Assessment of cardiac function and hemodynamics in children and adults with right ventricular pressure overload: role of cardiac magnetic resonance imaging
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Assessment of cardiac function and hemodynamics in children and adults with right ventricular pressure overload: role of cardiac magnetic resonance imaging

Soha Romelh

I am proud to belong to the generation that dreamed of a new Egypt, and decided to make their dream a reality; yet nobody said it going to be easy, but as the Dutch would say, "Waar een wil is, is een weg."

Soha Romelh

ROLE OF CARDIAC MAGNETIC RESONANCE IMAGING

ASSESSMENT OF CARDIAC FUNCTION AND HEMODYNAMICS IN CHILDREN AND ADULTS WITH RIGHT VENTRICULAR PRESSURE OVERLOAD

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ASSESSMENT OF CARDIAC FUNCTION AND HEMODYNAMICS IN CHILDREN AND ADULTS WITH RIGHT VENTRICULAR PRESSURE OVERLOAD: ROLE OF CARDIAC MAGNETIC RESONANCE IMAGING

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Faculteit der Geneeskunde
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Chapter 1

Introduction and outline of the thesis
In congenital heart disease (CHD), the right ventricle (RV) is subject to pressure overload in patients with obstruction of the right ventricular outflow tract (RVOT), elevated pulmonary pressure, or when the RV supports the systemic circulation. Approximately 10% to 20% of CHD cases involve RV pressure overload.\textsuperscript{1-5}

RV adaptation to pressure overload is complex and depends on the course (acute versus chronic) and onset (childhood versus adulthood) of the disease. In general, the RV adapts better to volume than to pressure overload and to chronic than to acute stressors.\textsuperscript{6-8}

Long term follow-up studies demonstrate that chronic pressure overload on the RV often leads to RV dysfunction, ventricular arrhythmias and sudden cardiac death. Therefore, appropriate RV evaluation is essential because timely intervention may preserve RV function and prevent irreversible RV damage.\textsuperscript{7, 9, 10}

Angiographic assessment previously was the gold standard for RV evaluation; however, it is an invasive method involving radiation hazards and the use of contrast agents.\textsuperscript{11, 12}

Radionuclide angiography provides a reliable quantitative measurement of ventricular function that is not based upon assumptions of ventricular geometry. However, it requires acquisition of views of the ventricles that exclude counts from other chambers. Counts can usually be achieved for the left ventricle (LV) but are often not satisfactorily for the RV. Moreover, radionuclide imaging uses ionizing radiation and its resolution is poor compared to other imaging modalities. Thus, radionuclide angiography has played only a limited role in RV evaluation.\textsuperscript{13, 14}

Due to its widespread availability, echocardiography is often used as the first imaging modality to evaluate the RV.\textsuperscript{15} Tricuspid annular plane systolic excursion (TAPSE) provides a reproducible echocardiographic quantitative assessment of RV systolic function and is a prognostic indicator of the outcome of heart failure.\textsuperscript{16} However, echocardiographic quantitative assessment of the RV is challenging due to its anterior position. Poor acoustic windows and an inability to adequately image the RV anterior wall also present challenges when obtaining a TAPSE measurement. Three-dimensional (3D) echocardiography may improve and expand the diagnostic capabilities of cardiac ultrasound. 3D echocardiography is less limited by the geometric assumptions needed to assess ventricular function and anatomy.\textsuperscript{17} However, it is still dependent on achieving adequate acoustic windows: four high-resolution subvolumes are required for a complete dataset. In an optimal setting, it is possible to encompass the entire RV in a one full-volume dataset. In clinical practice, however, it is difficult to incorporate both the RV inflow and outflow tracts in one volume dataset due to the limited angle of 3D echocardiography, especially when the RV is dilated or hypertrophied.\textsuperscript{18, 19} Therefore, evaluation of the RV by 3D echocardiography is not currently part of standard clinical practice.

Alternative 3D "non-geometric" techniques such as cardiac magnetic resonance (CMR) and multi-detector computed tomography (MDCT) for patients with contraindications for CMR, permit an accurate assessment of RV volume, mass, and function. CMR is now the imaging modality of choice for RV evaluation.\textsuperscript{19-27} CMR provides the ability to image the
heart, systemic and pulmonary veins and arteries, the airway, and to evaluate flow and myocardial function, thereby having an important diagnostic role in patients with CHD. However, the challenges for CMR in infants and children are significant because of the much smaller structures being imaged, the faster heart rates, and the inability of children to hold still during the relative long scan time requiring sedation and general anesthesia. Despite these challenges, CMR becomes more integrated in clinical practice.\textsuperscript{28, 29}

In this review we discuss the role of CMR in evaluating RV in patients with RVOT obstruction and in patients with systemic RV. Assessment of RV in pressure overload caused by elevated pulmonary pressure is beyond the scope of this review.

**The Role of CMR in RV evaluation**

RV volume and mass can be reproducibly measured by CMR without the need for computational assumptions. The ESC and AHA/ACC guidelines recommend the use of CMR when knowledge of RV function is essential for patient management.\textsuperscript{30, 31} The current guidelines recommend that a stack of slices is orientated along the RV short axis.\textsuperscript{32} This approach is highly accurate and does not rely on geometrical assumptions. However, until now, no commercial software has been available to automatically detect the RV contours; therefore, they still have to be drawn manually.

Phase-encoded flow imaging is an accurate and extensively validated method that is used for assessing cardiac valve flow.\textsuperscript{33} This technique is used to measure flow volumes, regurgitation fraction and peak flow velocities and can be performed in any direction, or in a combination of directions (i.e., 2D in-plan encoding or 3D encoding).\textsuperscript{34} Phase-encoded flow imaging measures the relative flow volume to each lung and assesses the hemodynamic significance of branch pulmonary stenosis.\textsuperscript{35, 36} CMR flow imaging of the pulmonary arteries has been validated against perfusion scintigraphy to accurately assess differential lung flow over both branch pulmonary arteries.\textsuperscript{37}

3D gadolinium enhanced angiography (3D-MRA) provides 3D images of the pulmonary artery tree from the centrally located main pulmonary artery to the small sub-segmental branches (< 1 mm) in the lung periphery.\textsuperscript{38-40} (Figure 1) However, 3D-MRA underestimates the size of vascular structures as it is non-gated sequence and the size of the pulmonary arteries change during the cardiac cycle.\textsuperscript{35} Comparable to echocardiography, the greatest limitation of 3D-MRA in the assessment of pulmonary circulation is its inability to directly measure pressures.

Delayed contrast enhancement MRI (DCE-MRI) was first described more than 20 years ago as an excellent choice to visualise myocardial fibrosis due to its excellent endocardial visualisation.\textsuperscript{41, 42} Most studies with DCE-MRI have focused on the assessment of fibrosis in the LV. In 1995, the feasibility of using DCE-MRI for the assessment of RV fibrosis has been introduced.\textsuperscript{43} Compared to the LV, there is a large discrepancy in the published
results regarding fibrosis detection in the RV. This might be because the RV has a thinner wall (less myocardium compared with the LV), so it is difficult to detect an accurate nulling time.

Dobutamine, a relatively selective b-1-adrenoreceptor agonist, can be used as a pharmacological stress agent during CMR investigation. The increased cardiac output in response to dobutamine is due to both increased heart rate and stroke volume. In CHD patients dobutamine stress (DS)-MRI has become a valuable for the assessment of cardiac response to stress 44-46. In this group impaired RV cardiac reserve can be an early sign of RV dysfunction even in asymptomatic patients. 44, 45, 47-51

Novel CMR techniques such as simultaneous quantification of RV pressure with MRI-compatible catheters to derive RV volume/pressure loops, 52 and strain-encoded MRI to detect abnormal regional RV strain patterns have been developed with the aim of improving RV evaluation.53-55 They have thus far only been evaluated in a research setting and the clinical implications are unclear.

**RVOT obstruction**

RVOT obstruction may be isolated (such as subvalvular, valvular, supravalvular, or branch pulmonary artery stenosis) or associated with other lesions, such as a ventricular septal defect (VSD) in tetralogy of Fallot (TOF), pulmonary atresia with ventricular septal defect (PA-VSD), or a small abnormal tricuspid valve in pulmonary atresia with intact ventricular
Chapter 1

septum (PA-IVS).\textsuperscript{5, 56, 57} In each case, the specific type of lesion, degree of obstruction, and the presence of associated defects will influence the RV geometry, mass, and function. Echocardiography is used, in clinical practice, to visualize the obstruction level in the RVOT and to evaluate the RV function. However, CMR is a useful imaging modality for pre-, post-operative assessment and clinical follow up.

1- Preoperative assessment

CMR obtains images of RV in any desired orientation and, therefore, provides better morphological images of the RVOT due to an excellent spatial resolution and absence of acoustic window limitations.\textsuperscript{24-26, 28} Regardless of the level of RVOT obstruction, the RV exerts a hypertrophic response. Previous CMR studies demonstrated that RV mass in pressure overloaded RV correlates well with the degree of RVOT obstruction.\textsuperscript{58-61}

Complete assessment of the pulmonary blood supply source and accurate delineation of the pulmonary arteries morphology are essential for determining a management plan in TOF and PA-VSD patients. Patients with confluent and good-sized pulmonary arteries undergo complete repair, while patients with non-confluent pulmonary arteries often require a staged unifocalization approach and undergo repair at a later stage.\textsuperscript{5, 62, 63} 3D-MRA is the best imaging modality to assess the origin, size, and course of the pulmonary arteries and collaterals. It is also very useful in the assessment of the sometimes tortuous systemic to pulmonary collateral arteries.\textsuperscript{38, 62, 64-67} Although the need for catheterization cannot be completely avoided in this patient group, 3D-MRA provides a “roadmap” for diagnostic catheterization and for catheter intervention thereby decreasing catheterization time, contrast, radiation exposure, and potentially, diagnostic errors.\textsuperscript{38, 63, 68, 69}

2- Postoperative assessment and clinical follow up

Patients with surgically corrected TOF form the largest group of patients undergoing relief of RVOT obstruction. Among patients with surgically corrected TOF, the rate of long-term survival after the postoperative period is excellent but remains lower than that in the general population. Late re-interventions, mostly pulmonary valve replacement (PVR), occur in around one-third of operated TOF patients.\textsuperscript{70-72} Pulmonary regurgitation after initial TOF repair initially was not considered very harmful, however, in recent years a more aggressive approach to PVR is advocated in these patients to prevent long term RV failure due to chronic volume overload of the RV.\textsuperscript{73} Many studies have shown beneficial effects of PVR, including improvement in functional class and exercise capacity, reduction of RV size, and decrease in QRS duration. However, timing still remains difficult because the advantages of PVR have to be weighed against the risks of repeat replacement of homografts or other biological valved conduits.\textsuperscript{73-76} More than 50% of the TOF patients develop a significant stenosis or regurgitation within 10 years after PVR.\textsuperscript{74}
Studies on long-term clinical outcome after relief of RV obstruction in the absence of pulmonary regurgitation as well as studies on the effect of isolated chronic RVOT obstruction are very limited. A recent study showed that postoperative mild residual pulmonary stenosis reduces the risk of PVR during follow-up of corrected TOF patients suggesting that a conservative pulmonary stenosis relief during initial TOF repair may prevent development of severe pulmonary regurgitation and volume overload of the RV. However, moderate to severe RVOT obstruction due residual stenosis after initial surgical repair or due to stenosed biological conduits eventually will lead to right ventricular hypertrophy and RV dysfunction. Therefore, timely restoration of the RVOT either by surgical or percutaneous PVR is important to avoid irreversible RV damage. Studies have shown that, after surgical or percutaneous PVR, RV systolic function usually recovers early within the first weeks. In contrast, RV diastolic function recovers relatively late because this requires long-term RV remodelling and regression of RV mass. Changes in the vascular geometry after PVR lead to local changes in pulmonary blood flow patterns, which might affect RV function. Available 2D imaging modalities, including the standard MRI flow acquisitions, do not provide a complete evaluation of flow patterns. Recent CMR studies using 4D flow have also looked in more detail at abnormal pulmonary flow in relation to RV function and pulmonary artery geometry. In corrected TOF, altered pulmonary flow patterns, including vortical flow in the RVOT and abnormal flow ratios between the right and left pulmonary arteries were demonstrated by 4D flow. During clinical follow-up of CHD patients DS-CMR has become more of interest because it allows assessment of RV (and LV) cardiac reserve by evaluating ventricular function during pharmacological stress. This enables early detection of RV dysfunction and possible identification of asymptomatic patients at risk for future RV failure. DS-MRI studies have been performed in asymptomatic patients with RVOT obstruction. In PA-IVS patients it remains difficult to determine whether a small and hypertrophied RV at birth is able to lifelong support the pulmonary circulation after surgical or interventional opening of the atretic valve. Myocardial fibrosis due to prolonged RV pressure overload or due to surgical scars may also play a role in development of RV failure and may form substrates for ventricular arrhythmia long-term after relief of RVOT obstruction in both isolated and combined lesions. Studies in both corrected TOF and PA-IVS patients demonstrated the presence of RV myocardial fibrosis by DCE-MRI. The presence of fibrosis in the RVOT and basal interventricular septum (Figure 2) was related to adverse clinical outcome, including restrictive pattern of RV dysfunction, exercise intolerance, and neurohormonal activation, and ventricular arrhythmia.
Systemic RV

The RV supports the systemic circulation in patients with congenitally corrected transposition of the great arteries (ccTGA) and in patients with transposition of the great arteries (TGA) after an atrial switch correction; the atrial switch involves the creation of an atrial baffle to direct venous return to the contralateral atrioventricular ventricle.\textsuperscript{3, 95} Echocardiographic assessment of these patients is usually of limited value due to an inability to adequately image the anterior wall of the hypertrophied RV, or to visualize the atrial baffles as they are placed remotely from the transducer and are thus inaccessible to the ultrasound beam. CMR provides a superior imaging modality in patients with systemic RV.\textsuperscript{96-99}

Overall low mortality and good functional status are up to the fourth decade of age in adult survivors of TGA after an atrial switch or ccTGA. Furthermore, mortality is remarkably similar between the two cohorts. This suggests that for the majority of patients, it is actually the systemic RV itself, rather than the nature of any prior surgery, that determines true long-term prognosis.\textsuperscript{100, 101} Early detection of systemic RV failure and tricuspid valve regurgitation are essential in deciding the need for medical or surgical intervention to prevent further deterioration.\textsuperscript{98, 102} The systemic RV works as a high pressure pump with increased oxygen demand which makes it vulnerable for failure and/or ischemia, however, the exact cause of the systemic RV dysfunction remains unclear.\textsuperscript{103} CMR is considered

Figure 2: Delayed contrast hyperenhancement (arrow) in the RVOT in a corrected TOF patient using DCE-MRI sequence.
as the gold standard imaging modality for the systemic RV volumes and function assessment.\textsuperscript{96, 97, 104} However, accurate and reproducible assessment of the systemic RV function is still a great challenge as delineation of the RV boundary relative to the trabeculations and papillary muscles is difficult in hypertrophied and trabeculated RVs. Delineation outside the papillary muscles and trabeculations is recommended for routine clinical measurements of systemic RV volumes as this approach takes less time and produces more reproducible measurements.\textsuperscript{105} (Figure 3) 20\% of patients with a systemic RV are pacemaker or implantable cardioverter-defibrillator dependent,\textsuperscript{106, 107} and an increasing number of patients with a failing systemic RV benefit from cardiac resynchronisation therapy.\textsuperscript{108} As most intracardiac devices are considered to be CMR incompatible, these patients are unsuitable to undergo CMR. MDCT provides a reliable alternative to assess the systemic RV volumes in these patients.\textsuperscript{109} However, patient selection should be restrictive to avoid unnecessary exposure to radiation and contrast agents.

CMR, especially stress CMR and delayed contrast hyperenhancement, enables prognostic classification in patients with systemic RV. Impaired cardiac reserve and myocardial fibrosis are correlated with poor exercise tolerance, ventricular arrhythmia, and inversely correlated with the RV systolic function.\textsuperscript{44, 46, 50, 51, 110-112}

Tricuspid regurgitation is a very common finding in adult patients with systemic RV and tends to progressively worsen. Tricuspid regurgitation is an independent factor of systemic RV dysfunction.\textsuperscript{113} Occasionally the tricuspid valve apparatus may be intrinsically abnormal or may have been damaged at the time of prior VSD repair or by endocarditis.\textsuperscript{114}

**Figure 3:** Assessment of RV volumes in a patient with hypertrophied systemic RV after atrial switched for transposition. Short-axis view from a multi-phase steady state free precision sequence in end systole (left) and end diastole (right) showing inclusion of trabeculations and papillary muscles in the ventricular cavity. LV = left ventricle, RV = right ventricle.
In this circumstance, tricuspid valve replacement may be warranted, but in most cases the regurgitation is secondary to annular dilatation from RV failure, and tricuspid valve replacement is not helpful. Evaluation of the tricuspid valve with standard 2D MRI sequence is hampered by cardiac motion because the imaging plane is fixed throughout the cardiac cycle, but the tricuspid valve may move up to 24 mm toward the apex during systole. 4D flow resolves the problem of valvular annulus motion, owing to retrospective valve tracking and velocity encoding in three orthogonal directions. There are no published data evaluating the tricuspid valve flow in patients with systemic RV; however it has been performed in other CHD.

Currently, the arterial switch operation is the surgical procedure of choice to correct patients with TGA. However, still many adult TGA patients with atrial switch undergo clinical follow up. Atrial baffles are not free from complications although the materials and surgical techniques are improved. Systemic or pulmonary venous baffles obstruction is the most common. It has been shown that CMR provides excellent visualisation of both extra cardiac venous structures as well as intracardiac baffles, and can detect obstruction with good sensitivity and excellent specificity. (Figure 4) Compared to echocardiography, CMR offers a 3D tomographic modality that allows imaging and reconstruction of the venous pathways in any orientation, and is not limited by body mass or poor acoustic penetration.

![Figure 4: Coronal multi-planer reconstruction of 3D-MRA in a patient after atrial switch for transposition, showing a stenosis of the SVC baffle (arrow). SVC = superior vena cava, LV = left ventricle, LA = left atrium.](image-url)
Moreover, CMR can quantify the hemodynamic impact of baffle failure on the RV: thus, CMR assists in determining the type and also, most importantly, the optimal timing of re-intervention.\textsuperscript{121-126}

**Conclusion**

Evaluation of the pressure overloaded RV in congenital heart disease, with its complex geometry and unique adaptive mechanisms, remains challenging. Recent advances in CMR techniques have improved the ability to better investigation of the RV anatomy and function. Currently, CMR has been incorporated into the management of patients with a pressure overloaded RV.

**Outline of the thesis**

The aim of this thesis is to assess cardiac function and hemodynamics in children and adults with pressure overloaded RV using CMR. Clinical outcomes of biventricular repair of PA-IVS patients seem favourable to univentricular palliation, but data on superiority of biventricular repair regarding exercise capacity are conflicting. In Chapter 2, we compare the difference in response to physical and pharmacologic stress, using DS-MRI, in surgically corrected PA-IVS patients. In Chapter 3, we study the age-related changes in exercise capacity and biventricular response to pharmacological stress, using DS-MRI in children and young adults with PA-IVS after biventricular repair to determine whether the relatively hypoplastic RV in PA-IVS is capable of adequately supporting the pulmonary circulation in the long-term.

There are few data on the long-term effects of moderate pulmonary valve stenosis on RV function. In Chapter 4, we compared the cardiac response to physical and pharmacological stress between adult patients with native moderate pulmonary valve stenosis and restenosis after prior surgical or catheter intervention.

In recent years, percutaneous PVR has been launched to relieve RVOT obstruction in patients with congenital heart disease. It has been shown that RV systolic function improved early after percutaneous PVR. In Chapter 5 both early and late changes in systolic and diastolic RV function and RV mass after percutaneous PV are evaluated.

The natural history of RV recovery after acute PE is largely unknown. In Chapter 6, we evaluate the biventricular function recovery after 6 months of treatment for acute PE. Evaluation of the systemic RV volumes and function remains a challenge. Chapter 7 provides a comparison between the axial and the short axis measurements, using CMR, of the systemic RV volumes and function. A large number of systemic RV patients have a pacemaker and an increasing number of patients with a failing systemic RV benefits from cardiac resynchronization therapy. These patients are unsuitable to undergo CMR.
Chapter 1

Cardiac CT may provide a reliable alternative for CMR in these patients. In **Chapter 8**, we evaluate intra- and interobserver variability of the RV volumes and function measurements by cardiac CT, in comparison with CMR, in patients with a systemic RV. Children represent a great challenge in obtaining arterial imaging using MRA, due to the widely variations in terms of size, circulation time, and the ability to cooperate. **Chapter 9** investigates the safety and accuracy of 3D-MRA in children with pulmonary artery atresia for evaluation of pulmonary artery anatomy and pulmonary blood supply.

Pulmonary flow can be qualitatively and quantitatively assessed by phase contrast (PC) MRI. In **Chapter 10**, we describe the pulmonary flow profile and distensibility in patients with acute PE treated for 6 months. Unexplained turbulent pulmonary flow patterns in distal to percutaneously PVR are often seen by standard 2D MRI flow. In **Chapter 11**, using 4D flow, we illustrate the pulmonary flow patterns in patients with a percutaneous PVR and compare them with patients who underwent surgical PVR.
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Exercise capacity and cardiac reserve in children and adolescents with corrected pulmonary atresia with intact ventricular septum after univentricular palliation and biventricular repair

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Abstract

Objective: Management of pulmonary atresia with intact ventricular septum is challenging and depends on severity of right ventricular hypoplasia. Clinical outcomes of biventricular repair seem favorable to univentricular palliation, but data on superiority of biventricular repair regarding exercise capacity are conflicting. We investigated the response to physical and pharmacological stress in patients with surgically corrected pulmonary atresia with intact ventricular septum.

Methods: Sixteen patients (7 patients after univentricular palliation, age 11.8 ± 2.6 years, 7 patients after biventricular repair, age 12.9 ± 2.7 years, and 2 patients after 1.5 ventricular repair, age 12 and 19 years) underwent cardiopulmonary exercise test, dobutamine stress magnetic resonance imaging, and delayed contrast-enhanced magnetic resonance imaging.

Results: The univentricular group showed impaired exercise capacity in contrast with normal exercise capacity in the biventricular group. Left ventricular ejection fraction increased in both groups. With dobutamine, left ventricular stroke volume increased only in the biventricular group (+11.3 ± 5.0 mL, P < 0.001) and not in the univentricular group (-0.04 ± 3.6 mL, P = 0.9). Heart rate increase was inadequate in the univentricular group. Maximum oxygen consumption and oxygen pulse were strongly correlated with left ventricular stroke volume during stress but not at rest. The results of the 2 patients after 1.5 ventricular repair were comparable to those of the univentricular group. No myocardial fibrosis was detected.

Conclusion: Impaired exercise capacity in children and adolescents with pulmonary atresia with intact ventricular septum after univentricular palliation is related to decreased cardiac reserve and inadequate chronotropic response. Young patients with pulmonary atresia with intact ventricular septum after biventricular repair show normal exercise capacity and cardiac reserve.
Introduction

Pulmonary atresia with intact ventricular septum (PAIVS) is a rare congenital cardiac anomaly constituting 1% to 3% of congenital heart disease (CHD). Surgical treatment of PAIVS is challenging, and treatment strategies differ among surgical centers. If the right ventricle (RV) and tricuspid valve (TV) grow adequately after initial palliation in the first years of life, biventricular repair may be considered. Patients with a hypoplastic RV or TV may be considered for univentricular palliation (Fontan operation) or a so-called 1.5 ventricular repair: patent right ventricular outflow tract (RVOT) with superior cavopulmonary anastomosis.1, 2 Theoretically, biventricular repair is superior to univentricular palliation because blood flow to the pulmonary arteries is actively sustained by the RV rather than passive as seen in the univentricular circulation. However, studies comparing long-term clinical outcomes of univentricular palliation and biventricular repair in patients with PAIVS are limited. Decreased exercise capacity after surgical repair of PAIVS has been demonstrated.3, 4 The underlying mechanisms for impaired exercise tolerance after surgical repair of PAIVS, including biventricular repair, are unclear and may be caused by impaired left ventricle (LV) performance, coronary perfusion abnormalities, or RV hypoplasia.3, 4 It is currently uncertain whether biventricular repair leads to superior exercise performance. Comprehensive assessment of cardiac reserve may provide information on the mechanism of impaired exercise tolerance. Pharmacological stress test facilitates noninvasive quantitative assessment of cardiac reserve.5, 6 Dobutamine stress magnetic resonance imaging (DS-MRI) is an attractive imaging modality for assessment of cardiac reserve because of excellent endocardial visualization and the lack of radiation. Delayed contrast enhancement (DCE)-MRI using gadolinium-based contrast media is a technique which allows the direct visualization of myocardial fibrosis.7

The present study analyzed differences in exercise capacity in patients with surgically corrected PAIVS after univentricular palliation, 1.5 ventricular repair, and biventricular repair. The presence of myocardial fibrosis was assessed using DCE-MRI. Subsequently, LV response to pharmacological stress was evaluated using DS-MRI, and the potential role of impaired LV stress-response in diminished exercise capacity was studied by correlating parameters of exercise performance to functional LV parameters at rest and during pharmacological stress.

Patients and methods

The local medical ethics committee approved the study, and informed consent was obtained from all participants and/or parents before their enrolment. Patients with surgically corrected PAIVS, aged more than eight years, followed up at our institutions, and with no contra-indication for MRI examination were included in the study. Patients.
were recruited from the pediatric cardiology database of the “Center for Congenital Heart Disease Amsterdam Leiden” (www.CAHAL.nl) and the national database and DNA data bank of adult patients with a congenital heart disease” (www.CONCOR.nl). The database identified 31 eligible PAIVS patients after surgical repair. Eleven patients were not enrolled, 10 because of family refusal to participate and 1 because of pregnancy. After univentricular palliation for PAIVS, 7 patients were identified, and out of 11 patients after biventricular repair, 7 age- and sex-matched patients after biventricular repair were selected for comparison. Furthermore, 2 patients after 1.5 ventricular repair of PAIVS were included in the study.

All patients underwent a symptom limited cardiopulmonary exercise test with determination of maximum oxygen consumption (VO_{2max}), and a MRI examination including DCE-MRI, and DS-MRI.

Cardiopulmonary exercise test
A symptom-limited cardiopulmonary exercise test to assess maximal exercise capacity was performed, according to the guidelines of the American Thoracic Society, by means of graded exercise testing on a motor-driven treadmill (Jaeger, Wuerzburg, Germany) using a modified Bruce protocol with a continuous 12 lead electrocardiographic monitoring system. At baseline and during the exercise tests, heart rate (HR) was continuously measured and maximum heart rate (MHR) was reported. VO_{2max} was defined as the highest value of oxygen uptake measured twice during the last 15 seconds of exercise. Oxygen (O_{2}) pulse is an indirect index of combined cardiopulmonary oxygen transport, and thus stroke volume. O_{2} pulse is measured by O_{2} consumption per minute divided by HR. Exercise tests were considered valid if the patient reached the anaerobic threshold, defined as having a respiratory exchange ratio (RER) greater than 1.0. Measured cardiopulmonary exercise test parameters were compared with predicted normal values from Wasserman and co-workers, and impaired exercise tolerance was defined as VO_{2} max lower than 85% of the predicted values.

Magnetic resonance imaging
MRI was performed using an open MRI 1.0 T MRI-scanner (Panorama; Philips Medical Systems, Best, The Netherlands). Long-axis, 2- and 4-chamber views and short-axis views consisting of 12 to 14 contiguous slices, covering the LV from the base of the heart to the apex, were acquired using a retrospective electrocardiogram-gated, steady-state free precession sequence during breath-holding at end-expiration. Scan parameters were: repetition time = 3.2-3.8 ms; echo time = 1.6-1.9 ms; flip angle = 50-70 degrees; slice thickness = 8 mm without slice gap; matrix = 160 x 256; field of view = 350-400 mm. Temporal resolution was approximately 25 ms. Short-axis images
were repeated at maximum dobutamine infusion to assess LV dimensions and function during pharmacological stress.

**Dobutamine infusion**

An intravenous line was inserted into the antecubital vein before the MRI procedure. Dobutamine was administrated by a digital MRI compatible infusion pump. After the MRI acquisition at rest, dobutamine was infused in serial incremental doses of 5, 10, and 15 μg/kg/min in 3-minute stages. Infusions were performed under continuous monitoring with electrocardiogram, automated blood pressure measurements. The end point for termination of dobutamine infusion was reaching a target HR, 85% of age-predicted MHR (220-age in years), or 15 μg/kg/min of dobutamine infusion.

**Delayed contrast enhanced MRI**

Ten to 15 min after injection of a gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany; 0.2 mmol/kg), DCE images were acquired in the same orientation as the cine short-axis images using a segmented inversion-recovery gradient-echo pulse sequence: repetition time / echo time = 4.01/1.25 ms, flip angle = 15 degrees, matrix = 208 x 256 and a typical voxel size of 1.6x1.3x5.0 mm, inversion time (T1) = 180-200 ms.

