yukimura T, Miura K, Iwao H. Effects of an AT1 receptor antagonist, an ACE inhibitor and a calcium channel antagonist on cardiac gene expressions in hypertensive rats. Br J Pharmacol 1996;118:549-556.
29. Yu C-M, Tipoe GL, Wing-Hon Lai K, Lau C-P. Effects of combination of angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist on inflammatory cellular infiltration and myocardial interstitial fibrosis after acute myocardial infarction. J Am Coll Cardiol 2001;38:1207-1215.
30. Babu-Narayan SV, Uebing A, Davlouros PA, et al. Randomised trial of ramipril in repaired tetralogy of Fallot and pulmonary regurgitation: the APPROPRIATE study (Ace inhibitors for Potential PRevention Of the deleterious effects of Pulmonary Regurgitation In Adults with repaired TEtralogy of Fallot). Int J Cardiol 2012;154:299-305.





Chapter 10

General discussion

Although patients with repaired tetralogy of Fallot (TOF) have been studied extensively, it remains a challenge to predict right ventricular (RV) dysfunction at an early stage. Therefore, the optimal timing to perform pulmonary valve replacement (PVR) is still a subject for debate and no uniform guidelines exist for asymptomatic TOF patients in particular. We performed a serial follow-up study with a 5-year interval in patients who have not undergone PVR already (referred to as "non-PVR" patients) to gain insight in the course of RV dilatation and functional changes over time, since this information is currently lacking. Biventricular size, systolic and diastolic function were assessed using magnetic resonance imaging (MRI), and contractile reserve, the ability to increase ejection fraction (EF) during stress, was assessed using low-dose dobutamine stress MRI. Furthermore, serial measurements of exercise capacity, electrocardiographic (ECG) parameters, and biomarkers were obtained. Results were compared to a group of PVR patients who were studied before and after PVR. We also assessed parameters of bi-atrial size and function in a cross-sectional study, in order to evaluate the associations with ventricular and functional parameters and the clinical value of these bi-atrial parameters. Additionally, we studied biomolecular pathways that are involved in the process of progressive RV dilatation, because a better understanding of the pathways involved in this process might aid in earlier recognition of patients at risk for RV failure and better treatment options.

In this chapter, we will give an overview of our most relevant results and their clinical and prognostic implications. We will discuss the outcomes against the background of the published literature and provide suggestions for future research if applicable.

Magnetic resonance imaging and parameters of ventricular function

Observer variability

Routine evaluation of biventricular size and function is essential in the follow-up of patients after TOF repair. Since parameters of biventricular size and function have a main contribution to decision making with regard to timing of PVR, it is of crucial importance that MRI measurements of biventricular size and function are reproducible. To reduce observer variability, all MRI contours in this thesis had been drawn by the same observer (SL), except for the studies about atrial function (chapter 6) and RV diastolic function during dobutamine stress (chapter 8). In these 2 studies, part of the contours had been drawn by students and were supervised by SL.

Before the start of our study in 2007, observer variability had been tested in various studies using steady-state free precession (SSFP) MRI. These studies had mostly been done in healthy controls or patients with acquired heart disease[1-4], but not in patients with congenital heart disease (CHD). In patients with CHD, observer variability had only been assessed using the older gradient echo imaging pulse sequences[5]. Observer variability, using SSFP MRI, had never been studied in a heterogeneous group of patients with CHD, representative for the total spectrum in a clinical program.

We speculated that observer variability would be higher in patients with CHD, since the shape of their ventricles is often changed due to different loading conditions. In **chapter 3**, we found that intra-observer variability for biventricular size and function was between 3% and 7% and interobserver variability between 4% and 10% in patients with different types of CHD, including

patients after TOF repair. These results were adequate and were comparable to reported results in the literature for healthy controls, patients with acquired heart disease, and patients with different types of CHD, which were reported in the meanwhile[1-4,6-10], Despite the adequate and comparable results, this variation should be taken into account when interpreting MRI results in clinical practice.

Observer variability may be caused by differences in the inclusion or exclusion of papillary muscles and trabeculations[10-11]. For example, the inclusion of papillary muscles and trabeculations in the ventricular cavity will lead to an overestimation of the ventricular volumes and an underestimation of the EF. However, in patients with a systemic RV, this method has been proven to be more reproducible than the inclusion of papillary muscles and trabeculations in the ventricular wall mass[10]. Correctly identifying the atrioventricular valve borders and the pulmonary valve in the basal slice are other sources of observer variation. This would be less difficult if an axial image orientation would be used. However, correctly identifying the blood-myocardial boundary on the inferior wall of both ventricles is more difficult if an axial image orientation is used. Most centers prefer the use of a short axis set. It has been reported that using the long-axis images in addition to the short axis images reduces interstudy variability, because it makes identification of the atrioventricular valve planes easier[12]. This should be incorporated in clinical practice.

Parameters of ventricular function

Although ejection fraction is the most commonly used parameter of systolic function, it might be questioned if it is the best marker reflecting ventricular function in patients with altered loading conditions, as in patients after TOF repair. Right ventricular performance depends on several intrinsic and extrinsic factors, like contractility, preload, afterload, heart rate, and ventricular-ventricular interactions. It has been reported that in mitral regurgitation, augmented preload increases left ventricular (LV) EF and may cause an overestimation of contractility, which may lead to the false assumption that contractility is normal, because LVEF is normal[13]. This also applies to patients with repaired TOF, in whom increased preload due to pulmonary regurgitation (PR) causes an increased RVEF, which may overestimate true RV performance[14]. Several studies have tried to provide more sensitive parameters of ventricular function in patients with repaired TOF. For example, Vliegen and collegues have proposed to measure the RVEF corrected for regurgitation of the tricuspid valve and pulmonary valve by dividing the net pulmonary flow by the RV end-diastolic volume (EDV): RVEFcor = net pulmonary flow (pulmonary forward flow – pulmonary backward flow) / RVEDV[15]. Others have suggested to measure RV effective stroke volume (eff.SV), which is stroke volume (SV) corrected for pulmonary regurgitant volume: RVeff.SV = RVSV – PR volume[16-17].

In order to provide more insight in the adaptive response of the RV to chronic volume overload and to improve measures of ventricular function in TOF patients, Bodhey et al. have suggested to analyze the function of the RV inlet part, the RV apical trabecular part, and the RV outlet part separately using MRI[18]. In their TOF patients, the RV apical trabecular part showed significant enlargement as compared to healthy controls, but the EF of this part of the RV, which contributes most to global RVEF, was maintained at control levels. The outlet part showed a

significant increase in RV end-systolic volume (ESV), and a reduced EF[18]. These results were confirmed by van der Hulst et al., who performed the same analysis using three-dimensional (3D) echocardiography[19]. In addition, Greutmann and collegues also studied RV regional function with two-dimensional (2D) echocardiography[20]. In their adult TOF patients, the function of the right ventricular outflow tract (RVOT) was impaired in all TOF patients, which is in agreement with results of the aforementioned studies. Furthermore, Greutmann et al. found that TOF patients with preserved RVEF on MRI (RVEF ≥ 50%), could compensate for this loss of RVOT function with an increased function of the RV body, while patients with an impaired RVEF on MRI could not[20]. This preserved contractile function of the RV apical trabecular part or RV body might explain the good clinical outcome that has been reported in TOF patients, operated on at a young age, in whom global RVEF is often only mildly reduced. Our TOF patients operated at a young age also had a good clinical condition and adequate exercise capacity, despite significant RV enlargement (**chapters 4 – 6, 8, and 9**). It might therefore be useful to incorporate the assessment of the size and function of the RV apical trabecular part in future follow-up studies that focus on seeking prognostic criteria for preventing RV failure.

In recent years, strain measurements have also been proposed as additional parameters of ventricular performance. Strain imaging measures the degree of myocardial deformation during the cardiac cycle, whereas strain rate is the rate of myocardial deformation over time. These parameters can be calculated using different echocardiographic techniques, like tissue Doppler imaging and speckle tracking[21-24], but also using MRI tagging or MRI tissue tracking[25-30]. Using these techniques, information about global and regional myocardial performance can be acquired. It has been shown that global and regional RV longitudinal strain decreased significantly over a 4-year period in TOF patients with mild to moderate RV dilatation, whereas RVEF remained unchanged during this follow-up period[22]. This demonstrates that RVEF may not be the first parameter to decline in TOF patients with subclinical RV dysfunction and that strain parameters might be used as markers to detect early deterioration in RV performance, particularly in asymptomatic TOF patients.

Strain measurements were not included in our research protocol. It may be useful to incorporate this in future research protocols.

Pulmonary regurgitation and pulmonary valve replacement

Methods for RVOT reconstruction

The detrimental effects of longstanding PR on RV function and clinical outcome have become clear over the last decades. Furthermore, the association between a transannular patch (TAP) and the amount of PR has been increasingly recognized[31-33]. The general opinion about surgical repair in TOF patients has shifted from the need for complete relief of the RVOT obstruction towards a policy to reduce the TAP size and the amount of TAPs used, despite the risk of some residual pulmonary stenosis (PS)[34-39].

Stewart and collegues reported that an annulus sparing surgical strategy could be performed in 80% of TOF patients[38]. Transannular patches could therefore be avoided in many patients, in whom subvalvular and supravalvular RVOT obstruction was aggressively approached during

intracardiac repair. These results were confirmed by Voges et al., who reported the need for a TAP in 32% of their patients, in whom an annulus sparing technique had been proposed[36]. Significant markers for success in the study by Stewart et al. were a larger pulmonary annulus size (Z-score greater than or equal to -4, calculated from a published nomogram[40]), a tricuspid pulmonary valve, and a postoperative RV to LV pressure ratio of less than 0.7. At short-term follow-up, postoperative peak RVOT gradients or peak RVOT flow velocities were not different between the annulus sparing groups and the patients who underwent TAP repair[36,38]. The need for reoperation for significant residual RVOT stenosis in the annulus sparing groups was 4% – 6% in these studies, which was higher, but not significantly different from the patients undergoing TAP repair[36,38].

In a large study by Park et al., preservation of the pulmonary annulus during surgery was found to reduce the reoperation rate at long-term follow-up[41]. In their total population of TOF patients, reoperation or reintervention was required in 32% of the patients (224 of 707). The most common causes for reintervention were PR and branch pulmonary artery stenosis. Reconstruction of the RVOT with a TAP was one of the risk factors associated with later reoperation and reintervention[41]. Hua and collegues have even proposed a more aggressive pulmonary annulus preservation strategy, in which pulmonary root enlargement at the supra-annular level was accomplished, as well as augmentation of the native pulmonary valve tissue with autologous pericardium[39]. However, despite all these encouraging attempts in recent years to reduce the number of TAPs used and therefore the amount of PR at long-term follow-up, there are still a large number of TOF patients who suffer from severe PR and subsequent RV dilatation, and face long-term morbidity.

Predictors for early right ventricular dysfunction – serial follow-up measurements

Although PR and RV dilatation can be tolerated well for many years, deterioration of clinical condition and ventricular function, and the risk of life-threatening arrhythmias and cardiac-related death have been reported to increase with increasing age, particularly after the third decade of life[42-48]. Patients with severe PR and severe RV dilatation can be treated with PVR, but the optimal timing to undergo PVR remains controversial, particularly in asymptomatic patients[14-16,42,49-61]. We know from previous reports that the lifespan of a homograft is limited[62-65], which means that patients are at risk for subsequent surgeries and interventions later in life if PVR is performed at an early stage. However, irreversible RV dysfunction may have occurred already if PVR is performed too late. Tetralogy of Fallot patients have been studied extensively to identify predictors for early RV dysfunction. Various parameters have been proposed as parameters that may have prognostic value, like parameters of RV size and biventricular function, RVOT motion, parameters of exercise tests, QRS duration, and (N-terminal prohormone) brain natriuretic peptide ((NT-pro)BNP)[14,31-32,47,56,58,66-73]. Despite extensive research in TOF patients, serial follow-up measurements, including MRI measurements of biventricular size and function, in non-PVR TOF patients are limited. This means that the progression rate of RV dilatation, deterioration of RV function, and the change in clinical condition over time, have not been clarified yet in patients who have not undergone PVR

already. This information could contribute to clinical decision making with regard to timing of PVR, but also to follow-up strategies, like for example in establishing MRI intervals.

In recent years, only a few studies have been published describing serial follow-up measurements in non-PVR TOF patients. In a study by Grothoff and collegues, a relatively young population of non-PVR TOF patients underwent an MRI study twice within 4 years[74]. The authors found a significant increase in RVEDV during the follow-up period, but only in patients who had undergone TAP repair. RVEF did not change during follow-up in this study. Limitations to this study included the heterogeneous patient population with regard to age at repair and follow-up duration since repair, and the lack of clinical tests[74].

In **chapter 5**, we demonstrated a significant increase in PR fraction and RV size over the course of 5-years time in non-PVR TOF patients, but the increase in RVEDV was limited, i.e. 1.6 ± 3.0 ml/m^2/year. Right ventricular EF and RVeff.SV did not change during follow-up in our non-PVR patients, but were lower than in healthy controls. We had hypothesized that the increase in RVEDV over time (RVEDV slope) would be related to the RVEDV at baseline and that there would be a RVEDV cut-off point above which the increase in RV size during follow-up would be significantly steeper. Unexpectedly, we found that the RVEDV slope was not associated with the RVEDV at baseline. In multivariate analysis, we found that a smaller RVeff.SV at baseline was an independent predictor for a steeper increase in RV size during follow-up. This emphasizes the need for routine measurement of RVeff.SV in TOF patients, which can be easily obtained from standard MRI measurements.

Kipps and co-workers published serial exercise test results in non-PVR TOF patients[75]. In their study, 70 adult TOF patients were examined twice with a mean interval of 2.8 years. The authors reported a significant decrease in peak oxygen uptake (peak VO_2) during the follow-up period, from 78 ± 19% of predicted values (28 ± 9 ml/kg/min) to 73 ± 16% of predicted values (25 ± 7 ml/kg/min), i.e. -1.4 ± 9.2%/year. The ventilatory response to carbon dioxide production (VE/VCO_2 slope) remained unchanged during this follow-up period. A higher peak VO_2 at baseline was associated with a more rapid decrease in peak VO_2 during follow-up. The rate of decrease in peak VO_2 was not related to age, gender, a TAP repair, or any baseline MRI parameters. The authors conclude that the deterioration in exercise capacity is difficult to predict in TOF patients[75]. A limitation of this study was the lack of serial MRI measurements.

In our non-PVR TOF patients, peak VO_2 also decreased during follow-up (**chapter 5**), from 96 ± 19% of predicted values (39 ± 7 ml/kg/min) to 91 ± 17% of predicted values (34 ± 7 ml/kg/min), which was equal to an annual decrease of 1.4 ± 2.9%/year. A higher peak VO_2 at baseline was the only independent predictor for a steeper decrease in peak VO_2 during follow-up in multivariate analysis, which is comparable with the results of Kipps et al[75].

Gatzoulis and co-workers studied serial ECG measurements and found that the QRS duration increased with 1.5 ± 1.2 msec/year in adult TOF patients free of arrhythmias. The rate of change per year increased to 3.5 ± 1.2 msec/year in patients who died suddenly during follow-up and to 4.1 ± 2.2 msec/year in TOF patients with ventricular tachycardia (VT)[66]. In our non-PVR TOF patients, QRS duration increased significantly from 132 ± 27 msec at baseline to 139 ± 27 msec at follow-up, i.e. 1.1 ± 1.8 msec/year (**chapter 5**). This is comparable to the increase of 1.5 ± 1.2 msec/year reported by

Gatzoulis et al. for TOF patients free of arrhythmias. In our patients, VT runs were rarely seen and none of the VT runs lasted ≥ 30 sec or required cardioversion. This might be due to our younger patient population, younger age at repair, and different surgical approach in comparison with the population of Gatzoulis et al.

With regard to biomarker results, we found that NT-proBNP levels were higher in our TOF patients than in healthy controls, but remained stable over the course of 5 years, despite an increase in RV size during this time period (**chapters 5 and 8**). Our NT-proBNP levels also could not discriminate between non-PVR patients and baseline results of patients who underwent PVR during follow-up (referred to as "pre-PVR" patients), despite significantly larger RVs and worse RV function in pre-PVR patients (**chapter 5**). In addition to this, we were unable to demonstrate an association between NT-proBNP levels and parameters of RV size and function. Combined, these observations tend to limit the prognostic value of NT-proBNP measurements in the current population of TOF patients, in contrast to previously reported more encouraging results[71,76-79]. In these studies, (NT-pro)BNP levels have been reported to be positively associated with RV size, and negatively associated with RVEF[71,76-77,79]. In addition to these reports, (NT-pro)BNP levels were also reported to be elevated in patients with RV dysfunction after acute RV volume overload due to acute pulmonary embolism[80-82]. In our patient population, severe RV dysfunction was uncommon, which might be an explanation for the lack of an association between RV function and NT-proBNP level. It may also be speculated that acute RV volume overload and subsequent acute RV dysfunction may lead to more release of (NT-pro)BNP, while a more gradual process of RV dilatation and deterioration of RV function, as in our TOF patients, does not. Apitz and collegues conclude that early RV dysfunction cannot be predicted accurately with BNP levels in TOF patients[83], which is in agreement with our results. The prognostic value of (NT-pro)BNP levels in the current population of TOF patients is therefore still undetermined.

Despite the fact that changes over time in RV size, peak VO_2, and QRS duration were limited in our non-PVR patients, they are unfavourable, as is the decrease in RV mass/EDV ratio during follow-up in our non-PVR TOF patients (**chapter 5**).

Predictors for early right ventricular dysfunction – stress imaging parameters

In order to find better predictors of early RV dysfunction, stress imaging has been proposed as additional tool in TOF patients. Stress imaging has been proven to have prognostic value in patients with coronary artery disease, since it may be used to identify wall motion abnormalities indicative of myocardial ischemia[84-85], which has been related to an increased risk of experiencing a subsequent cardiac event[84]. In patients with CHD, stress imaging is mostly used to determine ventricular contractile reserve. In different patient populations, absent contractile reserve has been proven to have clinical and prognostic value[86-87]. In patients with a systemic RV after Mustard or Senning operation for transposition of the great arteries, the inability to decrease RVESV during stress or increase RVEF during stress was predictive for future cardiac events[87]. In TOF patients, abnormal stress responses have been reported[88-92], but its prognostic value has not been established yet.

In **chapter 7b**, we demonstrated that low-dose dobutamine stress imaging is feasible and safe in children and young adults with CHD. Minor side effects were reported in only a limited number of patients with complex CHD and no major side effects were observed. Major side effects, such as serious rhythm disturbances, have been reported with dobutamine stress testing, although most of these arrhythmias occurred with higher doses of dobutamine[85,92-95]. In our experience, a dosage of 7.5 µg/kg/min is safe and should limit the number of major side effects, but is also high enough to elicit a significant cardiovascular response[89,96-100].

In **chapter 8**, we performed low-dose dobutamine stress testing in a homogenous young TOF population twice, with a 5-year interval. In our study, 26 of our 27 non-PVR patients were able to increase RVEF during stress and to decrease RVESV during dobutamine stress at both time points. Furthermore, the relative increase in RVEF during stress (i.e. $((RVEF_{stress} – RVEF_{rest})/RVEF_{rest})*100\%$) and the relative decrease in RVESV during stress (i.e. $((RVESV_{stress} – RVESV_{rest})/RVESV_{rest})*100\%$) remained unchanged during the 5-year follow-up period (relative increase in RVEF during stress: +25 ± 9% (baseline) to +27 ± 10% (follow-up), not significant; relative change in RVESV during stress: -30 ± 10% (baseline) to -32 ± 10% (follow-up), not significant). This well preserved RV contractile reserve is in agreement with the good clinical condition and adequate exercise capacity in our patients and probably relates to the young age of the patient population and reflects excellent mid-term to long-term results in TOF patients operated on at a young age[68].