**MRI post-processing**

All images were analyzed on a workstation with an Intel Pentium 4 processor (Intel, Santa Clara, Calif). LV functions were analyzed with the software package MASS® (Medis BV, Leiden, The Netherlands).

LV systolic function was assessed by drawing endocardial contours at end-diastole and end-systole in all sections of the cine short-axis data. End-diastolic volume (EDV) and end-systolic volume (ESV) were obtained. Stroke volume (SV) was calculated by subtracting ESV from EDV. Ejection fraction (EF) was calculated by dividing SV by EDV × 100. Cardiac output (CO) was calculated by multiplying SV by HR.

Two observers (S.R. and M.G. with 4 and 15 years of experience in cardiac MRI, respectively) agreed on the presence or absence of DCE in the LV and in the interventricular septum (IVS).

**Statistical analysis**

The study patients were categorized in 2 groups based on the surgical repair of PAIVS: univentricular repair, and biventricular repair. Between both PAIVS groups, age-matched results of cardiopulmonary exercise test, DCE-MRI and DS-MRI were compared. The studies of 2 patients with 1.5 ventricular repair were not statistically analyzed. Differences between groups were evaluated employing the Student t test or Mann-Whitney test for pairwise comparisons. Variables that were normally distributed are presented as mean
and standard deviation, variables with skewed distribution as medians and range. The presence of normal distribution was tested using the Shapiro-Wilk test. All statistical testing and data analysis was performed with SPSS version 16 (SPSS inc, Chicago, Ill). The correlations were assessed between maximal achieved LV-SV during DS-MRI and cardiac work indices during the exercise test. The Pearson correlation coefficient was calculated.

Results

Patient characteristics

Characteristics of the patients are shown in Table 1. All patients were in New York Heart Association class I or II and received no heart failure medication. All patient with univentricular palliation received aspirin. At our institution, patients with PAIVS with a normal or moderately hypoplastic RV and a TV diameter z score of -2.0 or more are generally considered candidate for biventricular exercise test.

Table 1: Patients’ characteristics and results of cardiopulmonary exercise test

<table>
<thead>
<tr>
<th></th>
<th>Univentricular palliation group (N=7)</th>
<th>Biventricular repair group (N=7)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.8 ± 2.6</td>
<td>12.9 ± 2.7</td>
<td>0.6</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5(72%)</td>
<td>6(86%)</td>
<td>0.2</td>
</tr>
<tr>
<td>II</td>
<td>2 (28%)</td>
<td>1(14%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Previous AP shunt (n, %)</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>Oxygen saturation %</td>
<td>92.6 ± 2.3</td>
<td>97.5 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RER</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Rest heart rate (b/m)</td>
<td>87 ± 10</td>
<td>85 ± 11</td>
<td>0.4</td>
</tr>
<tr>
<td>MHR (b/m)</td>
<td>143 ± 13</td>
<td>186 ± 7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MHR (% of predicted)</td>
<td>73.5 ± 6.8</td>
<td>94.9 ± 5.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>VO2max (ml/kg/min)</td>
<td>25.9 ± 6.3</td>
<td>45.4 ± 6.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>VO2max (% of predicted)</td>
<td>55.7 ± 10.8</td>
<td>92.7 ± 6.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>O2 pulse (ml/beat)</td>
<td>6.7 ± 1.3</td>
<td>11.2 ± 2.6</td>
<td>0.006</td>
</tr>
<tr>
<td>O2 pulse (% of predicted)</td>
<td>59.6 ± 11.6</td>
<td>100.2 ± 18.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Work load (METS)</td>
<td>7.9 ± 1.9</td>
<td>12.4 ± 2.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Exercise test time (minutes)</td>
<td>10.1 ± 1.3</td>
<td>15.1 ± 0.6</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are (mean ± SD), NYHA = New York heart association, AP = aortopulmonary, b/m = beat per minute, MHR= maximum heart rate, RER= respiratory exchange rate, VO2max = maximum O2 consumption. METS = metabolic equivalents.
repair, and patients with TV diameter z scores of less than -2.0 are considered for univentricular palliation or 1.5 ventricular repair.

The neonatal TV diameter z scores, available in 13 patients, were -1.7 ± 0.3 in the biventricular group (6/7 patients) and -3.7 ± 0.6 in the univentricular palliation group and 1.5 ventricular repair group (7/9 patients).

All patients with univentricular palliation had an aorto-pulmonary (AP) shunt neonatally. Two patients (28%) had RV- dependent coronary circulation. One patient (14%) had attempted RV decompression in the neonatal period but was ultimately managed with univentricular repair because of inadequate RV growth. Two patients (28%) had Ebstein’s malformation of TV. All patients had completion of the univentricular repair at mean age of 3.1 ± 0.7 years. The Fontan circulation had been completed by means of a lateral tunnel technique in 2 patients (28%) and an extracardiac conduit in 5 patients (72%). A fenestration was performed in 4 patients (57%), which was closed later in 3 patients (43%).

In the biventricular repair group, all patients had a surgical RVOT reconstruction in the neonatal period. Six patients (86%) required AP shunts due to cyanosis and RV failure. Age at complete surgical repair was 2.5 ± 0.5 years. At the time of complete repair, 3 patients (42%) had an interatrial communication in the form of an atrial septal defect. Surgical or catheter–directed closure of atrial septal defect was performed at a later stage in all of them.

All patients completed the cardiopulmonary exercise test, DCE-MRI, and DS-MRI with no adverse events. In particular, none of the patients had episodes of hypotension or sustained arrhythmia leading to early termination of any test. None of the participants experienced headache, chest pain, or palpitations, and no ST-T changes or premature ventricular complexes were recorded on the electrocardiogram.

Cardiopulmonary exercise test

All patients reached an RER greater than 1.0, which indicates that all patients reached the anaerobic threshold. The cardiopulmonary exercise parameters of both groups are summarized in Table 1.

The univentricular palliation group showed impaired exercise capacity, defined as VO2max less than 85% of predicted. In contrast, the biventricular repair group showed normal exercise capacity. O2 pulse in response to physical exercise was significantly lower in the univentricular repair group. (Table 1) During exercise testing, all patients remained in sinus rhythm. There was no significant difference between both groups in the resting HR. HR increase, in response to physical exercise, was significant in both groups. However, the biventricular repair group had a good chronotropic response (MHR >85% of predicted), whereas the univentricular palliation group had inadequate chronotropic response (MHR < 85% of predicted). (Table 1)
Magnetic resonance imaging

MRI scans of good quality were obtained in all patients at rest and during dobutamine infusion. LV dimensions and function at rest are shown in Table 2 and Figure 1. None of the patients showed DCE in the LV or IVS. There were no differences in the functional indices (LV-SV, LV-EF and CO) between both groups at rest. In the univentricular group, the LV-EDV at rest was within the normal range but smaller compared to the biventricular group.

During DS, HR significantly increased in both groups. However, the biventricular repair group had a statistically significant better chronotropic response. LV-EF increased and LV-ESV decreased in both groups. However, during DS, patients with univentricular palliation showed abnormal decrease of LV-EDV compared with no change in patients with biventricular repair. This resulted in a significant increase in LV-SV in patients with biventricular repair whereas LV-SV did not change in patients with univentricular

Table 2: Results of dobutamine stress magnetic resonance imaging univentricular palliation group versus biventricular repair group.

<table>
<thead>
<tr>
<th></th>
<th>Univentricular palliation group</th>
<th>Biventricular repair group</th>
<th>P value of difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Stress</td>
<td>P value</td>
</tr>
<tr>
<td>MHR (b/m)</td>
<td>88 ± 18</td>
<td>128 ± 18</td>
<td>0.01</td>
</tr>
<tr>
<td>LV-EDV (mL/m²)</td>
<td>71.4 ± 7.8</td>
<td>63.5 ± 10.8</td>
<td>0.002</td>
</tr>
<tr>
<td>LV-ESV (mL/m²)</td>
<td>32.5 ± 5.8</td>
<td>25.6 ± 6.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV-SV (mL/m²)</td>
<td>38.2 ± 7.2</td>
<td>38.2 ± 6.5</td>
<td>0.9</td>
</tr>
<tr>
<td>LV-EF (%)</td>
<td>53.4 ± 7.3</td>
<td>60.57 ± 6.0</td>
<td>0.003</td>
</tr>
<tr>
<td>LV-CO (L)</td>
<td>3.8 ± 1.4</td>
<td>4.8 ± 1.6</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Values are mean ± SD, MHR = maximum heart rate, b/m = beat per minute, LV = left ventricle, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, EF = ejection fraction, CO = cardiac output.

Figure 1 Changes of left ventricular end diastolic volume (LV-EDV), left ventricular end systolic volume (LV-ESV), left ventricular stroke volume (LV-SV), left ventricular ejection fraction (LV-EF) and left ventricular cardiac output (LV-CO) during maximum dobutamine infusion in patients after univentricular palliation (white bars) and in patients after biventricular repair (black bars).
palliation (+11.3 ± 5.0 mL, -0.04 ± 3.6 mL respectively, P = .004). LV-CO increased in both groups, but LV-CO increase was significantly greater in the biventricular repair group compared with the univentricular palliation group. VO₂max and O₂ pulse during maximum physical exercise were strongly related to LV-SV during peak dobutamine infusion (r = 0.73, P = 0.003, and r = 0.79, P = 0.001 respectively; while no correlation was observed with LV-SV at rest (r = 0.05, P = 0.4, and r = 0.15, P = 0.1 respectively). (Figure 2)

**Figure 2** A) Correlation between change in LV-SV during maximum dobutamine infusion and maximum oxygen consumption (VO₂max). B) Correlation between change in LV-SV during maximum dobutamine infusion and oxygen-pulse (O₂-pulse).

**PAIVS Patients after 1.5 ventricular repair**

Two female patients of 12 and 19 years of age underwent 1.5 ventricular repair. Both patients had a surgical RVOT reconstruction and AP shunts in the neonatal period and had a superior cavopulmonary anastomosis at 2 years of age. Both patients reached RER greater than 1.0; however, both had impaired exercise capacity; VO₂max was 73% and 75% of predicted and O₂ pulse was 56% and 63% of predicted. However, both patients had a good chronotropic response; maximum HR was 95% and 87% of predicted. During pharmacological stress test, LV function resembled the reaction to DS that was observed in the univentricular group. LV-EDV decreased abnormally from 75 to 65 mL/m² and from 59 to 56 mL/m² respectively. LV-ESV response was normal and decreased from 38 to 26 mL/m² and from 25 to 20 mL/m² respectively; LV-SV remained unchanged before and after dobutamine, from 37 to 36 mL/m² in one patient and 35 mL/m² in the other patient. LV-EF increased from 51 to 60% and from 58 to 64%. LV-CO increased from 4.0 to 5.7 L and from 2.5 to 4.2 L. None of the 2 patients showed DCE of the LV or IVS.
Discussion

The present study showed that children and adolescents with PAIVS after univentricular palliation have an impaired exercise capacity that is related to decreased cardiac reserve. Of note, in all children with PAIVS exercise capacity and cardiac reserve were found to be completely normal after biventricular repair.

Management of PAIVS is difficult, and surgical and interventional therapies are associated with significant mortality and morbidity. Different treatment options have to be considered, including biventricular repair, 1.5 ventricular repair, or Fontan-type operation. The major problem when planning a strategy for a definitive repair is the fact that RV function and growth are difficult to predict before the operation. Currently, follow-up data on cardiac function and exercise capacity in PAIVS patients after different types of repair remain limited.

Our results demonstrate that increase in both SV and HR in response to physical and pharmacological stress was normal in the biventricular repair group. In contrast, the univentricular palliation group had an impaired exercise capacity because of the inability to increase SV and inadequate chronotropic response. The SV response to physical stress in patients with univentricular palliation, as measured by O₂ pulse, was inadequate, as well as the increase of HR. During pharmacological stress using DS-MRI, we confirmed that LV-SV failed to increase and that the HR increase was inadequate in the univentricular palliation group. We showed a strong correlation between indices of LV-SV augmentation during physical stress and pharmacological stress, but not with LV-SV at rest. (Figure 2) In the absence of myocardial fibrosis, the inability to increase LV-SV in spite of a normal EF could be explained by unfavorable ventricular filling, evidenced by abnormally decreased LV-EDV in response to pharmacological stress. This is the first study to investigate the mechanism of impaired exercise capacity in this group of patients.

Cardiopulmonary exercise test is a strong predictor of survival in patients with chronic heart failure, and decreased VO₂max is related to adverse long-term outcome. Furthermore, poor exercise capacity has been used as a predictor for identifying CHD patients who are at risk for hospitalization or death. In patients with surgically corrected PAIVS, decreased exercise capacity has been reported, but controversy exist whether biventricular repair leads to superior exercise performance as compared to univentricular palliation. Published data on assessment of exercise capacity in patients after surgical repair of PAIVS are limited. Few studies are available on exercise capacity assessment exclusively in this group of patients. Our results are in line with the results of Ekman-Joelsson and colleagues, who showed that patients with PAIVS after biventricular repair have a better exercise capacity compared with those after univentricular palliation. In contrast, Sanghavi and colleagues showed that exercise capacity varied widely within the 2 postoperative PAIVS groups and found no difference.
after univentricular palliation and after biventricular correction. Sanghavi and colleagues even question whether biventricular repair had been the optimal treatment option in some of the patients in their study cohort. The exact mechanism of impaired exercise capacity in patients with surgically corrected PAIVS is not clear. Although several factors have been suggested to influence exercise capacity, such as age at surgical repair, RV size at birth, TV abnormalities, presence of RV-dependent coronary circulation, and cardiac function parameters at rest, no correlations were found in earlier studies. Both previous studies showed inadequate chronotropic response in the univentricular palliation group. Univentricular palliation often involves surgery near sinus node, and sinus node dysfunction is a recognized complication of these procedures. However, as shown in our results, the magnitude of the difference in chronotropic response was insufficient to have a significant impact on the exercise capacity.

In the present study, the patients with PAIVS after the Fontan operation had similar results regarding the degree of impairment of exercise performance and reduction of VO2max as compared with large Fontan cohorts with a variety of underlying CHD. The importance of assessment of cardiac reserve is stressed by the observation that the most important predictor for development of cardiac dysfunction is not a depressed cardiac function at rest, but an abnormal response to stress. The evaluation of cardiac reserve is of special interest in patients with CHD because it is an early predictor for cardiac dysfunction and assessment of cardiac reserve may reveal cardiac dysfunction, which is not present at rest. There is no previously published data on evaluation of cardiac reserve exclusively in surgical treated patients with PAIVS after biventricular repair or univentricular palliation. Previous studies evaluated cardiac reserve in patients after univentricular palliation with several underlying diagnoses by DS imaging. In general, impaired cardiac reserve was observed in patients after univentricular palliation. However, the clinical impact of impaired cardiac reserve has not been unveiled in this heterogeneous group of Fontan patients. Our results confirmed the impaired exercise capacity in univentricular palliation patients by demonstrating significant decrease in LV-EDV in response to pharmacological stress, which indicates improper LV filling. The present study for the first time demonstrates that reduced exercise functional capacity is strongly related to cardiac reserve in a group of young patients with PAIVS after the Fontan operation. Possible explanations for improper LV filling are that loss of flow pulsatility augmentation in the univentricular circulation reduces the release of endothelium-derived nitric oxide, thereby attenuating the lowering of pulmonary vascular resistance induced by nitric oxide, leading to reduced preload. Moreover, specifically in patients with PAIVS, the presence of a high-pressure residual RV may have an adverse effect on ventricular-ventricular interaction, leading to further impairment of LV filling.

No LV or RV myocardial fibrosis was detected by DCE in this PAIVS cohort, including 2 patients who underwent the Fontan procedure with RV coronary-dependent
circulation. These findings are in contrast with the study by Liang and colleagues,\textsuperscript{25} who showed the presence of DCE in several patients with PAIVS after biventricular repair, perhaps because the majority of their patients had received an RVOT patch. However, because the DCE acquisition parameters were not mentioned in this study, it is difficult to compare results. In another study by Ekman-Joelsson and colleagues,\textsuperscript{26} perfusion defects were demonstrated in patients with PAIVS after the Fontan operation using myocardial perfusion scintigraphy. Perfusion defects were present in the septum and LV free wall and appeared to be related with ventriculo-coronary arterial connections and late age of univentricular palliation. They also demonstrated septal or LV hypokinesia or dyskinesia using echocardiography. These findings are clearly in contrast with those of our DS-MRI study, in which none of the patients were found to have segmental wall motion abnormalities at rest or during stress, and none of them had signs or symptoms of ischemia, indicating adequate coronary artery perfusion. This difference may be explained by younger age at Fontan operation in the present study or by differences in patient selection.

The present study found normal results regarding cardiac reserve during pharmacological stress and normal exercise capacity tests in the biventricular PAIVS group, which is encouraging. After birth, the majority of children in this cohort required an additional AP shunt and interatrial communication to maintain adequate pulmonary blood flow, indicating severe RV dysfunction in the first months of life. Our data indicate that cardiac function appears to recover and remains preserved in this biventricular group during midterm follow-up.

Data on the response to physical stress in patients after 1.5 ventricular repair is limited. Only 2 studies are available, and both studies showed that exercise capacity was impaired and correlated with impaired RV function in this group,\textsuperscript{27,28} similar to our 2 patients. In the present study, both patients showed abnormal response to pharmacological stress with failure to increase LV-SV after 1.5 ventricular repair. More studies on patients with PAIVS after 1.5 ventricular repair are needed for better understanding of the 1.5 ventricular physiology.

Study Limitations

The present study included relatively few patients; however, significant differences were observed between the patients with PAIVS after univentricular or biventricular correction. Furthermore, the age at MRI examination and exercise test was relatively young. Long-term follow-up is needed to evaluate whether the observed differences between the different ways of PAIVS correction remain.
Conclusion

Impaired exercise capacity in children and adolescents with PAIVS after univentricular palliation is related to decreased cardiac reserve caused by impaired LV filling during stress and inadequate chronotropic response. In contrast, young patients with PAIVS after biventricular repair show normal exercise capacity and cardiac reserve. These findings support the superiority of biventricular correction of PAIVS over univentricular palliation during mid-term follow-up.
Reference List


(5) 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(9):1077-81.


Chapter 3

Effect of age on exercise capacity and cardiac reserve in patients with pulmonary atresia with intact ventricular septum after biventricular repair

Soha Romeih 1,3,6,7, Maarten Groenink 1,3,6, Mart N van der Plas 8, Anje M Spijkerboer 3, Mark G Hazekamp 5, Saskia Luijnenburg 9, Barbara JM Mulder 1,6, Nico A Blom 2,4


ABSTRACT

Objectives: In patients with pulmonary atresia with intact ventricular septum (PAIVS), biventricular repair is considered to be the optimal treatment option in the absence of significant right ventricular (RV) hypoplasia. However, long-term clinical outcome studies are limited. We evaluated exercise capacity and cardiac function during pharmacological stress in children and young adults with PAIVS after biventricular repair.

Methods: Ten PAIVS patients after biventricular repair, with a median age of 12 years (range 9 – 42 years), underwent a cardiopulmonary exercise test, dobutamine stress magnetic resonance imaging (DS-MRI) and delayed contrast enhancement (DCE) MRI.

Results: The patients’ age negatively correlated with exercise capacity (r = - 0.72, P = 0.01) as well as left (LV) and right ventricular stroke volume (SV) response to pharmacological stress (r = - 0.72, P = 0.02; and r = - 0.64, P = 0.04; respectively). Furthermore, older age was associated with decreased RV E/A volume ratio and increased pulmonary late diastolic forward flow percentage (r = 0.65, P = 0.04, r = 0.66, P = 0.03, respectively). RV E/A volume ratio positively correlated with RV-SV response to DS-MRI (r = 0.77, P = 0.009). VO2max and O2 pulse during physical stress correlated with biventricular SV response to DS-MRI. No RV or LV ventricular myocardial fibrosis was detected.

Conclusion: In PAIVS patients after biventricular repair exercise capacity and cardiac reserve decrease with age. These findings appear to be related to impaired diastolic RV function and decreased RV filling, indicating that the function of the relatively small RV deteriorates with time.
Chapter 3

Introduction

Pulmonary atresia with intact ventricular septum (PAIVS) is an uncommon congenital heart disease (CHD) with variable grades of right ventricular (RV) hypoplasia and tricuspid valve (TV) abnormalities. Management of PAIVS is challenging due to the wide anatomic variations requiring different treatment strategies. RV decompression by means of transcatheter opening of pulmonary valve surgical pulmonary valvotomy or transannular patch is usually the first treatment step after birth if the size of the RV and the TV are adequate and if the coronary circulation is not RV-dependent. In PAIVS patients with mild – to- moderate RV hypoplasia, biventricular repair can usually be achieved although some patients require aortopulmonary shunts early in life. It is generally believed that cardiac function in PAIVS patients is better after biventricular repair than after univentricular repair or so-called one- and half ventricular repair. However, there is limited evidence to support this.

In contrast, studies showed that following a biventricular repair, patients with PAIVS still have abnormal RV diastolic function and atrial dilatation, which may negatively influence exercise capacity. It has been reported that peak exercise capacity did not differ between patients with PAIVS after biventricular or univentricular repair. In this study, there was a trend towards impaired exercise performance in older patients with PAIVS irrespective of the type of operation. The question then arises whether the relatively small and hypertrophied RV in PAIVS is capable of effectively supporting the pulmonary circulation in the long term. Thus far, detailed studies on biventricular function in PAIVS patients in relation to exercise performance are lacking. Dobutamine stress magnetic resonance imaging (DS-MRI) is an important imaging modality for accurate assessment of cardiac reserve as an early predictor of cardiac dysfunction. Delayed contrast enhancement (DCE)-MRI using gadolinium-based contrast media allows direct visualization of myocardial fibrosis.

In the present study, we evaluated exercise capacity and biventricular response to pharmacological stress using DS-MRI in children and young adults with PAIVS after biventricular repair. Furthermore, the presence of myocardial fibrosis was assessed using DCE-MRI.

Patients and methods

The local medical ethics committee approved the study, and informed consent was obtained from all participants and /or parents prior to enrolment. Patients with PAIVS after biventricular repair followed at our institutions, older than 8 years, and with no contra-indication for MRI examination were included in the study. Patients were recruited from the institutional pediatric cardiology database and the national database and DNA data bank of adult patients with a CHD (www.CONCOR.nl). The database identified 19
eligible patients. Nine patients were excluded for the following reasons; 7 patients refused to participate, one patient was pregnant and one patient has percutaneous pulmonary valve implantation at this time. Thus, 10 patients between 9 and 42 years of age were included. All patients underwent a symptom-limited cardiopulmonary exercise test with determination of maximum oxygen consumption ($\text{VO}_2\text{max}$) and MRI examination including DCE-MRI, and DS-MRI.

Cardiopulmonary exercise test

A symptom-limited cardiopulmonary exercise test, to assess maximal exercise capacity, was performed, according to the guidelines of the American Thoracic Society.\textsuperscript{15} Graded exercise testing on a motor-driven treadmill (Jaeger, Wuerzburg, Germany) using a modified Bruce protocol was performed in children, and a cycle ergometer (Jaeger Oxyconpro, Wuerzburg, Germany) was used in adults. Continuous heart rate monitoring was done and maximum heart rate (MHR) documented. $\text{VO}_2\text{max}$ was defined as the highest value of oxygen uptake measured twice during the last 15 seconds of exercise. Oxygen ($O_2$) pulse was assessed as it is an indirect index of combined cardiopulmonary oxygen transport, and thus stroke volume (SV). Exercise tests were considered valid if the patient reached the anaerobic threshold, defined as having a respiratory exchange ratio (RER) greater than 1.0. Measured cardiopulmonary exercise test parameters were compared with predicted normal values from Wasserman and co-workers.\textsuperscript{16} Impaired exercise capacity was defined as $\text{VO}_2\text{max}$ less than 85% of the predicted values.\textsuperscript{16}

Magnetic resonance imaging

MRI was performed using an open MRI 1.0 Tesla MRI-scanner (Panorama, system Philips Medical Systems, Best, The Netherlands). Long-axis, 2- and 4-chamber views and short-axis views consisting of 12 to 14 contiguous slices, covering both the ventricles from the base of the heart to the apex were acquired using a retrospective electrocardiogram-gated steady-state free precession (SSFP) sequence during breath holding at end-expiration. Scan parameters were: repetition time = 3.2 - 3.8 ms; echo time = 1.6 - 1.9 ms; flip angle = 50 - 70°; slice thickness = 8 mm without slice gap; matrix = 160 x 256; field-of-view = 350 - 400 mm. Temporal resolution was approximately 25 ms. A retrospective electrocardiogram-gated phase-contrast cine sequence with a through-plane velocity encoding was used to assess the flow across pulmonary valve and TV during a breath hold. Scan parameters were: repetition time = 9 ms, echo time = 5 ms, flip angle = 15 - 20°, slice thickness = 6 - 8 mm, matrix = 128 x 256, temporal resolution = 20 ms. Short-axis images were repeated at maximum dobutamine infusion.
Dobutamine infusion

An intravenous line was inserted into the antecubital vein before the MRI procedure. Dobutamine was administrated by a digital MRI-compatible infusion pump. After the MRI acquisition at rest, dobutamine was infused in serial incremental doses of 5, 10, and 15 μg/kg/min in three minutes stages. Infusions were performed under continuous monitoring with electrocardiogram and automated blood pressure measurements. The end point for termination of dobutamine infusion was reaching a target heart rate, 85% of age-predicted maximal heart rate (220 - age in years) or 15 μg /kg/min of dobutamine infusion.

Delayed contrast enhancement MRI

Ten to 15 minutes after injection of a gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany; 0.2 mmol/kg), DCE images were acquired in the same orientation as the cine short-axis images using a segmented inversion-recovery gradient-echo pulse sequence. Scan parameters were: repetition time/echo time = 4.01/1.25 ms, flip angle = 15°, matrix = 208 x 256 and a typical voxel size of 1.6x1.3x5.0 mm, inversion time (T1) = 180 - 200 ms.

MRI post processing

All images were analyzed on a workstation with an Intel Pentium 4 processor (Intel, Santa Clara, Calif). Left ventricle (LV) and RV volumes and function were analyzed with the software package MASS ® (Medis, Leiden, Netherlands). Flow velocity–encoded MRI data were analyzed using the software package FLOW ® (Medis, Leiden, the Netherlands). Vascular contours were drawn for the pulmonary trunk to generate flow versus time curves throughout the cardiac cycle. Peak flow velocity was measured; the presence of pulmonary regurgitation (PR) was assessed and regurgitation fraction (RF) was calculated as percent backward flow over forward flow. The presence of late diastolic forward flow (DFF) in the pulmonary artery was assessed, late DFF% was defined as percentage of late DFF over the total pulmonary artery forward flow. Flow versus time curves for TV flow were analyzed to assess RV E/A volume ratio.

Biventricular systolic function was assessed by drawing endocardial contours at end-diastole and end-systole in all sections of the cine short axis data. End-diastolic volumes (EDV) and end-systolic volumes (ESV) were obtained. Stroke volumes (SV) were calculated by subtracting ESV from EDV. In presence of significant PR, defined as PR fraction > 20%, the effective RV-SV was calculated, defined as RV-SV minus regurgitant flow, assessed with flow mapping. Ejection fraction (EF) was calculated by dividing SV by EDV x 100%, LV-EF > 50 % and RV-EF > 47% was defined as normal. Cardiac output (CO) was calculated by multiplying SV by HR. All volumetric parameters were indexed for body surface area according to the Mosteller formula: (√ Height (cm) x weight (kg)/3600). Two observers
(S.R. and M.G. with 4 and 15 years of experience in cardiac MR imaging, respectively) agreed on presence or absence of DCE in the LV and RV.

Statistical analysis
All statistical testing and data analysis was performed with SPSS version 16 (SPSS inc, Chicago, Ill). The cardiac response to the physical exercise test was assessed. The cardiac function parameters at rest and during the maximum pharmacological stress were compared using the paired student’s t-test in case of normal distribution or the Wilcoxon test for pairwise comparisons. Variables that were normally distributed are presented as mean and standard deviation; variables with skewed distribution are presented as medians and range. The presence of normal distribution was tested using the Shapiro-Wilk test. Finally, the correlation between the patients’ age and cardiac work indices during the physical stress, cardiac function parameters at rest and during maximum pharmacological stress was evaluated. The Pearson correlation coefficient was calculated if the variables were normally distributed otherwise Spearman rank correlation was calculated. Differences were accepted as statistically significant at P < 0.05.

Results
Patient characteristics
Characteristics of the patients are displayed in Table 1. All patients were asymptomatic, New York Heart Association class I or II and received no medication. Systolic pulmonary artery pressures at rest were normal in all patients (26 ± 7 mmHg) as assessed by echocardiographic flow velocity measurements of the tricuspid regurgitation.
At birth, all patients had a Z-value of TV diameter of greater than -2.5, and a tripartite or bipartite RV. None of them had RV-dependent coronary circulation, or Ebstein’s malformation of TV.
All patients had a surgical RV outflow tract (RVOT) reconstruction in the neonatal period, nine patients had pulmonary valvotomy and one patient had a RVOT patch. Aortopulmonary shunts were placed in seven patients (70%). Age at complete surgical repair was 2.5 ± 0.5 years. At the time of complete repair, five patients (50%) had an interatrial communication in the form of an atrial septal defect (ASD). Surgical or catheter-directed closure of ASD was performed in all of them at a later stage.
All patients completed the cardiopulmonary exercise test, DCE-MRI, and DS-MRI with no adverse events. In particular, none of the patients had episodes of hypotension or sustained arrhythmia leading to early termination of any test. None of the participants experienced headache, chest pain or palpitations, and no ST-T changes or premature ventricular complexes were recorded on the ECG.
Cardiopulmonary exercise test

The cardiopulmonary exercise parameters are summarized in Table 1. All patients achieved a RER > 1.0, indicating that all patients reached the anaerobic threshold. Median VO\textsubscript{2max}.

### Table 1: Patients’ characterization and results of the cardiopulmonary exercise test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (male - %)</td>
<td>10 (3 - 30%)</td>
</tr>
<tr>
<td>Median age (years, range)</td>
<td>12.0 (9.0 – 42.0)</td>
</tr>
<tr>
<td>Median follow up period after surgical repair</td>
<td>11.0 (8.0 – 40.0)</td>
</tr>
<tr>
<td>NYHA functional classification</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Class II</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>RER</td>
<td>1.1 ± 0.05</td>
</tr>
<tr>
<td>Rest heart rate (b/m)</td>
<td>80.0 ± 4.0</td>
</tr>
<tr>
<td>MHR (b/m)</td>
<td>182.0 ± 4.0</td>
</tr>
<tr>
<td>MHR (% of predicted)</td>
<td>95.0 ± 2.0</td>
</tr>
<tr>
<td>Median VO\textsubscript{2max} (ml/kg/min, range)</td>
<td>45.2 (19.1 - 51.0)</td>
</tr>
<tr>
<td>Median VO\textsubscript{2max} (% of predicted, range)</td>
<td>92.0 (60.0 – 100.0)</td>
</tr>
<tr>
<td>Median O\textsubscript{2} pulse (ml/beat, range)</td>
<td>10.6 (7.0 - 10.0)</td>
</tr>
<tr>
<td>Median O\textsubscript{2} pulse (% of predicted, range)</td>
<td>97.0 (65.0 – 130.0)</td>
</tr>
</tbody>
</table>

NYHA = New York heart association, MHR = maximum heart rate, bpm = beat per minute, RER = respiratory exchange rate, VO\textsubscript{2max} = maximum oxygen consumption, O\textsubscript{2}-pulse = oxygen pulse.

![Graph A](image1.png)  \( R^2 = 0.6324 \)

![Graph B](image2.png)  \( R^2 = 0.905 \)

![Graph C](image3.png)  \( R^2 = 0.5028 \)

![Graph D](image4.png)  \( R^2 = 0.5318 \)

**Figure 1:** Correlation between the patients’ age and cardiac work indices in response to the physical stress (A) VO\textsubscript{2max}, (B) O\textsubscript{2}-pulse. Correlation between the patients’ age and biventricular SV response to the pharmacological stress; (C) LV-SV, (D) effective RV SV.
was 92% of predicted (range, 60 -100%); median \( O_2 \) pulse was 97% of predicted (range, 65 -130%). During the exercise test all patients remained in sinus rhythm and showed an adequate chronotropic response, MHR was 95 ± 2 % of the predicted. A strong negative correlation was observed between the patients’ age and VO\(_2\) max and \( O_2 \) pulse (\( r = -0.72, P = 0.01 \) and \( r = -0.74, P = 0.01 \) respectively; Figures 1-A, 1-B) but not with MHR (\( r = 0.01, P = 0.9 \)).

**Magnetic resonance imaging**

MRI images of good quality were obtained in all patients at rest and during dobutamine infusion. Data are presented in Table 2. Remarkably, none of the patients showed DCE in RV or LV. All patients had normal LV and RV systolic function at rest. All patients had a significant pulmonary regurgitation (RF = 24.7 ± 6.2 %), and relatively large RV-EDV. None of the patients had a residual RVOT obstruction (maximum velocity = 2.3 ± 0.7 m/sec). Late DFW in the pulmonary artery was present in 70% of patients and late DFF% strongly correlated with patients’ age (\( r = 0.66, P =0.03 \)). RV E/A volume ratio is negative correlated with the patients’ age (\( r = 0.65, P = 0.04 \)), indicating impaired RV diastolic function with age.

**Table 2:** Results of DS-MRI and correlation between patients’ age and cardiac parameters at rest and at maximum dobutamine infusion.

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Stress</th>
<th>P value</th>
<th>Correlation between age and rest parameters</th>
<th>Correlation between age and stress parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>74.0 ± 8.0</td>
<td>130.0 ± 23.0</td>
<td>&lt; 0.001</td>
<td>-0.29 NS</td>
<td>0.30 NS</td>
</tr>
<tr>
<td>RV EDV (mL/m(^2))</td>
<td>103.4 ± 20.3</td>
<td>99.0 ± 21.8</td>
<td>NS</td>
<td>-0.20 NS</td>
<td>-0.33 NS</td>
</tr>
<tr>
<td>RVEF (mL/m(^2))</td>
<td>47.4 ± 15.4</td>
<td>32.9 ± 12.9</td>
<td>&lt; 0.001</td>
<td>-0.22 NS</td>
<td>-0.12 NS</td>
</tr>
<tr>
<td>Effective RV-SV (mL/m(^2))</td>
<td>42.1 ± 3.4</td>
<td>50.0 ± 10.1</td>
<td>0.002</td>
<td>0.52 NS</td>
<td>-0.73 0.01</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>53.8 ± 6.6</td>
<td>67.7 ± 8.8</td>
<td>&lt; 0.001</td>
<td>-0.06 NS</td>
<td>-0.09 NS</td>
</tr>
<tr>
<td>RVCO (L)</td>
<td>6.2 ± 1.8</td>
<td>9.9 ± 3.9</td>
<td>&lt; 0.001</td>
<td>0.15 NS</td>
<td>0.20 NS</td>
</tr>
<tr>
<td>RV E/A volume ratio</td>
<td>1.0 ± 0.3</td>
<td>0.9 ± 2.3</td>
<td>0.80 0.005</td>
<td>0.39 NS</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary late DFF%</td>
<td>7.4 ± 2.3</td>
<td>7.4 ± 2.3</td>
<td>0.39 0.005</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PVF (%)</td>
<td>24.7 ± 6.2</td>
<td>24.7 ± 6.2</td>
<td>NS</td>
<td>-0.52 NS</td>
<td>-0.67 NS</td>
</tr>
<tr>
<td>LV EDV (mL/m(^2))</td>
<td>85.4 ± 10.4</td>
<td>80.2 ± 12.8</td>
<td>NS</td>
<td>-0.52 NS</td>
<td>-0.67 NS</td>
</tr>
<tr>
<td>LVESV (mL/m(^2))</td>
<td>42.1 ± 6.5</td>
<td>29.9 ± 6.6</td>
<td>&lt; 0.001</td>
<td>-0.22 NS</td>
<td>-0.36 NS</td>
</tr>
<tr>
<td>LVS (mL/m(^2))</td>
<td>43.0 ± 8.3</td>
<td>51.5 ± 10.2</td>
<td>0.001</td>
<td>-0.44 NS</td>
<td>-0.69 0.02</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.5 ± 6.2</td>
<td>68.8 ± 6.4</td>
<td>&lt; 0.001</td>
<td>-0.12 NS</td>
<td>-0.16 NS</td>
</tr>
<tr>
<td>LVCO (L)</td>
<td>4.6 ± 0.9</td>
<td>7.5 ± 2.8</td>
<td>0.003</td>
<td>-0.05 NS</td>
<td>0.11 NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD, LV = left ventricle, RV = right ventricle, bpm = beat per minute, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, EF = ejection fraction, CO = cardiac output, DFF = diastolic forward flow, PRF = pulmonary regurgitation fraction.
In response to pharmacological stress, there was an adequate chronotropic response, and adequate RV-EF increase. This resulted in a significant increase in RV-SV and RV-CO. LV showed a similar response. (Table 2) There was a positive correlation between RV E/A ratio and Δ RV-SV \((r = 0.77, P = 0.009)\).

There was a negative correlation between the patients’ age and LV-SV, and RV-SV during peak dobutamine infusion, \((r = -0.72, P = 0.02; \text{ and } r = -0.64, P = 0.04, \text{ respectively}; \text{ Figures 1-C, 1-D})\), whereas there was no correlation with the other RV or LV function parameters during dobutamine infusion. (Table 2)

VO\textsubscript{2,max} and \(\text{O}_2\) pulse during physical exercise correlated with LV-SV response to pharmacological stress \((r = 0.74, P = 0.01, \text{ and } r = 0.65, P = 0.04, \text{ respectively}; \text{ Figures 2-A, 2-C})\), and to RV-SV response \((r = 0.73, P = 0.01, r = 0.84, P = 0.002, \text{ respectively}; \text{ Figures 2-B, 2-D})\) but not to LV-SV at rest \((r = 0.48, P = \text{NS}, r = 0.34, P = \text{NS}, \text{ respectively})\) and to RV-SV at rest \((r = 0.47, P = \text{NS}, r = 0.39, P = \text{NS}, \text{ respectively})\).

**Figure 2:** Correlation between VO\textsubscript{2,max} and biventricular SV response to the pharmacological stress; (A) LV-SV (B) effective RV-SV. Correlation between \(\text{O}_2\)-pulse and biventricular SV response to the pharmacological stress; (C) LV-SV (D) effective RV-SV.

**Discussion**

Biventricular repair for PAIVS provides satisfactory results in terms of survival and clinical outcome during early follow up period. However, comprehensive long term follow-up studies on RV performance are still limited.\(^{1-3,5}\)
In the present study in asymptomatic PAIVS patients, we demonstrated that both exercise capacity and biventricular SV response to pharmacological stress decreased with age. Furthermore, we demonstrated that RV diastolic function decreased with age in PAIVS patients correlating well with impaired RV-SV response to pharmacological stress. Finally, we showed a strong correlation between cardiac work indices during physical stress (VO₂max, O₂ pulse) and biventricular SV response to pharmacological stress, but not biventricular SV at rest.

Impaired exercise capacity in patients with CHD, even among asymptomatic patients, is a useful predictor for adverse long term clinical outcomes. In PAIVS patients few studies are available on exercise capacity evaluation.

Our results are in line with the results of Sanghavi et al. who investigated exercise capacity in PAIVS patients after univentricular and biventricular repair. Exercise capacity did not appear to differ between PAIVS patients after biventricular and univentricular repair. However, older PAIVS patients tended to have decreased exercise capacity irrespective of the type of surgical repair. Ekman-joelsson et al. demonstrated a better exercise capacity in PAIVS patients after biventricular repair as compared to PAIVS patients after univentricular repair. In contrast to our findings no correlation was found between patients’ age and exercise capacity, which may be explained by the younger age of their patient cohort. Comparable to our data, both studies showed that cardiac function parameters at rest did not predict exercise capacity in this specific group of patients.

In patients with CHD, including children, cardiac reserve can be assessed accurately and safely using DS-MRI, allowing for detection of cardiac dysfunction, which is not present at rest. Thus far, there is no previously published data on cardiac reserve assessment in PAIVS patients after biventricular repair.

In the present study, we demonstrated that with age PAIVS patients failed to increase RV-SV despite adequate increase in RV-EF in response to dobutamine even in the absence of myocardial fibrosis. This could be explained by unfavorable ventricular filling due to impaired RV diastolic function in older PAIVS patients. Deterioration of diastolic function with age is well-known and is mainly due to increasing ventricular stiffness. Several causative factors may play a role in the early onset of RV diastolic dysfunction. These include size and dysplasia of the TV, endocardial and myocardial abnormalities of the RV such as major RV hypertrophy, extensive myocardial fiber disarray, and endocardial fibroelastosis at the time of birth. Surgical procedures, such as pulmonary valvulotomy or RVOT patch reconstruction, may allow RV growth but probably do not allow normalization of these significant myocardial abnormalities.

A recent study in PAIVS patients following biventricular repair showed that the presence of RV myocardial fibrosis using DCE correlated with both the occurrence of late pulmonary DFF and reduced myocardial tissue velocities, indicating impairment of RV diastolic function. In contrast to this study, we were unable to detect any RV or LV myocardial fibrosis by DCE.
in our group of PAIVS patients. A possible explanation may be that in the study by Liang et al., the majority of patients had a RVOT patch compared to only one patient in our cohort. Furthermore, the DCE acquisition parameters were not mentioned in the study of Liang et al., which makes it difficult to compare the DCE sequences of the two studies. We also showed that in older PAIVS patients, LV-SV failed to increase in response to pharmacological stress despite normal contractility. This finding correlated with reduced RV-SV augmentation and could be well explained by reduced LV preload due to impaired RV diastolic function. Although there was no reason to assume significant impairment of LV diastolic function in this PAIVS cohort, we cannot exclude this because LV diastolic function parameters were not measured in the study.

Conclusion

In PAIVS patients after biventricular repair, exercise capacity and cardiac reserve decrease with age. These findings are related to impaired diastolic RV function and decreased RV filling during stress, indicating that the function of the RV deteriorates with time. These results indicate that the relatively small and hypertrophied RV at birth may not be capable of maintaining normal ventricular performance in the long term. This does not imply that long-term prognosis of PAIVS patients after univentricular repair is better than after biventricular repair since comparison of the two treatment strategies was not part of this study.
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Impaired cardiac reserve in asymptomatic patients with moderate pulmonary restenosis late after relief of severe pulmonary stenosis: evidence for diastolic dysfunction

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Abstract

Objective: Patients with moderate pulmonary valve restenosis late after relieve of severe pulmonary stenosis (PS) may show decreased exercise tolerance. To elucidate the mechanism of decreased exercise tolerance, we evaluated cardiac response to physical and pharmacological stress in these patients and compared results with those of patients with native moderate PS.

Methods: Twenty asymptomatic patients with moderate PS were divided into 2 groups: Group I (late after relief of severe PS, n=9), and Group II (no previous intervention, n=11). All patients underwent an exercise test, dobutamine stress (DS) MRI, and delayed contrast enhanced MRI. The response to physical and pharmacological stress was compared between both groups.

Results: Group I showed impaired exercise capacity compared to Group II (VO₂max = 72.8% ± 3.5% vs. 102.5% ± 16.3%, P < 0.001). During DS-MRI, RV-SV increased in Group II, but not in Group I (+13 ± 8 mL, - 5 ± 8 mL, P < 0.001). RV- end diastolic volume decreased significantly in Group I patients (P = 0.006) while it did not significantly change in Group II patients. The amount of RV-SV increase (Δ RV-SV) correlated negatively with the period of moderate PS existence in Group I (r =-0.82, P = 0.007) but not in Group II (r = 0.45, P = 0.1). Furthermore, Δ RV-SV correlated negatively with the PG before valvuloplasty (r = -0.76, P = 0.02).

Conclusion: Impaired exercise capacity in patients with moderate pulmonary restenosis after relief of severe PS is probably caused by inability to increase RV-SV. Disturbed RV filling properties, worsening in time, might play a role.
Introduction

Isolated pulmonary valve stenosis (PS) is a relatively common abnormality occurring in 7-12% of all congenital heart diseases (CHD).\textsuperscript{1,2} Traditionally, pulmonary valve replacement was the most effective management choice.\textsuperscript{3} However, due to the excellent results of balloon valvuloplasty,\textsuperscript{4,5} low thresholds are currently being employed for intervention in adults. By current guidelines, any PS with a transvalvular pressure gradient > 64 mmHg is now considered a candidate for valvuloplasty. In case of a pressure gradient < 64 mmHg, management of patients is more complicated. Intervention is advocated (as a class IIa recommendation) in symptomatic patients, in patients with decreased right ventricular (RV) function and in patients with additional right to left shunting (i.e. atrial septal defect or ventricular septal defect).\textsuperscript{2} The New York Heart Association functional (NYHA) classification is generally used to assess symptoms, with exercise testing as an additional tool. Reduced exercise capacity has been shown in asymptomatic (according to the NYHA scale) patients with moderate PS,\textsuperscript{6,7} although it may be difficult in clinical practice to assign this feature to the condition of PS alone. Moreover, the condition of moderate PS may differ between patients with restenosis after relief of severe PS and patients with native moderate PS. Especially patients with moderate pulmonary restenosis have shown reduced exercise capacity in previous studies.\textsuperscript{6,7} The underlying mechanisms for decreased exercise capacity in these patients are incompletely understood. RV function is generally normal at rest. However, assessment of cardiac reserve may unmask pathological conditions that could be responsible for decreased exercise capacity, as has been shown in several other conditions with RV pressure overload.\textsuperscript{8-11} Accordingly, we compared exercise capacity and cardiac reserve between patients with moderate pulmonary restenosis, late after relieve of severe PS, and patients with native moderate PS.

Patients and methods

The local medical ethics committee approved the study, and informed consent was obtained from all participants before their enrolment. Adult asymptomatic patients (NYHA class I) with isolated moderate PS, with no more than a mild degree of pulmonary regurgitation (PR), as indicated by transthoracic echocardiography, were included in the study. Patients were recruited from the national database and DNA data bank of adult patients with CHD (www.CONCOR.net).\textsuperscript{12} The database identified 34 eligible patients. Fourteen patients refused to participate, 20 patients were included in the study: 9 patients late after relief of severe PS (Group I) and 11 patients with native moderate PS (Group II). All patients underwent a symptom-limited cardiopulmonary exercise test with determination of maximum oxygen consumption (VO\textsubscript{2}max), dobutamine stress MRI (DS-MRI) and delayed contrast enhancement MRI (DCE-MRI).
Chapter 4

Cardiopulmonary exercise test
A symptom-limited cardiopulmonary exercise test was performed to assess maximal exercise capacity, according to the guidelines of the American Thoracic Society\textsuperscript{13} by means of a cycle ergometer (Jaeger Oxyconpro, Wuerzburg, Germany). VO\textsubscript{2}max, maximum heart rate (MHR), maximum work (watt) and oxygen (O\textsubscript{2}) pulse were measured and calculated. O\textsubscript{2} pulse is an indirect index of combined cardiopulmonary oxygen transport and thus stroke volume. Workload was increased by 5 to 15 watt, depending on the predicted maximum exercise capacity and in such a way that maximal effort was attained within approximately 10-15 minutes. Exercise tests were considered valid if the patient reached the anaerobic threshold, defined as having a respiratory exchange ratio (RER) greater than 1.0. Measured cardiopulmonary exercise test parameters were compared with predicted normal values from Wasserman and co-workers.\textsuperscript{14} Calibration of the system occurred prior to every test according to manufacturer specifications.

Magnetic resonance imaging
MRI was performed using an open 1.0 T MRI-scanner (Panorama, Philips Medical Systems, Best, The Netherlands). An intravenous line was inserted into the antecubital vein prior to the MRI procedure. Long-axis 2- and 4-chamber views and short-axis views consisting of 12 to 14 contiguous slices, covering both ventricles from the base of the heart to the apex were acquired using a retrospective electrocardiogram-gated steady-state free precession (SSFP) sequence during breath hold. Scan parameters were: repetition time = 3.2 - 3.8 ms; echo time = 1.6 - 1.9 ms; flip angle = 50 - 70°; slice thickness = 8 mm without slice gap; matrix = 160 x 256; field of view = 350 - 400 mm. Temporal resolution was approximately 25 ms. Dobutamine was administrated by a digital MRI compatible infusion pump with an initial dose of 10 ug/kg/min. Hereafter, the dobutamine infusion rate was incremented by 10 ug/kg/min every 3 minutes depending on individual subject response, until the target heart rate (THR), 85% of the age-predicted MHR (220-age in years), was achieved. The maximum dobutamine dose administered was 40ug/kg/min. During each MRI measurement, the electrocardiogram and heart rate were monitored. Short-axis CINE imaging was repeated at maximum dobutamine infusion. Ten to 15 minutes after injection of a gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany; 0.2 mmol/kg), DCE images were acquired in the same orientation as the cine short axis images using a segmented inversion-recovery gradient-echo pulse sequence. Scan parameters; repetition time/echo time= 4.01/1.25 ms, flip angle = 15°, matrix = 208 x 256, inversion time = 180 - 200 ms.

MRI post processing
All images were analyzed on a workstation with an Intel Pentium 4 processor (Intel, Santa Clara, USA). RV function and mass were analyzed with the software package MASS®
RV and left ventricle (LV) systolic function were assessed by drawing endocardial contours at end-diastole and end-systole in all sections of the cine short axis data. Biventricular end-diastolic volumes (LV-EDV, RV-EDV) and end-systolic volumes (LV-ESV, RV-ESV) were obtained. Biventricular stroke volumes (LV-SV, RV-SV) were calculated by subtracting ESV from EDV. Biventricular ejection fractions (LV-EF, RV-EF) were calculated by dividing SV by EDV. Cardiac output (CO) was calculated by multiplying SV by heart rate (HR). RV mass was assessed using the software package MASS® (Medis, Leiden, The Netherlands). All contours were drawn manually by one observer (A.M.S., with 5 years of experience with CMR) and supervised by M.G (with 16 years of experience with CMR). Both were unaware of the patient conditions, although sternal wires could be visible in the two operated patients. All volumetric measurements were indexed for body surface area according to the Mosteller formula: $(\sqrt{\text{Height (cm)} \times \text{weight (kg)}}/3600)$. Two observers (S.R. and M.G) agreed on the presence or absence of delayed myocardium enhancement.

**Statistical analysis**

All statistical testing and data analysis was performed with SPSS version 16 (SPSS inc, Chicago, Ill). The cardiac functional parameters at rest and during maximum pharmacological stress were compared using the paired student’s $t$-test in case of normal distribution or else by the Wilcoxon test for pairwise comparisons. Variables that were normally distributed are presented as mean and standard deviation, variables with skewed distribution as medians and range. The presence of normal distribution was tested using the Shapiro-Wilk test. To assess the validity of DS-MRI as a surrogate for physical exercise, linear correlations were made between maximal achieved RV-SV during DS-MRI and indices of cardiac work during the exercise test. The Pearson correlation coefficient was calculated. Differences were accepted as statistically significant at $P < 0.05$.

**Results**

**Patient characteristics**

Patient characteristics are summarized in the top part of Table 1. All patients were in NYHA class I, with no medical treatment. All patients in Group I underwent a single isolated procedure for relief of severe PS. Age at intervention time was $13.4 \pm 8.3$ years. Two patients had surgical valvulotomy and 7 patients had a balloon dilatation when this procedure became a clinical routine. PG before intervention was $57.3 \pm 4.2$ mmHg; all patients had a successful relief of pulmonary obstruction, defined by a reduction of the PG after intervention to $25.2 \pm 2.9$ mmHg. During the follow up period, PG gradually increased and within $5.9 \pm 4.5$ years after pulmonary intervention, the PS was considered moderate, with a PG of $38.4 \pm 3.5$ mmHg. The period of moderate PS existence was $13.9$
± 6.3 years. Group II patients were diagnosed to have mild PS during childhood. The PG gradient increased gradually until the PS was considered moderate, with a PG of 38.0 ± 4.2 mmHg. The period of moderate PS existence was 12.7 ± 6.2 years. All patients completed the symptom-limited cardiopulmonary exercise test, DCE-MRI, and DS-MRI without adverse events. In particular, none of the patients had episodes of hypotension or sustained arrhythmia leading to early termination of any test. None of the participants experienced headache, chest pain or palpitations, and no premature ventricular complexes were recorded on the electrocardiogram.

Cardiopulmonary exercise test

All patients reached an RER greater than 1.0, which indicates that all patients reached the anaerobic threshold. Data are summarized in Table 1. Group I showed impaired exercise capacity, defined by VO$_2$max < 85% of the predicted value. In contrast, Group II showed a normal exercise capacity (P < 0.001). O$_2$ pulse in response to the physical exercise was significantly lower in Group I patients than in Group II (P < 0.001). There was no significant difference between both groups in HR at rest. With exercise, all patients remained in sinus rhythm and both groups had a good chronotropic response (MHR was > 85% of predicted). However, HR response to exercise was significantly less in Group I compared to Group II (P < 0.02).

| Table 1: Patients’ characteristics and results of the cardiopulmonary exercise test |
|---------------------------------|-------------------------------|-------------------------------|-------------------|
|                                | Group I N = 9                | Group II N = 11               | P value          |
| Mean age (years)              | 34.5 ± 8.6                   | 33.2 ± 6.4                   | 0.1              |
| Sex (male, %)                 | 5 (55%)                      | 6 (54%)                      | 0.9              |
| The current PG (mmHg)         | 38.4 ± 3.5                   | 38.0 ± 4.2                   | 0.7              |
| Period of moderate PS existence (years) | 13.9 ± 6.3               | 12.7 ± 6.2                   | 0.8              |
| RER                            | 1.2 ± 0.1                    | 1.2 ± 0.1                    | 0.8              |
| Load (watts)                  | 186.0 ± 19.0                 | 222.0 ± 57.0                 | 0.1              |
| Rest hear rate (bpm)          | 73.0 ± 11.0                  | 83.0 ± 14.0                  | 0.3              |
| MHR (bpm)                     | 166.0 ± 17.0                 | 187.0 ± 7.0                  | 0.02             |
| MHR (% of predicted normal values) | 88.0 ± 9.0                   | 97.0 ± 4.0                   | 0.01             |
| VO$_2$ max (ml/kg/min)        | 18.5 ± 4.8                   | 30.6 ± 6.2                   | < 0.001          |
| VO$_2$ max (% of predicted normal values) | 72.8 ± 3.5                  | 102.5 ± 16.3                 | < 0.001          |
| O$_2$ pulse (ml/beat)         | 10.0 ± 3.0                   | 20.5 ± 4.4                   | 0.005            |
| O$_2$ pulse (% of predicted normal values) | 80.0 ± 3.0                  | 108.0 ± 13.0                 | < 0.001          |

Values are mean ± SD, N = number, PG = pressure gradient, PS = pulmonary stenosis, RER = respiratory exchange ratio, bpm = beat per minute, MHR = maximum heart rate.
Magnetic resonance imaging

MRI images of good quality were obtained in all patients at rest and during dobutamine infusion. Data are presented in Table 2. None of the patients showed delayed contrast enhancement in the RV or LV. Both groups showed RV hypertrophy and RV mass was comparable in both groups. At rest there was a significantly smaller ESV (P = 0.04) and a significantly greater EF (P = 0.04) in the patients in Group I. During DS-MRI, both groups showed a good and comparable chronotropic response, although less than during physical exercise. RV-EF increased and RV-ESV decreased in both groups. RV-EDV decreased significantly in Group I patients (P = 0.006) while it did not significantly change in Group II patients. This resulted in a significant increase in RV-SV in Group II patients but not in Group I patients (+13 ± 8 mL, -5 ± 8 mL, respectively, P < 0.001). RV-CO increased in both groups, although RV-CO increase was greater in Group II compared to Group I. LV dimensions showed a similar response to dobutamine infusion. The amount of RV-SV increase (Δ RV-SV) correlated negatively with the period of moderate PS existence (r = -0.82, P = 0.007, Figure 1-A), and positively with the current PG (r = 0.68, P = 0.04, Figure 1-C) in Group I but not in Group II (r = 0.45, P = 0.1, and r = 0.40, P = 0.2, Figures 1-B and 1-D, respectively). Furthermore, Δ RV-SV correlated negatively with the PG before valvuloplasty (r = -0.76, P = 0.02, Figure 2).
Figure 1: Correlation between $\Delta$ RV-SV and the time of moderate PS existence (years): (A) in Group I, and (B) in Group II. Correlation between $\Delta$ RV-SV and the current PG (mmHg): (C) in Group I, and (D) in Group II.

Figure 2: Correlation between $\Delta$ RV-SV and the PG before intervention (mmHg) in Group I.

Figure 3: A) Correlation between RV-SV during maximum dobutamine infusion and maximum oxygen consumption ($VO_2$max). B) Correlation between changes in RV-SV during maximum dobutamine infusion and oxygen–pulse ($O_2$-pulse)
The VO\textsubscript{2}max and O\textsubscript{2} pulse during maximum physical exercise were strongly related to RV-SV during peak dobutamine infusion ($r = 0.71$, $P < 0.001$, and $r = 0.73$, $P < 0.001$, respectively; Figure 3).

**Discussion**

We showed impaired exercise capacity in asymptomatic patients with moderate pulmonary restenosis, late after relieve of severe PS. Regarding the volumetric data of pharmacological stress, this might be caused by the inability to increase stroke volume and thereby cardiac output, despite a good chronotropic response. In contrast, patients with native moderate PS, without a history of severe PS, showed a normal exercise capacity and a normal cardiac reserve.