In the study of Winter and colleagues, the inability to increase RVEF during stress or decrease RVESV during stress were predictors for future cardiac events (e.g. hospitalization for heart failure, cardiac surgery, aborted cardiac arrest, or death)[87]. Since no such major events occurred in our young TOF population during the follow-up period, we evaluated the additional value of dobutamine stress testing by assessing relations between stress imaging parameters and parameters that have been shown to have prognostic relevance in the TOF population (**chapter 8**)[31,33,47,66,68,71,76,101]. These included parameters of RV size, exercise test results, ECG parameters, and NT-proBNP levels. Several significant relations were found between the relative increase in RVEF during stress or the relative decrease in RVESV during stress and these parameters. For example, at the baseline as well as at the follow-up study, a smaller relative increase in RVEF during stress was significantly associated with a longer QT interval, corrected for heart rate (QTc interval) ($r = -0.62$, $p < 0.001$ at baseline; $r = -0.54$, $p = 0.004$ at follow-up). This relation was also found for the relative decrease in RVESV during stress and the QTc interval, i.e. a smaller relative decrease in RVESV during stress was significantly associated with a longer QTc interval ($r = 0.42$, $p = 0.028$ at baseline; $r = 0.51$, $p = 0.007$ at follow-up). Furthermore, a smaller relative decrease in RVESV during stress at follow-up related significantly to a longer QRS duration at follow-up ($r = 0.50$, $p = 0.008$). However, the relative increase in RVEF during stress or the relative decrease in RVESV during stress at baseline could not predict the relative increase in QRS duration or the relative increase in QTc interval during the 5-year follow-up period. An important finding was that a smaller relative increase in RVEF during stress at baseline was predictive for a larger relative decrease in peak VO_2 during the 5-year follow-up period ($r = 0.59$, $p = 0.004$) (**chapter 8**). Since several studies have

established the prognostic value of peak VO_2 with regard to adverse outcomes and mortality in patients with CHD[47,70], this finding is of additional value in the follow-up of TOF patients.

We also found that a smaller relative decrease in RVESV during stress at baseline was significantly associated with a larger RVEDV at baseline (r = 0.42, p = 0.028) and with a larger RVEDV at follow-up (r = 0.49, p = 0.010). We were unable however to establish a significant relation between the relative decrease in RVESV during stress at baseline and the relative increase in resting RVEDV during the 5-year follow-up period (r = 0.26, p = 0.20), or between the relative increase in RVEF during stress at baseline and the relative increase in resting RVEDV during follow-up (r = -0.22, p = 0.28). The small number of patients may have limited statistical power and further studies are needed to establish if the increase in RV size over time could be predicted from stress imaging parameters at baseline.

A limitation to our study was that the patient population was most likely biased towards patients with a more favourable outcome, since our patients were relatively young and the patients who underwent PVR during the follow-up period (N = 9) were excluded from the analysis. We concluded that dobutamine stress imaging has additional value in the follow-up of patients after TOF repair, but larger studies are required to determine the extent of this additional value.

Additional analyses showed that the relative increase in RVEF during stress at baseline could not discriminate between non-PVR patients and pre-PVR patients (relative increase in RVEF during stress at baseline: +25 ± 9% (non-PVR patients) vs. +21 ± 10% (pre-PVR patients), not significant), despite significantly larger RVs in pre-PVR patients (RVEDV at baseline: 136 ± 34 ml/m^2 (non-PVR patients) vs. 177 ± 42 ml/m^2 (pre-PVR patients), p = 0.006). However, the relative decrease in RVESV during stress was significantly smaller in pre-PVR patients than in non-PVR patients (relative change in RVESV during stress at baseline: -30 ± 10% (non-PVR patients) vs. -20 ± 11% (pre-PVR patients), p = 0.016) (chapter 8 – data not shown). In addition to this, pre-PVR patients were unable to significantly increase RVeff.SV during stress, whereas RVeff.SV significantly increased during stress in non-PVR patients (**chapter 8**). This again emphasizes the need for assessment of additional parameters of RV function other than RVEF only.

An unexpected finding in our study was that a lower resting RVEF was related to a larger relative increase in RVEF during stress. However, there was no such association between resting RVEF and the relative decrease in RVESV during stress, which makes this result difficult to interpret. Uebing et al. observed a more pronounced response to dobutamine in TOF patients with a lower resting RVEF[88]. In addition to this, Robbers-Visser et al. found that the relative increase in EF during stress was highest in patients with a dominant RV after Fontan operation, in whom the resting EF was lower than in patients with a dominant LV[96]. An explanation for these results is difficult. It may be speculated that there could be a compensatory augmented response to dobutamine in patients with reduced RV function, which may precede RV dysfunction. Future studies are necessary to elucidate the mechanisms of deteriorating RV function. An upregulation of the β1-adrenergic-receptor pathway may be involved in this augmented response to dobutamine[102], but future studies are necessary to verify this.

A very recent report by Parish and co-workers suggested that a dobutamine dosage of 10 μg/kg/min may not be high enough to elicit discriminative responses in subgroups of patients with repaired TOF[103]. A normal response to dobutamine, i.e. decrease in RVESV and increase in RVEF, was demonstrated with a dobutamine dosage of 10 μg/kg/min in their patients. In a small number of their patients, an increase to a dobutamine dosage of 20 μg/kg/min resulted in either lack of further reduction or even increase in RVESV, and a significant worsening of RV contractile reserve[103]. A limitation to this study is the lack of clinical parameters. Further research is required to determine the prognostic value of dobutamine stress imaging in TOF patients and the optimal dobutamine dosage.

Endpoints

One of the limitations in our patient population is the lack of hard endpoints. The most powerful primary endpoint, death, is rare in young adult patients with repaired TOF, since long-term survival is excellent nowadays[104]. Surrogate endpoints are expected to predict a primary endpoint, and have a higher incidence in the population studied[105]. Therefore, surrogate endpoints may be used in clinical studies in TOF patients, thereby reducing the number of patients needed and reducing the length of the study. Detailed information about RV size and function, exercise capacity, biomarker assessment, 12-lead ECGs, and 24-hour Holter monitorings may provide surrogate endpoints. However, many of these parameters interact, or are influenced by other factors than ventricular function only, which makes the predictive value of the individual parameters less clear.

Knauth and co-workers identified LVEF < 55%, RVEF < 45%, and RVEDV Z ≥ 7 as independent predictors for adverse clinical outcomes in their adult population of TOF patients. RVEDV Z ≥ 7 corresponded to ≥ 172 ml/m^2 in women and ≥ 185 ml/m^2 in men in their population. Adverse clinical outcomes were defined as death (N = 4), sustained VT lasting > 30 seconds or requiring cardioversion (N = 8), and deterioration to New York Heart Association (NYHA) class III or IV (N = 10)[68]. The only independent predictor for no clinical deterioration during follow-up was age at TOF repair < 3 years, which is current practice in most centers nowadays, as it was for most of our TOF patients. We used the cut-off values for LVEF, RVEF, and RVEDV as surrogate endpoints in our serial follow-up study (**chapter 5**). The following baseline parameters were independent predictors for LVEF < 55% at follow-up: a palliative shunt before corrective surgery, larger LVEDV at baseline, and lower LVEF at baseline. It seems clear that a lower baseline LVEF is related to LVEF < 55% at follow-up. The fact that a palliative shunt before corrective surgery is related to LVEF < 55% at follow-up might be related to older age at repair, which has been reported to be related to adverse clinical outcome[66,68]. The relation between a larger LVEDV at baseline and LVEF < 55% at follow-up is less clear, but will be discussed in more detail in the section on ventricular-ventricular interactions. A palliative shunt before corrective surgery, larger RVEDV, larger RV mass, lower RVEF, lower LVEF, longer QRS duration, and lower peak VO_2 at baseline were all associated with RVEF < 44% at follow-up in univariate analysis. This emphasizes the association between a longer QRS duration and lower RVEF, and between worse exercise capacity and lower RV function, although these parameters were not independently associated with RVEF < 44% at follow-up. A lower RVEF at baseline was the only

independent predictor for RVEF < 44% at follow-up in multivariate analysis. A larger RVEDV at baseline was the only independent predictor for RVEDV at follow-up up ≥ 172 ml/m^2 in women and ≥ 185 ml/m^2 in men in our non-PVR TOF population.

We also performed multivariate analysis with PVR as surrogate endpoint. A worse NYHA class, larger RVEDV at baseline, and higher PR fraction at baseline were independent predictors for PVR during follow-up (chapter 5 – data not shown). Although these parameters were statistically independent predictors for PVR, it may be questioned whether these parameters are also clinically independent predictors for PVR. A worse clinical condition, a large RV, and severe PR are among others parameters on which the decision to replace the pulmonary valve is usually made.

In addition to the surrogate endpoints defined by Knauth and collegues, a prolonged QRS duration, a decreased peak VO_2, an increased VE/VCO_2 slope, and an elevated (NT-pro)BNP level have also been reported in the literature as surrogate endpoints. We will discuss these surrogate endpoints below. Gatzoulis and co-workers have reported that a QRS duration ≥ 180 msec is a powerful predictor for life-threatening arrhythmias[67]. In our patients (**chapter 5**), a QRS duration ≥ 180 msec was observed in only a very limited number of patients (1 non-PVR patient (1%) and 7 PVR patients (13%) at baseline, and 3 non-PVR patients (4%) and 7 PVR patients (13%) at follow-up), which hampers its use as surrogate endpoint in our study.

A lower peak VO_2 and a higher VE/VCO_2 slope have been related to impaired survival in patients with heart failure and different types of CHD, including patients after TOF repair. Cut-off values which are related to poorer prognosis have been reported to be between 10 and 20 ml/kg/min for peak VO_2 and between 34 and 45 for the VE/VCO_2 slope[47,70,106-110]. Only a limited number of our patients (**chapter 5**) had a peak VO_2 below 20 ml/kg/min or a VE/VCO_2 slope above 34, which again hampers the use of these parameters as surrogate endpoints in our population (peak VO_2 < 20 ml/kg/min: 0 non-PVR patients and 1 of 20 PVR patients (5%) at baseline; 0 non-PVR patients and 1 of 9 PVR patients (11%) at follow-up; VE/VCO_2 slope > 34: 5 of 37 non-PVR patients (14%) and 4 of 20 PVR patients (20%) at baseline; 13 of 50 non-PVR patients (26%) and 2 of 9 PVR patients (22%) at follow-up).

Cut-off values for NT-proBNP have been inconsistent in the literature[72-73]. Cowie et al. have proposed to use NT-proBNP levels ≥ 12 pmol/l for men and ≥ 18 pmol/l for women as cut-off values for the detection of heart failure[72]. In our patients (**chapter 5**), 20 of 36 non-PVR patients (56%) and 5 of 12 PVR patients (42%) had NT-proBNP levels above this cut-off value at baseline and 28 of 71 non-PVR patients (39%) and 8 of 17 PVR patients (47%) at follow-up. However, Smith et al. have reported that NT-proBNP levels can range up to 46 pmol/l in healthy teenagers between 3 and 14 years and up to 27 pmol/l between 15 and 18 years[73]. In our patients, NT-proBNP levels above these age-dependent cut-off values were observed in 2 of 30 non-PVR teenagers (7%) and in none of the PVR teenagers (N = 3) at baseline. At follow-up, NT-proBNP levels were below these cut-off values in all non-PVR (N = 17) and PVR (N = 2) teenagers. This again hampers its use as surrogate endpoint in our study. In addition to this, we were unable to demonstrate an association between NT-proBNP level and parameters of RV size and function, which limited the additional value of NT-proBNP levels in our study.

One of the limitations of our study was the incomplete exercise and biomarker data, particularly in PVR patients, which limited statistical power. Moreover, especially our older non-PVR patients may be interpreted as patients with a favourable outcome after TOF repair, because it may be speculated that PVR may have already been performed in older TOF patients with a less favourable outcome. Larger numbers of patients and longer follow-up duration is required in future research protocols.

Outcome after pulmonary valve replacement

In recent years, multiple reports have been published on outcome after PVR[15-17,49,51,53-58,60,111-121]. After PVR, an improvement in NYHA class is observed, as well as a significant decrease in PR fraction and RV volumes. Our results (**chapter 5**) are in agreement with these findings. However, it should be taken into account that the decrease in RV volumes after PVR will partly be due to surgical reduction of the RVOT during PVR. In many patients, the insertion of a pulmonary homograft is accompanied by resection of the large, or aneurysmatic, transannular or RVOT patch. In our PVR patients, almost half of the patients underwent RVOT remodeling during PVR.

Results with regard to functional ventricular recovery after PVR are less consistent. In some reports, an improvement in RVEF after PVR has been observed, which has not been confirmed in other reports. A meta-analysis of Cheung and collegues was unable to demonstrate an increase in RVEF after PVR[49]. As mentioned before, RVEF may not be the first parameter to decline in TOF patients with subclinical RV dysfunction. In line with this hypothesis, RVEF may also not be the first parameter to improve after PVR. In our PVR patients, RVEF did not improve after PVR, but RVeff.SV did significantly increase after PVR (**chapter 5**). This has also been reported in some other studies[16-17].

In several studies, a decline in QRS duration has been observed after PVR [55,57,112,114,117]. Scherptong et al. reported that the absence of reduction in QRS duration after PVR was a major determinant of adverse outcome during follow-up[57]. Others reported stabilization, but no reduction, in QRS duration after PVR [116,118]. This is also concluded by the meta-analysis of Cheung et al.[49], and is in agreement with our results. Since QRS duration increased significantly in our non-PVR patients during the 5-year follow-up period, stabilization of QRS duration after PVR in our PVR patients could therefore be considered a favourable result of the PVR (**chapter 5**).

Results about improvement of exercise capacity after PVR are equivocal in the reported literature[16-17,51,55,113,121]. In one of the largest studies, peak VO_2 did not improve in 57 patients after PVR, but the VE/VCO_2 slope did[16]. In our PVR patients, exercise capacity did not improve after PVR, or even tended to deteriorate further. Since results were only available in a very limited number of patients, adequate conclusions cannot be drawn in our patients.

Several studies have tried to provide thresholds for RV size, above which PVR should be performed in order to achieve adequate reduction in RV size after PVR and a favourable outcome. Threshold values of between 150 – 200 ml/m^2 for RVEDV have been proposed as cut-off values[16,56,58,60]. We performed a subgroup analysis in our PVR patients, based on the cut-off

value of 170 ml/m^2 for RVEDV at baseline (**chapter 5**). We found that RV volumes decreased in both subgroups, but did not return to normal in patients with RVEDV ≥ 170 ml/m^2 before PVR, which is in agreement with previous reports[56,58]. Furthermore, RVEF did not improve in both our subgroups after PVR, although RVEF was significantly better in patients with the smaller RVs. However, RVeff.SV and LVSV did significantly improve in patients with a pre-PVR RVEDV < 170 ml/m^2, whereas this was not observed in patients with the larger RVs. Additionally, we found that NYHA class only significantly improved after PVR in patients with a pre-PVR RVEDV < 170 ml/m^2. These results may indicate that some of our PVR patients may have been operated too late. We therefore performed a subgroup analysis in our non-PVR patients too, in whom we used 142 ml/m^2 for RVEDV at baseline as cut-off point. This cut-off point was chosen because Frigiola et al. has reported improvement in biventricular function and exercise capacity in their TOF population, in whom PVR was performed with a mean RVEDV of 142 ml/m^2[16]. The subgroup analysis in our non-PVR patients showed no differences in change of RVEDV, RVeff.SV, and RVEF during the 5-year follow-up period, although RVEF was significantly higher in patients with RVEDV < 142 ml/m^2 at baseline. Moreover, clinical condition deteriorated and the VE/VCO_2 slope significantly increased during follow-up in patients with RVEDV ≥ 142 ml/m^2 at baseline, whereas these unfavourable changes were not observed in patients with the smaller RVs.

The mean RVEDV at follow-up was 176 ± 25 ml/m^2 for patients with a baseline RVEDV ≥ 142 ml/m^2. Despite the unfavourable changes, which were limited, most patients were still asymptomatic, biventricular function and exercise capacity were still adequate, serious arrhythmias were rarely seen, and only a small number of patients reached surrogate endpoints. This again indicates how difficult it is to adequately predict patients who are at risk for adverse outcomes. Harrild and co-workers studied the long-term effect of PVR on VT and mortality in adult non-PVR and PVR patients and found that PVR did not reduce the incidence of VT or death[53]. This emphasizes the need for additional parameters that can adequately predict early RV dysfunction or indicates that PVR should be performed earlier.

Homograft survival

As mentioned before, the lifespan of any valved conduit, including a homograft, is limited, which makes the optimal timing to perform a PVR an ongoing discussion. Freedom from conduit replacement has been reported to be between approximately 50% – 70% at 10 years and between 30% – 45% at 15 years in some of the earlier studies[62,122-125]. Some of these studies included patients with a wide spectrum of CHDs, including patients in whom the conduit had been placed during the initial surgery. Different types of conduits had been used in these studies, as well as different preservation techniques. Al these factors make it difficult to predict the longevity of homografts used in our current TOF population, in whom PVR is mostly performed at long-term follow-up due to severe PR.

Recent reports, describing homograft survival in TOF patients requiring PVR after the initial intracardiac repair and thus excluding patients in whom a homograft is placed during the initial surgery, are more encouraging[64-65,126]. A PVR can be performed with low operative risk, with

hospital mortality reported to be < 3%[49,65,126]. Freedom from valve-related events or replacement has been reported to be approximately 80% at 10 years and 70% at 15 years in these studies[64-65,126]. Factors that have been reported to be related to early homograft dysfunction include a smaller diameter of the pulmonary homograft, severe pre-PVR PR, and a higher homograft gradient 1 month after surgery [64,126].

Percutaneous pulmonary valve implantation

In the year 2000, the first percutaneous pulmonary valve implantation (PPVI) was performed in a 12-year old boy, who suffered from stenosis and insufficiency of his prosthetic conduit in the RVOT[127]. Bonhoeffer and collegues developed a system for percutaneous stent implantation combined with valve replacement[127]. Since the introduction of this procedure, over 800 PPVIs had already been performed by the year 2009, and this number continues to increase. The device is composed of a trileaflet bovine jugular vein sutured to a platinum-iridium balloon-expandable stent, the so-called Melody valve[128].

Mid-term results from the first 155 patients who underwent PPVI, most of them with TOF, were encouraging: survival at 83 months was 97%, and a significant reduction of RV systolic pressure could be accomplished. Freedom from reoperation was 93% at 10 months, and 70% at 70 months; freedom from transcatheter re-intervention was 95% at 10 months, and 73% at 70 months[129]. Freedom from reoperation in the latest 100 patients was significantly longer than in the first 50 patients, due to device modifications that had been implemented, the improvements of the delivery system, the learning curve of the operators, better patient selection, postdilatation of the stent in case of significant residual gradients over the implanted valve, and by changed strategies to deal with device failures. Stent fractures were the most common complication during follow-up occurring in 21% of the patients. Prestenting is performed in the majority of the patients nowadays, which might lead to better immediate hemodynamic results, but might also reduce the number of stent fractures[128]. Furthermore, functional and clinical outcome have been evaluated in 65 patients after PPVI[130]. Right ventricular size and PR decreased significantly after PPVI in all patients; RVEF only improved in patients who had predominantly PS before PPVI, but not in patients who had predominantly PR before PPVI. However, RVeff.SV increased significantly after PPVI in all patients. In the PS group, the peak VO_2 and the VE/VCO_2 slope significantly improved after PPVI, whereas these parameters remained unchanged after PPVI in the PR group, although the VE/VCO_2 slope seemed to improve 1 year after PPVI in these patients[130].

One of the limitations of the Melody valve is that it can be implanted only in RVOTs that range from 14 – 22 mm. The device can be expanded to a maximum diameter of 22 mm, because otherwise valve leaflet coaptation may fail, which precludes PPVI in many TOF patients who have not undergone surgical PVR already[128]. In many TOF patients, a TAP or RVOT patch is used in the initial intracardiac repair, which becomes dilated many years later, often exceeding a diameter of 22 mm. This again emphasizes the need for restrictive enlargement of the pulmonary annulus and RVOT in TOF patients undergoing initial surgical repair. The development of a percutaneous valved conduit for larger RVOTs has not been achieved until now.