Herewith, the importance of cardiopulmonary exercise testing has once again been emphasized as an objective tool to assess functional class in CHD patients with PS who are considered to be ‘asymptomatic’\textsuperscript{16,17}. Patients in Group I, who were comparable with patients in Group II in age, sex, NYHA class and PG, performed significantly worse during the exercise test, even in the presence of a significantly higher RV-EF at rest. Published data on exercise capacity in PS patients are very limited\textsuperscript{6,7}. Johnson et al. showed impaired exercise capacity in asymptomatic patients with moderate pulmonary restenosis late after relief of severe PS. However, these (older) studies did not investigate the mechanism of the impaired exercise capacity in these patients. Our study is the first to investigate the mechanism of impaired exercise capacity in these patients by DS-MRI. We believe that the correlation between indices of SV augmentation during physical stress and pharmacological stress, as shown in the present study, allow us to make this assumption. Although we could not find published data on cardiac reserve evaluation in PS patients, DS-MRI has shown to be safe and feasible to assess cardiac reserve in patients with CHD\textsuperscript{8-10,18,19}. In the absence of myocardial fibrosis (as shown in the present study), systolic dysfunction at rest or during exercise (EF increased similarly in both groups), failure to increase RV-SV might be explained by unfavorable RV filling, due to decreased RV compliance. This phenomenon could also explain the significant decrease in RV-EDV during dobutamine stress in the Group I patients. Persistence of impaired RV diastolic function directly after successful relief of severe PS has been demonstrated in earlier studies, where RV hypertrophy and subendocardial ischemia were suggested to be the cause\textsuperscript{4}. However, RV masses were comparable between the two groups and myocardial fibrosis could not be demonstrated in our study. Nevertheless, diffuse fibrosis, which cannot be visualized by MRI, could be present in Group I patients. Longstanding pressure overload may cause degenerative myocardial changes, which could be responsible for altered RV filling properties, and indeed we showed a negative correlation between $\Delta$RV-SV and the PG before intervention. After relief of severe PS, moderate restenosis may continue to cause progressive diastolic failure as shown by the
negative correlation of $\Delta RV-SV$ with the period of moderate PS existence in Group I (which could not be demonstrated in Group II).

Our finding that adult patients with native moderate PS have a normal exercise capacity and a normal cardiac reserve, support the general consensus that moderate pressure overload on the RV is well tolerated and support the current guidelines not to treat patients with native moderate PS.

Study limitations

Because we did not actually assess RV diastolic function directly, we can only provide ‘indirect’ evidence of diastolic dysfunction. However, the significant decrease in RV-EDV during pharmacological stress strongly suggests at least ‘exercise induced’ diastolic dysfunction. This phenomenon remains to be investigated properly.

We have also shown that the LV response to the DS-MRI was similar to RV response. In Group I, LV-SV failed to increase and thereby cardiac output, despite a good chronotropic response. In contrast, in Group II, LV-SV increased. We have demonstrated that LV systolic function was normal at rest and no myocardial fibrosis was detected. We assume that the LV response to DS-MRI, in the absence of LV structural abnormality, was a manifestation of diastolic ventricular interdependence. However, a comprehensive evaluation of LV diastolic function in this group of patients is still needed.

Patients in Group I showed a significantly lower MHR than patients in Group II during exercise, which could be responsible for decreased exercise tolerance. During pharmacological stress chronotropic response was also less (although not significantly) in Group I patients. However, all further hemodynamic data indicate inability to increase stroke volume (which seems to be only negatively affected by increased heart rates) and preservation of systolic function, with comparable increases in EF.

Conclusion

Exercise capacity and cardiac reserve are decreased in patients with moderate pulmonary restenosis and a history of severe PS, which might be caused by diastolic dysfunction. The extent of diastolic dysfunction seems to be dependent on the PG before intervention and duration of moderate restenosis existence. Patients with native moderate PS show a normal exercise tolerance and cardiac reserve.
Reference List


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Delayed improvement of right ventricular diastolic function and regression of right ventricular mass after percutaneous pulmonary valve implantation in patients with congenital heart disease

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Abstract

**Objective:** Percutaneous pulmonary valve implantation (PPVI) has been introduced as therapy for right ventricular (RV) to pulmonary artery conduit dysfunction in patients with congenital heart disease. It has been shown that RV systolic function improved early after PPVI. The effects of PPVI on RV diastolic function and RV hypertrophy have not yet been studied. The object of this study is to assess early and late changes in systolic and diastolic RV function and RV mass after PPVI.

**Methods:** Fourteen patients underwent PPVI (7 male, median age 15 years). Cardiac MRI was performed before and at 2 time points after PPVI (at 1 and at 16 months). RV volume and systolic and diastolic function as well as RV mass were assessed.

**Results:** At 1 and 16 months after PPVI, the RV mass decreased from $28.6 \pm 2.1$ g/m$^2$ to $25.6 \pm 2.2$ g/m$^2$ ($P = 0.03$) and to $22.3 \pm 2.1$ g/m$^2$ ($P = 0.002$). E/A volume ratio increased from $1.91 \pm 0.4$ to $2.6 \pm 0.4$ (NS) and to $3.3 \pm 0.4$ ($P = 0.01$). E/A peak flow ratio increased from $1.34 \pm 0.14$ to $1.48 \pm 0.16$ (NS) and to $1.73 \pm 0.14$ ($P = 0.04$). E wave deceleration time increased from $142 \pm 25$ ms to $160 \pm 27$ ms (NS) and to $211 \pm 26$ ms ($P = 0.007$). At one month RV end-diastolic volume decreased from $124 \pm 8$ ml to $113 \pm 8$ ml ($P = 0.01$) and RV ejection fraction increased from $36 \pm 2\%$ to $46 \pm 2\%$ ($P = 0.001$) without further improvement at 16 months.

**Conclusion:** After PPVI, in contrast to rapid improvement of RV systolic function, the improvement of RV diastolic function is delayed. The reduction of RV mass appears to be the underlying mechanism for improvement of RV diastolic function. Long follow up for patients with PPVI is recommended.
Introduction

Right ventricle (RV) to pulmonary artery conduit dysfunction is a common problem in patients with repaired congenital heart disease (CHD).\textsuperscript{1-3} Degeneration of the valve in the conduit and patient growth can result in valve incompetence and /or stenosis. Prolonged pressure or volume overload may lead to impaired RV systolic and diastolic function presenting as decreased ejection fraction (EF) and impaired relaxation or restriction to ventricular filling.\textsuperscript{4}

Percutaneous pulmonary valve implantation (PPVI) has recently been introduced into clinical practice as an effective treatment for RV to pulmonary artery conduit dysfunction.\textsuperscript{5-8} A great advantage of PPVI is that it provides a nonsurgical means to restore effective valve function and prolong the functional life of prosthetic conduits, thereby reducing the number of open- heart surgeries for these patients through their lifetime. Cardiac magnetic resonance imaging (MRI) studies in patients with RV pressure or volume overload have demonstrated that RV systolic function improves in the first weeks after PPVI.\textsuperscript{6;8;9} The time-related changes in RV diastolic function after PPVI have not yet been studied. A recent cardiac MRI study in adult patients with volume overload late after repair of Tetralogy of Fallot (TOF) revealed that surgical pulmonary valve replacement leads to late improvement of RV diastolic function.\textsuperscript{10} In these patients delayed improvement of RV diastolic function is expected to coincide with long-term remodeling of the RV.

Our hypothesis is that improvement of diastolic function occurs over time after PPVI in patients with CHD with RV to pulmonary artery conduit dysfunction. Accordingly, the purpose of this study using cardiac MRI was to assess early and late changes in systolic and diastolic RV function as well as changes in RV mass in patients undergoing PPVI for RV-pulmonary artery conduit dysfunction.

Materials and Methods

Patients

Between June 2006 and March 2008, 14 patients with CHD were considered for PPVI based on previous repair on the right ventricular outflow tract (RVOT) and on having a conventional surgical indication for RVOT revision.\textsuperscript{11;12} The indication was based on the following parameters: RV pressure \( \geq 2/3 \) of the systemic pressure with outflow obstruction, significant pulmonary regurgitation (PR > 20\%) and RV dilatation, or RV ejection fraction (EF) < 47\%.\textsuperscript{13} The medical ethical committee at our institution approved the study protocol. Written informed consent was obtained from patients and parents as appropriate. No extramural funding was used to support this work. The authors are solely responsible for the design
and conduct of this study; all study analyses, the drafting and editing of the paper and its final contents.

Percutaneous pulmonary valve implantation

The design of the valved stent graft and technique of delivery have been reported previously. Under general anesthesia, vascular access was achieved through a femoral vein (n = 11) or the right internal jugular vein (n = 3). Standard right-side heart catheterization with invasive systemic arterial pressure monitoring was undertaken for hemodynamic evaluation (RV peak systolic and end-diastolic pressure with simultaneous measurement of the left ventricular systolic and end-diastolic pressure, pulmonary artery peak systolic pressure, transpulmonary pressure gradient). Angiography was used to obtain the RVOT dimensions. Projections were selected depending on RVOT morphology. Multi-track catheters with platinum image bands (placed 10 mm apart) were used to calibrate angiographic measurements. Immediate hemodynamic changes after stent graft placement were measured.

Magnetic resonance imaging

MRI was performed at 1.5 T with 1 of 2 MRI scanners (either Intera [Philips Medical System, Best, the Netherlands] or Avanto [Siemens Medical System, Erlangen, Germany]). Images were obtained 2.6 ± 2.7 months before PPVI and at 2 time points after PPVI: at 1 ± 0.7 months and at 16 ± 3.4 months. Systolic and diastolic volumes were assessed using a retrospective electrocardiogram-gated steady-state free precession sequence during breath holding. Vertical long-axis 2- and 4-chamber views and transverse or short-axis views consisting of 12 to 14 contiguous slices were acquired, covering both ventricles from the base of the heart to the apex. Scan parameters were: repetition time = 3.2 to 3.8 ms; echo time = 1.6 to 1.9 ms; flip angle = 50-70°; slice thickness = 6-8 mm without slice gap; matrix = 160 x 256; field of view = 350-400 mm, and temporal resolution approximately 25 ms.

Stent graft valve function and flow dynamics across the pulmonary trunk were assessed using a free-breathing retrospective electrocardiogram-gated velocity-encoded MRI sequence. Image planes were located at the midpoint of the conduit before PPVI and approximately at the same level just distal to the stent graft after PPVI to avoid stent artifacts. The sequence was encoded for a through-plane velocity 150 cm/s or higher according to the degree of main pulmonary artery / conduit stenosis. Scan parameters were: repetition time = 9 ms, echo time = 5 ms, flip angle = 15-20°, slice thickness = 6-8 mm, matrix = 128 x 256, temporal resolution approximately 20 ms. Velocity mapping across the tricuspid valve was used for assessment of diastolic RV function. Scan parameters were: repetition time = 9 ms, echo time = 5 ms, flip angle 15-20°, slice
thickness 6-8 mm, matrix 128 x 256, temporal resolution 20 ms. The sequence was encoded for a through-plane velocity up to 100 cm/s.

Post processing
All images were analyzed on a workstation with an Intel Pentium 4 processor (Intel, Santa Clara, Calif). RV systolic function and mass were analyzed with the software package MASS® (Medis, Leiden, the Netherlands). Flow velocity encoded MRI data were analyzed using the software package FLOW® (Medis, Leiden, the Netherlands). All contours were manually drawn by an observer (with 1 year of experience) and supervised by a radiologist (11 years of experience with cardiac MRI) or a cardiologist (11 years of experience with cardiac MRI). The supervisors were unaware of the patient conditions.

Vascular contours were drawn for the pulmonary trunk to generate flow-versus-time curves throughout the cardiac cycle. The presence of substantial (> 5%) PR was assessed. Peak flow velocity was measured. Increased peak flow velocity in the pulmonary trunk was defined as maximum blood flow velocity (V max) exceeding 1.5 m/s.

RV systolic function was assessed by drawing endocardial RV contours at end-diastole and end-systole in all sections of the cine transverse or short axis data. RV end-diastolic volumes (RV-EDV) were obtained and indexed for body surface area according to the Mosteller formula: \( \sqrt{\text{Height (cm) x weight (kg)/3600}} \). RV stroke volume indexed for body surface area (RV-SV) was calculated by subtracting RV-ESV from RV-EDV. The RV ejection fraction (RV-EF) was calculated by dividing RV-SV by RV-EDV. Decreased RV-EF <47% was defined as abnormal. In presence of significant PR (PR fraction >20%), the RV-EF corrected for regurgitation was calculated by dividing the net pulmonary flow (forward flow minus diastolic regurgitate flow) by the RV-EDV.

**Figure 1:** Midventricular slice in transverse (A) and short axis (B) views with the right ventricular endocardial and epicardial edges traced.
RV mass was assessed using the software package MASS © (Medis, Leiden, The Netherlands). RV epicardial borders were traced for each slice level where the area of the interventricular septum was allocated to the LV. (Figure 1) Masses were summed for each segment from apex to base with subsequent indexation for body surface area.19 Flow versus time curves for RV inflow across the tricuspid valve were analyzed using Microsoft Excel (version 2007) for the following diastolic function parameters: E peak filling rate (Epfr), A peak filling rate (Apfr), E/A peak flow ratio, E-wave volume (Evol), A wave volume (Avol), Evol/Avol ratio. The Evol and Avol were calculated by integration of the flow curves.20;21 In addition, the E-wave deceleration time was measured.

Statistical analysis
Statistical evaluation was performed using SPSS version 16 (SPSS inc, Chicago, Ill). Data were expressed as mean ± SD and medians with interquartile range where appropriate. We used a linear mixed model analysis with least significant difference criterion for post-hoc comparisons for all MRI parameters at 1 month and 16 months after PPVI versus baseline (pre-PPVI). Correlations between pre-PPVI RV mass and pulmonary Vmax were expressed using Pearson’s test. P values < 0.05 were considered statistically significant.

Results
Most patients (n=11) had surgical repair of TOF or pulmonary atresia with ventricular septal defect, one patient had pulmonary atresia and intact ventricular septum, one patient had undergone Rastelli operation, and one patient had undergone Ross operation. Conduit dysfunction presented predominantly as obstruction with peak systolic gradient ≥ 50 mmHg in 5 patients, as significant PR with RV dilatation in 2 patients (more than grade 2 by echocardiography and/or PR fraction >20% by MRI), and a combination of both obstruction and PR > 20% in 7 patients. All but one patient had complete right bundle branch block. One patient with TOF had significant PR had an implantable cardioverter-defibrillator and was excluded from the MRI study, so our study included 13 patients. Clinical parameters of the patients studied are provided in Table 1.

Percutaneous pulmonary valve implantation
All patients (male/female 7/7) underwent successful PPVI. The median age at implantation was 15 years, the median body surface area was 1.61 m². (Table 1) Five patients additionally had a single bare stent placed in the RVOT and one patient in the left pulmonary artery to relieve a localized stenosis before PPVI. After stent graft implantation, RVOT gradients significantly decreased from 33 ± 12 mmHg to 12 ± 6 mmHg (P < 0.001). RV/aorta pressure ratio’s significantly decreased from 0.60 ± 0.11 to
0.35 ± 0.05, (P < 0.001). Pulmonary regurgitation was absent or trivial (< 5%) after PPVI in all patients.

Magnetic resonance imaging

The MRI results of 13 PPVI patients are shown in Table 2. No statistically significant differences in heart rate were observed during acquisitions before or after PPVI.

**Stent graft valve function:** The pulmonary trunk Vmax reduced from 3.7 ± 0.2 m/s before PPVI to 2.5 ± 0.2 m/s at 1 month after PPVI (P = 0.001), without further change at 16 months follow up (2.3 ± 0.2 m/s, P = 0.5). Thus, PPVI significantly decreased pulmonary stenosis with mild residual stenosis remaining during follow-up. Six of 13 (46%) patients had PR > 20%. In this group the percent PR decreased significantly from 20 ± 2% before to 2 ± 2% at 1 month after PPVI (P = 0.008), without further changes at 16 months follow up (1 ± 2%, P = 0.8). Thus, PR was successfully treated by PPVI.

**RV mass:** RV mass decreased early from 28.6 ± 2.1 gm/m² before to 25.6 ± 2.2 gm/m² at 1 month after PPVI (P =0.03) with further decreases to 22.3 ± 2.1 gm/m² (P =0.002) at 16 months after PPVI. Interestingly, before PPVI the RV mass was positively correlated with Vmax as measured across the pulmonary trunk (r = 0.57, P = 0.04),

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/ Female</td>
<td>6/71</td>
</tr>
<tr>
<td>Median age at PPVI (years, range)</td>
<td>15 (10-46)</td>
</tr>
<tr>
<td>Median age at MRI (years, range)</td>
<td>15 (10-46)</td>
</tr>
<tr>
<td>Median BSA m²</td>
<td>1.61 (0.94-2.34)</td>
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<tr>
<td>Diagnosis:</td>
<td></td>
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<tr>
<td>TOF-PA/VSD</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>PA/IVS</td>
<td>1</td>
</tr>
<tr>
<td>Rastelli operation</td>
<td>1</td>
</tr>
<tr>
<td>Ross operation</td>
<td>1</td>
</tr>
<tr>
<td>Type of RV conduit:</td>
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</tr>
<tr>
<td>Homograft</td>
<td>12</td>
</tr>
<tr>
<td>Contegra</td>
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</tr>
<tr>
<td>RV conduit lesions</td>
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</tr>
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<td>Obstructive</td>
<td>5</td>
</tr>
<tr>
<td>Regurgitation</td>
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</tr>
<tr>
<td>Combined</td>
<td>7</td>
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</table>

BSA = body surface area as calculated according to the Mosteller formula: Ö Height (cm) x weight (kg)/3600). PPVI = percutaneous pulmonary valve implantation; TOF= Tetralogy of Fallot; PA/VSD= pulmonary atresia with ventricular septum defect; PA/IVS= pulmonary atresia with intact ventricular septum.
indicating that RV hypertrophy was associated with the severity of conduit obstruction. The relation between RV mass and V max across the stent graft was no longer present after PPVI (r = 0.24, P = 0.56). Thus, after PPVI, RV mass (i.e. hypertrophy caused by pulmonary stenosis) reduced together with reduction in pulmonary stenosis.

**RV systolic function:** MRI results of RV systolic function are displayed in Table 2. At 1 month follow up, the mean RV-EDV significantly reduced (P = 0.01), without further change at 16 months follow up (P = 0.1). RV-ESV did not significantly change at one month follow up (P = 0.1), but was reduced significantly at 16 months (P = 0.03). The RV-EF corrected for pulmonary regurgitation improved at one month follow up (P = 0.001), that remained unchanged at 16 months follow up (P =0.1). The results indicate that RV systolic function improved early after PPVI and that further improvement was found at mid-term follow up. Of note is the normalization of the RV-EF from 36% to 50% (P = 0.001) after PPVI.

**RV diastolic function:** MRI results of RV diastolic function are displayed in Table 2. E/A volume ratio and E/A peak flow ratio did not significantly change 1 month after PPVI. However, at 16 months follow-up both E/A volume ratio as well as E/A peak flow ratio showed significant increase (P = 0.01 and P = 0.04, respectively). A peak filling rate showed no significant change after PPVI (at 1month P = 0.8, at 16 months P = 0.3). E peak filling rate showed no significant increase at 1 month after PPVI (P = 0.9), but significantly increased at 16 months (P = 0.02). E-wave volume remained unchanged

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**Table 2: MRI results before and after PPVI**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before PPVI Mean ±SD</th>
<th>1 month after PPVI Mean ±SD</th>
<th>p-value before versus 1 month after PPVI</th>
<th>16 months after PPVI Mean ±SD</th>
<th>p-value before versus 16 months after PPVI</th>
<th>p-value at 1 month versus 16 months after PPVI</th>
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</thead>
<tbody>
<tr>
<td><strong>RV systolic function</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EDV (ml/m²)</td>
<td>124 ± 8</td>
<td>113 ± 8</td>
<td>0.01*</td>
<td>105 ± 8</td>
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</tr>
<tr>
<td>ESV (ml/m²)</td>
<td>62 ± 6</td>
<td>58 ± 6</td>
<td>0.1</td>
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<tr>
<td>EF% (corrected for PR)</td>
<td>35.5 ± 2.4</td>
<td>46 ± 2.5</td>
<td>0.00*</td>
<td>50 ± 3.5</td>
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<tr>
<td><strong>RV diastolic function</strong></td>
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</tr>
<tr>
<td>Evol (ml)</td>
<td>40 ± 6</td>
<td>48 ± 6</td>
<td>0.1</td>
<td>59 ± 6</td>
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<tr>
<td>Avol (ml)</td>
<td>23 ± 3</td>
<td>24 ± 3</td>
<td>0.8</td>
<td>20 ± 3</td>
<td></td>
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<tr>
<td>E/A volume ratio</td>
<td>1.91 ± 0.4</td>
<td>2.6 ± 0.4</td>
<td>0.3</td>
<td>3.3 ± 0.4</td>
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</tr>
<tr>
<td>Epfr (ml.s⁻¹)</td>
<td>305 ± 30</td>
<td>327 ± 31</td>
<td>0.9</td>
<td>345 ± 30</td>
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<tr>
<td>Apfr (ml.s⁻¹)</td>
<td>243 ± 30</td>
<td>236 ± 32</td>
<td>0.8</td>
<td>212 ± 30</td>
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<td></td>
</tr>
<tr>
<td>E/A peak flow ratio</td>
<td>1.34 ± 0.14</td>
<td>1.48 ± 0.16</td>
<td>0.4</td>
<td>1.73 ± 0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-wave deceleration time (ms)</td>
<td>142 ± 25</td>
<td>160 ± 27</td>
<td>0.4</td>
<td>211 ± 26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = significant

PPVI = percutaneous pulmonary valve implantation; PR = pulmonary regurgitation; EDV= end diastolic volume indexed to body surface area, ESV = end systolic volume indexed to body surface area, EF= ejection fraction; Evol = E volume; Avol= A volume; Epfr= E peak filling rate, Apfr= A peak filling rate.
1 month after PPVI (P = 0.1), but significantly increased at 16 months (P = 0.001). A-wave volume did not change after PPVI at 1 month or 16 months (P = 0.8 and P = 0.4, respectively). E-wave deceleration time was not significantly prolonged at 1 month after PPVI (P = 0.4) but prolongation was found statistical significant at 16 months (P = 0.007). **Figure 2** shows an example of change in RV inflow curves after PPVI as compared to pre-PPVI.
**Discussion**

In this study, cardiac MRI was used for follow-up patients who underwent PPVI for RV to pulmonary artery conduit dysfunction. We found delayed reduction of RV mass and delayed improvement of RV diastolic function together with early improvement of RV systolic function.

Several studies in patients with CHD have shown improvement of RV function after surgical pulmonary valve replacement using a valved conduit. Most of these studies focus on recovery of systolic RV function after surgical pulmonary valve replacement in patients with RV volume overload due to PR late after repair of TOF.\(^{17,22}\)

Studies on improvement of RV function in patients with RV pressure overload or with combined RV pressure and volume overload are limited. Recent studies in patients with CHD undergoing PPVI for obstruction relief of the RV showed early improvement of systolic RV function.\(^{6,8,9}\) In the present study, we have also evaluated the time course of changes in RV diastolic function and regression of RV hypertrophy in young patients with CHD after PPVI.

**RV systolic function**

RV systolic function improved early after PPVI; RV-EDV significantly reduced after 1 month without further reduction later on. Also, RV corrected EF percentage increased substantially and was normalized at 1-month follow up.\(^{23}\) It has been demonstrated that the corrected EF percentage is better than uncorrected RV-EF percentage in reflecting the RV functional status after pulmonary valve replacement in patients with TOF.\(^{22}\)

These results are in agreement with previous MRI studies on RV systolic function in patients undergoing PPVI.\(^{6,9,10}\) This supports the theory, as mentioned in these studies, that early improvement of EF combined with the fall in EDV implies that before PPVI, the RV is on the decompensating limb of the Starling curve and returns to the compensatory limb immediately after valve replacement.

**RV mass and RV diastolic function**

All but one patient in the study cohort had pressure overload of the RV alone or combined with pulmonary valve regurgitation. RV hypertrophy in this group correlated with the severity of RVOT obstruction before PPVI as measured by maximal flow velocity across the pulmonary trunk. In this study cohort, the RV mass decreased almost 25 % during follow-up. These data, indicating ongoing regression of RV mass, are comparable with histological studies in postoperative TOF patients showing that RV hypertrophy regresses in the absence of significant residual stenosis.\(^{24}\)

In the present study, we demonstrated that regression of RV mass is associated with improvement of RV diastolic function despite the presence of mild residual stenosis. In patients with CHD, diastolic dysfunction of the RV can occur in the presence of both
volume or pressure overload of the RV. MRI studies have demonstrated impairment of RV diastolic function as early sign of RV failure in patients with PR late after repair of TOF.

RV hypertrophy may be one of the most important underlying mechanisms for impaired relaxation or restriction to RV filling. Recent cardiac MRI studies have shown that RV diastolic dysfunction was related to RV mass and RVOT obstruction in patients long term after the arterial switch operation and after the Ross operation for aortic valve replacement.

In the present study, we demonstrated that RV diastolic function recovers relatively late after obstruction relief and elimination of volume overload and that recovery of RV diastolic function recovery is associated with the regression of RV mass. These findings on RV diastolic function improvement are comparable with previous echocardiographic reports in patients with pulmonary valve stenosis. These studies have revealed that RV diastolic dysfunction did not improve immediately after relief of RVOT obstruction by balloon valvuloplasty, suggesting that afterload mismatch was not the direct cause of the diastolic abnormalities of the RV. A long-term follow up of this group of patients by echocardiography demonstrated late improvement of RV diastolic function which was assumed to be due to decrease of RV hypertrophy.

**Study limitations**

The available sample was small, and patients had various types of CHD. However, still, substantial improvement could be found in systolic and diastolic function after PPVI treatment on short and midterm follow-up.

**Conclusion**

This study shows that both systolic and diastolic RV function improved and RV hypertrophy reduced after PPVI in patients with RV to pulmonary artery conduit dysfunction. However, in contrast to the early normalization of systolic function, improvement of diastolic function is delayed. Long-term follow-up for patients with PPVI is recommended for complete assessment of RV function.


Chapter 5

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Recovery of right and left ventricular function after acute pulmonary embolism

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Abstract

Objective: To evaluate recovery of cardiac function after acute pulmonary embolism (PE).

Methods: Routine breath-held computed tomography (CT)-pulmonary angiography was performed in patients with suspected PE to confirm or exclude the diagnosis of PE at initial presentation. Electrocardiogram (ECG)-triggered cardiac CT was performed to assess biventricular function. After 6 months, cardiac magnetic resonance imaging (MRI) was performed. In total, 15 consecutive patients with PE and 10 without were studied. A significant change in ventricular volume was defined as a >15% change in end-diastolic or systolic volumes (EDV, ESV), and significant ventricular function improvement as a >5% increase in ejection fraction (EF) as based on reported cut-off values.

Results: Right and left ventricular (RV and LV) EDV and ESV changed non-significantly (<1.3%) in the patients without PE, indicating good comparability of those values measured by CT and MRI. PE patients with baseline normal RV function (RVEF ≥ 47%) revealed a >5% improvement in the RVEF (+5.4 ± 3.1%) due to a decrease in the RVESV. Patients with baseline abnormal RV function showed a >5% improvement in the RVEF (+14 ± 15%) due to decreases in both the RVESV and RVEDV. Furthermore, the LVEDV increased in this latter patient group.

Conclusion: The present study demonstrated an improvement in RV function in the majority of patients with PE, independent of baseline RV function. The degree of RV and LV recovery was dependent on the severity of baseline RV dysfunction.
Chapter 6

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by intraluminal thrombus organization and fibrous stenosis or complete obliteration of the pulmonary arteries, and has frequently been associated with acute pulmonary embolism (PE). This obstruction of the pulmonary artery causes an increase in pulmonary vascular resistance and as a consequence chronic right ventricular (RV) dysfunction. Although CTEPH is considered to be a rare disease after acute PE, signs of RV dysfunction can be observed in half of the patients with acute PE. This acute RV function impairment is caused by increased afterload of the RV by the pulmonary embolus. The natural history of RV recovery after acute PE is largely unknown and, therefore, complicates the diagnostic management of CTEPH. Detailed information of the cardiac function at the time of the PE and general understanding of the subsequent ventricular recovery mechanisms might simplify the diagnostic workup of patients with persistent dyspnoea or heart failure after acute PE. Magnetic resonance imaging (MRI) is widely accepted as the reference standard for evaluating cardiac volumes. Also electrocardiogram (ECG)-gated multidetector computed tomography (MDCT) has been shown to be a reliable method to assess ventricular volumes and ejection fraction (EF) and can be combined with CT pulmonary angiography to establish the diagnosis of PE. Furthermore, CT and MRI can be used interchangeably as ventricular volumes assessed by both techniques show excellent correlation. The hypothesis of the present study was that acute RV dysfunction associated with acute PE will improve in the majority of patients over time after anticoagulant treatment, except for those patients who develop CTEPH. The rate of this recovery is dependent on individual patient characteristics, such as prior cardiac function, embolus load, and fibrinolytic potential. A further hypothesis was that cardiac MRI would be a feasible tool to study the RV function recovery after acute PE and additionally would involve less radiation exposure than MDCT. Accordingly, the aim of the present study was to evaluate biventricular cardiac function using cardiac MDCT at baseline and MRI at 6 months follow-up in consecutive patients with suspected PE.

Patients and methods

Patients

Consecutive normotensive outpatients with clinically suspected acute PE and an indication for CT pulmonary angiography were enrolled in this prospective observational study. PE suspicion was based on clinical signs and symptoms including sudden onset dyspnoea, deterioration of existing dyspnoea, and/or sudden onset pleuritic chest pain. An indication for CT pulmonary angiography was defined as a likely clinical probability for PE according to the Wells rule or an abnormal VIDAS D-dimer (BioMerieux, Marcy L’Etoile, France) test.
Patients with confirmed PE were treated according to hospital policy, initially with therapeutic unfractioned or low-molecular-weight heparin, followed by vitamin K antagonists for 6 months. Exclusion criterion was a contraindication for MRI, e.g., pregnancy, aneurysm clip in the brain, implanted neural stimulator, implanted cardiac pacemaker or defibrillator, or severe claustrophobia. As this was a proof of concept study, the aim was to study 15 consecutive patients with PE and 10 consecutive patients without PE. The Institutional Review Board approved the study and all participants consented to participation.

Baseline MDCT examination

All patients underwent MDCT (Aquilion 64; Toshiba Medical Systems, Otawara, Japan) of the chest during breath holding. Section collimation of 0.5- or 1 mm was used for acquisition. A separate image acquisition using retrospective ECG-synchronized dynamic cardiac MDCT was performed to assess RV and left ventricular (LV) function. All examinations were performed according to a standardized protocol as described previously. The diagnosis of PE was confirmed by the presence of at least one filling defect in the pulmonary artery tree. For cardiac analysis, 2 mm thick sections focused on the heart were reconstructed and analysed with dedicated cardiac function analysis software MASS® (Medis, Leiden, The Netherlands). The phase in which the ventricular sizes were maximal and minimal were selected to represent the end-diastolic and end-systolic phase. End-diastolic and end-systolic endocardial border contours were drawn for both ventricles on every other transverse section (i.e., each 4 mm) covering the entire ventricles up to the pulmonary valve and aortic valve. All contours were manually drawn by an observer (2 years experience with cardiac CT), supervised by a radiologist (8 years experience with cardiac CT) who were both blinded for the patients’ conditions. End-diastolic volume (EDV), end-systolic volume (ESV), stroke volume, and EF were calculated for both the right and left ventricles. (Figure 1a) Patients with PE were categorized in two groups characterized by normal or abnormal baseline systolic RV function. RV ejection fraction < 47% was defined as abnormal. Patients without PE comprised a third study group.

Follow-up MRI

MRI examinations were performed using a 1.5 T MRI system (Intera, Philips Medical Systems, Best, The Netherlands). A five-element, phased-array cardiac coil placed on the chest was used for signal reception. After a series of thoracic scout images that were used for planning purposes, a stack of 14-18 transverse sections (dependent on the size of the heart) was obtained using a steady-state free-precession sequence for biventricular volume measurements. Each section was acquired with breath holding at end-expiration. Scan parameters were: section thickness = 10 mm with no gap, field of view = 450 mm, scan matrix = 256 x 195, with reconstructed voxels = 1.37 x 1.37 x 8.0 mm, flip angle =
35°, repetition time = 3.2 ms, echo time = 1.6 ms, one signal average was used. Gated cardiac synchronization was used with 30 reconstructed phases per cardiac cycle; yielding a temporal resolution of 20 - 35 ms. Parallel imaging was used (Sensitivity encoding SENSE, with sense factor 2). Endocardial contours at end-systole and end-diastole were manually drawn using the MASS software package. All endocardial contours were manually drawn by an observer (2 years experience with cardiac MRI), supervised by a radiologist (11 years experience with cardiac MRI) who were both blinded for the patients’ conditions. (Figure 1b)

Statistical analysis
Ventricular volume changes were studied in 3 subgroups, i.e., patients with PE and abnormal baseline RV function, patients with PE and normal baseline RV function, and patients without PE. Significant change in ventricular volumes was defined as a decrease in volumes of more than 15%. Significant ventricular function improvement was defined as an increase in ejection fraction greater than 5%. Differences in ventricular recovery between the three study groups were assessed by post hoc least significant difference (LSD) testing for parameters that proved statistically significant on analysis of variance (ANOVA). P values less than 0.05 were considered significant.
Results

Study patients
To achieve the required sample size 27 consecutive patients with acute PE and 15 consecutive patients in whom PE was ruled out were recruited into the study. Of these patients, three had died during the 6 months follow-up period and 14 were excluded because of implanted cardiac pacemaker, unwillingness to cooperate, or claustrophobia. The remaining 15 patients diagnosed with PE and 10 patients without PE underwent both a CT examination at entry and MRI at 6 months follow-up, and were included for analysis. The baseline characteristics of patients with PE and without were comparable (Table 1); overall mean age was 53 ±11 years and 11 (40%) of the patients were male. There was no difference in the presence of cardiopulmonary comorbidity. Median follow-up duration was 205 days (range, 165 ± 301 days).

Table 1: General characteristics of study patients

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Patients without PE (n = 10)</th>
<th>Patients with PE (n = 15)</th>
<th>Total population (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years, ± SD)</td>
<td>52 ± 13</td>
<td>53 ± 10</td>
<td>53 ± 11</td>
</tr>
<tr>
<td>Male gender (n, %)</td>
<td>3 (30)</td>
<td>8 (53)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>History of venous thrombosis (n, %)</td>
<td>0 (0)</td>
<td>6 (40)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>COPD (n, %)</td>
<td>2 (20)</td>
<td>3 (20)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Pre-existent left heart failure (n, %)</td>
<td>0 (0)</td>
<td>1 (6.7)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Qanadli score [median, IQ range (max 40)]</td>
<td>NA</td>
<td>15 (2-26)</td>
<td>NA</td>
</tr>
<tr>
<td>Follow-up duration (days; mean, ± SD)</td>
<td>202 ± 36</td>
<td>226 ± 42</td>
<td>217 ± 41</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; COPD, chronic obstructive pulmonary disease; IQ, interquartile; NS, not significant; NA, not applicable.

Of the 15 PE patients, seven were diagnosed with RV dysfunction at time of the PE (47%, 95% CI 21-73). RV dysfunction was not found in any of the patients without PE (0%, 95% CI 0-30). None of the patients with PE or without PE experienced a clinical event or medication change other than the acute PE that could have influenced their cardiac function in the follow-up period. The PE patients with baseline RV dysfunction did not differ in age, gender, or the prevalence of cardiopulmonary comorbidity from the PE patients with baseline normal RV function.

Ventricular volume changes
Patients with RV dysfunction had higher right ventricular ESV and EDV at baseline than the patients with normal RV function and patients without PE. LV volumes were not different between the three groups. (Table 2) In the cohort without PE, the overall relative change in the EDV (+ 0.48 ± 6.0 mL for the RV and 0.93 ± 5.7 mL for the LV) and ESV (+0.88 ± 4.3
In both ventricles did not meet the previously stated definition of significant volume changes. (Table 2) Also, none of the individual patients without PE was found to have changed RV or LVEF after 6 months. PE patients with normal RV function at baseline showed a >5% overall increase in the RVEF (+5.4 ± 3.1%) due to a relative decrease in the ESV (-17 ± 7.9%). Overall, no volume changes of the LV were observed in these patients. (Table 2) Individually, of the eight PE patients with normal RV function at baseline, one (13%) showed significant decrease in the RVEDV, six (75%) in the RVESV, and two showed no volume changes. The LVESV increased in four patients (50%). A > 5% increase in the RVEF was found in five of these eight patients (63%), with a concomitant increase of >15% in the LVEDV in one patient.

<table>
<thead>
<tr>
<th>Table 2: Ventricular volume changes during follow-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without PE (n = 10)</td>
</tr>
<tr>
<td>Baseline RV ESV (ml; mean ± SD)a,b</td>
</tr>
<tr>
<td>Baseline RV EDV (ml; mean ± SD)a,b</td>
</tr>
<tr>
<td>Baseline RV EF (%; mean ± SD)a,b</td>
</tr>
<tr>
<td>Follow-up RV EF (%; mean ± SD)</td>
</tr>
<tr>
<td>Deltac RV EF (%; mean ± SD)a</td>
</tr>
<tr>
<td>Deltac RV EDV (ml; mean ± SD)a,b</td>
</tr>
<tr>
<td>Relative RVEDV change (%; mean ± SD)a,b</td>
</tr>
<tr>
<td>Deltac RVESV (ml; mean ± SD)a,b</td>
</tr>
<tr>
<td>Relative LVESV change (%; mean ± SD)a,b,e</td>
</tr>
<tr>
<td>Baseline LV ESV (ml; mean ± SD)</td>
</tr>
<tr>
<td>Baseline LV EDV (ml; mean ± SD)</td>
</tr>
<tr>
<td>Baseline LV EF (%; mean ± SD)a,b</td>
</tr>
<tr>
<td>Follow-up LV EF (%; mean ± SD)a</td>
</tr>
<tr>
<td>Deltac LV EF (%; mean ± SD)a</td>
</tr>
<tr>
<td>Deltac LVEDV (ml; mean ± SD)</td>
</tr>
<tr>
<td>Relative LVEDV change (%; mean ± SD)a</td>
</tr>
<tr>
<td>Deltac LVESV (ml; mean ± SD)</td>
</tr>
<tr>
<td>Relative LVESV change (%; mean ± SD)</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; RV, right ventricular; LV, left ventricular; SD, standard deviation; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume.

a Significant differences between patients without PE and PE patients with baseline RV dysfunction (P < 0.05).
b Significant differences between PE patients with baseline normal RV function and PE patients with baseline RV dysfunction (P < 0.05).
c Delta = follow-up scan - baseline scan.
d Significant ventricular volume changes (delta EF >5%; delta volume >15%).
e Significant differences between patients without PE and PE patients with baseline normal RV function (P < 0.05).
Overall, the seven patients with abnormal RV function at baseline had a >5% improvement in the RVEF (+14 ±15%) due to a relative decrease in both the ESV (-34 ± 27%) and EDV (-20 ± 19%). Furthermore, the LVEDV increased > 15% (15 ± 11%, Figure 1). On an individual basis, five out of seven patients (71%) with RV dysfunction at baseline were found to have a > 15% decrease in the RVEDV and six patients (86%) were found to have a > 15% decrease in the RVESV after 6 months of treatment. The LVEDV increased by > 15% in four patients (57%) and the LVESV in two patients (29%). As a result, a > 5% increase in the RVEF was found in six patients (86%) and in the LVEF in two patients (29%). Three patients with PE had a RVEF < 47% after the treatment period. In only one patient, this RVEF remained unchanged and poor. After further clinical work-up, this patient was diagnosed with peripheral, inoperable CTEPH.

Discussion

This study shows that the degree of RV recovery after 6 months treatment of acute PE is dependent on the severity of RV dysfunction at the time of the acute event. RVEF improved due to a decrease in end-systolic volumes and, although to a lesser extent, a decrease in end-diastolic volumes. Patients with more severe RV dysfunction at baseline were additionally shown to have LV volume changes due to an increase in end-diastolic volumes. This indicates that restoration of LV function is dependent on the restoration of the RV, which is a manifestation of inter-ventricular dependence.

The following explanations are proposed to explain the findings of the present study: the concept of ventricular recovery starts with the initial effect of an obstruction of the pulmonary artery by a thrombus, causing a sudden rise in afterload of the RV. RV ESVs and EDVs increase, followed by reduced RV EF and stroke volume.2,16 Depending on prior cardiopulmonary status and the extent of embolic obstruction, the impending resulting reduction of pulmonary blood flow leads to a decrease in LV filling and eventually decreased LV stroke volume. During the naturally occurring thrombolysis of the embolus, RV afterload will be reduced leading to RV and LV volume changes and improvement of stroke volume and ventricular output.2,16 Notably, all but three patients with acute PE from this study were found to have a decrease in RV ESV after 6 months of treatment, even with baseline RVEF within the normal range. One of the three patients that showed no RV ESV change was subsequently diagnosed with CTEPH; the other two had low PE-obstruction scores (data not presented) and excellent RV function (EF > 60%) at baseline. These observations suggest that in most patients acute PE is associated with increased RV volumes although not clinically relevant in all cases. Data from a recent study suggest that approximately 50% of first time patients diagnosed with sub massive PE have RV dysfunction at time of diagnosis, of whom 36% continue to have RV dysfunction at 6-month follow-up.17,18 The results of the present study, combining cardiac MDCT and MRI, confirm these data. It has
been previously shown that cardiac evaluation after PE by echocardiography helps predict future pulmonary hypertension. One potential advantage of using cardiac MRI as opposed to echocardiography in cardiac evaluation after PE is the possibility of direct comparison of the cardiac volumes to MDCT images, as demonstrated in this study. As CT is the current imaging method of choice for diagnosing PE, patients are not required to undergo additional echocardiography in the acute phase of the disease, although ECG-gated MDCT of the heart involves increased radiation and contrast medium exposure. Furthermore, MRI has been demonstrated to accurately measure pulmonary haemodynamic parameters that correlate closely to invasive measurements. The strengths of the present study include the prospective design and the inclusion of consecutive patients. The CT and MRI protocols performed were well validated. Furthermore, the previously described reliable assessment of RV and LV function with MDCT when compared to MRI is underlined by the present study. A limitation of the study is that as this was a proof of concept study, only a limited number of patients were selected to test the hypothesis.

In summary, this study demonstrates improvement in RV function in the majority of patients with acute PE, independent of baseline RV function. The extent of the RV and LV function recovery related to the severity of RV dysfunction at the time of the acute event. Further investigation is required in larger patient cohorts to study the potential clinical value of cardiac MRI in the clinical follow-up of patients with acute PE.
Chapter 6

References


Evaluating the systemic right ventricle by cardiovascular magnetic resonance; short axis or axial slices?

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Submitted 2013
Abstract

Objective: To evaluate differences in functional parameters and reproducibility between short axis and axial slice orientation in the quantitative evaluation of the systemic right ventricle by cardiac magnetic resonance (CMR).

Patients and Methods: Twenty-three patients (mean age 32 ± 7 years) with systemic right ventricle (3 with congenitally corrected transposition of the great arteries and 21 with atrially switched transposition of the great arteries) underwent CMR. Short axis and axial slice stacks were analysed by two observers. Differences in end-diastolic and end-systolic volumes, mass and ejection fraction between the two slice orientations were analysed. In addition, intra and interobserver variances were compared to determine which of the two methods is more reliable.

Results: Compared to short axis slices, analysis of axial slices resulted in higher end-systolic volume (6.6%, \( P < 0.01 \)), while mass (-10.8%, \( P < 0.01 \)) and ejection fraction (-8.9%, \( P < 0.01 \)) turned out lower. Intraobserver and interobserver reproducibility were similar for both methods when measuring end-diastolic and end-systolic volumes. However, ejection fraction, stroke volume were measured more consistently in axial orientation, while ventricular mass was measured more consistently in short axis orientation.

Conclusion: There are significant differences in volume, mass and function between measurements in axial and short axis orientation. Ejection fraction and stroke volume, which have a high clinical relevance, were measured more consistently in axial slice orientation. Consequently, we recommend using axial slice orientation in patients with a systemic right ventricle.
Chapter 7

Introduction

A substantial portion of the growing population of patients with congenital heart disease has a morphological right ventricle (RV) that supports the systemic circulation (e.g. patients with an atrially or congenitally corrected transposition of the great arteries).\(^1\) While mid term survival is excellent, progressive right ventricular dilatation, hypertrophy and dysfunction seems inevitable and underlies impaired exercise tolerance, arrhythmia, progression to heart failure, or premature death.\(^2\)–\(^6\)

Consequently, it is essential to monitor ventricular volumes, mass and function closely in these patients. Cardiac magnetic resonance (CMR) is considered the gold standard for the evaluation of patients with a systemic RV.\(^7\)–\(^12\) The European Society of Cardiology and American Heart Association/ American College of Cardiology guidelines consider CMR imaging an important addition to echocardiography and recommend it should be regularly used when the information is essential for patient management.\(^13\),\(^14\) Moreover, decisions on the timing of surgical intervention or feasibility of pregnancy often based on RV function in these patients.\(^15\)–\(^17\) What is more, RV volumes and mass have been shown to predict outcome.\(^18\) The current guidelines recommend a stack of slices orientated along the RV short axis.\(^19\) However, recent studies in predominantly patients with a subpulmonary RV have shown that evaluation of RV volumes using axial slices has a better reproducibility than short axis slices.\(^20\)–\(^23\) As a consequence, in clinical practice the emphasis has shifted more towards the use of axial slices, also in patients with a systemic RV, whose dilated, hypertrophied RVs are considerably different from subpulmonary RVs.

The aim of the present study was to assess whether there are systematic differences in systemic RV volumes and mass between short axis and axial orientations in patients with a systemic RV. Moreover, intraobserver and interobserver variability was compared in order to assess reproducibility.

Methods

Study population

A total of 22 adult patients (16 (72%) male, mean age 33±7 years, mean body surface area 1.89 ± 0.20) with systemic right ventricle were included. CMR imaging was performed in the setting of a double blind randomized placebo controlled trial on the efficacy of valsartan in 88 patients with a systemic RV.\(^24\),\(^25\) The study population (n=22) comprised of all patients in whom both short axis and axial stacks were acquired. Adult patients with a systemic RV due to ccTGA or surgically corrected TGA were eligible. Exclusion criteria were hypersensitivity to valsartan, renal impairment, treatment with ACE or ARB that could not be discontinued, pregnancy or a wish to get pregnant during follow-up, recent myocardial infarction, stroke or heart surgery, (planned or imminent) heart transplantation,
and contraindications to MRI. Three patients (14%) had cc TGA and 19 (86%) had atrially corrected TGA. The review board of all participating centres approved the study protocol. Written and informed consent was obtained from all patients prior to participation in the study.

Image acquisition

Image acquisition was performed by CMR, using a 1.5 Tesla scanner (Siemens Avanto, Erlangen, Germany). Imaging was performed in a supine position, using breath holds. After acquisition of localizer views in three orthogonal planes, multi-phase steady-state free precession with retrospective electrocardiographic gating was performed in 2-chamber, 3-chamber, and 4-chamber views. The axial slices were acquired using coronal and sagittal localizing images to plan a stack of orthogonal slices that covered the heart from a level just below the diaphragm to the pulmonary artery. Short axis slices were obtained from the 2-, and 4-chamber multiphase images, by planning a stack of short axis slices perpendicular to the ventricular septum, encompassing the total heart. Scan parameters were: flip angle = 50-70°; repetition time = 40 msec, echo time = 2 msec; temporal resolution = 20 msec; in-plane spatial resolution = 2 x 2 mm, slice thickness = 8 mm with 1mm inter slice gap.

Image analysis

Two independent observers (T.B and S.R) used MASS ® analytical Software System (Medis, Leiden, the Netherlands) for CMR image analysis. The first observer (TB) was a research fellow with 2 years of experience in CMR of patients with CHD. The second observer (SR) was a cardiologist with advanced training in CMR of patients with CHD and 4 years of CMR experience. Mid ventricular cine loops were used to choose end-diastolic and end-systolic phases. These were defined as the phase with the largest and smallest right ventricular area respectively. In both axial and short-axis data sets, contours were drawn manually in each end-diastolic and end-systolic phase. For each slice and phase, first the endocardial contour of the left ventricle was traced, followed by the left ventricular epicardial contour, including the ventricular septum. Next, the right ventricular endocardial contour was drawn, followed by the epicardial contour. Trabeculae and papillary muscles were considered to be part of the ventricular cavity, according to the method described by Winter et al. and Papavassiliu et al.8,26 Cine loops of axial and short axis slices were examined to determine the difference between ventricular wall and impacted trabeculae and papillary muscles. Cine loops of the heart in 2-chamber, 3-chamber, and 4-chamber views in phase with short axis and axial datasets were used for orientation when distinction between atria, ventricle and great vessels was unclear.
Ventricular end-diastolic and end-systolic volumes and mass were computed using a modified Simpson’s rule. Stroke volume was calculated as the difference between end-diastolic and end-systolic volume. Ejection fraction was calculated as the stroke volume divided by the end diastolic volume multiplied by 100%. Mass was measured in end-diastole.

Both axial and short axis data sets were analyzed once by S.R and twice by T.B, with a gap of minimally 2 weeks between measurements. The observers were blinded to each other and prior measurements. To evaluate systematic error and agreement between axial and short axis methods, the median of the 3 measurements (1 by S.R and 2 by T.B) was compared to the median of the measurements in short axis orientation. For the evaluation of intraobserver variance, the variance between the first and second analysis in axial slices were compared to the variance between the first and second analysis in the short axis slices. To determine the interobserver reliability for each method, we randomly selected one of the 2 measurements of T.B which was then compared with the results of the analysis by S.R.

Statistical analysis

For statistical analysis SPSS version 16 (SPSS inc, Chicago, Ill) was used. The agreement between the axial and short axis orientation was assessed using the method described by Bland and Altman. The limits of agreement were defined as mean difference ± 2SD. Due to the large variation in ventricular volumes and mass between patients we focused on relative rather than absolute differences, expressed as a percentage.

The differences between the axial and short axis slice orientation were assessed using a 2 -tailed paired t test. The agreement between two measurements of observer 2 (intraobserver) and between the measurements of observer 1 and 2 (interobserver) were evaluated using the Lin’s concordance correlation coefficient (CCC) and Bland and Altman plots. P values < 0.05 were considered statistically significant.

Results

Figure 1 shows the different slice orientations of the 2 methods, with examples of the endo- and epicardial contours defined for right and left ventricle.

Differences in volume, function, and mass

Table 1 lists the mean and standard deviation for the volume and mass measurements of both axial and short axis methods. Bland Altman plots were used to visualize systematic differences and agreement. (Figure 2) The axial method resulted in significantly higher right ventricular end –systolic volumes then the short axis method. This resulted in a
Table 1. Comparison of ventricular volumes, mass and function between axial and short-axis slices in patients with a systemic right ventricle

<table>
<thead>
<tr>
<th>Variable</th>
<th>RVEDV (ml)</th>
<th>RVESV (ml)</th>
<th>RSVV (ml)</th>
<th>RVEF (%)</th>
<th>RVM (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial mean ± SD</td>
<td>278 ± 108</td>
<td>188 ± 88</td>
<td>91 ± 28</td>
<td>34.8 ± 7.1</td>
<td>67 ± 25</td>
</tr>
<tr>
<td>Short axis mean ± SD</td>
<td>273 ± 112</td>
<td>177 ± 85</td>
<td>97 ± 34</td>
<td>38.2 ± 6.9</td>
<td>75 ± 26</td>
</tr>
<tr>
<td>Mean difference</td>
<td>5.2 ± 19.5</td>
<td>10.9 ± 14.9</td>
<td>-5.6 ± 11.0</td>
<td>-3.4 ± 3.8</td>
<td>-8.3 ± 8.7</td>
</tr>
<tr>
<td>% difference</td>
<td>2.5</td>
<td>6.6</td>
<td>-4.5</td>
<td>-8.9</td>
<td>-10.8</td>
</tr>
<tr>
<td>Limits of agreement (%)</td>
<td>-12 to 17</td>
<td>-12 to 25</td>
<td>-23 to 14</td>
<td>-28 to 10</td>
<td>-36 to 14</td>
</tr>
<tr>
<td>Standard deviation (%)</td>
<td>7.1</td>
<td>9.5</td>
<td>9.4</td>
<td>9.5</td>
<td>12.4</td>
</tr>
<tr>
<td>p Value (t-test axial vs short-axis)</td>
<td>0.20 &lt; 0.01 &lt; 0.03 &lt; 0.01 &lt; 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EDV end-diastolic volume; EF ejection fraction; ESV end-systolic volume; LV left ventricular; M mass; RV right ventricular; positive difference indicates variable measured in axial slices are larger than those derived from short axis slices, and vice versa.

Figure 1: Title: Overview of axial and short axis slice orientation and contour placement
Caption: Both images are in end-diastole; red: left ventricular endocardial contour; green: left ventricular epicardial contour; yellow: right ventricular endocardial contour; blue: right ventricular epicardiac contour.
significantly lower RV stroke volume and ejection fraction. RV mass, on the other hand was lower when using the axial method.

Observer reproducibility

Intra- and interobserver agreement is displayed in the form of Bland Altman plots in Figure 3 and 4. CCC values for intra- and interobserver agreement were similar for ventricular end-diastolic and end-systolic volumes measured with axial and short axis methods (Table 2 and 3). However, notably, ejection fraction was measured with a higher consistence when using the axial method (intraobserver CCC axial 0.90 vs short axis 0.75, interobserver axial 0.86 vs short axis 0.72). Moreover, observer agreement of RV mass was better when measured using axial slices (intraobserver CCC axial 0.94 vs short axis 0.90, interobserver axial 0.71 vs short axis 0.88).
Discussion

The present study addresses the issue of CMR slice orientation in the population of patients with a systemic RV. Axial slice orientation resulted in higher end-systolic volumes and consequently lower stroke volume and ejection fraction compared to short axis orientation.
Intra and interobserver reliability of measurements of stroke volume and ejection fraction was higher in axial slice orientation. In contrast to a recent study by Jimenez et al.,\textsuperscript{23} who found differences between the 2 slice orientations in end-diastolic and end-systolic volumes, but not in stroke volume and ejection fraction, the present study did find significant differences in stroke volume and ejection fraction. This is an important finding, as right ventricular ejection fraction often guides clinical decisions. Consequently, when drawing conclusions concerning the volumes or function of the systemic RV using serial measurements, it is important to take into account the slice orientation.

Several other studies\textsuperscript{21,22,28,29} in predominantly patients with a subpulmonary RV reported differences in RV volumes, while ejection fraction remained unaffected. In contrast, Alfakih et al. showed even larger ejection fraction in the axial orientation.\textsuperscript{20}

The difference between the systemic RV and subpulmonary RV in bias between short-axis and axial slice orientation is in all probability caused by the severe hypertrophy of the systemic RV. Axial slices give more oblique cross sections of the hypertrophied RV. This may result in a larger cross sectional area, in which distinction between intraventricular structures (papillary muscles and trabeculae) and myocardium can be made more accurately. In the present study, drawing the endocardial contour in axial slices led to larger volumes, especially in end-systole. Moreover, RV mass derived from the difference between epi- and endocardial contours, was accordingly smaller in axial orientation, suggesting, that, indeed, the endocardial contour is responsible for the differences between slice orientations.

In line with previous studies\textsuperscript{20,21}, the present study found ejection fraction measured by axial orientation to be more reproducible than the short axis method. In contrast, observer agreement of RV volumes between axial and short axis methods was similar. As has been suggested before, the differences in reproducibility are probably due to the through-plane motion of the tricuspid valve that occurs at the basal slices in the short axis orientation.

**Study limitations**

As in most studies concerning CHD, the number of patients that could be included was relatively small. We did not assess the accuracy of each slice orientation as a reliable gold standard for the in vivo measurement of ventricular volumes is not available and reliable aortic flow measurements were not available in all patients. However, the evaluation of RV size and volume by cardiovascular magnetic resonance has been validated extensively in previous studies.\textsuperscript{12,30} Moreover, the present study did not evaluate the impact of excluding trabeculae and papillary muscles from the ventricular cavity on the agreement between axial and short axis slice orientation.
Table 2. Intraobserver variance (single observer’s first versus second measurements using axial and short-axis slices)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RVEDV</th>
<th>RVESV</th>
<th>RVSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias (%)</td>
<td>-1.9</td>
<td>-0.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Standard deviation (%)</td>
<td>3.2</td>
<td>4.0</td>
<td>10.8</td>
</tr>
<tr>
<td>Limits of agreement (%)</td>
<td>-8 to 4</td>
<td>-9 to 7</td>
<td>-20 to 24</td>
</tr>
<tr>
<td>CCC (95% CI)</td>
<td>1.00 (0.99-1.00)</td>
<td>1.00 (0.99-1.00)</td>
<td>0.93 (0.86-0.97)</td>
</tr>
<tr>
<td>Short-axis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference (%)</td>
<td>-3.2</td>
<td>-2.8</td>
<td>-2.9</td>
</tr>
<tr>
<td>Standard deviation (%)</td>
<td>4.5</td>
<td>-6.5</td>
<td>18.8</td>
</tr>
<tr>
<td>Limits of agreement (%)</td>
<td>-12 to 6</td>
<td>10 to -16</td>
<td>-41 to 35</td>
</tr>
<tr>
<td>CCC (95% CI)</td>
<td>0.99 (0.97-0.99)</td>
<td>0.99 (0.98-1.00)</td>
<td>0.83 (0.67-0.92)</td>
</tr>
</tbody>
</table>

95% CI 95 percent confidence interval; CCC Lin’s concordance correlation coefficient; EDV end-diastolic volume; EF ejection fraction; ESV end-systolic volume; LV left ventricular; M mass; RV right ventricular.