The successful introduction of the PPVI has the potential to reduce the number of open-heart surgeries. Combined with the more encouraging results of the survival pattern of homografts in TOF patients requiring PVR during follow-up and the unfavourable changes in non-PVR patients over time, this may improve the outlook for earlier intervention in TOF patients.

Ventricular-ventricular interaction

Systolic function

Ventricular-ventricular interactions refer to the concept that the size, shape, and function of 1 ventricle may affect the other ventricle, which has been recognized since the beginning of the 19th century. Factors that contribute to these complex ventricular-ventricular interactions are the common interventricular septum, the shared epicardial myocardial fibers, the common pericardial sac, and series interaction through the pulmonary arterial and systemic vascular bed[119,131-135]. Ventricular-ventricular interactions occur during systole and diastole and occur in both directions[135]. Interactions during systole are mediated mainly through the interventricular septum, whereas the pericardium is more important in diastolic interactions[132-133]. Close relationships have been demonstrated between RV and LV function in TOF patients[31,33,136], which we also observed in our study: the correlation coefficient (r) between RVEF and LVEF was 0.41, $p < 0.001$ (chapter 5 – data not shown).

In recent years, an increasing number of studies have focused on the LV in patients after TOF repair[23,25,30,69,115,119,136-140], because it has been suggested that LV dysfunction may be a stronger predictor for adverse events and arrhythmias than RV dysfunction[33,43,68-69]. In addition to an increasing number of studies describing results of global and regional strain, several studies have reported on torsional mechanics of the LV with the use of speckle tracking echocardiography. During systole, the LV performs a wringing motion with a counterclockwise rotation of the apex and a clockwise rotation at the base of the ventricle. Left ventricular twist is then characterized as the maximal net difference in rotation between the LV apex and the LV base. It has been shown that LV twist and parameters of LV strain are decreased in TOF patients and closely correlate with RV size and RV strain patterns[23,136,138-140]. It has been suggested that alteration of LV configuration, e.g. by distortion of septal geometry secondary to RV volume overload, may contribute to abnormal LV torsional mechanics, indicating the presence of adverse ventricular-ventricular interactions[30,140]. Future research regarding regional RV and LV function using MRI or echocardiographic measurements of strain and twist is needed to evaluate the ability of these techniques to detect early biventricular dysfunction in patients after TOF repair. This then could contribute to clinical decision making with regard to timing of PVR.

In our PVR patients, LVEDV increased after PVR, which seems to reflect better LV filling resulting from increased RV effective output (**chapter 5**). This is in agreement with results from other studies[16,56,60] Surprisingly, we also found an increase in LVEDV during follow-up in our non-PVR patients, as well as a relationship between a higher LVEDV at baseline and a lower LVEF at follow-up in multivariate analysis. Although the LVEDV at follow-up was still comparable to results in healthy controls, these findings may be interpreted as unfavourable in these non-PVR patients, in whom a

steady increase in RV size was observed concurrently. This unfavourable relation between a higher LVEDV and lower LVEF in non-PVR TOF patients has also been recognized by others[119,137,139]. In these 3 studies, LVEDV was significantly higher in patients with a lower LVEF than in patients with a preserved LVEF. In addition to this, Tobler and collegues found that LVEDV did not increase after PVR in patients with a poor pre-PVR LVEF (< 45%), whereas LVEDV increased significantly after PVR in patients with a preserved pre-PVR LVEF (> 45%). This is in agreement with our results: the majority of our PVR patients had a preserved pre-PVR LVEF and showed an increase in LVEDV after PVR (**chapter 5**). The preserved LVEF in our patients might also explain the fact that no serious adverse events have been observed in our patients during follow-up, since LV dysfunction has been shown to be related to adverse outcome[43,68-69].

The exact mechanisms for increased LV size in patients with longstanding PR and RV dilatation are not fully elucidated, but may relate to an increase in RV size, as has been suggested by Tzemos and co-workers[139]. Pericardial constraint seems to play an important role in LV adaptation to RV dilatation. In an animal study, induction of acute RV dilatation with intact pericardium resulted in a decrease in LV size, whereas an increase in LV size occurred in animals with acute RV dilatation and an open pericardium[134]. This phenomenon needs to be further elucidated.

Diastolic function

The presence of ventricular-ventricular interactions is further strengthened by our observation of LV diastolic dysfunction in TOF patients with significant RV dilatation and reduced RV function (**chapter 6**).

Diastolic dysfunction has been reported to precede systolic dysfunction[141-142] and may therefore be an important marker in the serial follow-up of patients after TOF repair. In patients with acquired heart disease, diastolic dysfunction is present in nearly all patients with symptomatic (systolic) heart failure, although isolated diastolic heart failure, i.e. with preserved LVEF, has also been recognized[142-143]. Measurement of diastolic function can be divided into those that reflect the process of active relaxation and those that reflect passive stiffness[142].

In our cross-sectional study, we found signs of impaired RV relaxation in our TOF patients at long-term follow-up, i.e. a decreased early peak filling rate and a prolonged deceleration time (**chapter 6**). However, the other parameters of RV diastolic function did not show much difference compared with healthy controls, despite significant RV enlargement and reduced RV systolic function in our patients. This seems contradictory to the hypothesis of diastolic dysfunction preceding systolic dysfunction. However, whether these observations represent true normal diastolic function or a pseudonormal state[142] cannot be directly determined from our data.

Atrial size and function may provide useful information when assessing ventricular diastolic function. The function of the atria is to assist in the filling of the RV and LV during diastole. Increased atrial volumes usually reflect elevated ventricular filling pressures and atrial size has therefore been suggested to be a reliable indicator of the severity of ventricular diastolic dysfunction[144-146]. In our patients, right atrial (RA) minimal volume was significantly larger than in healthy controls (**chapter 6**), which is in agreement with recent results of Riessenkampf et al.[147]. Furthermore, RA

size positively related to RV size. These results may indicate that RV end-diastolic pressure (EDP) is elevated in patients with enlarged RA and RV size, which would point towards abnormal RV diastolic function in our patients.

Another sign of abnormal RV diastolic function in our TOF patients was the presence of end-diastolic forward flow (EDFF), defined as late diastolic forward flow in the pulmonary artery coinciding with atrial contraction, which was present in 60% of our patients (**chapter 6**). This has been recognized as a sign of restrictive RV physiology or impaired compliance[148-149]. The effects of the presence of EDFF on long-term outcome have been equivocal[61,98,148,150-157]. In some studies, the presence of EDFF has been related to favourable long-term outcome results as been represented by less PR, smaller RV size, shorter QRS duration, and better exercise capacity[148,157], but others have related EDFF to more PR, larger RV volumes, and worse exercise capacity[98,154-155]. Our patients with EDFF had more PR, larger RV volumes, a higher (worse) VE/VCO_2 slope, and a higher NT-proBNP level. QRS duration and other parameter of exercise testing were not different between patients with or without EDFF. Lu and collegues argue that the presence of EDFF in the current TOF population represents an overdistended RV, in which excessive RV dilatation leads to poor compliance and the presence of EDFF. The authors state that this may be a different phenomenon than the classical definition of restriction, in which the restriction to filling may be caused by fibrotic changes of the ventricular wall due to delayed and different surgical strategies[155]. These patients may present with smaller RV volumes. Surprisingly, parameters of RV diastolic function were not significantly different between our patients with and without EDFF (**chapter 6**), but our patients with EDFF had larger RA volumes and more abnormal RA emptying, which may point towards abnormal RV diastolic function in these patients.

Interestingly, we observed signs of impaired LV compliance in our TOF patients, in whom we found a significantly increased LV early-to-atrial filling (E/A) ratio, despite only mildly reduced LV systolic function. This increased LV E/A ratio has also been observed by Riessenkampf and collegues[147]. We speculate that this LV diastolic dysfunction relates in part to adverse RV-LV interactions[23,132,139-140]. Recent experimental and clinical studies have demonstrated a relation between RV pressure overload and impaired LV compliance, but also between RV volume overload and LV diastolic dysfunction[143,158]. In an animal study, Kitahori and collegues demonstrated that RV pressure overload caused LV diastolic dysfunction through mechanical and molecular effects on the interventricular septum and LV myocardium, emphasizing the presence of this interventricular coupling[143]. In the study by Schwartz and co-workers, a linear relation was found between RVEDV and LVEDP in patients after TOF repair[158]. This is in agreement with the results in our patients, in whom the most abnormal LV diastolic function was observed in patients with the largest RV size, i.e. the patients with EDFF.

In addition to RA size, parameters of abnormal RA empyting also related to RV size and clinical parameters, underlining the usefulness of assessment of RA size and function in the follow-up of TOF patients (**chapter 6**).

Biomolecular pathways

Although TOF patients have been studied extensively, information about the myocardial metabolism and biomolecular pathways that are involved in the process of progressive RV dilatation and the transition from a state of compensated RV volume overload to RV failure is limited. A better understanding of the molecular biology that governs this process might aid in earlier recognition of patients at risk for RV failure and better treatment options.

Chronic hypoxemia adversely affects myocardial function[159-160], but the exact effects on myocardial metabolism and long-term ventricular performance are less clear. Najm and collegues demonstrated decreased preoperative and postoperative adenosine triphosphate (ATP) levels and ventricular function in TOF patients with the most severe cyanosis before corrective surgery[159]. In **chapter 4**, we compared long-term results of patients after treatment for isolated PS with those after corrective surgery for TOF. One of the differences between patients with isolated PS and TOF is the presence of hypoxemia in TOF patients before treatment. In our patients, biventricular function and exercise capacity were not significantly different between PS and TOF patients 13 years after the initial treatment. However, RVEF was lower in both patient groups than in healthy controls, although only mildly reduced. This may indicate that the relatively short hypoxemic period before corrective surgery in TOF patients does not have detrimental effects on long-term ventricular function and exercise capacity. However, we did not include measurements of the myocardial metabolism, which could have provided additional information. An explanation for the mildly reduced RVEF and mildly reduced exercise capacity in PS patients, who had undergone percutaneous balloon valvuloplasty of the pulmonary valve, might be the longstanding mild PR, which we found in these patients.

In addition to the effects of hypoxemia on myocardial metabolism, it has been recognized that upregulation or downregulation of biomolecular pathways and altered gene expression occur in response to different overload conditions or myocardial infarction[160-183]. Different stressors may result in the development of different biomolecular phenotypes regulating processes such as inflammation, extracellular matrix (ECM) degradation, fibroblast proliferation, and cardiomyocyte apoptosis. This may affect ventricular remodeling processes such as the development of hypertrophy and fibrosis, dilatation, dysfunction, and eventually heart failure.

It is well known that increased matrix metalloproteinase (MMP) activity is involved in the process of adverse LV remodeling and heart failure[162,172-173,177,179,184-185]. Under normal conditions, MMP activity, which promotes ECM degradation and therefore ventricular dilatation, is regulated by their specific inhibitors, i.e. tissue inhibitors of metalloproteinases (TIMPs). The normal balance between MMP and TIMP expression is lost in cardiac pathologies and adverse LV remodeling is generally associated with enhanced MMP activity and reduced TIMP activity, although this pattern is not held universally and varies with the type and stage of disease[184]. Janicki and collegues describe 3 distinct phases to the process of adverse LV remodeling, i.e. an initial phase, which involves the activation of MMPs, collagen degradation, ventricular dilatation, and hypertrophy. The initial phase is followed by a compensated phase, in which MMP levels return to normal, but hypertrophy progresses and cardiac function is reduced. Following the transition to a decompensated phase, MMP activity becomes elevated again[162]. Most research has been done in

animal models of LV pressure or volume overload or after myocardial ischemia and less is known about RV pathologies. Sharma and co-workers studied biopsies of the RV myocardium in a small group of TOF patients undergoing initial intracardiac repair or homograft implantation late after initial repair. An increase in various biomolecules was found, but most MMPs remained unchanged, whereas TIMPs showed a downregulated pattern[180]. In our patients, serum MMP levels did not discriminate between TOF patients with smaller or larger RVs using a protein array analysis (chapter 9 – data not shown). However, TIMP2 levels decreased with increasing follow-up duration in patients with severe RV enlargement, whereas these levels increased in patients with only mildly dilated RVs or healthy controls. This may point towards an imbalance in MMP / TIMP expression favouring MMP activity in our patients with severe RV dilatation. It may be speculated that MMP activity was not elevated in our TOF patients and those of Sharma et al., because they may still be in a compensated state of RV overload and therefore do not show increased MMP activity, according to the aforementioned hypothesis. This may be supported by the finding that the RV mass/volume ratio in our patients was higher than in healthy controls (**chapter 5**), which may indicate that the RV is still capable of adapting to the elevated wall stress caused by the volume overload[162].

The process of adverse ventricular remodeling seems to be a complex interplay between many different biomolecules, which also includes inflammatory and anti-inflammtory cytokines[163-164,168,171,174,176,183,186-189]. In fibroblasts, the inflammatory cytokines interleukin (IL)6 and tumor necrosis factor (TNF)-α decrease collagen synthesis, increase MMP activity and decrease TIMP expression and therefore contribute to adverse ventricular dilatation[162,184]. Transforming growth factor (TGF)-β is an anti-inflammatory cytokine and a potent stimulator of collagen synthesis[183-184], which has also been shown to play an important role in the process of adverse LV remodeling[163,168,174,187,189], but also in aortic root dilatation in patients with Marfan syndrome[190-192]. It has been reported that interruption of TGF-β signaling decreased interstitial fibroblast proliferation and collagen deposition, which led to LV dilatation and dysfunction in the pressure-overloaded heart[168]. However, less is known about the role of TGF-β in RV volume overload settings. In our patients, progressive RV enlargement during 5-year follow-up was associated with declining serum levels of TGF-β (**chapter 9**). In our cross-sectional group of patients, a trend towards lower serum levels of TGF-β was found in patients with severe RV dilatation. This coincided with an augmented inflammatory state (e.g. increased serum levels of TNF-α) and loss of cardiac protection, as growth and survival factors were reduced (e.g. decreased levels of TIMP2) and markers of hypertrophy were increased. These may suggest a role for TGF-β in the setting of longstanding RV volume overload, indicating that diminished TGF-β signaling disrupts the complex process of cardiac healing, leading to progressive RV dilatation. We were unable to confirm our results in RV myocardium, since biopsies were not taken. Furthermore, late gadolinium enhancement MRI was not performed in our patients, which may have provided additional information regarding fibrotic areas in the RV myocardium. However, this would not have provided information on the time of occurrence of fibrosis. In operated TOF patients, these changes may have occurred before, during, or at different time-points after the intracardiac repair.

Angiotensin converting enzyme (ACE)-inhibitors, angiotensin II type-1 receptor blockers, β-blockers, and spironolactone are widely used in the prevention of heart failure, also of the RV, although these drugs have not been studied extensively for their effects in the RV. Previous experimental studies have evaluated the effects of these drugs on various biomolecules involved in the process of heart failure[163-164,193-198]. Some studies reported that the exact role of TGF-β, regarding its up or downregulation in remodeling processes, and the exact way by which ACE inhibitors act on this pathway and other pathways, have not been fully elucidated yet[163,168,190,193-194]. A first clinical trial in TOF patients treated with ramipril did not show major differences with regard to the rate of RV enlargement or change in MRI-derived RVEF during follow-up. However, biventricular long-axis shortening improved after ramipril treatment[199].

A better understanding of the pathways involved in the adaptive processes to chronic RV volume overload in patients after TOF repair and their interactions may lead to the identification of biomarkers that may be used in risk stratification and may provide targets for the development of specific therapies and future research.

Directions for future research

Future research protocols should continue to include serial follow-up measurements in all TOF patients in order to obtain more information on the rate of changes with regard to RV size, biventricular function, regional function, exercise capacity, QRS duration, arrhythmias, and biomarker levels in patients with different degrees of RV volume overload after TOF repair. Serial measurements of exercise capacity and NT-proBNP assessment were incomplete in our patients, which may have limited statistical power. Furthermore, the increase in RV size over time was limited in our non-PVR TOF patients. It may be speculated that patients with a more rapid increase in RV size may have undergone PVR already during the 5-year follow-up period. Unfortunately, serial MRI measurements before PVR were lacking in our PVR patients. This may have provided additional insight in the progression of RV size and the rate of deterioration of RV function in TOF patients with different degrees of RV volume overload. Future serial follow-up studies are needed to evaluate if this information could be used in risk stratification of TOF patients.

These serial measurements may be obtained most easily when standardized protocols would be incorporated in all tertiary referral centers in the Netherlands. All TOF patients should undergo an extensive set of studies at standardized time points after birth, for example every 5 years starting at the age of 8 years and continuing into adulthood, even after PVR or PPVI. Ideally, tests included in this extensive set should be: cardiac MRI, including dobutamine stress imaging and measurements of diastolic function and regional function, echocardiography including measurements of strain and twist, a maximal bicycle exercise test, including measurements of peak VO_2 and the VE/VCO_2 slope, 12-lead ECG, 24-hour Holter monitoring, and blood withdrawal for assessment of NT-proBNP, but also for further biomolecular pathway analyses. Additional parameters of RV function should be evaluated, since ejection fraction may not be the best parameters of RV function in patients with RV volume overload as in patients after TOF repair.

If standardized serial follow-up protocols could be accomplished in all TOF patients, important information will be acquired, which should give insight in many aspects of the disease progression, such as the rate of RV dilatation, (sub)clinical biventricular systolic and diastolic dysfunction, regional function, ventricular-ventricular interactions, biomolecular changes during chronic RV volume overload, long-term clinical outcome, and homograft function and survival. This may lead to better understanding of the process of adverse RV remodeling, as well as better predictors for early RV failure and better treatment options.

Conclusions

We have demonstrated that MRI is an accurate and reproducible method for the assessment of biventricular size and global biventricular function at rest and during low-dose dobutamine stress, although interobserver variability exceeded 10% for biventricular ESV with stress testing. Serial measurements with a 5-year interval demonstrated unfavourable changes in TOF patients who have not undergone PVR already. These unfavourable changes included a limited increase in RV size and QRS duration, and a deterioration of exercise capacity. However, clinical condition was still adequate in the majority of the patients and RV systolic function was only mildly reduced, despite important PR and RV dilatation. Left ventricular systolic function was preserved.

Signs of impaired biventricular diastolic function were observed in our non-PVR patients. Right atrial enlargement, and abnormal RA emptying were related to signs of impaired clinical condition, as was the presence of end-diastolic forward flow in the pulmonary artery. These parameters may serve as useful markers for clinically relevant RV diastolic dysfunction. The presence and significance of ventricular-ventricular interactions has been demonstrated. We observed LV diastolic dysfunction in patients with severe RV dilatation.

Right ventricular contractile reserve, i.e. the ability to increase RVEF during dobutamine stress, was preserved in the majority of our patients. This parameter may be useful to predict the deterioration in exercise capacity over time, since a smaller increase in RVEF during stress at baseline was predictive for a larger decrease in peak VO_2 during 5-year follow-up. Serum levels of NT-proBNP were higher than in healthy controls, but remained unchanged during 5-year follow-up and were not discriminative in our study.

Our results in non-PVR TOF patients may not be representative for all TOF patients, since our patients were relatively young and the majority of the patients had been operated according to current surgical guidelines at a young age.

In our PVR patients, NYHA class improved after PVR and QRS duration stabilized. RV volumes did not return to normal values after PVR in the subgroup of patients with RVEDV ≥ 170 ml/m^2 before PVR. Biventricular EF remained unchanged after PVR, but RVeff.SV improved after PVR in patients with RVEDV < 170 ml/m^2 before PVR. Combined with the more encouraging results of current studies on homograft survival and the successful introduction of PPVI, this may improve the outlook for earlier intervention. However, long-term results of PPVI are still awaited for.