Table 3. Interobserver variance (first observer versus second observer measurements using axial and short-axis slices)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RVEDV</th>
<th>RVESV</th>
<th>RVSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference (%)</td>
<td>0.1</td>
<td>0.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Standard deviation (%)</td>
<td>7.2</td>
<td>10.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Limits of agreement (%)</td>
<td>-14 to 15</td>
<td>-22 to 22</td>
<td>-23 to 26</td>
</tr>
<tr>
<td>CCC (95% CI)</td>
<td>0.98 (0.96-0.99)</td>
<td>0.98 (0.94-0.99)</td>
<td>0.90 (0.80-0.96)</td>
</tr>
<tr>
<td>Short-axis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference (%)</td>
<td>-2.1</td>
<td>2.3</td>
<td>-0.4</td>
</tr>
<tr>
<td>Standard deviation (%)</td>
<td>5.4</td>
<td>8.5</td>
<td>18.2</td>
</tr>
<tr>
<td>Limits of agreement (%)</td>
<td>-13 to 9</td>
<td>-15 to 19</td>
<td>-37 to 36</td>
</tr>
<tr>
<td>CCC (95% CI)</td>
<td>0.98 (0.96-0.99)</td>
<td>0.98 (0.97-0.99)</td>
<td>0.80 (0.58-0.91)</td>
</tr>
</tbody>
</table>

95% CI 95 percent confidence interval; CCC Lin’s concordance correlation coefficient; EDV end-diastolic volume; EF ejection fraction; ESV end-systolic volume; LV left ventricular; M mass; RV right ventricular.

Conclusion

There are significant differences in volume, mass and function between measurements in axial and short axis orientation. Consequently, slice orientation should be taken into account when evaluating serial CMRs. Intraobserver and interobserver reliability of RV stroke volume and ejection fraction was higher when using the axial slice orientation. Consequently we recommend the use of the axial slice orientation in patients with a systemic RV.
<table>
<thead>
<tr>
<th>Variable</th>
<th>RVEDV</th>
<th>RVESV</th>
<th>RVSV</th>
<th>RVEF</th>
<th>RVM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias (%)</td>
<td>-1.9</td>
<td>-0.9</td>
<td>2.1</td>
<td>2.2</td>
<td>-1.7</td>
</tr>
<tr>
<td>Standard deviation (%)</td>
<td>3.2</td>
<td>4.0</td>
<td>10.8</td>
<td>8.9</td>
<td>17.3</td>
</tr>
<tr>
<td>Limits of agreement (%)</td>
<td>-8 to 4</td>
<td>-9 to 7</td>
<td>-20 to 24</td>
<td>-16 to 20</td>
<td>-36 to 33</td>
</tr>
<tr>
<td>CCC (95% CI)</td>
<td>1.00 (0.99-1.00)</td>
<td>1.00 (0.99-1.00)</td>
<td>0.93 (0.86-0.97)</td>
<td>0.90 (0.79-0.96)</td>
<td>0.90 (0.78-0.96)</td>
</tr>
<tr>
<td><strong>Short-axis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference (%)</td>
<td>-3.2</td>
<td>-2.8</td>
<td>-2.9</td>
<td>-0.2</td>
<td>-4.8</td>
</tr>
<tr>
<td>Standard deviation (%)</td>
<td>4.5</td>
<td>6.5</td>
<td>18.8</td>
<td>15.7</td>
<td>11.4</td>
</tr>
<tr>
<td>Limits of agreement (%)</td>
<td>-12 to 6</td>
<td>10 to -16</td>
<td>-41 to 35</td>
<td>-32 to 31</td>
<td>-28 to 18</td>
</tr>
<tr>
<td>CCC (95% CI)</td>
<td>0.99 (0.97-0.99)</td>
<td>0.99 (0.98-1.00)</td>
<td>0.83 (0.67-0.92)</td>
<td>0.75 (0.50-0.89)</td>
<td>0.94 (0.87-0.97)</td>
</tr>
</tbody>
</table>

95% CI 95 percent confidence interval; CCC Lin’s concordance correlation coefficient; EDV end-diastolic volume; EF ejection fraction; ESV end-systolic volume; LV left ventricular; M mass; RV right ventricular.

Table 3.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RVEDV</th>
<th>RVESV</th>
<th>RVSV</th>
<th>RVEF</th>
<th>RVM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference (%)</td>
<td>0.1</td>
<td>0.3</td>
<td>1.4</td>
<td>1.5</td>
<td>19.2</td>
</tr>
<tr>
<td>Standard deviation (%)</td>
<td>7.2</td>
<td>10.9</td>
<td>12.3</td>
<td>12.0</td>
<td>35.8</td>
</tr>
<tr>
<td>Limits of agreement (%)</td>
<td>-14 to 15</td>
<td>-22 to 22</td>
<td>-23 to 26</td>
<td>-23 to 25</td>
<td>-52 to 91</td>
</tr>
<tr>
<td>CCC (95% CI)</td>
<td>0.98 (0.96-0.99)</td>
<td>0.98 (0.94-0.99)</td>
<td>0.90 (0.80-0.96)</td>
<td>0.86 (0.67-0.94)</td>
<td>0.71 (0.48-0.84)</td>
</tr>
<tr>
<td><strong>Short-axis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference (%)</td>
<td>-2.1</td>
<td>2.3</td>
<td>-0.4</td>
<td>1.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Standard deviation (%)</td>
<td>5.4</td>
<td>8.5</td>
<td>18.2</td>
<td>15.4</td>
<td>17.7</td>
</tr>
<tr>
<td>Limits of agreement (%)</td>
<td>-13 to 9</td>
<td>10 to 19</td>
<td>-37 to 36</td>
<td>-29 to 32</td>
<td>-29 to 42</td>
</tr>
<tr>
<td>CCC (95% CI)</td>
<td>0.98 (0.96-0.99)</td>
<td>0.98 (0.97-0.99)</td>
<td>0.80 (0.58-0.91)</td>
<td>0.72 (0.45-0.87)</td>
<td>0.88 (0.75-0.95)</td>
</tr>
</tbody>
</table>

95% CI 95 percent confidence interval; CCC Lin’s concordance correlation coefficient; EDV end-diastolic volume; EF ejection fraction; ESV end-systolic volume; LV left ventricular; M mass; RV right ventricular.

References


(11) 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;89:1077–81.


Is cardiac CT a reproducible alternative for cardiac MR in adult patients with a systemic right ventricle?

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c. Department of Radiology, Academic Medical Center, Amsterdam, the Netherlands.
d. Department of Paediatrics, Academic Medical Center, Amsterdam, the Netherlands.

Abstract

Objective: 20% of patients with a systemic right ventricle (RV) are pacemaker dependent, and unsuitable to undergo cardiac magnetic resonance (CMR). Multidetector row computed tomography (MDCT) could provide a reproducible alternative for CMR in these patients. The aim of this study was to compare variability of MDCT with CMR.

Methods: Thirty-five patients with systemic RV underwent either MDCT (n=15), or CMR (n=20). Systemic RV volumes, and ejection fraction were obtained, and intra- and interobserver variability for both modalities were assessed and compared.

Results: We found the intra-, and the interobserver variability of volumes and function measurements of the systemic RV obtained with MDCT to be higher compared to those obtained with CMR. However, these differences in variability were not significant, the only exception being the interobserver variability of systemic RV stroke volume.

Conclusions: MDCT provides a reproducible alternative for CMR for volumes and function assessment in patients with a systemic RV.
Introduction

Patients with a complete transposition of the great arteries (TGA) who had undergone an atrial switch operation in the past and patients with a congenitally corrected transposition of the great arteries (ccTGA) have a morphologic right ventricle (RV) supporting the systemic circulation. Due to improvements in the palliative cardiac surgery early in life, the number of adult patients with a systemic RV has increased dramatically over the past few decades.¹ Although long-term outcome in these patients is unknown, morbidity is worrisome, with tricuspid valve regurgitation, arrhythmias, and RV dysfunction being the main constituents.²;³ Reliable assessment of systemic RV volumes and function is important for clinical decision making, to follow-up therapeutic intervention, and to properly execute clinical research.⁴;⁵ Currently, cardiac magnetic resonance (CMR) is considered the gold standard for accurate and reproducible systemic RV volumes and function assessment.⁵;⁶ However, 20% of patients with a systemic RV are pacemaker or implantable cardioverter-defibrillator (ICD) dependent,⁷;⁸ and an increasing number of patients with a failing systemic RV benefits from cardiac resynchronization therapy.⁹ As most intracardiac devices are considered to be CMR incompatible, these patients are unsuitable to undergo CMR. Multidetector row computed tomography (MDCT) may provide a reliable alternative for CMR in these patients.

Although the accuracy of MDCT measurements of cardiac volumes and function is relatively well documented, no studies have been performed on the reproducibility of measurements.¹⁰;¹¹ Therefore, the objective of our study was to evaluate intra- and inter-observer variability of the right ventricular volumes and function measurements by MDCT, in comparison to CMR, in patients with a systemic RV.

Patients and methods

Patient characteristics

A cross-sectional prospective study was performed among 35 consecutive patients with a systemic RV, 23 patients with an atrially switched TGA, and 12 with a ccTGA. All patients had RV volumes and function evaluation either by CMR (n = 20; mean age = 35 ± 12 yrs) in patients without, or by MDCT (n =15; mean age = 32 ± 8 yrs) in patients with a pacemaker or ICD. The Human Research Committees of all participating institutions approved the study protocol, and the study protocol conforms the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients prior to participation in the study.
Image acquisition

For MDCT image acquisition, Contrast-enhanced retrospective electrocardiogram–gated MDCT was performed using Philips Brilliance-64 Computed Tomography scanner. All scans were obtained during breath-hold at the end of inspiration. Patients received 90 ml of a contrast medium (70 mL at a flow rate of 5.0 mL/s, followed by a 20 mL at a flow rate of 3.5 mL/s, and a 40 mL bolus of saline at a flow rate of 3.5 mL/s) containing 300 mg of iodine (Iomeron 300, Bracco Imaging SpA, Milan, Italy). No B-Blocker preparation was used. The scan was automatically commenced after contrast detection in the systemic RV. The contrast detection threshold was set at 150 Hounsfield Units. The rotation time was 0.4 sec, and the pitch factor was 0.2. The tube current was 600 MA, and the tube voltage was 120 kV, and the effective radiation dose per scan was around 14 mSv. Two-millimeter thick contiguous slices were reconstructed in 512 x 512 matrix using a 100 mm filed of view. The whole heart was covered within 60-80 slices per cardiac phase. Data in steps of 10% of R-R interval (ranging from 0% to 90% for each investigation) were obtained using a segmental reconstruction algorithm. From these axial images, multi-planar reformations in the short-axis orientation, with a slice-thickness of 6 mm, without slice gap, were done. This resulted in 12 to 15 short-axis slices, which were used for functional analysis.

CMR was performed using 1.5 Tesla scanner (Siemens Avanto, Erlangen, Germany), 2-, 4- chamber and short-axis views covering both ventricle from the base of the heart to the apex were acquired using a retrospective electrocardiogram-gated steady-state free precession sequence during breath holding at expiration. Short-axis view is consisting of 12 to 15 contiguous slices. Scan parameters were: repetition time = 3.2 - 3.8 ms; echo time = 1.6 - 1.9 ms; flip angle = 50 - 70°; slice thickness = 6 mm without slice gap; matrix = 160 x 256; field of view = 350 - 400 mm. Temporal resolution was approximately 25 ms. All the data were stored in DICOM format and transferred to a PC workstation running a MASS ® program.

Image analysis

For MDCT and CMR image analysis we used the MASS ® Analytical Software System (Medis, Leiden, The Netherlands). Cine loops were used to choose end-diastole and end-systole. End diastole was defined as the phase with the largest RV and left ventricular (LV) volume and end systole as the phase with the smallest RV and LV volume. The slices at the base of the heart were considered to be in the ventricle if the blood was at least half surrounded by ventricular myocardium. To optimize differentiation between ventricle and atria and vessels in the basal slices, using 2- and 4-chamber views simultaneously with short-axis views was possible only in the CMR group. Trabeculations and papillary muscles were considered part of the ventricular cavity.5 The sums of the traced contours in end diastole en end systole were used to calculate end diastolic volume and end systolic volume using a disc summation technique. End diastolic volumes and end systolic volumes
were used to calculate stroke volume and ejection fraction. Stroke volume was defined as end diastolic volume – end systolic volume, and ejection fraction as [(end diastolic volume – end systolic volume) / end diastolic volume] × 100%. All ventricular volumes were indexed for body surface area according to the Mosteller formula: (√ Height (cm) × weight (kg)/3600).

Contours were traced in total 3 times by 2 independent observers (M.W, S.R) The first observer analyzed all scans twice, with a minimal interval of 2 weeks between the first and second scan analysis, and blinded to the previous results. The second observer analyzed the scans once, blinded to the results of the first observer.

**Statistics**

For statistical analyses SPSS 16.0 (SPSS Inc., Chicago, Illinois) for Windows was used. P values < 0.05 were considered statistically significant. The descriptive data are presented as mean with standard deviation if normally distributed, or as median with range as appropriate. Intra- and interobserver measurement variability was determined from the mean values and the differences between the 2 measurements, and visualized with the methods and plots as described by Bland and Altman. The coefficient of variability (CV) was calculated as the standard deviation of the difference of the paired measurements divided by the mean of the average of the paired measurements, and expressed as a percentage. The statistical comparison of any differences in reproducibility of MDCT and CMR measurements was assessed with an extension of the Bland-Altman methods. Therefore, a log transformation of the squared differences between the 2 measurements was performed. If the squared difference was 0, we replaced the value by the next smallest value multiplied by 0.5, before log transformation. A 2-tailed unpaired t-test of the logged squared differences of MDCT versus CMR was performed thereafter.12

**Results**

**Patient characteristics**

A total of 35 adult patients (66% male, mean age 33.6 ± 10.7 years) with a systemic RV were included in the study, 23 patients with an atrially switched TGA, and 12 patients with a ccTGA.

CMR was performed in 20 patients, whereas 15 patients underwent MDCT due to implantation of pacemaker or ICD (14 patients with pacemakers, and 1 patient with an ICD). There were no statistically significant differences in age, type of TGA, and NYHA functional class between patients who underwent CMR and who underwent MDCT. All CMR and MDCT scans were undertaken without complications. Patient characteristics are summarized in **Table 1**.
Systemic RV volumes and function assessment

We found no statistically significant differences in intra-observer variability of end diastolic volume, end systolic volume, stroke volume and ejection fraction between measurements obtained by CMR, compared to MDCT. Moreover, we found no statistically significant differences in interobserver variability of end diastolic volume, end systolic volume, and ejection fraction between measurements obtained by CMR, compared to MDCT. However, CMR had a superior interobserver variability for stroke volume measurements compared to MDCT (12% variability with CMR vs. 32% variability with MDCT; P < 0.01), Figure 1. These differences were statistically non-significant, except for the interobserver variability for stroke volume measurements. However, the coefficient of variability was higher for all measurements performed with MDCT, except for the inter-observer variability of end systolic volumes (13% with CMR vs. 12% with MDCT; P = NS). Intra- and interobserver variability data are summarized in Table 2.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients* (n=35)</th>
<th>CMR* (n=20)</th>
<th>MDCT* (n=15)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.6 ± 10.7</td>
<td>34.8 ± 12.5</td>
<td>31.9 ± 8.0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Male</td>
<td>23 (66%)</td>
<td>16 (80%)</td>
<td>7 (47%)</td>
<td>0.05</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 ± 0.04</td>
<td>1.8 ± 0.2</td>
<td>1.9 ± 0.3</td>
<td>N.S.</td>
</tr>
<tr>
<td>Heart Rate (b/m)</td>
<td>71 ± 2</td>
<td>71 ± 16</td>
<td>70 ± 10</td>
<td>N.S.</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>77%</td>
<td>75%</td>
<td>80%</td>
<td>N.S.</td>
</tr>
<tr>
<td>II</td>
<td>14%</td>
<td>20%</td>
<td>7%</td>
<td>N.S.</td>
</tr>
<tr>
<td>III</td>
<td>9%</td>
<td>5%</td>
<td>13%</td>
<td>N.S.</td>
</tr>
<tr>
<td>IV</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Atrially switched TGA</td>
<td>23 (66%)</td>
<td>13 (65%)</td>
<td>10 (67%)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

* Data are mean value ± standard deviation, or as number of patients (percent). CMR = cardiovascular magnetic resonance; MDCT = multidetector rowcomputed tomography; TGA = transposition of the great arteries; p value indicates the difference between patients who underwent CMR vs. MDCT.

Figure 1. Bland-Altman plots depicting the intra- and interobserver variability between multidetector row computed tomography, and cardiac magnetic resonance. Bland-Altman plots demonstrating the intra-observer (left side), and inter-observer (right side) variability of right ventricular a). end diastolic volume, b). end systolic volume, c). stroke volume, and d). ejection fraction. On the X-axis the mean value of both measurements, and on the Y-axis the difference between measurements. The ▲ represent measurements performed with MDCT, the represents —— the mean of the differences between MDCT measurements. The ★ represent measurements performed with CMR, ——— the represent the mean of the differences between CMR measurements.
In the current study, we have shown for the first time that volumes and function measurement with MDCT is equally reproducible compared to assessment with CMR in patients with a systemic RV, and therefore provides an alternative for those patients who are unsuitable to undergo CMR.

In patients with normal cardiac anatomy MDCT is already considered to be a reliable alternative for CMR for biventricular volumes and function measurements.\(^1\,^0;^1^3\) However, the feasibility of routine use of MDCT in patients with a systemic RV cannot simply be extrapolated from these data, as the morphology of the systemic RV differs substantially from the subpulmonary RV. The complex geometric shape of the systemic RV, its extensive trabeculations and poor acoustic windows, make standard geometric assumptions impossible, and function assessment challenging.\(^1^4;^1^5\) Subsequently, quantitative assessment of the systemic RV with frequently used diagnostic modalities, such as echocardiography, is difficult.\(^1^6;^1^7\) MDCT, similar to CMR, has the ability to provide any desired imaging plane and does not rely on the geometric assumptions to calculate the RV volume. However, its role in patients with a systemic RV had not yet been established. The establishment of MDCT as a reproducible alternative for CMR is important, as 20% of patients with a systemic RV are pacemaker dependent, and an increasing number of patients are receiving cardiac resynchronization therapy or ICDs.\(^1^8\) Although data on CMR compatibility and safety of intra-cardiac devices remain limited and controversial, most

### Table 2. Intra- and inter-observer variability of measurements.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CMR (n=20)</th>
<th>MDCT (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Difference</td>
<td>CV</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>213</td>
<td>-7 ± 21</td>
<td>10%</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>139</td>
<td>-5 ± 18</td>
<td>13%</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>74</td>
<td>-2 ± 9</td>
<td>12%</td>
</tr>
<tr>
<td>EF (%)</td>
<td>36</td>
<td>-0,1 ± 3</td>
<td>8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CMR (n=20)</th>
<th>MDCT (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Difference</td>
<td>CV</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>212</td>
<td>-5 ± 13</td>
<td>6%</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>139</td>
<td>-4 ± 9</td>
<td>7%</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>74</td>
<td>-1 ± 7</td>
<td>9%</td>
</tr>
<tr>
<td>EF (%)</td>
<td>36</td>
<td>0 ± 2</td>
<td>6%</td>
</tr>
</tbody>
</table>

Data are mean values ± standard deviation of the average and the difference of the paired observations 
CV = coefficient of variability; EDV = end diastolic volume; EF = ejection fraction; ESV = end systolic volume; SV = stroke volume. P-value indicates difference in coefficient of variability between CMR and MDCT.

**Discussion**

In the current study, we have shown for the first time that volumes and function measurement with MDCT is equally reproducible compared to assessment with CMR in patients with a systemic RV, and therefore provides an alternative for those patients who are unsuitable to undergo CMR.

In patients with normal cardiac anatomy MDCT is already considered to be a reliable alternative for CMR for biventricular volumes and function measurements.\(^1^0;^1^3\) However, the feasibility of routine use of MDCT in patients with a systemic RV cannot simply be extrapolated from these data, as the morphology of the systemic RV differs substantially from the subpulmonary RV. The complex geometric shape of the systemic RV, its extensive trabeculations and poor acoustic windows, make standard geometric assumptions impossible, and function assessment challenging.\(^1^4;^1^5\) Subsequently, quantitative assessment of the systemic RV with frequently used diagnostic modalities, such as echocardiography, is difficult.\(^1^6;^1^7\) MDCT, similar to CMR, has the ability to provide any desired imaging plane and does not rely on the geometric assumptions to calculate the RV volume. However, its role in patients with a systemic RV had not yet been established. The establishment of MDCT as a reproducible alternative for CMR is important, as 20% of patients with a systemic RV are pacemaker dependent, and an increasing number of patients are receiving cardiac resynchronization therapy or ICDs.\(^1^8\) Although data on CMR compatibility and safety of intra-cardiac devices remain limited and controversial, most
intra-cardiac devices are currently considered to be CMR incompatible. One study reports encouraging results on device safety when scanning patients with certain devices, if the right precautions are taken. However, others have described a variety of mechanisms by which CMR could affect pacemaker- and ICD- function. The magnetic forces could attract and displace the pacemakers and ICDs, and could lead to “reed switch activation” in sporadic cases. Moreover, radiofrequent energy could cause heating of the intra-cardiac leads.

In summary, whether scanning patients with pacemakers and ICD is contraindicated remains disputable, as contraindications are predominantly theoretical, and clinical data are limited. To obtain valid and accurate information on CMR compatibility and safety of intra-cardiac devices further research is warranted.

There are several restrictions that should be taken into account before MDCT is performed. Firstly, we found remarkable differences in reproducibility between MDCT and CMR, although they were not statistically significant. These differences are most likely due to the differences in image acquisition and image analysis between the 2 modalities. In MDCT temporal resolution remains limited in comparison with CMR, making MDCT more sensitive to cardiac motion and making the definition of end systolic and end diastolic time points less precise. Using beta-blockers medication to lower a patient’s heart rate partially overcomes this problem, but is not desirable as this could change functional parameters. On the other hand, MDCT provides an excellent spatial resolution which, in combination with the administered contrast, enhances differentiation between blood and myocardium.

The lower reproducibility of MDCT parameters could also be due to differences in image analysis between MDCT and CMR. Although the protocol we used to draw contours was the same in the CMR group as in the MDCT group, the analytical software could provide us with 4-and 2-chamber views simultaneous with the short-axis view in the CMR group but not in MDCT group. This made differentiation between ventricles, atria and vessels in the basal slices challenging in MDCT group.

Another important difference with CMR is patients’ exposure to radiation and contrast agents during MDCT. Although the effective radiation dose per scan was around 14 mSv in our study, effective radiation doses of up to 32 mSv per scan have been reported. The possible impact of this large quantity of radiation should not be taken lightly. Einstein et al. and Hurwitz et al. have reported that MDCT derived coronary angiography, with an effective radiation dose ranging from 12 to 32 mSv, causes a significant increase in risk of both lung and breast cancer, especially in younger and female patients. There are strategies by which radiation dose can be reduced, without reducing image quality to an unacceptable level; patients should only be scanned when they have a stable sinus rhythm, tube voltage can be lowered to 100 or 80 kV in the small patients or the children, ECG-controlled tube current modulation can be used, and the scan volume should be accurately specified prior to scanning. Beside radiation, the administered contrast agent imposes a risk factor for patients undergoing MDCT. The risk of contrast-induced
nephropathy is significant, especially in patients with risk factors, such as pre-existing renal function impairment or diabetes mellitus. The risk of contrast-induced nephropathy can be reduced by prophylactic pre-hydration, but proper risk assessment of all patients prior to MDCT remains of key importance. However, reticence and thorough patient selection remain key to avoid any unnecessary exposure to radiation or contrast agents.

As with most studies on MDCT or CMR in patients with congenital heart diseases, our study is limited by a relatively small number of patients. Moreover, we compared two different groups of patients: those who underwent CMR and those who underwent MDCT. However, we found no differences in characteristics between patients who underwent CMR, compared to those who underwent MDCT, except for sex distribution. All patients who underwent MDCT were unsuitable to undergo CMR due to the presence of intra-cardiac devices. We could have performed MDCT in patients without intra-cardiac devices to overcome this limitation, but chose not to unnecessarily expose these young patients to radiation and contrast agents.

Conclusions

Multidetector row computed tomography provides a reproducible alternative for cardiovascular magnetic resonance for ventricular volumes and function assessment in patients with a systemic right ventricle, although larger variability between measurements should be taken into account. Patient selection should be restrictive, to avoid unnecessary exposure to radiation and contrast agents.


(19) Naehle CP, Kreuz J, Strach K et al. Safety, feasibility, and diagnostic value of cardiac magnetic resonance imaging in patients with cardiac pacemakers and implantable cardioverters/defibrillators at 1.5 T. Am Heart J 2011;161:1096-1105.


Comparison of Contrast Enhanced Magnetic Resonance Angiography with Invasive Cardiac Catheterization for evaluation of Children with Pulmonary Atresia

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Departments of: Cardiology, Tanta University Hospital, Tanta, Egypt (a), Cardiology, Academic Medical Center, Amsterdam, The Netherlands (b), Pediatric Cardiology, Leiden Medical University Center, Leiden, The Netherlands (c), Radiology, Mansoura University Hospital, Egypt (d), Pediatric Cardiology, Mansoura Children University Hospital, Egypt (e), Cardiology, Marshfield Clinic, Marshfield, WI (f)

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Abstract

**Objective:** Complete assessment of the source of pulmonary blood supply and delineation of the anatomy of pulmonary arteries are essential for management and prognostic evaluation of pulmonary atresia (PA) patients. Invasive cardiac catheterization is considered the gold standard imaging modality to achieve this. We investigated the role of contrast enhanced magnetic resonance angiography (MRA) to evaluate the pulmonary blood supply and the anatomy of the pulmonary arteries and compared with cardiac catheterization in children with PA.

**Methods:** We studied 20 children with PA. Median age was 2.5 years (range, 6 months - 13 years). All patients were examined with cardiac catheterization and contrast enhanced MRA, and the results of both modalities were compared.

**Results:** There was a complete agreement between both modalities in detection of the main pulmonary artery morphology and determination of the confluence state of the central pulmonary arteries. There was an 88% agreement for patency of the ductus arteriosus, and 66% for patency of the surgically placed shunt. There was a complete agreement between both techniques on determining the presence of collaterals larger than 2.5 mm. Twenty-eight collaterals smaller than 2.5 mm were detected only by contrast enhanced MRA. There was a strong correlation between both modalities in measuring the pulmonary arteries and collaterals diameters (P < 0.001).

**Conclusion:** Contrast enhanced MRA is a safe and accurate non-invasive technique to evaluate the pulmonary artery morphology and the sources of pulmonary blood supply in children with PA.
Introduction

Pulmonary atresia (PA) is defined as a complete obstruction between the right ventricle (RV) and the pulmonary artery with developmental abnormalities of the pulmonary valve or pulmonary arterial tree.\(^1\) Two anatomical “classification” have been identified: pulmonary atresia with ventricular septal defect (PAVSD) and pulmonary atresia with intact ventricular septum (PAIVS).\(^2\);\(^3\) The central pulmonary arteries may be hypoplastic, discontinuous, or entirely absent. The pulmonary vascular bed receives a blood supply from different sources, such as patent ductus arteriosus (PDA), systemic to pulmonary collaterals, or surgically placed shunts.

Complete assessment of the pulmonary blood supply source and accurate delineation of the morphology of the pulmonary arteries are essential for both optimal management and prognostic evaluation of patients with PA.\(^4\) Traditionally, cardiac catheterization is considered the gold standard method to achieve this. However, cardiac catheterization is invasive and involves radiation exposure and, therefore, serial investigations can be problematic.\(^5\);\(^6\) Echocardiography is of limited value in this group of patients due to the poor visualization of vascular structures outside the mediastinum with both a transthoracic and a trans-esophageal approach.\(^6\);\(^7\);\(^8\) The use of cardiac magnetic resonance imaging in complex congenital heart diseases is on the increase. The role of the contrast enhanced magnetic resonance angiography (MRA) in accurate delineation of complex pulmonary artery anatomy and evaluation of the pulmonary blood supply source in adult patients with PA has been previously reported.\(^9\);\(^10\);\(^11\) However, data on the efficacy and safety of the contrast enhanced MRA in children with PA are still limited. Pediatric patients often represent a special challenge for acquisition of arterial phase datasets because the children vary widely in size, circulation time and ability to cooperate. The aim of this study is to evaluate the role of contrast enhanced MRA, as compared to the cardiac catheterization, in the evaluation of the anatomy of the central pulmonary arteries and the pulmonary blood supply in children with PA.