Right ventricular eff.SV may be a better parameter of RV function than RVEF. Right ventricular eff.SV was an independent predictor for the increase in RVEDV over time in our non-PVR

patients. Furthermore, some patients who underwent PVR during follow-up were unable to augment RVeff.SV with dobutamine stress before PVR, whereas all PVR patients were able to increase RVEF with dobutamine stress before PVR. The lack of increase in RVeff.SV during dobutamine stress may be an indicator of impaired RV function that needs further study. Other parameters of RV function, such as parameters of regional function, should be evaluated as well. Ejection fraction may not be the best parameter of RV function in patients with altered loading conditions, as in patients after TOF repair.

We have linked, for the first time to our knowledge, the process of RV dilatation with declining serum levels of TGF-β. A trend towards lower levels of TGF-β in TOF patients with severe RV dilatation coincided with an increase in a significant number of immune regulatory factors that indicate an augmented inflammatory state. This cytokine may play an important role in the process of adverse RV dilatation. A better understanding of the molecular biology that governs this process might aid in earlier recognition of patients at risk for RV failure and better treatment options.

References

1. Clay S, Alfakih K, Messroghli DR, Jones T, Ridgway JP, Sivananthan MU. The reproducibility of left ventricular volume and mass measurements: a comparison between dual-inversion-recovery black-blood sequence and SSFP. Eur Radiol 2006;16:32-37.
2. Hudsmith LE, Petersen SE, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. J Cardiovasc Magn Reson 2005;7:775-782.
3. Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J 2006;27:2879-2888.
4. Plein S, Bloomer TN, Ridgway JP, Jones TR, Bainbridge GJ, Sivananthan MU. Steady-state free precession magnetic resonance imaging of the heart: comparison with segmented k-space gradient-echo imaging. J Magn Reson Imaging 2001;14:230-236.
5. Helbing WA, Rebergen SA, Maliepaard C, et al. Quantification of right ventricular function with magnetic resonance imaging in children with normal hearts and with congenital heart disease. Am Heart J 1995;130:828-837.
6. Catalano O, Antonaci S, Opasich C, et al. Intra-observer and interobserver reproducibility of right ventricle volumes, function and mass by cardiac magnetic resonance. J Cardiovasc Med (Hagerstown) 2007;8:807-814.
7. Karamitsos TD, Hudsmith LE, Selvanayagam JB, Neubauer S, Francis JM. Operator induced variability in left ventricular measurements with cardiovascular magnetic resonance is improved after training. J Cardiovasc Magn Reson 2007;9:777-783.
8. Mooij CF, de Wit CJ, Graham DA, Powell AJ, Geva T. Reproducibility of MRI measurements of right ventricular size and function in patients with normal and dilated ventricles. J Magn Reson Imaging 2008;28:67-73.
9. Robbers-Visser D, Boersma E, Helbing WA. Normal biventricular function, volumes, and mass in children aged 8 to 17 years. J Magn Reson Imaging 2009;29:552-559.
10. Winter MM, Bernink FJ, Groenink M, et al. Evaluating the Systemic Right Ventricle by CMR: the Importance of Consistent and Reproducible Delineation of the Cavity. J Cardiovasc Magn Reson 2008;10:40.
11. Hughes ML, Muthurangu V, Taylor AM. Cardiovascular MR imaging -- Indications, techniques and protocols. Progress in Pediatric Cardiology 2010;28:3-10.
12. Kirschbaum SW, Baks T, Gronenschild EH, et al. Addition of the long-axis information to short-axis contours reduces interstudy variability of left-ventricular analysis in cardiac magnetic resonance studies. Invest Radiol 2008;43:1-6.
13. Carabello BA. Evolution of the study of left ventricular function: everything old is new again. Circulation 2002;105:2701-2703.
14. Henkens IR, van Straten A, Schalij MJ, et al. Predicting Outcome of Pulmonary Valve Replacement in Adult Tetralogy of Fallot Patients. The Annals of Thoracic Surgery 2007;83:907-911.
15. Vliegen HW, van Straten A, de Roos A, et al. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of fallot. Circulation 2002;106:1703-1707.
16. Frigiola A, Tsang V, Bull C, et al. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? Circulation 2008;118:S182-190.
17. Ghez O, Tsang VT, Frigiola A, et al. Right ventricular outflow tract reconstruction for pulmonary regurgitation after repair of tetralogy of Fallot. Preliminary results. Eur J Cardiothorac Surg 2007;31:654-658.
18. Bodhey NK, Beerbaum P, Sarikouch S, et al. Functional Analysis of the Components of the Right Ventricle in the Setting of Tetralogy of Fallot. Circ Cardiovasc Imaging 2008;1:141-147.

19. van der Hulst AE, Roest AAW, Holman ER, et al. Real-Time Three-Dimensional Echocardiography: Segmental Analysis of the Right Ventricle in Patients with Repaired Tetralogy of Fallot. Journal of the American Society of Echocardiography 2011;24(11):1183-1190.
20. Greutmann M, Tobler D, Biaggi P, et al. Echocardiography for assessment of regional and global right ventricular systolic function in adults with repaired tetralogy of Fallot. Int J Cardiol 2012;157(1):53-58.
21. Eyskens B, Brown SC, Claus P, et al. The influence of pulmonary regurgitation on regional right ventricular function in children after surgical repair of tetralogy of Fallot. Eur J Echocardiogr 2010;11:341-345.
22. Scherptong RW, Mollema SA, Blom NA, et al. Right ventricular peak systolic longitudinal strain is a sensitive marker for right ventricular deterioration in adult patients with tetralogy of Fallot. Int J Cardiovasc Imaging 2009;25(7):669-676.
23. van der Hulst AE, Delgado V, Holman ER, et al. Relation of Left Ventricular Twist and Global Strain with Right Ventricular Dysfunction in Patients After Operative "Correction" of Tetralogy of Fallot. Am J Cardiol 2010;106:723-729.
24. Mertens LL, Friedberg MK. Imaging the right ventricle--current state of the art. Nat Rev Cardiol 2010;7:551-563.
25. Ordovas KG, Carlsson M, Lease KE, et al. Impaired regional left ventricular strain after repair of tetralogy of fallot. J Magn Reson Imaging 2012;35(1):79-85.
26. Fogel MA. Assessment of cardiac function by magnetic resonance imaging. Pediatr Cardiol 2000;21:59-69.
27. Roest AA, de Roos A. Imaging of patients with congenital heart disease. Nat Rev Cardiol 2012;9:101-115.
28. Helbing WA, de Roos A. Clinical applications of cardiac magnetic resonance imaging after repair of tetralogy of Fallot. Pediatr Cardiol 2000;21:70-79.
29. Scott CH, Sutton MS, Gusani N, et al. Effect of dobutamine on regional left ventricular function measured by tagged magnetic resonance imaging in normal subjects. Am J Cardiol 1999;83:412-417.
30. Ortega M, Triedman JK, Geva T, Harrild DM. Relation of Left Ventricular Dyssynchrony Measured by Cardiac Magnetic Resonance Tissue Tracking in Repaired Tetralogy of Fallot to Ventricular Tachycardia and Death. Am J Cardiol 2011;107(10):1535-1540.
31. Davlouros PA, Kilner PJ, Hornung TS, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol 2002;40:2044-2052.
32. van den Berg J, Hop WC, Strengers JL, et al. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of Fallot. J Thorac Cardiovasc Surg 2007;133:470-477.
33. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. J Am Coll Cardiol 2004;43:1068-1074.
34. Apitz C, Webb GD, Redington AN. Tetralogy of Fallot. Lancet 2009;374:1462-1471.
35. Carvalho JS, Shinebourne EA, Busst C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. Br Heart J 1992;67:470-473.
36. Voges I, Fischer G, Scheewe J, et al. Restrictive enlargement of the pulmonary annulus at surgical repair of tetralogy of Fallot: 10-year experience with a uniform surgical strategy. European Journal of Cardio-Thoracic Surgery 2008;34:1041-1045.
37. Boni L, Garcia E, Galletti L, et al. Current strategies in tetralogy of Fallot repair: pulmonary valve sparing and evolution of right ventricle/left ventricle pressures ratio. Eur J Cardiothorac Surg 2009;35:885-890.

38. Stewart RD, Backer CL, Young L, Mavroudis C. Tetralogy of Fallot: results of a pulmonary valve-sparing strategy. Ann Thorac Surg 2005;80:1431-8; discussion 1438-1439.
39. Hua Z, Li S, Wang L, Hu S, Wang D. A new pulmonary valve cusp plasty technique markedly decreases transannular patch rate and improves midterm outcomes of tetralogy of Fallot repair. Eur J Cardiothorac Surg 2011;40(5):1221-1226.
40. Kouchoukos NT BE, Doty DB, Hanley FL, Karp RB. Anatomy, dimensions, and terminology. In: Kirklin/Barratt-Boyes Cardiac Surgery 2003;Philadelphia:3-65.
41. Park CS, Lee JR, Lim HG, Kim WH, Kim YJ. The long-term result of total repair for tetralogy of Fallot. Eur J Cardiothorac Surg 2010;38:311-317.
42. Geva T. Indications and Timing of Pulmonary Valve Replacement After Tetralogy of Fallot Repair. Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual 2006;9:11-22.
43. Khairy P, Aboulhosn J, Gurvitz MZ, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation 2010;122:868-875.
44. Murphy JG, Gersh BJ, Mair DD, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. N Engl J Med 1993;329:593-599.
45. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-Term Survival in Patients With Repair of Tetralogy of Fallot: 36-Year Follow-Up of 490 Survivors of the First Year After Surgical Repair. J Am Coll Cardiol 1997;30:1374-1383.
46. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol 1998;32:245-251.
47. Giardini A, Specchia S, Tacy TA, et al. Usefulness of Cardiopulmonary Exercise to Predict Long-Term Prognosis in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2007;99:1462-1467.
48. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation 1995;91:2214-2219.
49. Cheung EW-Y, Wong WH-S, Cheung Y-F. Meta-Analysis of Pulmonary Valve Replacement After Operative Repair of Tetralogy of Fallot. Am J Cardiol 2010;106:552-557.
50. Davlouros PA, Karatza AA, Gatzoulis MA, Shore DF. Timing and type of surgery for severe pulmonary regurgitation after repair of tetralogy of Fallot. Int J Cardiol 2004;97 Suppl 1:91-101.
51. Gengsakul A, Harris L, Bradley TJ, et al. The impact of pulmonary valve replacement after tetralogy of Fallot repair: a matched comparison. Eur J Cardiothorac Surg 2007;32:462-468.
52. Grosse-Wortmann L, Redington A. Doing the right thing at the right time: is there more to pulmonary valve replacement than meets the eye? Eur Heart J 2009;30:2076-2078.
53. Harrild DM, Berul CI, Cecchin F, et al. Pulmonary valve replacement in tetralogy of Fallot: impact on survival and ventricular tachycardia. Circulation 2009;119:445-451.
54. Lim C, Young Lee J, Kim W-H, et al. Early replacement of pulmonary valve after repair of tetralogy: is it really beneficial? European Journal of Cardio-Thoracic Surgery 2004;25:728-734.
55. Meijboom FJ, Roos-Hesselink JW, McGhie JS, et al. Consequences of a selective approach toward pulmonary valve replacement in adult patients with tetralogy of Fallot and pulmonary regurgitation. J Thorac Cardiovasc Surg 2008;135:50-55.
56. Oosterhof T, van Straten A, Vliegen HW, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation 2007;116:545-551.
57. Scherptong RWC, Hazekamp MG, Mulder BJM, et al. Follow-Up After Pulmonary Valve Replacement in Adults With Tetralogy of Fallot: Association Between QRS Duration and Outcome. J Am Coll Cardiol 2010;56:1486-1492.

58. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. Am J of Cardiol 2005;95:779-782.
59. Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG, Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? Journal of the American College of Cardiology 2000;36:1670-1675.
60. Valsangiacomo Buechel ER, Dave HH, Kellenberger CJ, et al. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. Eur Heart J 2005;26:2721-2727.
61. van Straten A, Vliegen HW, Lamb HJ, et al. Time course of diastolic and systolic function improvement after pulmonary valve replacement in adult patients with tetralogy of Fallot. J Am Coll Cardiol 2005;46:1559-1564.
62. Brown JW, Ruzmetov M, Rodefeld MD, Vijay P, Turrentine MW. Right Ventricular Outflow Tract Reconstruction With an Allograft Conduit in Non-Ross Patients: Risk Factors for Allograft Dysfunction and Failure. The Annals of Thoracic Surgery 2005;80:655-664.
63. Caldarone CA, McCrindle BW, Van Arsdell GS, et al. Independent factors associated with longevity of prosthetic pulmonary valves and valved conduits. The Journal of Thoracic and Cardiovascular Surgery 2000;120:1022-1031.
64. Oosterhof T, Meijboom FJ, Vliegen HW, et al. Long-term follow-up of homograft function after pulmonary valve replacement in patients with tetralogy of Fallot. Eur Heart J 2006;27:1478-1484.
65. van de Woestijne PC, Mokhles MM, de Jong PL, Witsenburg M, Takkenberg JJM, Bogers AJJC. Right Ventricular Outflow Tract Reconstruction With an Allograft Conduit in Patients After Tetralogy of Fallot Correction: Long-Term Follow-Up. The Annals of Thoracic Surgery 2011;92(1):161-166.
66. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975-981.
67. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation 1995;92:231-237.
68. Knauth AL, Gauvreau K, Powell AJ, et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart 2008;94:211-216.
69. Ghai A, Silversides C, Harris L, Webb GD, Siu SC, Therrien J. Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of fallot. J Am Coll Cardiol 2002;40:1675-1680.
70. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation 2012;125:250-259.
71. Bolger AP, Sharma R, Li W, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation 2002;106:92-99.
72. Cowie MR, Jourdain P, Maisel A, et al. Clinical applications of B-type natriuretic peptide (BNP) testing. European Heart Journal 2003;24:1710-1718.
73. Smith J, Goetze JP, Andersen CB, Vejlstrup N. Practical application of natriuretic peptides in paediatric cardiology. Cardiol Young 2010:1-11.
74. Grothoff M, Hoffmann J, Lehmkuhl L, et al. Time course of right ventricular functional parameters after surgical correction of tetralogy of Fallot determined by cardiac magnetic resonance. Clin Res Cardiol 2011;100(4):343-350.
75. Kipps AK, Graham DA, Harrild DM, Lewis E, Powell AJ, Rhodes J. Longitudinal Exercise Capacity of Patients With Repaired Tetralogy of Fallot. Am J Cardiol 2011;108(1):99-105.
76. Oosterhof T, Tulevski, II, Vliegen HW, Spijkerboer AM, Mulder BJ. Effects of volume and/or pressure overload secondary to congenital heart disease (tetralogy of fallot or pulmonary

stenosis) on right ventricular function using cardiovascular magnetic resonance and B-type natriuretic peptide levels. Am J Cardiol 2006;97:1051-1055.
77. Cheung EW, Lam WW, Chiu CS, Chau AK, Cheung SC, Cheung YF. Plasma brain natriuretic peptide levels, right ventricular volume overload and exercise capacity in adolescents after surgical repair of tetralogy of Fallot. Int J Cardiol 2007;121:155-162.
78. Ishii H, Harada K, Toyono M, Tamura M, Takada G. Usefulness of Exercise-Induced Changes in Plasma Levels of Brain Natriuretic Peptide in Predicting Right Ventricular Contractile Reserve After Repair of Tetralogy of Fallot. The American Journal of Cardiology 2005;95:1338-1343.
79. Festa P, Ait-Ali L, Prontera C, et al. Amino-terminal fragment of pro-brain natriuretic hormone identifies functional impairment and right ventricular overload in operated tetralogy of Fallot patients. Pediatr Cardiol 2007;28:339-345.
80. Binder L, Pieske B, Olschewski M, et al. N-terminal pro-brain natriuretic peptide or troponin testing followed by echocardiography for risk stratification of acute pulmonary embolism. Circulation 2005;112:1573-1579.
81. Choi HS, Kim KH, Yoon HJ, et al. Usefulness of cardiac biomarkers in the prediction of right ventricular dysfunction before echocardiography in acute pulmonary embolism. J Cardiol 2012;60(6):508-513.
82. Mikulewicz M, Lewczuk J. Importance of cardiac biomarkers in risk stratification in acute pulmonary embolism. Cardiol J 2008;15:17-20.
83. Apitz C, Sieverding L, Latus H, Uebing A, Schoof S, Hofbeck M. Right Ventricular Dysfunction and B-Type Natriuretic Peptide in Asymptomatic Patients After Repair for Tetralogy of Fallot. Pediatr Cardiol 2009;30(7):898-904.
84. Jahnke C, Nagel E, Gebker R, et al. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007;115:1769-1776.
85. Wahl A, Paetsch I, Gollesch A, et al. Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases. Eur Heart J 2004;25:1230-1236.
86. Wahi S, Haluska B, Pasquet A, Case C, Rimmerman CM, Marwick TH. Exercise echocardiography predicts development of left ventricular dysfunction in medically and surgically treated patients with asymptomatic severe aortic regurgitation. Heart 2000;84:606-614.
87. Winter MM, Scherptong RW, Kumar S, et al. Ventricular response to stress predicts outcome in adult patients with a systemic right ventricle. Am Heart J 2010;160:870-876.
88. Uebing A, Fischer G, Schlangen J, Apitz C, Steendijk P, Kramer HH. Can we use the end systolic volume index to monitor intrinsic right ventricular function after repair of tetralogy of Fallot? Int J Cardiol 2011;147:52-57.
89. van den Berg J, Strengers JLM, Wielopolski PA, et al. Assessment of biventricular functional reserve and NT-proBNP levels in patients with RV volume overload after repair of tetralogy of Fallot at young age. Int J of Cardiol 2009;133:364-370.
90. Roest AA, Helbing WA, Kunz P, et al. Exercise MR imaging in the assessment of pulmonary regurgitation and biventricular function in patients after tetralogy of fallot repair. Radiology 2002;223:204-211.
91. Tulevski, II, Hirsch A, Dodge-Khatami A, Stoker J, van der Wall EE, Mulder BJ. Effect of pulmonary valve regurgitation on right ventricular function in patients with chronic right ventricular pressure overload. Am J Cardiol 2003;92:113-116.
92. Brili S, Stamatopoulos I, Barbetseas J, et al. Usefulness of dobutamine stress echocardiography with Tissue Doppler imaging for the evaluation and follow-up of patients with repaired tetralogy of Fallot. J Am Soc Echocardiogr 2008;21:1093-1098.
93. Kuijpers D, van Dijkman PR, Janssen CH, Vliegenthart R, Zijlstra F, Oudkerk M. Dobutamine stress MRI. Part II. Risk stratification with dobutamine cardiovascular magnetic resonance in patients suspected of myocardial ischemia. Eur Radiol 2004;14:2046-2052.

94. Hui L, Chau AK, Leung MP, Chiu CS, Cheung YF. Assessment of left ventricular function long term after arterial switch operation for transposition of the great arteries by dobutamine stress echocardiography. Heart 2005;91:68-72.
95. Tulevski, II, van der Wall EE, Groenink M, et al. Usefulness of magnetic resonance imaging dobutamine stress in asymptomatic and minimally symptomatic patients with decreased cardiac reserve from congenital heart disease (complete and corrected transposition of the great arteries and subpulmonic obstruction). Am J Cardiol 2002;89:1077-1081.
96. Robbers-Visser D, Jan ten Harkel D, Kapusta L, et al. Usefulness of Cardiac Magnetic Resonance Imaging Combined With Low-Dose Dobutamine Stress to Detect an Abnormal Ventricular Stress Response in Children and Young Adults After Fontan Operation at Young Age. The American Journal of Cardiology 2008;101:1657-1662.
97. Robbers-Visser D, Helderman F, Strengers JL, et al. Pulmonary artery size and function after Fontan operation at a young age. J Magn Reson Imaging 2008;28:1101-1107.
98. van den Berg J, Wielopolski PA, Meijboom FJ, et al. Diastolic function in repaired tetralogy of Fallot at rest and during stress: assessment with MR imaging. Radiology 2007;243:212-219.
99. De Wolf D, Suys B, Verhaaren H, Matthys D, Taeymans Y. Low-Dose Dobutamine Stress Echocardiography in Children and Young Adults. The American Journal of Cardiology 1998;81:895-901.
100. Berg RA, Padbury JF, Donnerstein RL, Klewer SE, Hutter JJ, Jr. Dobutamine pharmacokinetics and pharmacodynamics in normal children and adolescents. J Pharmacol Exp Ther 1993;265:1232-1238.
101. Ishizaka T, Ichikawa H, Sawa Y, et al. Prevalence and optimal management strategy for aortic regurgitation in tetralogy of Fallot. European Journal of Cardio-Thoracic Surgery 2004;26:1080-1086.
102. Wang X, Sentex E, Saini HK, Chapman D, Dhalla NS. Upregulation of beta-adrenergic receptors in heart failure due to volume overload. Am J Physiol Heart Circ Physiol 2005;289:H151-H159.
103. Parish V, Valverde I, Kutty S, et al. Dobutamine stress MRI in repaired tetralogy of Fallot with chronic pulmonary regurgitation A comparison with healthy volunteers. Int J Cardiol 2011;Dec 8 [Epub ahead of print].
104. Hickey EJ, Veldtman G, Bradley TJ, et al. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. European Journal of Cardio-Thoracic Surgery 2009;35:156-164.
105. Mahony L, Sleeper LA, Anderson PA, et al. The Pediatric Heart Network: a primer for the conduct of multicenter studies in children with congenital and acquired heart disease. Pediatr Cardiol 2006;27:191-198.
106. Francis DP, Shamim W, Davies LC, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2)slope and peak VO(2). Eur Heart J 2000;21:154-161.
107. Poggio R, Arazi HC, Giorgi M, Miriuka SG. Prediction of severe cardiovascular events by VE/Vco(2) slope versus peak Vo(2) in systolic heart failure: A meta-analysis of the published literature. Am Heart J 2010;160:1004-1014.
108. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. American Heart Journal 2004;147:354-360.
109. Dimopoulos KMD, Okonko DOBM, Diller G-PMD, et al. Abnormal Ventilatory Response to Exercise in Adults With Congenital Heart Disease Relates to Cyanosis and Predicts Survival. Circulation 2006;113:2796-2802.
110. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 2005;112:828-835.

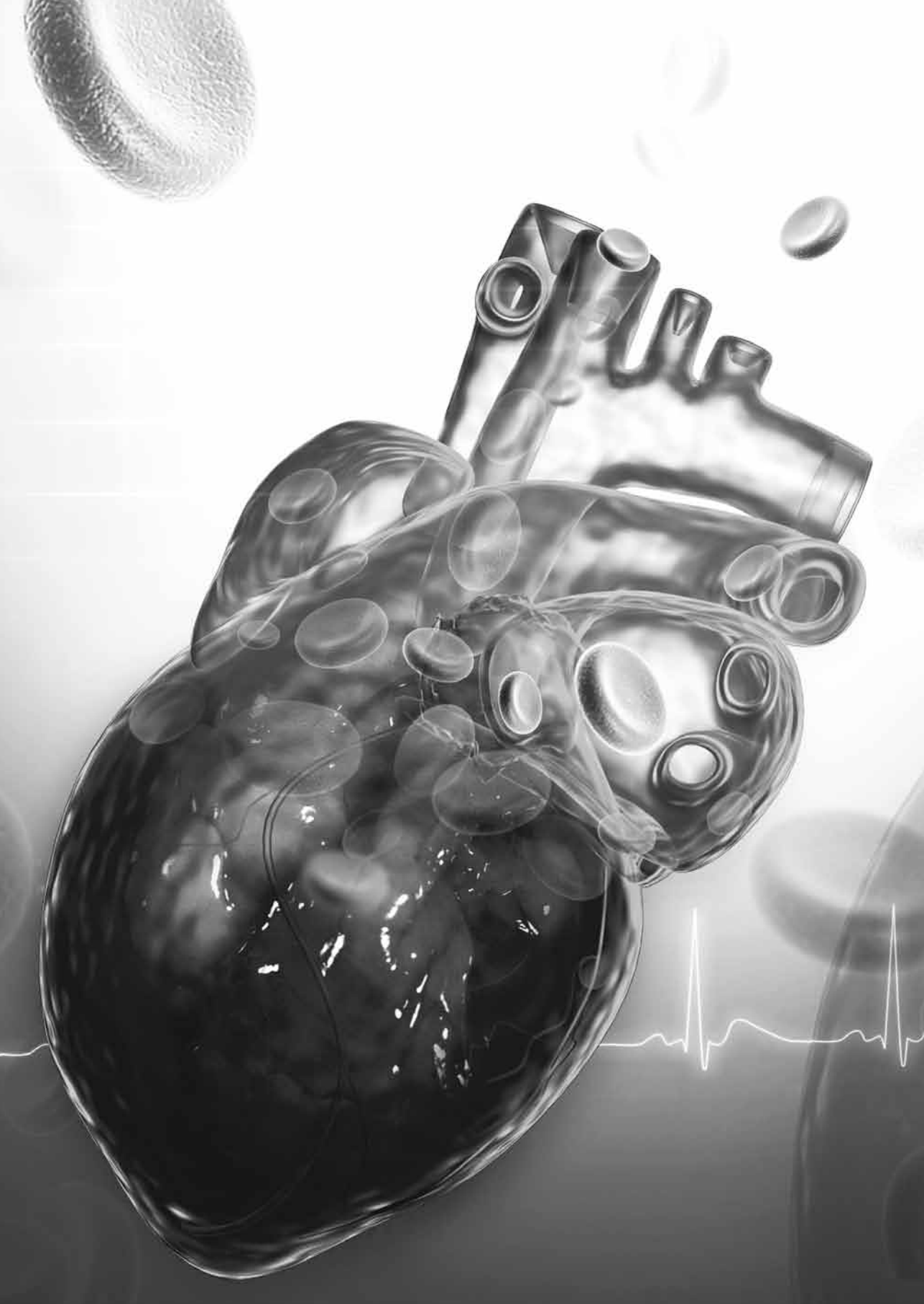
111. Adamson L, Vohra HA, Haw MP. Does pulmonary valve replacement post repair of tetralogy of Fallot improve right ventricular function? Interact CardioVasc Thorac Surg 2009;9:520-527.
112. Doughan AR, McConnell ME, Lyle TA, Book WM. Effects of Pulmonary Valve Replacement on QRS Duration and Right Ventricular Cavity Size Late After Repair of Right Ventricular Outflow Tract Obstruction. The American Journal of Cardiology 2005;95:1511-1514.
113. Eyskens B, Reybrouck T, Bogaert J, et al. Homograft insertion for pulmonary regurgitation after repair of tetralogy of Fallot improves cardiorespiratory exercise performance. The American Journal of Cardiology 2000;85:221-225.
114. Hooft van Huysduynen B, van Straten A, Swenne CA, et al. Reduction of QRS duration after pulmonary valve replacement in adult Fallot patients is related to reduction of right ventricular volume. Eur Heart J 2005;26:928-932.
115. Kane C, Kogon B, Pernetz M, et al. Left ventricular function improves after pulmonary valve replacement in patients with previous right ventricular outflow tract reconstruction and biventricular dysfunction. Tex Heart Inst J 2011;38:234-237.
116. Kleinveld G, Joyner RW, Sallee D, Kanter KR, Parks WJ. Hemodynamic and Electrocardiographic Effects of Early Pulmonary Valve Replacement in Pediatric Patients After Transannular Complete Repair of Tetralogy of Fallot. Pediatric Cardiology 2006;27:329-335.
117. Oosterhof T, Vliegen HW, Meijboom FJ, Zwinderman AH, Bouma B, Mulder BJ. Long-term effect of pulmonary valve replacement on QRS duration in patients with corrected tetralogy of Fallot. Heart 2007;93:506-509.
118. Therrien J, Siu SC, Harris L, et al. Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. Circulation 2001;103:2489-2494.
119. Tobler D, Crean AM, Redington AN, et al. The left heart after pulmonary valve replacement in adults late after tetralogy of Fallot repair. Int J Cardiol 2012;160(3):165-170.
120. van Straten A, Vliegen HW, Hazekamp MG, et al. Right Ventricular Function after Pulmonary Valve Replacement in Patients with Tetralogy of Fallot. Radiology 2004;233:824-829.
121. Warner KG, O'Brien PKH, Rhodes J, Kaur A, Robinson DA, Payne DD. Expanding the indications for pulmonary valve replacement after repair of tetralogy of fallot. The Annals of Thoracic Surgery 2003;76:1066-1071.
122. Discigil B, Dearani JA, Puga FJ, et al. Late pulmonary valve replacement after repair of tetralogy of Fallot. Journal of Thoracic and Cardiovascular Surgery 2001;121:344-351.
123. Kanter KR, Budde JM, Parks WJ, et al. One hundred pulmonary valve replacements in children after relief of right ventricular outflow tract obstruction. The Annals of Thoracic Surgery 2002;73:1801-1807.
124. Stark J, Bull C, Stajevic M, Jothi M, Elliott M, de Leval M. Fate of subpulmonary homograft conduits: determinants of late homograft failure. J Thorac Cardiovasc Surg 1998;115:506-14; discussion 514-516.
125. Tweddell JS, Pelech AN, Frommelt PC, et al. Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. Circulation 2000;102:III130-III135.
126. Troost E, Meyns B, Daenen W, et al. Homograft survival after tetralogy of Fallot repair: determinants of accelerated homograft degeneration. Eur Heart J 2007;28:2503-2509.
127. Bonhoeffer P, Boudjemline Y, Saliba Z, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet 2000;356:1403-1405.
128. Lurz P, Bonhoeffer P, Taylor AM. Percutaneous pulmonary valve implantation: an update. Expert Rev Cardiovasc Ther 2009;7:823-833.
129. Lurz P, Coats L, Khambadkone S, et al. Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. Circulation 2008;117:1964-1972.
130. Lurz P, Nordmeyer J, Giardini A, et al. Early versus late functional outcome after successful percutaneous pulmonary valve implantation are the acute effects of altered right ventricular loading all we can expect? J Am Coll Cardiol 2011;57:724-731.

131. Geva T. Repaired tetralogy of Fallot: the roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. J Cardiovasc Magn Reson 2011;13:9.
132. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. Circulation 2008;117:1436-1448.
133. Lee FA. Hemodynamics of the right ventricle in normal and disease states. Cardiol Clin 1992;10:59-67.
134. Brookes C, Ravn H, White P, Moeldrup U, Oldershaw P, Redington A. Acute right ventricular dilatation in response to ischemia significantly impairs left ventricular systolic performance. Circulation 1999;100:761-767.
135. Santamore WP, Dell'Italia LJ. Ventricular interdependence: significant left ventricular contributions to right ventricular systolic function. Prog Cardiovasc Dis 1998;40:289-308.
136. Kempny A, Diller GP, Orwat S, et al. Right ventricular-left ventricular interaction in adults with Tetralogy of Fallot: A combined cardiac magnetic resonance and echocardiographic speckle tracking study. Int J Cardiol 2011;154(3):259-264.
137. Broberg CS, Aboulhosn J, Mongeon FP, et al. Prevalence of Left Ventricular Systolic Dysfunction in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2011;107(8):1215-1220.
138. Takayasu H, Takahashi K, Takigiku K, et al. Left ventricular torsion and strain in patients with repaired tetralogy of fallot assessed by speckle tracking imaging. Echocardiography 2011;28:720-729.
139. Tzemos N, Harris L, Carasso S, et al. Adverse Left Ventricular Mechanics in Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2009;103:420-425.
140. Cheung YF, Wong SJ, Liang XC, Cheung EW. Torsional Mechanics of the Left Ventricle in Patients After Surgical Repair of Tetralogy of Fallot. Circ J 2011;75(7):1735-1741.
141. Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part I. Physiologic and pathophysiologic features. Mayo Clin Proc 1989;64:71-81.
142. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105:1387-1393.
143. Kitahori K, He H, Kawata M, et al. Development of Left Ventricular Diastolic Dysfunction With Preservation of Ejection Fraction During Progression of Infant Right Ventricular Hypertrophy. Circ Heart Fail 2009;2:599-607.
144. Abhayaratna WP, Seward JB, Appleton CP, et al. Left Atrial Size: Physiologic Determinants and Clinical Applications. J Am Coll Cardiol 2006;47:2357-2363.
145. Maceira AM, Cosin-Sales J, Roughton M, Prasad SK, Pennell DJ. Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2010;12:65.
146. Do DH, Therrien J, Marelli A, Martucci G, Afilalo J, Sebag IA. Right atrial size relates to right ventricular end-diastolic pressure in an adult population with congenital heart disease. Echocardiography 2011;28:109-116.
147. Riesenkampff E, Mengelkamp L, Mueller M, et al. Integrated analysis of atrio-ventricular interaction in tetralogy of Fallot. Am J Physiol Heart Circ Physiol 2010;299:H364-H371.
148. Gatzoulis MA, Clark AL, Cullen S, Newman CG, Redington AN. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot. Restrictive physiology predicts superior exercise performance. Circulation 1995;91:1775-1781.
149. Cullen S, Shore D, Redington A. Characterization of Right Ventricular Diastolic Performance After Complete Repair of Tetralogy of Fallot : Restrictive Physiology Predicts Slow Postoperative Recovery. Circulation 1995;91:1782-1789.

150. Apitz C, Latus H, Binder W, et al. Impact of restrictive physiology on intrinsic diastolic right ventricular function and lusitropy in children and adolescents after repair of tetralogy of Fallot. Heart 2010;96(22):1837-1844.
151. Cardoso SM, Miyague NI. Right ventricular diastolic dysfunction in the postoperative period of tetralogy of Fallot. Arq Bras Cardiol 2003;80:198-201, 194-197.
152. Choi JY, Kwon HS, Yoo BW, et al. Right ventricular restrictive physiology in repaired tetralogy of Fallot is associated with smaller respiratory variability. International Journal of Cardiology 2008;125:28-35.
153. Greenberg SB, Shah CC, Bhutta ST. Tricuspid valve magnetic resonance imaging phase contrast velocity-encoded flow quantification for follow up of tetralogy of Fallot. Int J Cardiovasc Imaging 2008;24:861-865.
154. Helbing WA, Niezen RA, Le Cessie S, van der Geest RJ, Ottenkamp J, de Roos A. Right ventricular diastolic function in children with pulmonary regurgitation after repair of tetralogy of Fallot: volumetric evaluation by magnetic resonance velocity mapping. J Am Coll Cardiol 1996;28:1827-1835.
155. Lu JC, Cotts TB, Agarwal PP, Attili AK, Dorfman AL. Relation of Right Ventricular Dilation, Age of Repair, and Restrictive Right Ventricular Physiology With Patient-Reported Quality of Life in Adolescents and Adults With Repaired Tetralogy of Fallot. Am J Cardiol 2010;106:1798-1802.
156. Munkhammar P, Cullen S, Jögi P, de Leval M, Elliott M, Norgård G. Early age at repair prevents restrictive right ventricular (RV) physiology after surgery for tetralogy of Fallot (TOF): Diastolic RV function after TOF repair in infancy. J Am Coll Cardiol 1998;32:1083-1087.
157. Norgard G, Gatzoulis MA, Moraes F, et al. Relationship between type of outflow tract repair and postoperative right ventricular diastolic physiology in tetralogy of Fallot. Implications for long-term outcome. Circulation 1996;94:3276-3280.
158. Schwartz MC, Rome JJ, Gillespie MJ, et al. Relation of Left Ventricular End Diastolic Pressure to Right Ventricular End Diastolic Volume After Operative Treatment of Tetralogy of Fallot. Am J Cardiol 2012;109(3):417-422.
159. Najm HK, Wallen WJ, Belanger MP, et al. Does the degree of cyanosis affect myocardial adenosine triphosphate levels and function in children undergoing surgical procedures for congenital heart disease? J Thorac Cardiovasc Surg 2000;119:515-524.
160. Reddy SMD, Osorio JCMD, Duque AMMD, et al. Failure of Right Ventricular Adaptation in Children With Tetralogy of Fallot. Circulation Cardiovascular Surgery Supplement 2006;114:I-37-I-42.
161. Toischer K, Rokita AG, Unsold B, et al. Differential cardiac remodeling in preload versus afterload. Circulation 2010;122:993-1003.
162. Janicki JS, Brower GL, Gardner JD, Chancey AL, Stewart JA. The Dynamic Interaction Between Matrix Metalloproteinase Activity and Adverse Myocardial Remodeling. Heart Failure Reviews 2004;9:33-42.
163. Bujak M, Frangogiannis NG. The role of TGF-β signaling in myocardial infarction and cardiac remodeling. Cardiovascular Research 2007;74:184-195.
164. Flesch M, Hoper A, Dell'Italia L, et al. Activation and functional significance of the renin-angiotensin system in mice with cardiac restricted overexpression of tumor necrosis factor. Circulation 2003;108:598-604.
165. Himeno W, Akagi T, Furui J, et al. Increased Angiogenic Growth Factor in Cyanotic Congenital Heart Disease. Pediatric Cardiology 2003;24:127-132.
166. Kawut SM, Barr RG, Johnson WC, et al. Matrix metalloproteinase-9 and plasminogen activator inhibitor-1 are associated with right ventricular structure and function: The MESA-RV Study. Biomarkers 2010;15(8):731-738.
167. Lai CTM, Chan K-W, Wong SJ, Chow P-C, Cheung Y-F. Circulating levels of biomarkers of collagen synthesis and ventricular function and dyssynchrony in adolescents and young adults after repair of tetralogy of Fallot. American Heart Journal 2011;162:467-473.

168. Lucas JA, Zhang Y, Li P, et al. Inhibition of transforming growth factor-beta signaling induces left ventricular dilation and dysfunction in the pressure-overloaded heart. Am J Physiol Heart Circ Physiol 2010;298:H424-H432.
169. Mital S, Chung WK, Colan SD, et al. Renin-angiotensin-aldosterone genotype influences ventricular remodeling in infants with single ventricle. Circulation 2011;123:2353-2362.
170. Norozi K, Buchhorn R, Yasin A, et al. Growth differentiation factor 15: An additional diagnostic tool for the risk stratification of developing heart failure in patients with operated congenital heart defects? American Heart Journal 2011;162:131-135.
171. Reifenberg K, Lehr HA, Torzewski M, et al. Interferon-gamma induces chronic active myocarditis and cardiomyopathy in transgenic mice. Am J Pathol 2007;171:463-472.
172. Nagatomo Y, Carabello BA, Coker ML, et al. Differential effects of pressure or volume overload on myocardial MMP levels and inhibitory control. Am J Physiol Heart Circ Physiol 2000;278:H151-161.
173. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. The Lancet 2006;367:356-367.
174. Sakata Y, Chancey AL, Divakaran VG, Sekiguchi K, Sivasubramanian N, Mann DL. Transforming growth factor-beta receptor antagonism attenuates myocardial fibrosis in mice with cardiac-restricted overexpression of tumor necrosis factor. Basic Res Cardiol 2008;103:60-68.
175. Spinale FGMDP, Coker MLBA, Heung LJBS, et al. A Matrix Metalloproteinase Induction/Activation System Exists in the Human Left Ventricular Myocardium and Is Upregulated in Heart Failure. Circulation 2000;102:1944-1949.
176. Sun M, Chen M, Dawood F, et al. Tumor necrosis factor-alpha mediates cardiac remodeling and ventricular dysfunction after pressure overload state. Circulation 2007;115:1398-1407.
177. Tziakas DN, Chalikias GK, Papaioakeim M, et al. Comparison of Levels of Matrix Metalloproteinase-2 and -3 in Patients With Ischemic Cardiomyopathy Versus Nonischemic Cardiomyopathy. The American Journal of Cardiology 2005;96:1449-1451.
178. Modesti PA, Vanni S, Bertolozzi I, et al. Different Growth Factor Activation in the Right and Left Ventricles in Experimental Volume Overload. Hypertension 2004;43:101-108.
179. Nishikawa N, Yamamoto K, Sakata Y, et al. Differential activation of matrix metalloproteinases in heart failure with and without ventricular dilatation. Cardiovasc Res 2003;57:766-774.
180. Sharma H, Peters T, Moorhouse M, van der Spek P, Bogers A. DNA microarray analysis for human congenital heart disease. Cell Biochemistry and Biophysics 2006;44:1-9.
181. Umar S, Hessel M, Steendijk P, et al. Activation of signaling molecules and matrix metalloproteinases in right ventricular myocardium of rats with pulmonary hypertension. Pathology - Research and Practice 2007;203:863-872.
182. Faber M, Agnetti G, Bezstarosti K, et al. Recent developments in proteomics. Cell Biochemistry and Biophysics 2006;44:11-29.
183. Gullestad L, Aukrust P. Review of Trials in Chronic Heart Failure Showing Broad-Spectrum Anti-Inflammatory Approaches. The American Journal of Cardiology 2005;95:17-23.
184. Kassiri Z, Khokha R. Myocardial extra-cellular matrix and its regulation by metalloproteinases and their inhibitors. Thromb Haemost 2005;93:212-219.
185. Spinale FG, Coker ML, Bond BR, Zellner JL. Myocardial matrix degradation and metalloproteinase activation in the failing heart: a potential therapeutic target. Cardiovasc Res 2000;46:225-238.
186. Jobe LJ, Melendez GC, Levick SP, Du Y, Brower GL, Janicki JS. TNF-alpha inhibition attenuates adverse myocardial remodeling in a rat model of volume overload. Am J Physiol Heart Circ Physiol 2009;297:H1462-H1468.
187. Lebastchi AH, Khan SF, Qin L, et al. Transforming growth factor beta expression by human vascular cells inhibits interferon gamma production and arterial media injury by alloreactive memory T cells. Am J Transplant 2011;11:2332-2341.