Patients and methods

There were 12 male and 8 females. Median age was 2.5 years (range, 6 months - 13 years). Eleven patients were younger than 2 years old, 10 patients weighed less than 10 kg. Sixteen patients had PAVSD, 2 patients had PAIVS and 2 patients had complex coronary heart disease (CHD) with atretic PA. Five patients had had previous surgical interventions; 4 had modified Blalock-Taussig (MBT) shunts and one patient had left-sided pulmonary unifocalization. Patients were prospectively recruited from Manasoura Children’s University Hospital, Egypt, from November 2004 till March 2008. The local medical ethics committee approved the study. Informed consent was obtained from all parents before enrolment. Twenty-five eligible children were identified through the database of the pediatric
cardiology department. Five patients were not enrolled; 4 had over NYHA class II and one patient’s family did not agree for the child to take part. Diagnosis was established by transthoracic echocardiography (Hewlett Packard, Philips Medical Systems, Best, The Netherlands.). All patients underwent cardiac catheterization followed by magnetic resonance imaging (MRI) examination within one week. No clinical events occurred during that interval.

Cardiac catheterization

Cardiac catheterization was performed on biplane catheter (System Philips Medical Systems, Best, The Netherlands). Contrast angiography was used and directed towards evaluation of the anatomy of pulmonary arteries and the source of pulmonary blood supply. Evaluation included upper descending aortography, right ventriculography, pulmonary vein wedge angiography, and selective injections in the surgical placed shunt and/or the collaterals. In each patient, the morphology and the size of MPA, LPA, RPA, the collaterals and the source of the pulmonary blood supply were evaluated.

Magnetic Resonance imaging

MRI was performed on 1.5 T MR scanner (Siemens Magnetom, Siemens Medical systems, Germany). A cardiac-phased array radiofrequency coil was used in patients weighting more than 10 kilograms. A head or surface coil was used in those with a body weight less than 10 kilograms. Young patients (under the age of 8 years) were sedated with chloral hydrate (100 mg/kg, maximum dose less than 2 g). Patients were monitored by pulse oximetry, electocardiogram, and closed circuit television. MRI examination includes HASTE (half Fourier acquisition single-shot turbo spin echo) sequence that was used to define the cardiac anatomy and to guide contrast enhanced MRA planning.

1- HASTE: Scan parameters: repetition time (TR) = the R-R cycle length; echo time (TE) = 15 - 26 ms; flip angle (FA) = 90°; matrix = 256 x 192; field of view (FOV) = 200 - 400 mm; number of signal averages = 2; slice thickness = 5 - 7 mm without slice gap. HASTE sequences were obtained in 3 orthogonal planes: transverse, sagittal and coronal.

2- Contrast enhanced MRA: A non ECG- triggered 3-dimensions spoiled gradient echo pulse sequence was used. Scan parameters: TR = 5.6 - 6.8 ms; TE = 1.18 - 1.7 ms; FA = 45°; number of signal averages = 1; FOV = 300 - 400 mm; matrix = 256 x 126; slice thickness = 1.2 – 1.5 mm; acquisition time = 18 - 20 seconds. MRA scanned in a coronal view from posterior (the spinal canal) to anterior (the ascending aorta). Gadopentetate dimeglumine contrast (0.2 mL/kg) was injected via a peripheral intravenous line either by hand (in patients weighting under 10 kilograms), or by a power injector at rates ranging from 3 - 5 mL/sec (in patients weighting over 10 kilograms). The time delay between the start of contrast injection and data acquisition was determined by the “best estimate” method and ranged between 6 - 8 seconds. MRA was reconstructed using 3-dimensional reformatting.
methods: multi-planer reformatting, maximum intensity projection, and 3-dimensional surface shading. In each patient the morphology and the size of MPA, LPA, RPA, the collaterals and the source of the pulmonary blood supply were evaluated.

**Post processing of images**

Cardiac catheterization and contrast enhanced MRA images were compared for the qualitative and the quantitative assessment of the anatomy of the pulmonary arteries and the source of pulmonary blood supply. For the qualitative assessment, the morphology of MPA and central pulmonary arteries, LPA and RPA was evaluated. The arteries were classified as atretic (luminal discontinuity), hypoplastic (diameter of the pulmonary vessel less than 60% of aorta diameter) or stenotic (discrete narrowing of the artery diameter with the distal part 40% less than the proximal part).\(^\text{12}\) The source of the pulmonary blood supply was determined by identification of PDA, surgically placed shunts or collaterals. To facilitate comparison between both modalities, the collaterals were labeled numerically according to their order of origin from the descending aorta or aortic arch vessels. For the quantitative assessment, the smallest caliber of the pulmonary arteries (MPA, LPA, and RPA) and the collaterals was measured. MPA was measured when it crossed posterior to the ascending aorta. The diameter of the distal portion of LPA and RPA was measured just before the takeoff of the first upper lobe branch. LPA was measured when it crossed the left main stem bronchus to avoid over-estimated measurement. Imbalance of growth is considered when the difference between distal LPA and RPA is more than 30%. The collaterals smaller than 2.5 mm were considered to be small collaterals and the collaterals larger than 2.5 mm were considered to be major collaterals.\(^\text{13}\)

Cardiac catheterization results were analyzed by H.A. (with 21 years experience with CHD) who ha not been informed of the results of the contrast enhanced MRA. The analysis of CMR/MRA was performed by A.A. and S.R (14 and 4 years experience with CMR, respectively) who had not been informed of the angiographic results.

**Statistical analysis**

All statistical testing and data analysis were performed with SPSS version 16 (SPSS Inc, Chicago, and III). Parametric data are expressed as mean ± SD, unless stated otherwise. The agreement between both modalities on the qualitative assessment was analyzed by calculating Kappa. Kappa < 0.4 is a poor concordance, Kappa between 0.4 to 0.75 is a moderate concordance, and Kappa between 0.76 to 1 is a strong concordance.\(^\text{14}\)

The agreement between both modalities on the quantitative evaluation was analyzed by calculating the mean difference ± SD as described by Bland and Altman and interclass correlation (ICC). ICC < 0.4 is a poor concordance, ICC between 0.4 to 0.75 is a moderate concordance, and ICC between 0.76 to 1 is a strong concordance.\(^\text{15}\) P < 0.05 was considered statistically significant.
Chapter 9

Results

All patients underwent cardiac catheterization with no adverse effect. Also, all patients underwent contrast enhanced MRA with no adverse effect. In particular, none of patients has change in the vital signs during examination. Only minor adverse effects have been observed; headache in 2 patients (10%) and nausea occurs in 3 patients (15%). These all resolved spontaneously and no treatment was required.

The morphology of MPA, LPA, RPA, and the collaterals

MPA was atretic in 7 patients, hypoplastic in 10 patients and absent in 3 patients. There was a complete agreement (Kappa = 1) between both modalities in delineation of MPA anatomy. Both modalities were also concordant (Kappa = 1) in defining the central pulmonary arteries as confluent in 15 patients, non-confluent in 4 patients, and absent in one patient. Kappa was 0.9 for the agreement between both modalities for PDA evaluation. There was a disagreement between both modalities in one of 3 patients with PDA: contrast enhanced MRA was not able to detect the presence of PDA while it was detected by the cardiac catheterization. Kappa was 0.7 for the agreement between both modalities in determining MBT shunts patency. There was a disagreement between both modalities in one of 4 patients with MBT shunt: the MBT shunt was found to be occluded by the cardiac catheterization while it was totally missed by contrast enhanced MRA. Figure 1 shows the agreement percentage between both modalities for the qualitative assessment.

![Figure 1](attachment:figure1.png)

**Figure 1:** Agreement of the qualitative assessment between the cardiac catheterization and contrast enhanced MRA. MPA= main pulmonary artery, CPA= central pulmonary artery, and PDA= patent ductus arteriosus.
Fifty-eight collaterals were detected by contrast enhanced MRA. Cardiac catheterization detected only 30 collaterals; therefore, overall Kappa was 0.6. All the 28 collaterals that were detected only by contrast enhanced MRA were smaller than 2.5 mm, i.e. small collaterals. (Figures 2 and 3)

For the 30 collaterals that were detected by both modalities, there was a complete agreement in visualization of the origin of the collaterals: 19 collaterals were described as

Figure 2: Comparison between both methods in evaluating a systemic to pulmonary artery collateral in a case of pulmonary atresia with ventricular septum defect. (A): Antero-posterior view of selective injection in the collateral demonstrating a direct collateral to the right lung taking origin from the upper part of descending aorta. (B): Antero-posterior view of 3-dimensional surface shading reconstruction of contrast enhanced magnetic resonance angiography demonstrating the same information. (Arrows show the collateral).

Figure 3: Three-dimensional surface shading of contrast enhanced magnetic resonance angiography demonstrating a large indirect collateral taking origin from the left subclavian artery going beneath the aortic arch to supply the right lung (solid arrow), giving small collaterals (< 2.5 mm) to the upper lobe of left lung (dashed arrow).
direct collaterals (taking origin from the descending aorta), 11 collaterals were described as indirect collaterals (5 collaterals taking origin from the right subclavian artery, 4 collaterals taking origin from the left subclavian artery, and 2 collaterals taking origin from the innominate artery). The Kappa was 0.9 for the agreement between both modalities for visualization of the collateral insertions. There was disagreement in visualization of 2 collateral insertions. By cardiac catheterization, the insertion point of the first collateral was diffuse to the entire right lung while by contrast enhanced MRA it was localized in the upper lobe of right lung. By cardiac catheterization, the insertion point of the second collateral was diffuse to the middle and lower lobe of right lung while by contrast enhanced MRA was more localized to the middle lobe.

The size of the LPA, RPA, and collaterals

Diameters of MPA, LPA, RPA and the collaterals are shown in Table 1. Bland-Altman analysis revealed no significant difference between both methods in measuring these diameters. (Figure 4)

### Table 1: Comparison between cardiac catheterization and contrast enhanced MRA measurement of the pulmonary arteries and the collaterals.

<table>
<thead>
<tr>
<th></th>
<th>Invasive Catheterization</th>
<th>Contrast enhanced MRA</th>
<th>ICC %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pulmonary artery</td>
<td>3.0 ± 2.4 mm</td>
<td>2.8 ± 2.5 mm</td>
<td>96</td>
</tr>
<tr>
<td>Left pulmonary artery</td>
<td>3.9 ± 1.6 mm</td>
<td>3.6 ± 1.7 mm</td>
<td>80</td>
</tr>
<tr>
<td>Right pulmonary artery</td>
<td>4.5 ± 1.6 mm</td>
<td>4.2 ± 1.9 mm</td>
<td>85</td>
</tr>
<tr>
<td>Collaterals</td>
<td>1.7 ± 0.7 mm</td>
<td>1.8 ± 0.7 mm</td>
<td>88</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. ICC = inter-class correlation.

### Discussion

The present study showed that contrast enhanced MRA is a safe and effective method that permits a rapid high-resolution imaging modality for complete assessment of the pulmonary blood supply and accurate delineation of the anatomy of the pulmonary arteries in children with PA. The large field of view and rapid data acquisition in one breath-hold after a single injection into a peripheral vein mean that a full delineation of the anatomy with the entire course of the collateral by using contrast enhanced MRA. There was a strong agreement between contrast enhanced MRA and the cardiac catheterization in measuring the diameter of pulmonary arteries and the collaterals. There was a complete agreement between both methods in delineation of MPA morphology and determining of the confluence state of the central pulmonary arteries. For the patency of PDA and
MBT shunt, there was an agreement in all cases except 2. PDA in one patient and MBT shunt in another patient were missed by contrast enhanced MRA, while they were clearly detected by the cardiac catheterization; this was probably due to incorrect timing of the contrast peak due to the jerky movements of the children during the contrast injection, even though they were sedated.

Optimal contrast timing in children is a problematic issue. A “Bolus track” technique was considered a reliable approach to ensure the acquisition of arterial phase and highly reproducible contrast enhanced MRA results in the pediatric population. However “Bolus track” requires greater operator expertise than the “best estimate” method that used in our study.

This study demonstrated the ability of contrast enhanced MRA to detect the small collaterals (< 2.5 mm) which were not completely detected by invasive cardiac catheterization. Contrast enhanced MRA offers a better spatial resolution and a good signal to noise ratio, so that vessels as small as 0.5 mm with a slow flow and the intra-parenchymal pulmonary vessels can be visualized. Detecting the small collaterals is of great clinical importance to avoid or to identify the possibility of having a bloody surgical filed.

**Figure 4:** Comparison between cardiac catheterization and contrast enhanced magnetic resonance angiography measurements of the pulmonary artery and branches diameter by the Bland Altman test. (A) Main pulmonary artery (MPA). (B): Left pulmonary artery (LPA). (C): Right pulmonary artery (RPA). (D): Collaterals.
Our results show that contrast enhanced MRA was a reliable non-invasive imaging modality to define pulmonary arteries and pulmonary blood supply. These results agree with pervious reports that compare contrast enhanced MRA with cardiac catheterization for assessment of the pulmonary artery anatomy and the pulmonary blood supply in Tetralogy of Fallot patients and PA patients.\textsuperscript{9-11} However, the median age in these studies was 28 years,\textsuperscript{9} 4.7 years,\textsuperscript{11} and a range of 3-30 years,\textsuperscript{10} respectively. Our patients were much younger, median age was 2.5 years (range; 6 months - 13 years). Our results suggest that contrast enhanced MRA can be used safely and effectively in children with PA.

\section*{Study limitations}

The present study had some limitations. The sample size was small; the contrast enhanced MRA sequence was not able to delineate the peripheral branches of the pulmonary arteries, beyond the 3\textsuperscript{rd} or 4\textsuperscript{th} generation. Also, the present study did not include the other MRI sequences that may be useful during a comprehensive examination of this group of patients, such as phase velocity cine MRI that can quantify blood flow, or fast gradient echo sequences that can measure ventricular volume, function and mass.

\section*{Conclusion}

Contrast enhanced MRA is a safe and accurate non-invasive technique to evaluate the pulmonary artery morphology and the sources of pulmonary blood supply in children with PA. Its high special resolution and 3-dimensional properties allow the course of collaterals and detection of the small sized collaterals to be better evaluated.
Reference List


Impaired cardiac reserve in asymptomatic patients with moderate pulmonary restenosis late after relief of severe pulmonary stenosis: evidence for diastolic dysfunction

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Abstract

Objective: Proof of concept study evaluating cardiac magnetic resonance (CMR) as screening tool for chronic thromboembolic pulmonary hypertension (CTEPH) in patients treated for acute pulmonary embolism (PE).

Methods: Right and left ventricular function of 15 consecutive patients treated for PE and 10 consecutive patients in whom PE was excluded was estimated at baseline by cardiac multi-detector row computed tomography (MDCT) and at 6 months follow-up by CMR. Additionally, during the follow-up visit, pulmonary artery (PA) hemodynamics were studied by CMR and the presence of pulmonary hypertension by echocardiography.

Results: CT measured right ventricular ejection fraction (RVEF) was lower in patients with PE compared to patients without PE at time of diagnosis (median 47%, interquartile range, 39-53 vs. 55%, 52-58; P = 0.014). After 6 months follow up, the RVEF between patients treated for PE and patients without PE were not statistically significant different (55%, 52-60 versus 54%, 51-57; P = 0.57), as were distensibility index (0.18 ± 0.18 versus 0.25 ± 0.18, P = 0.20), mean velocity (14.1 ± 3.9 cm/s versus 14.0 ± 2.5 cm/s, P = 0.81), peak velocity (86.5 ± 22 cm/s versus 89.6 ± 13 cm/s, P = 0.43) and time to peak PA blood flow velocity (142 ± 49 ms versus 161 ± 29 ms, P = 0.14). One patient was diagnosed with CTEPH and CMR revealed poor right systolic function, decreased PA distensibility and flow velocity, and a systolic notch in the PA flow profile consistent with persistent PA obstruction.

Conclusion: In this small series, right ventricular performance and PA flow profiles of patients treated for 6 months after PE are equivalent to those parameters in normal patients.
Chapter 10

Introduction

Acute right ventricular (RV) dysfunction associated with pulmonary embolism (PE), which can both be evaluated by multi-detector row CT, is caused by increased tension in the RV wall and may lead to RV dilatation and ischemia. The natural history of RV recovery after acute PE is largely unknown. Persistent RV dysfunction after PE might be a predictor of chronic thromboembolic pulmonary hypertension (CTEPH), a rare but serious long-term clinical complication of PE. Because the underlying pathophysiological mechanism leading to CTEPH is not fully established and its clinical presentation is not specific, the early identification of patients with CTEPH is very difficult. Consequently, the majority of CTEPH patients present with more advanced stage disease. The reference standard for diagnosing pulmonary hypertension is right heart catheterization. Currently, the most widely used non-invasive screening tool for pulmonary hypertension is echocardiography, although it has been shown that Doppler echocardiography may frequently be inaccurate in estimating pulmonary artery (PA) pressure and cardiac output in patients being evaluated for pulmonary hypertension. Cardiac magnetic resonance (CMR) is a non-invasive modality for evaluating pulmonary hypertension by evaluation of left and right systolic and diastolic function as well as by quantification of PA distensibility and pulmonary flow dynamics. CMR measured pulmonary flow dynamics are altered in acute PE as well as in pulmonary hypertension, and have been shown to correlate closely with invasive assessment of cardiac hemodynamic function and clinical outcome in patients with pulmonary hypertension. Especially PA distensibility has been suggested to be a sensitive (sensitivity 83%) and specific (specificity 82%) marker for pulmonary hypertension, even in early or mild clinical stages. We hypothesized that the pulmonary flow dynamics would restore to normal after 6 months of treatment following acute PE and therefore would not be different from patients without PE, except for those patients who develop CTEPH who will show decreased distensibility and flow velocity in the PA. Following this, flow profile analysis of the PA in the clinical follow-up of patients with acute PE might be a helpful screening tool for CTEPH. Accordingly, we performed a proof of concept study to evaluate PA hemodynamics and distensibility at 6 months follow-up in consecutive patients with PE, and in patients in whom PE was clinically suspected but ruled out as a control cohort.

Materials and methods

Patients

Since this was a proof of concept study to evaluate the restoration of PA hemodynamics, we aimed at studying 15 consecutive patients treated for and 10 consecutive patients...
in whom PE was ruled out. Consecutive, hemodynamically stable in- and outpatients suspected of acute PE were eligible. All patients underwent multi-detector row computed tomography (MDCT) of the chest to establish or rule out acute PE as described by Huisman et al.\textsuperscript{11} The presence of PE was defined as at least one filling defect in the \textit{PA} tree. Furthermore, in all patients, a separate image acquisition using retrospective electrocardiogram-gated dynamic cardiac MDCT was performed to assess RV and left ventricular (LV) function. All scans were performed according to a standardized protocol, described previously by Dogan et al in full detail.\textsuperscript{2} Scan parameters were: tube voltage 120 kV and tube current 200 mA. The optimal pitch factor and rotation time were automatically established to obtain optimal temporal resolution. Images for functional analysis were reconstructed in 20 cardiac phases by using a segmental reconstruction algorithm. The entire heart from aortic root to cardiac apex was covered within the reconstructed sections per cardiac phase point. The reconstructed volumes were transferred to a dedicated workstation running on Linux software.

Electrocardiogram-gated MDCT has been shown to be a reliable method to assess ventricular volumes and ejection fraction and can be combined with computed tomography pulmonary angiography to establish the diagnosis of PE.\textsuperscript{2,11-14} Finally, the severity of the pulmonary obstruction was measured following the method described by Qanadli and colleagues.\textsuperscript{15} Patients with confirmed PE were initially treated with therapeutic unfractioned or low-molecular-weight heparin, followed by vitamin K antagonists for 6 months.\textsuperscript{16} Study participants were excluded if they had a contraindication for CMR scanning, e.g. pregnancy, aneurysm clip in the brain, implanted neural stimulator, implanted cardiac pacemaker or defibrillator, or severe claustrophobia. The study was approved by an institutional review board and all participants consented to participation.

\textbf{Follow-up CMR}

After 6 months following initial presentation, CMR examinations were performed using a 1.5T CMR scanner (Intera, Philips Medical Systems, Best, the Netherlands). We used a 5-element phased-array cardiac coil placed on the chest for signal reception. First, a stack of 14-18 transverse slices (dependent on the size of the heart) was achieved during breath holding at end-expiration and by using a steady-state free-precession sequence for biventricular volume measurements. We used the following scan parameters: slice thickness = 10 mm with no gap, field of view = 450 mm (80% rectangular), scan matrix = 256 × 195, with reconstructed voxels of 1.37 × 1.37 × 8.0 mm, flip angle = 35°, repetition time (TR) = 3.2 ms and echo time (TE) = 1.6 ms. We utilized gated cardiac synchronization (30 reconstructed phases per cardiac cycle, temporal resolution 20-35 ms) and parallel imaging (Sensitivity encoding SENSE, sense factor 2). Using the MASS
software package, we drew the endocardial contours at end-systole and end-diastole manually. Second, the main pulmonary artery flow curve was obtained using velocity-encoded (VE) CMR, planned perpendicular to the pulmonary artery. The VE CMR acquisition was performed during breath holding, with the acquisition plane planned perpendicular to the pulmonary trunk distal to the pulmonary valve. Scan parameters: slice thickness = 8 mm; field of view = 300 mm (85% rectangular), scan matrix = 128 × 108, with reconstructed voxels = 1.17 × 1.17 × 8.0 mm, flip angle = 20°, TR/TE = 9.3 ms/6.1 ms, 2 signal averages, VENC = 100 cm/s with echo planar imaging (EPI) factor 7. PA time to peak velocity, peak velocity and mean velocity were assessed. PA contours were semi-automatically drawn using the FLOW ® software package (FLOW software package; Medis, Leiden, The Netherlands). Distensibility index [(Area max (systole) - Area min (diastole))/(Area min)] was determined from the lumen area measurements of the PA at the moment of maximal flow and at the moment of the isovolumetric contraction. Two gated acquisitions were performed to obtain the maximal and minimal luminal areas, using steady-state free precession sequences with a field of view = 220 mm, voxel size = 1.25 × 1.25 × 6.00 mm, flip angle = 50°; TR/TE = 3.2/1.2 and a gate width = 34.2 ms. The gate delay was accordingly set so that the middle of the acquisition window equals the moment of maximal flow or the moment of isovolumetric contraction, respectively. Also, in order to correct for through-plane motion of the acquisition plane, the location and angulation of this plane were manually adjusted on both orthogonal cine views of the right ventricular outflow tract, specifically on the two phases of the cardiac cycle nearest to the chosen gate delays as described by Grotenhuis et al.17 All contours were drawn by one observer (2 years experience with CMR) supervised by a radiologist (11 years experience with CMR) who were both blinded for the patients’ condition.

Echocardiography
To evaluate the presence of pulmonary hypertension in the study patients, all underwent transthoracic echocardiography after the CMR was performed. Echocardiography included cross sectional, M-mode and Doppler studies, and was performed by an experienced technician according to a standardized protocol. In case of suspected pulmonary hypertension (1) maximal tricuspid regurgitation velocity > 2.8 m/s, 2) estimated systolic PA pressure ≥ 35 mmHg, 3) estimated mean PA pressure ≥ 25 mmHg 4) borderline value of criterion 1 or 2 in combination with a RV TEI index > 0.36) or other echocardiographic abnormalities and if clinically indicated, further diagnostic work-up was performed under supervision of an independent expert panel. Criteria for the diagnosis of CTEPH were mean pulmonary artery pressures assessed by right heart catheterization exceeding 25 mmHg respectively and normal pulmonary capillary
wedge pressure in combination with an abnormal perfusion scintigram and signs for distal or central CTEPH on conventional pulmonary angiography.  

### Statistical analysis

Differences in baseline characteristics and CMR measurements between patients with and without PE were sought for using the Student’s *t*-test in case of normal distribution or else the Mann-Whitney U test for pairwise comparisons. Variables that were normally distributed are presented as mean and standard deviation, variables with skewed distribution as medians and inter-quartile range. The presence of normal distribution was tested using the Kolmogorov-Smirnov test. Finally, we compared the CMR test results of patients with to those without pulmonary hypertension. P-values < 0.05 were considered significant.

### Results

#### Study patients

To achieve our sample size goal, we followed 27 consecutive patients with acute PE and 15 consecutive patients in whom PE was ruled out. From these patients, 3 had died during the 6 months follow-up period and 14 were excluded because of implanted cardiac pacemaker, unwillingness to cooperate or claustrophobia, leaving 15 patients diagnosed with and 10 patients without PE for analysis. The demographic characteristics of the 2 patient cohorts were comparable (Table 1); overall mean age was 53 ± 11 years and 14 (60%) of the patients were of male gender. The distribution of cardiopulmonary comorbidity was comparable as well. None of the patients without PE had a history of venous thrombosis.

#### Table 1: Baseline characteristics of study patients

<table>
<thead>
<tr>
<th></th>
<th>PE patients (n = 10)</th>
<th>Patients without PE (n = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ([years] mean, ± SD)</td>
<td>53 ± 10</td>
<td>52 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Female gender (n, %)</td>
<td>7 (47)</td>
<td>7 (70)</td>
<td>NS</td>
</tr>
<tr>
<td>History of venous thrombosis (n, %)</td>
<td>6 (40)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>COPD (n, %)</td>
<td>3 (20)</td>
<td>2 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-existent left heart failure (n, %)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Qanadli score (median, IC range)</td>
<td>15 (2-26)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Right ventricular ejection fraction by CT (%; median, IC range)</td>
<td>47 (39-53)</td>
<td>55 (52-58)</td>
<td>0.014</td>
</tr>
<tr>
<td>Left ventricular ejection fraction by CT (%; median, IC range)</td>
<td>54 (31-63)</td>
<td>60 (55-65)</td>
<td>0.038</td>
</tr>
<tr>
<td>Follow-up duration (days; mean, ± SD)</td>
<td>226 ± 42</td>
<td>202 ± 36</td>
<td>NS</td>
</tr>
</tbody>
</table>

PE = pulmonary embolism, n = number, SD = standard deviation, NA = not applicable, IC = interquartile.
or developed venous thrombosis during the 6 months follow-up period. Median follow-up duration of the overall population was 205 days (range, 165-301 days), and was not different between the two study cohorts. (Table 1)

The median Qanadli score of the patients with PE was 15 with a range of 2 to 26. (Table 1) The systolic performance of both the RV and LV of the patients with PE was significantly impaired compared to the control patients without PE: median RV ejection fraction 47% (39-53%) versus 55 (52-58%; P = 0.014) and mean LV ejection fraction 54.1 ± 8.2% versus 60.1 ± 3.5% (P = 0.038) for patients with and without PE respectively.

Figure 1: Distribution of right and left ventricular ejection fraction, distensibility index and flow characteristics of the pulmonary artery in the study population. The patient with CTEPH is indicated with the open box. Medians (right ventricular ejection fraction) and means (all other parameters) are indicated. *P < 0.05.
Pulmonary artery flow dynamics

After 6 months follow up, RV ejection fraction was not statistically significant different between patients with PE and control patients without PE (median 54.5%; interquartile range 51.8-60.4 versus 54.3%; 51.0-56.6, P = 0.57, Figure 1). In contrast, patients with PE had statistically significant lower LV ejection fraction than patients without PE (mean 54.7% ± 5.8 versus 59.5% ± 3.5, P = 0.016). The PA distensibility index was not different between patients with and without PE (0.18 ± 0.18 versus 0.25 ± 0.18, P = 0.20). Also, the studied pulmonary hemodynamic parameters were not different between patients with and without PE: mean velocity 14.1 ± 3.9 cm/s versus 14.0 ± 2.5 cm/s (P = 0.81), peak velocity 86.5 ± 22 cm/s versus 89.6 ± 13 cm/s (P = 0.43), and time to peak velocity 142 ± 49 ms versus 161 ± 29 ms (P = 0.14; Figure 1).