188. Li P, Wang D, Lucas J, et al. Atrial natriuretic peptide inhibits transforming growth factor beta-induced Smad signaling and myofibroblast transformation in mouse cardiac fibroblasts. Circ Res 2008;102:185-192.
189. Werner F, Jain MK, Feinberg MW, et al. Transforming growth factor-beta 1 inhibition of macrophage activation is mediated via Smad3. J Biol Chem 2000;275:36653-36658.
190. Lin F, Yang X. TGF-beta signaling in aortic aneurysm: another round of controversy. J Genet Genomics 2010;37:583-591.
191. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355:788-798.
192. Moltzer E, Essers J, van Esch JH, Roos-Hesselink JW, Danser AH. The role of the renin-angiotensin system in thoracic aortic aneurysms: clinical implications. Pharmacol Ther 2011;131:50-60.
193. Brower GL, Levick SP, Janicki JS. Inhibition of matrix metalloproteinase activity by ACE inhibitors prevents left ventricular remodeling in a rat model of heart failure. Am J Physiol Heart Circ Physiol 2007;292:H3057-H3064.
194. Kim S, Ohta K, Hamaguchi A, Yukimura T, Miura K, Iwao H. Effects of an AT1 receptor antagonist, an ACE inhibitor and a calcium channel antagonist on cardiac gene expressions in hypertensive rats. Br J Pharmacol 1996;118:549-556.
195. Seeland U, Schaffer A, Selejan S, et al. Effects of AT1- and beta-adrenergic receptor antagonists on TGF-beta1-induced fibrosis in transgenic mice. Eur J Clin Invest 2009;39:851-859.
196. Tsukashita M, Marui A, Nishina T, et al. Spironolactone alleviates late cardiac remodeling after left ventricular restoration surgery. J Thorac Cardiovasc Surg 2008;136:58-64.
197. Yu C-M, Tipoe GL, Wing-Hon Lai K, Lau C-P. Effects of combination of angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist on inflammatory cellular infiltration and myocardial interstitial fibrosis after acute myocardial infarction. J Am Coll Cardiol 2001;38:1207-1215.
198. Peng H, Carretero OA, Vuljaj N, et al. Angiotensin-converting enzyme inhibitors: a new mechanism of action. Circulation 2005;112:2436-2445.
199. Babu-Narayan SV, Uebing A, Davlouros PA, et al. Randomised trial of ramipril in repaired tetralogy of Fallot and pulmonary regurgitation: the APPROPRIATE study (Ace inhibitors for Potential PRevention Of the deleterious effects of Pulmonary Regurgitation In Adults with repaired TEtralogy of Fallot). Int J Cardiol 2012;154:299-305.



Chapter 11

Summary – Samenvatting

Summary

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect (CHD) and includes pulmonary stenosis (PS), ventricular septal defect, overriding of the aorta, and right ventricular (RV) hypertrophy. The overall long-term survival has improved over the last decades due to an impressive decline in perioperative mortality. Patients with TOF are nowadays treated within their first year of life and long-term survival has become excellent for these patients. Despite excellent long-term survival, many patients encounter adverse sequelae at long-term follow-up, particularly pulmonary regurgitation (PR). Chronic PR leads to RV volume overload and subsequent RV dilatation. Although chronic PR and RV dilatation are tolerated well for many years, eventually it may lead to RV dysfunction, deterioration of clinical condition, and an increased risk of life-threatening arrhythmias and sudden cardiac death. Patients with severe PR can be treated with pulmonary valve replacement (PVR), but the optimal timing to perform PVR remains subject for debate, particularly for asymptomatic patients with severe PR and severe RV dilatation. Despite several recommendations, no uniform guidelines to perform PVR exist for these patients.

Although TOF patients have been studied extensively, current literature provides limited information on the course of ventricular and functional changes over time in patients who have not undergone PVR already (referred to as “non-PVR patients”). This means that the progression rate of RV enlargement and the deterioration of RV function over time have not been clarified yet. Serial follow-up studies in non-PVR patients may provide insight in this process, which could be useful in decision making on optimal timing of PVR, but also to determine follow-up strategies. We performed a serial follow-up study, in which we obtained serial measurements of biventricular size and function using magnetic resonance imaging (MRI), in addition to serial measurements of exercise capacity, electrocardiographic (ECG) parameters, 24-hour Holter monitorings, and N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels, with a 5-year interval.

Besides the lack of serial follow-up measurements, biomolecular pathways that are involved in the process of progressive RV dilatation and the transition from a state of compensated RV volume overload to RV failure have hardly been studied in TOF patients. Information about the pathways involved in these processes may lead to the identification of biomarkers that may be used in risk stratification and may provide targets for the development of specific therapies and future research.

Therefore, the aims of this thesis were:

- Assess the progression of RV dilatation and the deterioration of RV function over time, in relation to parameters of clinical condition, in patients after repair of tetralogy of Fallot. Systolic and diastolic ventricular function were assessed using cardiac MRI, as well as the ventricular response to dobutamine stress.
- Identify potential biomarkers with the use of high-density protein arrays and enzyme-linked immuno sorbent assays (ELISA), which may be used as diagnostic and prognostic tools. These markers were assessed in blood samples, obtained from tetralogy of Fallot patients at different stages of the development of RV volume overload.

This thesis is structured as follows:
In **chapter 1**, an overview is given on congenital heart defects in general and on tetralogy of Fallot more specifically. Current treatment options for TOF patients are described, as well as results of studies reporting on long-term outcome of biventricular function and clinical condition. The assessment of biventricular size and function by MRI is defined, as well as the quantification of pulmonary regurgitation. Finally, the aims and outline of this thesis are presented.

Chapter 2 provides an overview of the role of MRI in the long-term follow-up of patients with repaired TOF. MRI studies have identified risk factors for late adverse outcomes in patients after TOF repair. These include increased RV end-diastolic volume (EDV), reduced RV and left ventricular (LV) ejection fraction (EF), and abnormal RV outflow tract function. Based on MRI studies, PVR should be considered if RVEDV reaches a threshold of between 150 – 200 ml/m^2 in the presence of severe PR. Other MRI applications include stress imaging, assessment of diastolic function, and late gadolinium enhancement, which have provided additional insight in the function and adaptive responses of the RV.

Since MRI parameters are increasingly used with regard to clinical decision making and timing of reinterventions in TOF patients, good reproducibility is of crucial importance. Results of observer variability in patients with CHD, measured with steady-state free precession MRI, have hardly been reported in the literature. We therefore assessed observer variability in a cross-sectional study including 35 patients (mean age 22 ± 13 years, range 7 – 62 years) with different types of CHDs, including patients after TOF repair. In **chapter 3**, we reported that intra-observer variability (between 3% and 7%) and interobserver variability (between 4% and 10%) were good in patients with complex CHDs. The highest variations were found for biventricular end-systolic volume (ESV). We concluded that MRI is an accurate and reproducible method for assessment of biventricular size and function in patients with CHD, and should allow for adequate assessment of changes in ventricular size and global ventricular function over time.

In **chapter 4**, 21 patients (mean age 16 ± 5 years) after percutaneous balloon pulmonary valvuloplasty for isolated pulmonary valve stenosis were included (“PS patients”). These patients were compared to 21 patients (mean age 17 ± 6 years) after repair of TOF and to 21 healthy controls (mean age 17 ± 5 years), in a cross-sectional study. We concluded that the short hypoxemic period before intracardiac repair in TOF patients does not seem to have detrimental effects on long-term ventricular function and clinical condition. Biventricular function and exercise capacity were not significantly different between PS patients and TOF patients, despite significantly more RV dilatation in TOF patients than in PS patients. PS patients had mildly reduced RVEF and exercise capacity compared to healthy controls. This may be explained by the longstanding mild PR, which we found in PS patients after treatment.

In **chapter 5**, results of serial follow-up measurements in 78 non-PVR patients (median age at the baseline study 20 years, range 6 – 60 years) are reported. Non-PVR patients were studied twice with a 5-year interval and results were compared to results of 52 patients (median age at the baseline study 23 years, range 7 – 46 years) who were studied at a mean of 1 year before and 4 years after PVR. In the 78 non-PVR patients, we found a significant, but limited increase in RV size during 5-year follow-up, i.e. 1.6 ± 3.0 ml/m^2/year for RVEDV ("RVEDV slope"). Right ventricular EF remained stable during follow-up, but was lower than in healthy controls. We also found that a lower RV effective stroke volume (eff.SV) at baseline related to a steeper increase in RVEDV during follow-up, while RVEDV at baseline was not related to this RVEDV slope. In addition to the increase in RV size, we observed a significant increase in QRS duration and a significant decrease in peak oxygen uptake (peak VO_2) during 5-year follow-up.

In the 52 PVR patients, we observed a significant improvement in clinical condition after PVR (represented by an improvement of the New York Heart Association (NYHA) class), accompanied by a significant decrease in PR fraction and RV size, and stabilization of QRS duration. In our patients, biventricular EF did not improve after PVR, but a significant increase in RVeff.SV was observed after PVR. Exercise capacity did not improve after PVR, but because of the incomplete results, this should be interpreted with caution. We concluded that some of our patients may have undergone PVR too late, since RV size did not return to normal and RVeff.SV did not increase after PVR in patients with RVEDV ≥ 170 ml/m^2 before PVR.

Our subgroup analysis in non-PVR patients showed that NYHA class significantly deteriorated during 5-year follow-up in patients with a larger RV size at baseline (RVEDV ≥ 142 ml/m^2), while NYHA class was better and remained stable in patients with a smaller RV size at baseline. Our results suggest a less conservative approach towards PVR may be required.

Serum NT-proBNP levels were significantly higher in TOF patients than in age-matched healthy controls, but remained stable during 5-year follow-up. NT-proBNP levels could also not discriminate between results of non-PVR patients and baseline results of patients who underwent PVR during follow-up (referred to as "pre-PVR patients"), which tends to limit the prognostic value of NT-proBNP as biomarker in this relatively young TOF population.

Diastolic dysfunction may precede systolic dysfunction and is therefore useful to assess in the follow-up of TOF patients. However, assessment of RV diastolic function in the presence of PR is complex. Atrial size and functional measurements can be helpful in the assessment of ventricular diastolic function. The atrial play a crucial role in the filling of the ventricle during ventricular diastole and it has been suggested that atrial enlargement reflects the burden of ventricular diastolic dysfunction. In **chapter 6**, biventricular diastolic function was assessed in a cross-sectional study including 51 patients (mean age 21 ± 8 years) and 30 healthy controls (mean age 31 ± 7 years). In our TOF patients, we observed signs of impaired RV relaxation, reflected by a decreased early peak filling rate and a prolonged deceleration time. Furthermore, end-diastolic forward flow (EDFF), a sign of impaired RV compliance, was present in 60% of our patients. We observed enlarged right atrial (RA) size and abnormal RA emptying (decreased RA early emptying and increased RA late emptying),

which related to enlarged RV size and signs of impaired clinical condition, as did the presence of EDFF. These results reflect the presence of RV diastolic dysfunction in our young TOF patients and emphasize the usefulness of measuring parameters of RA size and function when RV diastolic function is assessed. In addition, we found signs of LV diastolic dysfunction (impaired compliance), particularly in patients with the most severe RV dilatation, despite only mildly reduced LV systolic function. These results underline the presence and importance of adverse RV – LV interactions.

Chapter 7a reviews the use of stress imaging in patients with CHD. The use of different types of stressors and imaging modalities is discussed, as well as results of stress imaging studies. In **chapter 7b**, we demonstrated that low-dose (7.5 μg/kg/min) dobutamine stress imaging is feasible and safe in patients with complex CHDs, including patients after TOF repair. In a series of 110 low-dose dobutamine stress studies in 91 patients (median age at first study 14 years, range 7 – 26 years), minor side effects occurred in only 3 patients, while major side effects, e.g. arrhythmias, did not occur. In addition, in 25 randomly selected patients, observer variability was assessed, which was still adequate, although interobserver variability of biventricular ESV exceeded 10% with stress testing.

Chapter 8 describes our results of serial measurements of low-dose dobutamine stress testing in 27 TOF patients (mean age at the baseline study 14 ± 4 years) with a 5-year interval. A normal response to dobutamine was defined as a decrease in RVESV during stress and an increase in RVEF during stress. Contractile reserve was defined as the ability to increase EF with dobutamine stress. We observed a normal response to dobutamine stress in the majority (26 of 27) of our TOF patients, which remained stable during 5-year follow-up. This conforms to the good clinical condition of these relatively young patients, despite significant RV enlargement. A smaller RV contractile reserve at baseline was predictive for a larger decrease in peak VO_2 during 5-year follow-up. This indicates the potential additional value of dobutamine stress imaging in the follow-up of TOF patients. RV contractile reserve could not discriminate between non-PVR patients and pre-PVR patients, but pre-PVR patients showed a smaller decrease in RVESV with stress than non-PVR patients. In addition, some pre-PVR patients were unable to increase RVeff.SV with dobutamine stress. These parameters may be indicators of impaired RV function that need further study.

In **chapter 9**, we focused on the biomolecular pathways and more specifically on the cytokine transforming growth factor (TGF)-β. In a cross-sectional study of 96 patients (median age 22 years, range 7 – 66 years), TGF-β levels were assessed using ELISA kits. A protein array analysis was performed in pooled subgroups to assess serum levels of various biomolecules that regulate inflammation, extracellular matrix degradation, fibroblast proliferation, and cardiomyocyte survival. Cardiac MRI was performed to assess RV size and function. In 36 patients (mean age at the baseline study 14 ± 5 years), serial follow-up measurements of TGF-β levels and RV parameters were available with a 5-year interval. We also included 70 healthy controls (median age 21 years, range 12 – 64 years). In the serial follow-up study, we observed an increase in RV size and a decrease in serum

levels of TGF-β levels over 5 years time. In the cross-sectional study, a trend towards lower TGF-β levels was observed in patients with the most severe RV dilatation, which coincided with an increase in a significant number of immune regulatory factors (e.g. tumor necrosis factor-α and interferon-γ), that indicate an augmented inflammatory state. In addition, the patients with severe RV dilatation also lost their long-term cardiac protection due to a decline in growth and survival factors (e.g. epidermal growth factor and metalloproteinase inhibitors), with increasing follow-up duration, while levels of hypertrophy inducers were increased. These patients may therefore be more susceptible for adverse RV dilatation with subsequent RV dysfunction and RV failure. A better understanding of the molecular biology that governs this process might aid in earlier recognition of patients at risk for RV failure and better treatment options. Future research is required to evaluate if biocomponents in the TGF-β pathway may be used as biomarkers for predicting the progression of the disease by long-term monitoring, and if specific TGF-β based therapy could be developed.

In **chapter 10**, an overview is given of our most relevant findings. Results of this thesis are discussed in the context of known literature and recently published studies. If applicable, directions for future research are described.

Samenvatting

Tetralogie van Fallot is de meest voorkomende cyanotische aangeboren hartafwijking en omvat een pulmonalis stenose, een ventrikel septum defect, een overrijdende aorta, en rechterkamer hypertrofie. De lange termijn overleving is door de jaren heen verbeterd, onder andere door een belangrijke daling van de sterfte tijdens en net na de operatie. Patiënten met een tetralogie van Fallot worden tegenwoordig geopereerd in het eerste levensjaar en de lange termijn overleving is nu uitstekend. Ondanks de uitstekende lange termijn overleving ondervinden veel patiënten negatieve gevolgen lange tijd na de operatie, met name een zekere mate van pulmonalis insufficiëntie. Chronische pulmonalis insufficiëntie leidt tot volume overbelasting van de rechterkamer en daaropvolgend tot rechterkamer dilatatie. Alhoewel chronische pulmonalis insufficiëntie en rechterkamer dilatatie gedurende lange tijd goed kunnen worden verdragen, kan het uiteindelijk leiden tot rechterkamer falen, verslechtering van de klinische conditie, en een verhoogde kans op levensbedreigende ritmestoornissen en plotse hartdood. Patiënten met ernstige pulmonalis insufficiëntie kunnen behandeld worden met een pulmonalisklepvervanging (PKV), maar het beste moment om deze operatie uit te voeren blijft onderwerp van discussie, met name bij asymptomatische patiënten die wel een ernstige pulmonalis insufficiëntie en een ernstig vergrote rechterkamer hebben. Ondanks diverse aanbevelingen zijn er nog geen (inter)nationale richtlijnen die aangeven wanneer een klepvervanging het beste kan worden uitgevoerd bij deze patiënten.

Alhoewel Fallot patiënten al uitgebreid onderzocht zijn, is er maar weinig informatie te vinden in de literatuur over de snelheid van veranderingen voor wat betreft de rechterkamer grootte en -functie bij patiënten die nog geen klepvervanging hebben ondergaan (de zogenaamde “niet-PKV patiënten”). Dit betekent dat de progressie van de rechterkamer dilatatie en de achteruitgang van de rechterkamer functie over het beloop van jaren nog niet inzichtelijk is. Seriële follow-up studies bij deze niet-PKV patiënten kunnen inzicht geven in dit beloop. Deze informatie zou gebruikt zou kunnen worden in de besluitvorming betreffende het wel of niet uitvoeren van een klepvervanging. Wij hebben een studie opgezet, waarbij de grootte- en functie van beide hartkamers 2x bepaald werd met behulp van magnetic resonance imaging (MRI), met een interval van 5 jaar. Daarnaast hebben wij seriële metingen verzameld van de inspanningscapaciteit (zoals de maximale zuurstofopnamecapaciteit (VO_2 max.)), electrocardiografische (ECG) parameters (zoals de QRS duur), 24-uurs Holter registraties voor de evaluatie van ritmestoornissen, en N-terminal prohormone brain natriuretic peptide (NT-proBNP) concentraties, een marker in het bloed die vaak verhoogd is bij patiënten met hartfalen.

Naast het feit dat seriële metingen tot op heden ontbreken, zijn ook de biomoleculaire signaalpaden, die betrokken zijn bij het proces van progressieve rechterkamer dilatatie en de overgang van een gecompenseerde volume overbelasting van de rechterkamer naar rechterkamer falen nauwelijks bestudeerd bij Fallot patiënten. Informatie over de betrokken signaalpaden zou mogelijk kunnen leiden tot het identificeren van biomarkers, die gebruikt zouden kunnen worden in het behandelbeleid. Tevens zou dit mogelijk aanknopingspunten op kunnen opleveren voor de ontwikkeling van specifieke therapieën en verder onderzoek.

Dit proefschrift had daarom de volgende doelstellingen:

- Het meten van de veranderingen in rechterkamer grootte en -functie over de tijd, in relatie tot klinische uitkomstmaten, bij patiënten met een gecorrigeerde tetralogie van Fallot. Systolische- en diastolische kamerfunctie werden bepaald met behulp van cardiale MRI's, zoals ook de respons van de hartkamers op dobutamine stress.
- Het identificeren van potentiële biomarkers met behulp van technieken als high-density protein arrays en enzyme-linked immune sorbent assays (ELISA), welke gebruikt zouden kunnen worden als diagnostische- en prognostische parameters. Deze markers werden bepaald in het bloed van een groep Fallot patiënten, waarbij de mate van volume overbelasting van de rechterkamer verschillend was.

Dit proefschrift is als volgt opgebouwd:
Allereerst wordt in **hoofdstuk 1** een overzicht gegeven van aangeboren hartafwijkingen in het algemeen en meer specifiek van de afwijkingen bij een tetralogie van Fallot. Huidige behandelstrategieën voor Fallot patiënten worden besproken, evenals de gerapporteerde resultaten over lange termijn uitkomsten van hartkamerfunctie en klinische uitkomstmaten. Er wordt beschreven hoe de grootte- en functie van beide hartkamers kan worden bepaald met behulp van MRI, als ook hoe de hoeveelheid pulmonalis insufficiëntie kan worden gekwantificeerd. Als laatste worden de doelstellingen van dit proefschrift beschreven en wordt een overzicht gegeven van de indeling daarvan.

In **hoofdstuk 2** wordt een overzicht gegeven van de rol van MRI in de lange termijn follow-up van patiënten met een gecorrigeerde tetralogie van Fallot. Door middel van MRI studies zijn risicofactoren geïdentificeerd die ongunstige uitkomsten op de lange termijn zouden kunnen voorspellen. Deze omvatten bijvoorbeeld een toegenomen rechterkamer eind-diastolisch volume, een verminderde linker- en rechterkamer functie (ejectie fractie), en een gestoorde rechterkamer uitstroombaan functie. Gebaseerd op deze MRI studies zou een klepvervanging moeten worden overwogen als het rechterkamer eind-diastolisch volume een waarde van tussen de 150 – 200 ml/m^2 bereikt, in de aanwezigheid van ernstige pulmonalis insufficiëntie. Andere MRI toepassingen omvatten onder andere het uitvoeren van stressmetingen, het bepalen van parameters van diastolische functie, en het meten van fibrose in het myocard na toediening van gadolinium (late gadolinium enhancement). Al deze MRI onderzoeken en -toepassingen hebben ervoor gezorgd dat we meer inzicht hebben gekregen in de functie- en de aanpassingsmechanismen van de rechterkamer.

MRI parameters worden in toenemende mate gebruikt in de klinische besluitvorming met betrekking tot het plannen van heroperaties bij Fallot patiënten. Een goede reproduceerbaarheid van de MRI metingen is daarom van cruciaal belang. Resultaten van observer variabiliteit bij patiënten met een aangeboren hartafwijking, gemeten met behulp van steady-state free precession MRI, zijn nauwelijks gerapporteerd in de literatuur. We hebben om die reden de observer variabiliteit

gemeten in een cross-sectionele studie. In deze studie werden 35 patiënten geïncludeerd (gemiddelde leeftijd 22 ± 13 jaar, bereik 7 – 62 jaar) met verschillende soorten aangeboren hartafwijkingen, waaronder Fallot patiënten. In **hoofdstuk 3** beschrijven we dat de intra-observer variabiliteit (tussen 3% en 7%) en de interobserver variabiliteit (tussen 4% en 10%) goed zijn. De hoogste variaties werden gevonden voor zowel het linker- als rechterkamer eind-systolisch volume. We concludeerden dat MRI een nauwkeurige en reproduceerbare methode is voor het meten van linker- en rechterkamer grootte en -functie bij patiënten met een aangeboren hartafwijking, en dat het veranderingen in hartkamer grootte en -functie over de tijd goed zou moeten kunnen weergeven.

In **hoofdstuk 4** beschrijven we resultaten van 21 patiënten (gemiddelde leeftijd 16 ± 5 jaar) met een geïsoleerde pulmonalisklep stenose die een percutane ballondilatatie van de pulmonalisklep hebben ondergaan ("PS patiënten"). Deze patiënten werden vergeleken met 21 patiënten (gemiddelde leeftijd 17 ± 6 jaar) met een gecorrigeerde tetralogie van Fallot en met 21 gezonde vrijwilligers (gemiddelde leeftijd 17 ± 5 jaar), in een cross-sectionele studie. We concludeerden dat de korte hypoxemische periode voorafgaand aan de initiële operatie in Fallot patiënten geen al te nadelige invloed lijkt te hebben op de linker- en rechterkamer functie en op de klinische uitkomstmaten op de lange termijn. De linker- en rechterkamer functie en inspanningscapaciteit waren niet significant verschillend tussen PS patiënten en Fallot patiënten, ondanks dat de Fallot patiënten duidelijk meer rechterkamer dilatatie hadden dan de PS patiënten. PS patiënten hadden wel een mild verlaagde rechterkamer functie en mild verlaagde inspanningscapaciteit ten opzichte van gezonde vrijwilligers. Dit zou mogelijk verklaard kunnen worden door de lang bestaande milde pulmonalis insufficiëntie die we vonden bij PS patiënten na de ballondilatatie.

In **hoofdstuk 5** hebben we resultaten weergegeven van onze seriële metingen bij 78 niet-PKV patiënten (mediane leeftijd ten tijde van de baseline studie 20 jaar, bereik 6 – 60 jaar). Niet-PKV patiënten werden 2x onderzocht met een interval van 5 jaar. De resultaten werden vergeleken met resultaten van 52 patiënten (mediane leeftijd ten tijde van de baseline studie 23 jaar, bereik 7 – 46 jaar), die werden onderzocht 1 jaar voorafgaand en 4 jaar na klepvervanging ("PKV patiënten"). Bij de 78 niet-PKV patiënten vonden we een significante, maar beperkte toename van de rechterkamer grootte over de tijd, namelijk van 1.6 ± 3.0 ml/m^2/jaar voor het rechterkamer eind-diastolisch volume. De rechterkamer ejectie fractie bleef onveranderd tijdens de 5-jaars follow-up, maar was wel lager dan in een groep gezonde vrijwilligers. Verder vonden we dat een lager rechterkamer effectief slagvolume ten tijde van de baseline meting voorspellend was voor een snellere toename van de rechterkamer grootte tijdens de follow-up periode, terwijl de rechterkamer grootte ten tijde van de baseline meting hier geen invloed op had. Naast de toename in rechterkamer grootte vonden we ook een duidelijke toename van de QRS duur en een significante afname van de inspanningscapaciteit (weergegeven als een afname van de VO_2 max.) tijdens de follow-up periode.

Bij de 52 PKV patiënten verbeterde de klinische conditie (weergegeven als een verbetering van de New York Heart Association (NYHA) klasse) na de klepvervanging. Daarnaast vonden we een

duidelijke afname van de hoeveelheid pulmonalis insufficiëntie, een afname van de rechterkamer grootte, en stabiliseerde de QRS duur na de klepvervanging. De linker- en rechterkamer ejectie fractie verbeterden niet, maar het rechterkamer effectief slagvolume nam wel significant toe na de klepvervanging. De inspanningscapaciteit verbeterde niet na de klepvervanging, maar deze inspanningsresultaten moeten met enige voorzichtigheid worden geïnterpreteerd, aangezien de data incompleet waren. We concludeerden dat sommige van onze PKV patiënten mogelijk toch te laat hun klepvervanging hebben ondergaan, omdat de rechterkamer grootte niet meer normaliseerde en tevens het rechterkamer effectief slagvolume niet toenam na de klepvervanging bij patiënten van wie het rechterkamer eind-diastolisch volume voorafgaand aan de klepvervanging meer dan 170 ml/m^2 was.

Subgroepanalyse bij onze niet-PKV patiënten liet zien dat de klinische toestand (NYHA klasse) duidelijk verslechterde tijdens de 5-jaars follow-up bij patiënten met een grotere rechterkamer ten tijde van de baseline meting (rechterkamer eind-diastolisch volume ≥ 142 ml/m^2), terwijl de klinische conditie beter was en onveranderd bleef tijdens de follow-up periode bij patiënten met een kleinere rechterkamer ten tijde van de baseline meting. Onze resultaten suggereren dat we mogelijk toch een wat minder conservatief beleid zouden moeten voeren ten aanzien van het uitvoeren van een klepvervanging.

Verder vonden we dat NT-proBNP concentraties duidelijk hoger waren bij Fallot patiënten dan bij gezonde vrijwilligers, maar dat deze onveranderd bleven tijdens de follow-up periode. Daarnaast kon op basis van de NT-proBNP concentraties ten tijde van de baseline studie geen onderscheid gemaakt worden tussen niet-PKV patiënten en patiënten die later een klepvervanging zouden ondergaan. Dit lijkt de prognostische waarde van NT-proBNP als biomarker te beperken bij deze relatief jonge groep Fallot patiënten.

Diastolische dysfunctie zou vooraf kunnen gaan aan systolische dysfunctie en is daarom belangrijk om te meten bij Fallot patiënten. Echter, het bepalen van rechterkamer diastolische functie is lastig in de aanwezigheid van pulmonalis insufficiëntie. Het meten van boezem grootte en -functie zou kunnen helpen bij het meten van de diastolische functie van de hartkamers. De boezems spelen namelijk een cruciale rol bij het vullen van de hartkamers tijdens diastole. Men denkt dat de mate van vergroting van de linkerboezem de mate van diastolische dysfunctie van de linkerkamer zou kunnen weerspiegelen. In **hoofdstuk 6** hebben we de diastolische functie van beide hartkamers bepaald in een cross-sectionele studie waarin 51 patiënten (gemiddelde leeftijd 21 ± 8 jaar) en 30 gezonde vrijwilligers (gemiddelde leeftijd 31 ± 7 jaar) werden geïncludeerd. Bij onze Fallot patiënten vonden we aanwijzingen voor een gestoorde rechterkamer relaxatie, weergegeven door een verlaagde vroege maximale vullingssnelheid van de rechterkamer (early peak filling rate) en een verlengde deceleratie tijd. Daarnaast zagen we eind-diastolische forward flow, wat wordt gezien als een teken van gestoorde rechterkamer elasticiteit, bij 60% van onze patiënten. Verder vonden we dat de rechterboezem vergroot was en tevens een gestoorde ledigingsfunctie vertoonde (verminderde vroege lediging en toegenomen late lediging). Dit was gerelateerd aan de mate van rechterkamer dilatatie en aan tekenen van een verminderde klinische conditie, zoals ook de

aanwezigheid van eind-diastolische forward flow. Deze resultaten geven aan dat er sprake is van een gestoorde rechterkamer diastolische functie bij onze patiënten, en geven tevens het nut aan van het meten van rechterboezem grootte en -functie wanneer rechterkamer diastolische functie wordt bepaald. Tevens vonden we tekenen van een gestoorde linkerkamer diastolische functie (verminderde elasticiteit), vooral bij patiënten met de meest ernstige rechterkamer dilatatie, ondanks dat de linkerkamer systolische functie slechts mild verlaagd was. Deze resultaten benadrukken de aanwezigheid en het belang van negatieve rechterkamer – linkerkamer interacties.

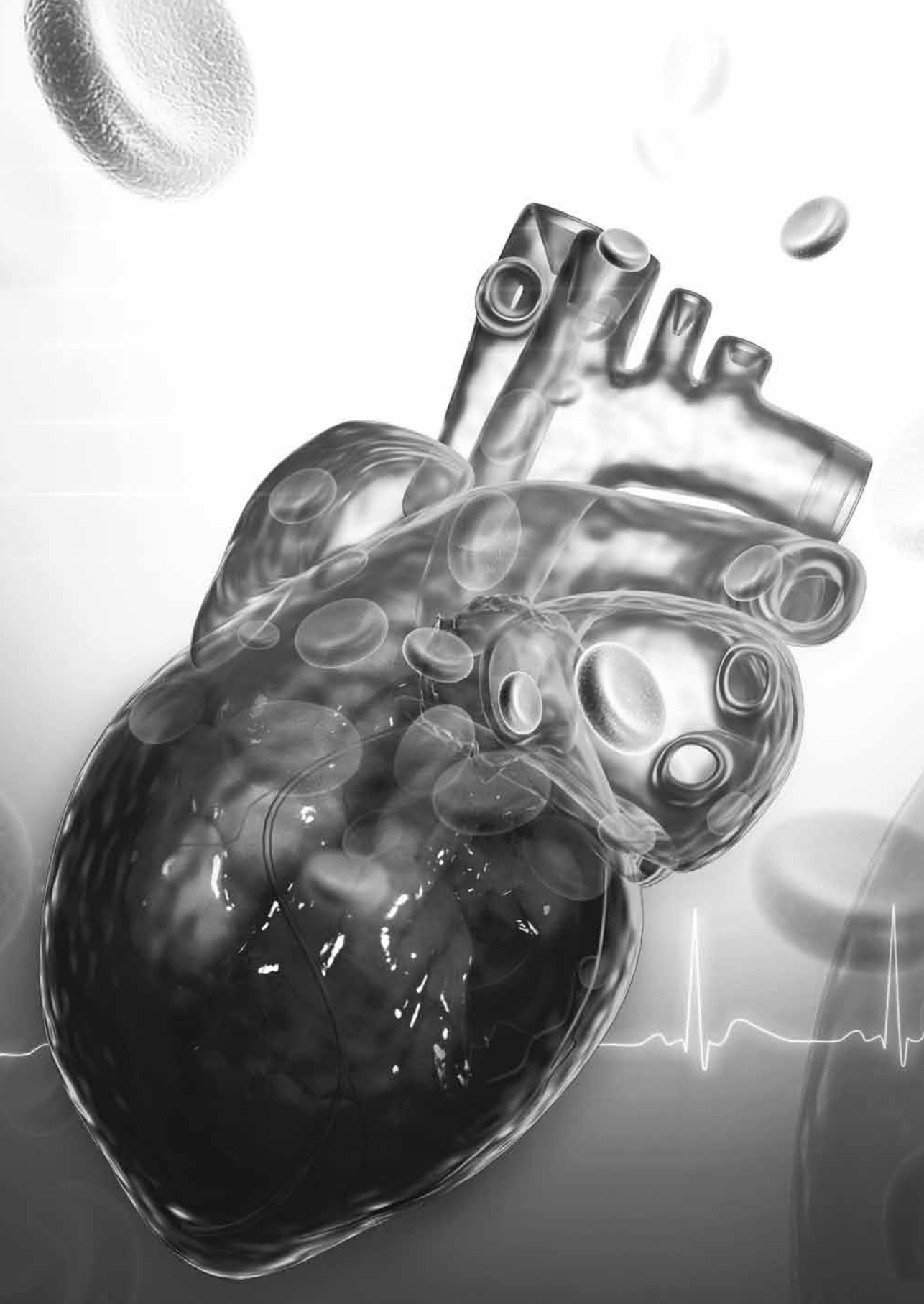
In **hoofdstuk 7a** wordt het nut van stress imaging bij patiënten met aangeboren hartafwijkingen geëvalueerd. Het gebruik van verschillende typen stressoren en verschillende soorten beeldvormende technieken wordt beschreven, als ook de resultaten van stress imaging studies. In **hoofdstuk 7b** hebben we aangetoond dat de zogenaamde stress MRI, met toediening van een lage dosering dobutamine (7.5 µg/kg/min), goed uitvoerbaar en veilig is bij patiënten met complexe aangeboren hartafwijkingen, waaronder patiënten na een gecorrigeerde tetralogie van Fallot. In een serie van 110 dobutamine stress studies bij 91 patiënten (gemiddelde leeftijd ten tijde van de eerste studie 14 jaar, bereik 7 – 26 jaar), vonden we geringe bijwerkingen bij slechts 3 patiënten, terwijl belangrijke bijwerkingen zoals ritmestoornissen, niet voorkwamen. Daarnaast hebben we de intra- en interobserver variabiliteit getest in 25 willekeurig geselecteerde patiëntenstudies. We vonden dat de observer variabiliteit nog steeds adequaat was, alhoewel de interobserver variabiliteit van het eind-systolisch volume tijdens dobutamine stress voor zowel linker- als rechterkamer toenam tot boven de 10%.

Hoofdstuk 8 beschrijft de resultaten van onze dobutamine stress MRI's, die 2x zijn verricht met een interval van 5 jaar bij 27 Fallot patiënten (gemiddelde leeftijd ten tijde van de baseline studie 14 ± 4 jaar). Een normale respons op dobutamine werd gedefinieerd als een afname van het rechterkamer eind-systolisch volume tijdens stress en een toename van de rechterkamer ejectie fractie tijdens stress. Contractiele reserve werd gedefinieerd als het vermogen om de ejectie fractie te laten toenemen tijdens stress. We vonden dat het grootste gedeelte van onze patiënten (26 van de 27) een normale respons op dobutamine vertoonde, welke ook niet veranderde tijdens de follow-up periode. Dit past bij de goede klinische conditie van deze relatief jonge Fallot patiënten, ondanks duidelijke rechterkamer dilatatie. Een lagere rechterkamer contractiele reserve ten tijde van de baseline meting was voorspellend voor een grotere afname van de VO_2 max. tijdens de 5-jaars follow-up periode. Dit geeft aan dat dobutamine stress MRI mogelijk van aanvullende waarde kan zijn tijdens de follow-up van Fallot patiënten. Op basis van de rechterkamer contractiele reserve ten tijde van de baseline studie kon echter geen onderscheid gemaakt worden tussen niet-PKV patiënten en patiënten die later tijdens de follow-up een klepvervanging zouden ondergaan. Echter, patiënten die later een klepvervanging zouden ondergaan vertoonden wel een kleinere afname van het rechterkamer eind-systolisch volume tijdens stress dan de niet-PKV patiënten. Daarnaast zagen we dat sommige patiënten die later een klepvervanging zouden ondergaan, niet in staat waren hun rechterkamer effectief slagvolume te verhogen tijdens dobutamine stress. Deze parameters zouden

erop kunnen wijzen dat er wel degelijk sprake is van een verminderde rechterkamer functie. Dit moet nader onderzocht worden.

In **hoofdstuk 9** hebben we ons geconcentreerd op de biomoleculaire signaalpaden en meer specifiek op het transforming growth factor (TGF)-β. In een cross-sectionele studie van 96 patienten (mediane leeftijd 22 jaar, bereik 7 – 66 jaar) werden TGF-β concentraties bepaald met behulp van ELISA kits. Een protein array werd uitgevoerd in gepoolde subgroepen om de concentraties van diverse eiwitten te bepalen die betrokken zijn bij processen als inflammatie, extracellulaire matrix afbraak, fibroblast proliferatie, en overleving van cardiomyocyten. MRI's werden verricht om de rechterkamer grootte en -functie te bepalen. Bij 36 patiënten (gemiddelde leeftijd ten tijde van de baseline studie 14 ± 5 jaar), konden we beschikken over seriële metingen van TGF-β concentraties en de rechterkamer grootte en -functie. Daarnaast werden 70 gezonde vrijwilligers geïncludeerd (mediane leeftijd 21 jaar, bereik 12 – 64 jaar). In onze seriële follow-up studie vonden we een toename van de rechterkamer grootte en een afname van de TGF-β concentraties tijdens de follow-up periode. In de cross-sectionele studie zagen we een trend tot lagere TGF-β concentraties bij patiënten met een ernstige rechterkamer dilatatie. Dit viel samen met een stijging van een belangrijk aantal ontstekingsfactoren (zoals tumor necrosis factor-α en interferon-γ). Daarbij zagen we bij deze patiënten een afname van een aantal beschermende groeifactoren (zoals epidermal growth factor en metalloproteinase remmers) met het toenemen van de follow-up duur, terwijl eiwitten die hypertrofie induceren toenamen. Dit alles wijst erop dat deze patiënten mogelijk gevoeliger zijn voor progressieve rechterkamer dilatatie en daaropvolgend rechterkamer dysfunctie en rechterkamer falen. Als we de biomoleculaire signaalpaden die bij deze processen betrokken zijn beter gaan begrijpen, zouden we de patiënten die het risico lopen op rechterkamer falen in de toekomst mogelijk in een eerder stadium kunnen herkennen en daardoor mogelijk ook beter kunnen behandelen. Nader onderzoek is nodig om te evalueren of componenten uit dit TGF-β signaalpad gebruikt zouden kunnen worden als biomarkers om de progressie van de rechterkamer dilatatie te kunnen voorspellen, en of specifieke TGF-β therapie ontwikkeld zou kunnen worden.

In **hoofdstuk 10** wordt een overzicht gegeven van onze belangrijkste bevindingen. De resultaten van dit proefschrift worden geëvalueerd in de context van de huidige literatuur en recent gepubliceerde studies. Daar waar mogelijk worden aanbevelingen gedaan voor nader onderzoek.



Appendices

List of abbreviations

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PhD portfolio

Dankwoord

About the author

List of abbreviations

2D = two-dimensional
3D = three-dimensional
ACE = angiotensin converting enzyme
APFR = atrial peak filling rate
AR = aortic regurgitation
AS = aortic stenosis
ASD = atrial septal defect
ASO = arterial switch operation
AT = anaerobic threshold
AT_1 = angiotensin II type-1
ATP = adenosine triphosphate
AVR = aortic valve replacement
BPV = balloon pulmonary valvuloplasty
BSA = body surface area
CCL = chemokine (C-C motif) ligand
ccTGA = congenitally corrected transposition of the great arteries
CHD = congenital heart disease / congenital heart defect
CMR = cardiovascular magnetic resonance
CO = cardiac output
CoV = coefficient of variability
CT = computed tomography
CTF1 = cardiotrophin 1
CXCL = chemokine (C-X-C motif) ligand
DCMR = dobutamine stress cardiac magnetic resonance
DORV = double outlet right ventricle
Dt = deceleration time
E/A emptying ratio = ratio of early-to-late emptying volume
E/A filling ratio = ratio of early-to-atrial filling volume
ECG = electrocardiography
ECM = extracellular matrix
EDFF = end-diastolic forward flow
EDP = end-diastolic pressure
EDV = end-diastolic volume
EF = ejection fraction
Eff.SV = effective stroke volume
EGF = epidermal growth factor
EGFR = epidermal growth factor receptor
EGVEGF = endocrine grand-derived vascular endothelial growth factor

ELISA = enzyme-linked immuno sorbent assay
EPER = early peak emptying rate
EPFR = early peak filling rate
ESV = end-systolic volume
FU = follow-up
HOCM = hypertrophic obstructive cardiomyopathy
HR = heart rate
hsCRP = high sensitive C-reactive protein
ICD = implantable cardioverter defibrillator
IFN-γ = interferon-γ
IL = interleukin
IL2R = interleukin 2 receptor
IL18BP = interleukin 18 binding protein
IP-10 = interferon-γ induced protein 10
IVC = inferior caval vein
LA = left atrium
LGE = late gadolinium enhancement
LPER = late peak emptying rate
LV = left ventricle
LVOT = left ventricular outflow tract
LVOTO = left ventricular outflow tract obstruction
Max.vol. = maximal volume
Min.vol. = minimal volume
MMP = matrix metalloproteinase
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
((NT-)pro)BNP = ((N-terminal) prohormone) brain natriuretic peptide
NYHA = New York Heart Association
PA = pulmonary artery
PA = pulmonary atresia (chapter 3)
Peak VO_2 = peak oxygen uptake
PPVI = percutaneous pulmonary valve implantation
PR = pulmonary regurgitation
PS = pulmonary (valve) stenosis
PV = pulmonary valve
PVR = pulmonary valve replacement
QTc = QT interval, corrected for heart rate
RA = right atrium
RBBB = right bundle branch block
ROC = receiver operating characteristic

RQ = respiratory quotient
RV = right ventricle
RVEFcor. = right ventricular ejection fraction, corrected for tricuspid regurgitation and pulmonary regurgitation
RVM = right ventricular mass
RVOT = right ventricular outflow tract
SCD = sudden cardiac death
SD = standard deviation
SE = standard error
SSFP = steady-state free precession
SV = stroke volume
SVC = superior caval vein
SVPB = supraventricular premature beat
SVT = supraventricular tachycardia
TAP = transannular patch
TAPSE = tricuspid annular plane systolic excursion
TDI = tissue Doppler imaging
TGA = transposition of the great arteries
TGF-β = transforming growth factor-β
TIMP = tissue inhibitor of metalloproteinase
TNF-α = tumor necrosis factor-α
TNFRSF21 = tumor necrosis factor receptor superfamily member 21
TOF = tetralogy of Fallot
VE/VCO_2 slope = ventilatory response to carbon dioxide production
VO_2 max. = peak oxygen uptake
VoSD = volumetric surface detection
VPB = ventricular premature beat
VSD = ventricular septal defect
VT = ventricular tachycardia
VTI = velocity time integral
WMA = wall motion abnormalities

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List of publications

Original papers

1. Abnormal right atrial and right ventricular diastolic function relate to impaired clinical condition in patients operated for tetralogy of Fallot
   Luijnenburg SE, Peters RE, van der Geest RJ, Moelker A, Roos-Hesselink JW, de Rijke YB, Mulder BJM, Vliegen HW, Helbing WA
   International Journal of Cardiology 2012 Mar 3 [Epub ahead of print]
2. Exercise capacity and ventricular function in patients treated for isolated pulmonary valve stenosis or tetralogy of Fallot
   Luijnenburg SE, de Koning WB, Romeih S, van den Berg J, Vliegen HW, Mulder BJM, Helbing WA
   International Journal of Cardiology 2012 Jul;158(3):359-363
3. Effect of age on exercise capacity and cardiac reserve in patients with pulmonary atresia with intact ventricular septum after biventricular repair
   Romeih S, Groenink M, Roest AAW, van der Plas MN, Spijkerboer AM, Hazekamp MG, **Luijnenburg SE**, Mulder BJM, Blom NA
   European Journal of Cardiothoracic surgery 2012 Jul;42(1):50-55
4. Safety and observer variability of cardiac magnetic resonance imaging combined with low-dose dobutamine stress-testing in patients with complex congenital heart disease
   Robbers-Visser D, **Luijnenburg SE**, van den Berg J, Roos-Hesselink JW, Strengers JLM, Kapusta L, Moelker A, Helbing WA
   International Journal of Cardiology 2011 Mar;147(2):214-218
5. Cardiac stress testing after surgery for congenital heart disease
   Helbing WA, **Luijnenburg SE**, Moelker A, Robbers-Visser D
   Current Opinion in Pediatrics 2010 Oct;22(5):579-586
6. Clinical value of real-time 3-dimensional echocardiography for right ventricular quantification in congenital heart disease: validation with cardiac magnetic resonance imaging
   Van der Zwaan HB, Helbing WA, McGhie JS, Geleijnse ML, **Luijnenburg SE**, Roos-Hesselink JW, Meijboom FJ
   Journal of the American Society of Echocardiography 2010 Feb;23(2):134-140
7. Tetralogy of Fallot – Does MR imaging have the answers?
   Luijnenburg SE, Vliegen HW, Mulder BJM, Helbing WA
   Progress in Pediatric Cardiology 2010 Jan;28:29-34
8. Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by CMR imaging
   Luijnenburg SE, Robbers-Visser D, Moelker A, Vliegen HW, Mulder BJM, Helbing WA
   International Journal of Cardiovascular Imaging 2010 Jan;26(1):57-64
9. Stress imaging in congenital heart disease
   Robbers-Visser D, **Luijnenburg SE**, van den Berg J, Moelker A, Helbing WA

Cardiology in the Young 2009 Dec;19(6):552-562

10. Postoperative hemicerebellar inflammation mimicking recurrent tumor after resection of a medulloblastoma
    Luijnenburg SE, Hanlo PW, Han KS, Kors WA, Witkamp TD, Verbeke JL
    Journal of Neurosurgery Pediatrics 2008 Apr;1(4):330-333
11. Mild pyelectasis diagnosed by prenatal ultrasound is not a predictor of urinary tract morbidity in childhood
    Damen-Elias HA, **Luijnenburg SE**, Visser GH, Stoutenbeek PH, de Jong TP
    Prenatal Diagnosis 2005 Dec;25(13):1239-1247

Submitted for publication

12. Ventricular response to dobutamine stress relates to the change in peak oxygen uptake during 5-year follow-up in patients with repaired tetralogy of Fallot
    Luijnenburg SE, van der Geest RJ, Mekic S, van den Berg J, Moelker A, Strengers JLM, Roos-Hesselink JW, Bogers AJJC, de Rijke YB, Mulder BJM, Vliegen HW, Helbing WA
13. Diminished TGF-β levels in patients with right ventricular dilatation after repair of tetralogy of Fallot
    Luijnenburg SE*, Cheng C*, van de Kamp EH, Schreuder MPR, Chrifi I, Roos-Hesselink JW, de Rijke YB, Mulder BJM, Vliegen HW, Duckers HJ[#], Helbing WA[#]
14. Serial follow-up of clinical condition and ventricular function in patients with and without pulmonary valve replacement after repair of tetralogy of Fallot
    Luijnenburg SE, Helbing WA, Moelker A, Kroft LJM, Groenink M, Roos-Hesselink JW, de Rijke YB, Hazekamp MG, Bogers AJJC, Vliegen HW, Mulder BJM
    In preparation

Abstracts

1. Impaired TGF-β mediated cardiac healing in patients with right ventricular dilatation after repair of tetralogy of Fallot
   Luijnenburg SE, Cheng C, van de Kamp EH, Schreuder MPR, Chrifi I, Roos-Hesselink JW, Rijke YB, Mulder BJM, Vliegen HW, Duckers HJ, Helbing WA
   Cardiology in the Young 2012;22(Suppl 1):abstract O5-3
   - Oral presentation Young Investigator Award session, 46th Scientific Sessions of the Association for European Pediatric Cardiology, 2011, Granada, Spain
2. Bi-atrial function and its relation with biventricular function and clinical parameters of patients operated for tetralogy of Fallot
   Luijnenburg SE, Peters RE, van der Geest RJ, Moelker A, Roos-Hesselink JW, de Rijke YB, Mulder BJM, Vliegen HW, Helbing WA
   Journal of Cardiovascular Magnetic Resonance 2012;14(Suppl 1):abstract P124
   - Posterpresentation, 15th Annual Scientific Sessions of the Society for Cardiovascular Magnetic Resonance, 2012, Orlando, USA

3. Serial follow-up of clinical condition and ventricular function in patients after repair of tetralogy of Fallot: we know when to operate, do we?
   Luijnenburg SE, Helbing WA, Moelker A, Kroft LJM, Groenink M, Roos-Hesselink JW, de Rijke YB, Hazekamp MG, Bogers AJJC, Vliegen HW, Mulder BJM
   Circulation 2011;124(Suppl 1):abstract 13161
   - Oral presentation, Scientific Sessions of the American Heart Association, 2011, Orlando, USA
   - Posterpresentatie, 33e congres van de Nederlandse Vereniging voor Kindergeneeskunde, 2011, Veldhoven, Nederland
4. Serial follow-up of biventricular function, contractile reserve, exercise capacity, and NT-proBNP measurements in repaired tetralogy of Fallot
   Luijnenburg SE, van den Berg J, Moelker A, Roos-Hesselink JW, Bogers AJJC, de Rijke YB, Mulder BJM, Vliegen HW, Helbing WA
   Journal of Cardiovascular Magnetic Resonance 2011;13(Suppl I):abstract P194
   Cardiology in the Young 2011;21(Suppl 1):abstract P201
   - Posterpresentation, 45th Scientific Sessions of the Association for European Pediatric Cardiology, 2011, Granada, Spain
   - Posterpresentation, Joint Scientific Sessions of the Society for Cardiovascular Magnetic Resonance / European Cardiovascular Magnetic Resonance, 2011, Nice, France
5. Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease using steady-state free precession magnetic resonance imaging
   Luijnenburg SE, Robbers-Visser D, Moelker A, Vliegen HW, Mulder BJM, Helbing WA
   Journal of Cardiovascular Magnetic Resonance 2009;11(Suppl 1):abstract P100
   - Posterpresentation, 12th Annual Scientific Sessions of the Society for Cardiovascular Magnetic Resonance, 2009, Orlando, USA
   - Posterpresentatie, Wetenschapsdag van de Nederlandse Hartstichting, 2008, Amsterdam, Nederland
6. Safety and accuracy of cardiac magnetic resonance imaging combined with low-dose dobutamine stress-testing in patients with congenital heart disease
   Luijnenburg SE, Robbers-Visser D, van den Berg J, Roos-Hesselink JW, Moelker A, Helbing WA
   Journal of Cardiovascular Magnetic Resonance 2009;11(Suppl 1):abstract P27
   - Posterpresentation, 12th Annual Scientific Sessions of the Society for Cardiovascular Magnetic Resonance, 2009, Orlando, USA
7. Enlarged right ventricular size at 11 years follow-up after closure of secundum type atrial septal defect in children
   de Koning WB**, Luijnenburg SE**, van Osch-Gevers M, ten Harkel ADJ, Robbers-Visser D, van Domburg RT, Bogers AJJC, Helbing WA
   Journal of Cardiovascular Magnetic Resonance 2009;11(Suppl 1):abstract P99

- Posterpresentation, 12th Annual Scientific Sessions of the Society for Cardiovascular Magnetic Resonance, 2009, Orlando, USA

PhD portfolio

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PhD period:	May 2007 – November 2011
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Title of thesis:	Outcome late after repair of tetralogy of Fallot

	Year	Workload (ECTS)
General academic skills		
- Research Integrity	2008	0.3
- Biomedical English Writing and Communication	2010	4.0
Research skills / In-depth courses		
Nihes:		
- Classical Methods for Data-analysis	2007	5.7
- Study Design	2008	4.3
- Courses for the Quantitative Researcher	2009	1.4
- Repeated Measurements in Clinical Studies	2010	1.9
Research School COEUR:		
- Arrhythmia Research Methodology	2009	1.5
- Congenital Heart Disease	2009	1.5
- Cardiovascular Imaging and Diagnostics	2010	1.5
- Heart Failure Research	2011	1.5
(Inter)national conferences / Presentations		
- Wetenschapsdag van de Nederlandse Hartstichting (posterpresentatie)	2008	0.3
- 11th Annual Scientific Sessions of the Society for Cardiovascular Magnetic Resonance (SCMR), Los Angeles, USA	2008	0.9
- 12th Annual Scientific Sessions of the Society for Cardiovascular Magnetic Resonance (SCMR), Orlando, USA (3x posterpresentation)	2009	0.9
- Coeur course on Congenital Heart Disease (oral presentation)	2009, 2011	0.6
- Joint Scientific Sessions of the Society for Cardiovascular Magnetic Resonance (SCMR) and the European Society of		

Cardiology (ESC), Nice, France (posterpresentation)	2011	1.2
- 45th Annual Meeting of the Association of European Paediatric Cardiology (AEPC), Granada, Spain (posterpresentation)	2011	1.2
- Coeur Research Seminar on Congenital Heart Disease (oral presentation)	2011	0.3
- 33e congres van de Nederlandse Vereniging voor Kindergeneeskunde (NVK), Veldhoven, Netherland (posterpresentatie)	2011	0.9
- Scientific Sessions 2011 of the American Heart Assocation (AHA), Orlando, USA (oral presentation)	2011	1.5
- 15th Scientific Sessions of the Society for Cardiovascular Magnetic Resonance (SCMR), Orlando, USA (posterpresentation)	2012	0.9
Seminars and workshops		
Research School COEUR:		
- Tetralogy of Fallot	2008	0.4
- Risk stratification and modelling	2008	0.4
- Gene and cell based therapies of cerebro and cardiovascular disease	2008	0.4
- Clinical decision making in cardiovascular intervention	2010	0.4
- Coarctation of the Aorta	2010	0.4
- Congenital Heart Disease	2011	0.4
Other:		
- Projectdag Interuniversitair Cardiologisch Instituut Nederland (ICIN)	2007	0.3
- Knowledge Day Interuniversitair Cardiologisch Instituut Nederland (ICIN): “Genetics in Cardiology”	2008	0.3
- Research Day Pediatrics	2008 – 2010	0.5
- Interactieve basis echocursus: aangeboren hartafwijkingen	2007	0.3
- Symposium “Behandeling van aangeboren hartafwijkingen: indicaties, technische aspecten en late gevolgen”	2009	0.3
Teaching activities		
- Supervising Research project 4th year medical student Erasmus MC Rotterdam (40 weeks)	2010 – 2011	1.5

Dankwoord

Eindelijk is het zover en is mijn proefschrift af! Wat een fantastisch gevoel. Graag wil ik iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit resultaat:

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About the author

Saskia Luijnenburg is geboren op 19 februari 1980 in Delft. Zij ging van 1992 tot 1998 naar het Huygens Lyceum te Voorburg, alwaar zij het Gymnasium afrondde met 9 vakken. Vervolgens startte zij haar Geneeskunde studie aan de Universiteit van Utrecht. Tijdens haar 4e jaar deed zij onderzoek op de afdeling Verloskunde van het Wilhelmina Kinderziekenhuis (begeleider Mevr. H. Damen-Elias, verloskundige-echografiste), alwaar zij keek naar de uitkomsten op kinderleeftijd van kinderen bij wie antenataal een milde pyelectasie (< 10 mm) was vastgesteld. In 2003 behaalde zij cum laude haar doctoraal examen. Voordat zij met haar co-schappen begon, deed zij 3 maanden vrijwilligerswerk in een kindertehuis in Ghana. Zij besloot haar studie met een keuze co-schap Kindergeneeskunde in het Wilhelmina Kinderziekenhuis.

Na haar studie werkte zij een half jaar als ANIOS kinderneurochirurgie en daarna nog anderhalf jaar als ANIOS kindergeneeskunde in het Wilhelmina Kinderziekenhuis, waarvan 1 jaar op de afdeling Neonatologie. In 2007 startte zij haar promotieonderzoek naar de lange termijn uitkomsten bij patiënten geopereerd aan een tetralogie van Fallot, onder supervisie van Prof. dr. W.A. Helbing (promotor), kindercardioloog in het Sophia Kinderziekenhuis te Rotterdam, Mevr. Prof. dr. B.J.M. Mulder (promotor), cardioloog in het Academisch Medisch Centrum te Amsterdam, en Dr. H.W. Vliegen (co-promotor), cardioloog in het Leids Universitair Medisch Centrum te Leiden, resulterend in dit proefschrift.

Tijdens haar studietijd, ANIOS periode en jaren als arts-onderzoeker heeft zij in het bestuur gezeten van een badmintonvereniging en heeft zij jarenlang diverse kinderkampen begeleid, waaronder kampen voor kinderen met een aangeboren hartafwijking. In haar vrije tijd speelt zij graag badminton en houdt zij van zeilen en reizen.

In 2012 is zij begonnen aan haar kindergeneeskunde opleiding. Momenteel is zij tot oktober 2013 werkzaam in het Amphia ziekenhuis te Breda (opleider Mevr. dr. A.A.P.H. Vaessen-Verberne), waarna zij haar opleiding zal voortzetten in het Sophia Kinderziekenhuis te Rotterdam (opleider Dr. M. de Hoog).