CMR as potential screening tool for CTEPH

All study participants underwent echocardiography after the CMR scan that revealed only one patient with PE suspected of having pulmonary hypertension. The diagnosis of inoperable CTEPH was confirmed after right heart catheterization and conventional angiography. This female patient was 59 years old, was diagnosed initially with idiopathic pulmonary embolism and expressed symptoms of exertional dyspnea and decreased exercise tolerance. At time of diagnosis of CTEPH, she was classified in NYHA class III and her mean pulmonary arterial pressure was 48 mmHg. Results from the CMR measurements in this patient indicated decreased systolic performance and increased stiffness of the pulmonary artery. Figure 1 Even more, she had the lowest RV ejection fraction (19.9%),

Figure 2: Pulmonary artery flow curve of the patient that was diagnosed with CTEPH and that of a healthy control without PE. Note the pulmonary flow systolic notch (arrow) and also diastolic forward flow as marker of restrictive physiology
distensibility index (0.03), mean PA velocity (7.11 cm/s), peak PA velocity (44.6 cm/s) and
time to peak velocity (97 ms) of all study patients. Strikingly, the PA flow curve of the patient
with CTEPH had an abnormal shape, i.e. a steep pulmonary flow systolic notch. Figure 2
This notch represents the increased wave reflection in the PA caused by a stiffened PA wall
or obstruction of the blood flow, and the timing of the notch distinguishes proximal from
distal obstruction of the PA in acute PE as well as in CTEPH.19

Discussion

The main finding of this study is that CMR measured PA flow profiles of patients treated
for acute PE do not differ from that of control patients without PE, whereas the same
patients with PE had significantly different systolic cardiac performance com-
pared to the same control patients without PE at time of diagnosis before treatment was initiated.
This observation possibly indicates normalization of the pulmonary flow dynamics in the
majority of patients after PE. One additional finding of this study is that CMR is a potentially
valuable screening tool for CTEPH after PE since measurements of the PA flow profile in
combination with RV function might be discriminative for pulmonary hypertension.
There is great need to develop tools for early identification of patients in early clinical
stages of CTEPH. Only in case of successful pulmonary endarterectomy, CTEPH is a
potentially curable but otherwise lethal disease.2 Early identification of CTEPH is likely
to improve the disease specific prognosis since even when pulmonary endarterectomy is
achievable, PA pressure and resistance as well as functional status of the patients remain
important prognostic factors.20 Because the incidence of CTEPH is reported to be as high
as 3.8% or even 8.8%,21,22 screening programs for CTEPH might be considered in the
clinical follow-up of patients with acute PE. Such screening programs should employ tools
that are non-invasive, widely available and applicable, and importantly, can distinguish
patients who are in early stages of CTEPH from those who are not at risk of developing
this condition. The results of this study support the potential role of CMR as early screening
tool for CTEPH after acute PE for 2 reasons. CMR is a widely available and non-invasive
imaging modality. Furthermore, since the hemodynamics of the PA are restored after
6 months of treatment for acute PE, and patients with CTEPH have a clearly different
flow profile,6-10 CMR may be able to distinguish patients with clinical relevant pulmonary
hypertension from those who are fully recovered, although the design and the number of
cases with pulmonary hypertension in our study does not allow to access the value of CMR
as a screening tool.

By design of our study, we were not able to evaluate the ability of CMR to identify patients
with very early stages of disease, who are likely to develop symptomatic CTEPH over time.
Nonetheless, previous reports have suggested that PA distensibility is decreased during
acute PE, but recovers over time after treatment.9 Furthermore, PA distensibility increases
early in the course of pulmonary hypertension, i.e. even when pulmonary hypertension is detectable only with exercise and before overt pressure elevations occur at rest.\textsuperscript{10} These reports as our results underline the potential of CMR as screening tool for CTEPH.

The strengths of our study include the prospective design and the inclusion of consecutive patients. We performed well-validated CMR scanning protocols and previous studies indicate excellent reproducibility for the used methods.\textsuperscript{19} In addition to accurate measurements of cardiac volumes, CMR is widely accepted as the reference standard for evaluating the PA flow. Study limitations are the limited sample size and only 6 months follow up without pulmonary flow measurements at the time of the acute event, which would have allowed evaluating the usefulness of CMR as early screening tool for CTEPH and possible changes of pulmonary flow profiles over time. Future studies should include larger patient cohorts and longer follow-up period. Furthermore, focus of these studies should not only be to detect patients with overt CTEPH but also on establishing relevant threshold values for pulmonary hemodynamic parameters to identify patients who are at risk of developing clinical relevant CTEPH in the following years. These patients then could be subjected to intensified clinical surveillance or referred to specialized pulmonary hypertension centers, to facilitate early diagnosis and treatment, leading to improved prognosis.

In summary, RV systolic performance and flow curve profiles of patients with PE after 6 months of treatment are generally comparable to those in patients in whom PE was suspected but ruled out. Furthermore, CMR may be helpful to identify patients with CTEPH. Further studies are needed to evaluate the potential role of CMR as screening tool for CTEPH after acute PE.
References


Nonuniformly distributed flow patterns after Melody ® implantation: implications for focal elevated pulmonary wall shear rates with right ventricular function

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Abstract

**Introduction:** Turbulent flow patterns distal to Melody ® valves are frequently observed by standard performed MRI. These turbulent flow patterns may have an impact on RV afterload conditions and RV function. The aim of this study was to compare pulmonary flow patterns between patients who underwent Melody ® and Contegra ® implantation and the impact of these flow patterns on pulmonary wall shear rates and right ventricular morphology and function.

**Patients and Methods:** Fifteen patients after Melody ® valve implantation (17.2 ± 2.0 years), 15 patients after Contegra ® implantation (15.8 ± 1.7 years), and 15 healthy volunteers, as a control group, (16.5 ± 1.5 years) were included. All subjects underwent a comprehensive cardiac MRI protocol, assessing RV morphology, function, pulmonary flow and vortices. From 3D flow analysis pulmonary flow eccentricity and pulmonary wall shear rate (WSR) were calculated.

**Results:** Patients in the Melody ® group showed reduced RVEF as compared to controls, eccentric pulmonary flow (deviation angle from the midline 31±10°) with vortex formation (vortex size 73±18 %), and a significant asymmetric elevated WSR at focal regions of the conduit. In contrast, those after surgical implantation showed a laminar pulmonary flow with no visible vortex and had symmetric, although elevated WSR in the conduit regions and an RV function comparable to controls.

**Conclusion:** Unfavorable pulmonary flow patterns with vortex formation distal from the Melody ® valve lead to abnormal hemodynamics that may influence the RV function and might be a predisposing factor for pulmonary aneurysm formation.
Introduction

Pulmonary valve stenosis and/or incompetence are common problems in patients after correction of congenital heart diseases.\(^1,2\) Prolonged pressure or volume overload may lead to irreversible right ventricular (RV) dysfunction.\(^3\) Therefore, right ventricular outflow tract (RVOT) repair by surgical implantation of a bovine jugular venous valve (Contegra \(^\circledR\) conduit) or a pulmonary homograft is commonly performed.\(^4\) Recently, percutaneous implantation of the same bovine jugular venous valve, sutured to a balloon-expandable platinum iridium stent (Melody \(^\circledR\) valve) has become a less invasive solution for patients with dysfunction of biological valve in the RVOT position. Herewith, the number of open-heart surgeries these patients have to undergo in their life may be reduced.\(^5-7\)

Although mid-term follow-up of patients who underwent percutaneous bovine valve implantation seems to be satisfactory\(^6,8\), turbulent flow patterns distal to the valve are often seen. (Figure 1) Recently, time resolved three dimensional magnetic resonance velocity mapping, also known as 4D flow, has gained considerable interest.\(^9,10\) By application of this technique it is feasible to assess blood flow velocities in all directions while simultaneously providing morphological information, which allows detailed insights into the local blood flow dynamics. In addition, 4D flow allows calculation of the wall shear rate (WSR) i.e., the force per unit area induced by the relative movement of blood at the endothelium, in the vessel upstream from the valve, which is considered an important determinant for vascular remodeling.\(^11-13\) We investigated RV morphology, RV function and 4D flow dynamics in patients with a percutaneously implanted bovine jugular venous valve (Melody \(^\circledR\) valve) and compared these parameters with patients who underwent surgical implantation of the bovine jugular venous valve (Contegra \(^\circledR\) conduit). We hypothesized that turbulent flow patterns would be more frequently present and that WSRs would be higher in patients with a percutaneously implanted

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**Figure 1:** 2D through plane flow just above the Melody \(^\circledR\) valve demonstrating turbulent flow with both forward (solid arrow) and backward (dashed arrow) directed flow during systole. Phase contrast image (left) and modulus image (right).
bovine jugular venous valve (Melody group) than in patients with a surgically implanted bovine jugular venous valve (Contegra group). Furthermore, we hypothesized that these unfavorable afterload conditions might influence RV morphology and function.

**Patients and Methods**

Informed consent was obtained from all participants and /or parents prior to enrolment. Patients who underwent Melody ® valve implantation at our institutions, older than 8 years, and without contra-indications for MRI examination, were included in the study. Patients were retrospectively recruited from the pediatric cardiology database of the “Center for Congenital Heart Disease Amsterdam Leiden” (www.CAHAL.nl). The database showed 15 eligible patients (8 male, 17.2 ± 2.0 years). Fifteen age and sex matched patients after Contegra conduit implantation (10 male, 15.8 ± 1.7 years) and 15 age matched healthy volunteers (6 male, 16.5 ± 1.5 years), as a control group, were included.

All subjects underwent a standard echocardiographic examination using Vivid 7.0.0 (GE Vingmed Ultrasound AS, Horten, Norway) to assess the maximum flow velocity (Vmax) of the pulmonary flow and a comprehensive cardiac MRI protocol including 4D flow of the pulmonary artery.

**Cardiac MRI**

Cardiac MRI was performed on a Philips Panorama 1.0 T open MRI scanner (Panorama, Philips Medical Systems, Best, the Netherlands). Two and 4-chamber views, RVOT views in two orthogonal planes, and short-axis views consisting of 12 to 14 contiguous slices, covering both ventricles from the base of the heart till the apex were acquired using a retrospective ECG-gated steady-state free precession (SSFP) sequence during breath holding at end-expiration. For choosing a correct velocity-encoded MRI in the 4D MRI flow sequence, the flow across the pulmonary/conduit valve was first assessed using a free-breathing retrospective 2D ECG-gated through plane velocity encoded MRI. Scan parameters were: repetition time/ echo time (TR/TE) = 9/5 msec, filed of view (FOV) = 370 – 400 mm, flip angle (FA)= 15 - 20°, slice thickness = 6-8 mm, matrix = 128 x 256, temporal resolution approximately 20 msec. Standard velocity encoding of 1.5 m/sec was initially chosen. When a higher velocity encoding was required based on the 2D velocity encoded sequence, this higher velocity encoding was used for the 4D flow acquisition.

For 4D flow mapping, a 60-mm slab was placed at the RVOT, from the pulmonary valve to the pulmonary bifurcation, verified to encompass this region throughout the cardiac cycle (this was visually verified in the two orthogonal views of the RVOT). Velocity was encoded in three orthogonal directions and the images were acquired during
free breathing by an imaging sequence with retrospective gating (10% acceptance window, 30 reconstructed cardiac phases). Imaging parameters were as follows: $TR/TE = 9.3/5.2$ msec, $FOV = 370 – 400$ mm, $FA = 10^\circ$, acquisition voxel size $= 2 \times 2 \times 4.0$ mm, reconstructed into a voxel size of $= 1.2 \times 1.2 \times 4.0$ mm, two signal averages, and a 237 Hz sampling bandwidth. The 60-mm slab was reconstructed into 15 sections of 4 mm thickness.

**Image post-processing**

Right ventricular systolic function and mass were analyzed using the MASS ® research software package (Version V2012-EXP, Leiden University Medical Center, the Netherlands). The RV systolic function was assessed by drawing endocardial contours at end-systole and end-diastole in all sections of the cine short axis data to obtain end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV) and ejection fraction (EF). An RVEF lower than 47% was defined as abnormal. RV mass was assessed by drawing RV epicardial borders for each slice level where the area of the interventricular septum was allocated to the LV. Masses were summed from apex to base with subsequent indexation for body surface area. A RV mass greater than 22 g/m$^2$ was defined as a hypertrophied RV. Diameters of the pulmonary artery/conduit were assessed as the mean of two measurements of the RVOT in two orthogonal cine imaging view at the pulmonary valve level, in the Melody group at the mid of the stent: $D_{proximal}$, just before the bifurcation: $D_{distal}$, and at half the distance between the pulmonary artery and the bifurcations: $D_{mid}$. In the Contegra group, the symmetry of the conduit valve opening was visually assessed, while this was not possible in the Melody group due to the stent artifacts. Pulmonary artery/conduit distension ($Pulm_{dis}$) was measured at the location of $D_{mid}$ as the difference between pulmonary artery/conduit area in the peak systolic and in the early diastolic phase.

Flow patterns were qualitatively and quantitatively assessed using color-coded streamlines visualization in both orthogonal RVOT views using in each individual time frame. All traces were color-coded according to the local blood flow velocity. Analysis focused on the presence of vortices and eccentricity of the pulmonary flow. A vortex was defined as particles revolving around a point within the vessel with a rotation direction deviating by more than $90^\circ$ from the physiological flow direction. The relative period of the vortex existence (number of cardiac phases with vortex divided by the total number of imaged cardiac phases) was determined visually. The vortex size was measured as a percentage of the vessel diameter in the phase showing the maximal diameter of the vortex. Eccentric pulmonary flow jets were defined as predominantly peripheral high-velocity vectors, away from the pulmonary artery midline; the flow deviation angle from the midline was measured.
Pulmonary flow quantification was directly derived from the measured 4D flow data and measured at the location of $D_{\text{mid}}$ (half the distance between the pulmonary valve and the bifurcation) in the control and the Contegra groups. In the Melody group pulmonary flow was quantified just distally to the stent to avoid stent artifacts, in all patients approximately at the same level as in the other groups. A reformatting plane was generated perpendicular to the pulmonary artery/conduit on both orthogonal RVOT cine views. The 4D velocity encoded images were reformatted to yield 30 through-plane velocity-encoded images with which the flow analysis was performed. For each phase the luminal border was traced and flow velocity curves were derived by multiplying the lumen area in each time frame by the average flow velocity to yield the following parameters: pulmonary forward flow volume, pulmonary backward flow volume, and pulmonary effective flow volume (forward minus backward flow volume).

Figure 2: (A) Quantification of wall shear rates (WSRs) in the phase of maximum velocity (phase 6), the luminal boundary of the pulmonary artery (green contour) was drawn and a concentric contour was generated automatically at a fixed distance of 5 mm inside the lumen (red contour). Radial velocity profiles within the region defined by the two contours were analysed to obtain local WSR values. WSRs were calculated at four local anatomical positions starting from the pulmonary wall facing the aorta (at the yellow cross) aorta wall (1), anterior wall (2), lateral wall (3), and posterior wall (4). (B) WSRs measurements.
and pulmonary Vmax. 18 WSRs were measured at the same site of the reformatting plane in the phase of maximum velocity as described by the Stalder et al. 19 WSRs were calculated at four local anatomical positions starting from the pulmonary artery/conduit wall facing the aorta (aorta wall), anterior wall, lateral wall, and posterior wall. (Figure 2)

**Statistical analysis**

A one-way analysis of variance (ANOVA) was used to analyze differences in quantitative parameters between groups. Post hoc least significant difference (LSD) testing was performed for parameters that proved statistically significant on ANOVA. The Pearson correlation coefficient was calculated to evaluate the potential correlation between RV systolic function, RV mass, time after Contegra conduit and Melody valve implantation, pulmonary artery/conduit diameters, pulmonary artery/conduit distension, pulmonary flow deviation angle, vortex existence, vortex size, pulmonary Vmax, and WSRs. P-values less than 0.05 were considered significant. SPSS® version 20 was used for statistical analysis.

**Results**

**Patient characteristics**

Baseline data are summarized in Table 1. All patients were in New York Heart Association (NYHA) class I or II and received no medication. Melody® valves were implanted in old homografts (13.5 ± 4 years); one patient (7%) had a second Melody® valve implantation. In the Contegra group, five patients (33%) had a replacement of the Contegra® conduit after previous Contegra placement. Time after Contegra® conduit implantation was 7.4 ± 4.3 years, and after Melody® valve implantation was 2.9 ± 1.3 years, (P < 0.001). All patients successfully underwent cardiac MRI examination.

**Comparison between the three groups**

Results are summarized in Table 2. Patients in the Contegra and the Melody groups had a normal RV systolic function. However, RV-EF in the Melody group was significantly lower than in the control group. Both the Contegra and the Melody groups showed RV hypertrophy and the RV mass was comparable in both groups. No correlation between RV-EF and time after Contegra® conduit implantation ($r = -0.17$, $P = 0.5$) or Melody® valve implantation ($r = 0.01$, $P = 0.9$) was observed. The conduit diameters were smaller in the Contegra group as compared to the Melody and the control groups. The conduit distension was lower in the Contegra group. (Table 2) Thirteen patients in the
Table 1: Baseline data over the Patients characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Contegra group (15 patients)</th>
<th>Melody group (15 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>15.8 ± 1.7</td>
<td>17.2 ± 2.0</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOF-PAVSD</td>
<td>7 (47%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>PAIVS</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rastelli operation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Ross operation</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Number of thoracotomies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One thoracotomy</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Two thoracotomies</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Three thoracotomies</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (67%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>II</td>
<td>5 (33%)</td>
<td>6 (40%)</td>
</tr>
</tbody>
</table>

TOF: Tetralogy of Fallot, PAVSD: pulmonary atresia and ventricular septum defect, PAIVS: pulmonary atresia and intact ventricular septum

Table 2: Comparison of MRI data between the three groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (15 subjects)</th>
<th>Contegra group (15 patients)</th>
<th>P value (Between Contegra and control groups)</th>
<th>Melody group (15 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV-EF (%)</td>
<td>55 ± 5</td>
<td>52 ± 7</td>
<td>0.3</td>
<td>50 ± 6</td>
</tr>
<tr>
<td>RV-EDV (mL/m²)</td>
<td>105 ± 14</td>
<td>114 ± 26</td>
<td>0.3</td>
<td>119 ± 20</td>
</tr>
<tr>
<td>RV mass (g/m²)</td>
<td>20 ± 2</td>
<td>30 ± 7</td>
<td>&lt; 0.001</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>Dproximal (mm)</td>
<td>23 ± 3</td>
<td>18 ± 5</td>
<td>&lt; 0.001</td>
<td>22 ± 2</td>
</tr>
<tr>
<td>Ddistal (mm)</td>
<td>23 ± 2</td>
<td>18 ± 4</td>
<td>&lt; 0.001</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>Dmid (mm)</td>
<td>23 ± 1</td>
<td>19 ± 6</td>
<td>&lt; 0.001</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>Pulmdis (cm)</td>
<td>1.7 ± 0.5</td>
<td>0.02 ± 0.09</td>
<td>&lt; 0.001</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>QF-PA (mL/heart beat)</td>
<td>75 ± 15</td>
<td>80 ± 9</td>
<td>0.9</td>
<td>76 ± 11</td>
</tr>
<tr>
<td>WSR of aorta wall (sec⁻¹)</td>
<td>16 ± 3</td>
<td>39 ± 22</td>
<td>&lt; 0.001</td>
<td>8 ± 9</td>
</tr>
<tr>
<td>WSR of anterior wall (sec⁻¹)</td>
<td>16 ± 4</td>
<td>38 ± 16</td>
<td>0.001</td>
<td>33 ± 19</td>
</tr>
<tr>
<td>WSR of lateral wall (sec⁻¹)</td>
<td>15 ± 4</td>
<td>37 ± 21</td>
<td>0.002</td>
<td>16 ± 18</td>
</tr>
<tr>
<td>WSR of posterior wall (sec⁻¹)</td>
<td>15 ± 3</td>
<td>34 ± 26</td>
<td>0.004</td>
<td>7 ± 5</td>
</tr>
</tbody>
</table>

Contegra group (87%) showed symmetrical opening of the conduit valve, while 2 patients (13%) showed an asymmetrical valve opening. None of the subjects had clinically relevant pulmonary valve incompetence. Contegra group patients had a significantly lower pulmonary Vmax, measured by 4D flow, as compared to those with Melody valve (2.6 ± 0.6 m/sec vs. 3.3 ± 0.6 m/sec respectively, P = 0.009). There was no difference between pulmonary Vmax measured by 4D flow and echocardiographic measurement (2.6 ± 0.6 m/sec vs. 2.5 ± 0.5 m/sec, respectively P = 0.6 in the Contegra group, and 3.3 ± 0.6 m/sec vs. 3.4 ± 0.3 m/sec, respectively P = 0.6 in the Melody group). (Figure 3) No correlation between pulmonary Vmax and the time after Contegra conduit implantation (r = 0.28, P = 0.4), or Melody valve implantation (r = 0.13, P = 0.6) was observed.

Pulmonary flow was laminar with no visible vortex, and without angle deviation of the pulmonary flow from the midline in all subjects in the control group (100%) and 13 patients (87%) in the Contegra group. The 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>Contegra group</th>
<th>Melody group</th>
</tr>
</thead>
<tbody>
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<td>RV-EF (%)</td>
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<td>50 ± 6</td>
</tr>
<tr>
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<td>114 ± 26</td>
<td>119 ± 20</td>
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<td>RV mass (g/m²)</td>
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<td>30 ± 7</td>
<td>33 ± 6</td>
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<tr>
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<td>15 ± 3</td>
<td>34 ± 26</td>
<td>7 ± 5</td>
</tr>
</tbody>
</table>

Figure 3: Bland Altman plot that show comparison maximum pulmonary flow velocity measured by 4D flow and echocardiographic measurements in Contegra and in Melody groups.
Figure 4: (A) Pulmonary artery in a normal subject; upper left (sagittal view), and upper right (coronal view). (B) Contegra ® conduit; upper left (sagittal view), upper right (coronal view). Lower rows show traces of color-coded streamlines demonstrating laminar flow, no visible vortex, and no deviation of the flow from the mid line. (C) Melody ® valve, upper left (sagittal view), upper right (coronal view). Middle rows show traces of colour-coded streamlines demonstrating eccentric flow, pulmonary flow is deviated from the midline, and vortex is seen. The lower rows are magnification of the vortex in a phase with the maximal vortex diameter.

Figure 5: Box plot shows the wall shear rate (WSRs) in the three groups.
patients (13%) in the Contegra group with an asymmetric conduit valve opening, and all the Melody group patients (100%) had an eccentric flow towards the anterior wall with a deviation angle from the midline of 31 ± 10°. Vortices were seen in all patients with eccentric flow. (Figure 4) Vortex size was positively correlated with pulmonary flow deviation angle (r = 0.97, p < 0.001) and with pulmonary Vmax (r = 0.54, P = 0.02). In the Contegra group, WSRs were symmetrical, but elevated, compared to the control and the Melody groups (Table 2, Figure 5). In the Melody group, the anterior wall WSR was elevated whereas the other wall regions (lateral, posterior, and aorta wall) showed no differences in comparison with the control group. (Table 2) There was no correlation between WSRs and pulmonary Vmax in the 3 groups.

Discussion

4D flow showed that pulmonary flow patterns differ significantly between patients with a surgical and percutaneously implanted bovine jugular venous valve in the RVOT. Notable findings were that all patients in Melody group (percutaneously implanted valve) showed an eccentric pulmonary flow with vortex formation and a significant asymmetric elevated WSR at focal regions of the conduit. In contrast, those in Contegra group (surgical implanted valve) and with symmetrical opening of the conduit valve showed a laminar pulmonary flow with no visible vortex and the WSR values, although elevated, were symmetric. The patients with asymmetrical opening of the Contegra ® conduit valve showed an eccentric pulmonary flow pattern with vortex formation. RV hypertrophy was present in both patients groups. RV systolic function was significantly lower in the Melody group compared to the controls, whereas no significant differences in RV systolic function between the controls and the Contegra group could be shown. Vortex formation leads to generation of dynamic actions on the surrounding structures and energy loss in forward flow. A vortex may thus be considered as an obstacle that partially obstructs the free flowing of the fluid inside a vessel. In the absence of any vortex formation, pressure would change as dictated by the Bernoulli balance. However, development of a vortex provokes an additional pressure drop (or energy loss) due to the transformation of energy into vortex inertia. These abnormal hemodynamics due to the vortex formation distal to the percutaneous implanted valve might be related to the development and growth of aneurysms. Previous studies reported that an asymmetric elevated WSR may be
regarded as a trigger for aneurysmal formation in the ascending aorta of patients with a bicuspid aorta valve exhibiting eccentric aorta flow.\textsuperscript{25, 26} Francois et al,\textsuperscript{27} confirmed the presence of vortices in the dilated segments of the pulmonary artery in surgical corrected TOF patients.

Elevated but symmetrical WSR values in the Contegra ® group are probably caused by the smaller lumen size and impaired distension of the venous conduit. Gober et al\textsuperscript{28} suggested that the foreign body reaction (excessive intimal peel formation, severe perigraft scarring reaction, fibrointimal proliferation) on the outside layer of the Contegra conduit could lead to an increase in stiffness of the Contegra ® conduit and therefore, impaired elasticity of the conduit.

The hypertrophied RV in both patients groups, as compared to the controls, is probably caused by the underlying disease and past pressure overload but probably also due to higher resistance to outflow; in the Contegra group due to relatively narrow unelastic conduits, and in the Melody group due to unfavorable flow patterns with vortex formation distal from the Melody ® valve.

It is worth mentioning that, in this study, the maximum flow velocities across the pulmonary valve determined by 4D flow were comparable to those determined by echocardiography. An important pitfall of standard 2D phase contrast magnetic resonance flow mapping is underestimation of the maximum flow velocity.\textsuperscript{29} More studies may help to validate this concept especially within the context of stenotic valves. However, measuring Vmax at the mid of the pulmonary artery/conduit is not representing the whole gradient over the long artery/conduit till the bifurcation.

Similarly to previous publications\textsuperscript{27, 30, 31}, normal healthy volunteers in this study exhibited a laminar pulmonary flow pattern with no visible vortex. Our findings contradict with findings of Bachler et al, who demonstrated two counter-rotating vortices in the pulmonary flow of healthy volunteers.\textsuperscript{32} However, a difference in vortex definition might explain this contradiction. Bachler et al defined the vortex as a rotation or swirling motion in the flow field, while in our study and in other studies\textsuperscript{27, 30, 31}, a vortex was defined as a regional circular flow pattern deviating by more than 90° from the physiological flow direction along the vessel lumen.

Study limitations

The relatively small number of patients in the cohort limits this study. Larger patient cohorts and more long term studies will be essential to learn more about the pathophysiological changes. A further difficulty of the 4D flow sequence is the long overall scan times of about 20 minutes. However, future improvement in scanning techniques will lead to a reduction in scanning time and hopefully the widespread use
of 4D flow to unravel the complex flow patterns after surgery for congenital heart disease.

**Conclusion**

4D flow showed that pulmonary flow patterns differ significantly between patients with a surgical and percutaneously implanted bovine jugular venous valve in the RVOT. Unfavorable pulmonary flow patterns with vortex formation distal from the Melody ® valve lead to abnormal hemodynamics that may influence the RV function and might be a predisposing factor for a pulmonary aneurysm formation. Longer follow up studies are required to determine the implications of such knowledge for prognosis and therapy.
Reference List


Chapter 12

Summary
Summary

Accumulating evidence suggests that pressure overload on the right ventricle (RV) leads to RV dysfunction, with considerable morbidity and mortality. Therefore, appropriate RV evaluation is essential because timely intervention may preserve RV function and prevent irreversible RV damage. Currently, cardiac magnetic resonance (CMR) is the imaging modality of choice for RV functional evaluation and cardiac flow quantification. Through its unlimited access to the chest, CMR permits a detailed morphological assessment of the whole RV and the pulmonary artery tree in a single comprehensive examination. CMR has several technical advantages: it is non-invasive, has excellent spatial resolution, images can be obtained in any desired orientation, and there are no acoustic window limitations or radiation risks. In this thesis, the assessment of cardiac function and hemodynamics in children and adults with right ventricular pressure overload using CMR will be discussed. A general introduction to the implications and limitations of CMR in evaluation of patients with congenitally pressure overloaded RV, particularly in the assessment of RV morphology, function, and cardiac flow pattern, is provided in Chapter 1. Following this general introduction and thesis outline, a series of studies addressing the relationship between exercise capacity and cardiac reserve using dobutamine stress (DS) MRI in asymptomatic patients with congenitally pressure overloaded RV is presented in Chapters 2 - 4. In Chapter 2, it was shown that impaired cardiac reserve, assessed by DS-MRI, is the underlying mechanism for impaired exercise capacity in patients with pulmonary atresia with intact ventricular septum (PAIVS) treated with univentricular palliation. By contrast, patients with PAIVS treated with biventricular repair have a normal exercise capacity and a normal cardiac reserve. These mid-term follow-up findings support the superiority of biventricular repair over univentricular palliation in PAIVS patients. However, the question then arises: whether these relatively small and hypertrophied RVs at birth capable of maintaining normal ventricular performance over the long-term? In Chapter 3, it was shown that exercise capacity decreases with age in PAIVS patients with biventricular repair. These findings were related to impaired cardiac reserve due to impaired diastolic RV function and decreased RV filling during stress, indicating that RV function deteriorates with time. Management of patients with moderate pulmonary stenosis is still controversial and depends mainly on symptoms of the patients that might present late in life. In Chapter 4, it was shown that patients with moderate pulmonary stenosis are not a homogenous group. Patients with native moderate PS showed normal exercise capacity and cardiac reserve, while patients with moderate pulmonary valve restenosis after the relief of severe pulmonary stenosis showed impaired exercise capacity that was correlated to impaired cardiac reserve, which is probably caused by RV diastolic dysfunction. The extent of RV diastolic dysfunction seems to be dependent on the pressure gradient before intervention and the duration of moderate restenosis.
CMR is a reproducible imaging modality to assess RV function that does not rely on geometrical assumptions. The post-treatment recovery of RV function in patients with pressure overloaded RV is evaluated in Chapters 5 and 6. In Chapter 5, the recovery of RV systolic and diastolic function after relief of RVOT obstruction by percutaneous pulmonary valve implantation (Melody ® valve) was assessed. It was shown that RV systolic function normalises early, within weeks, after pulmonary valve implantation. By contrast, RV diastolic function improvement and RV mass regression are delayed. These results indicate that long-term follow-up of patients with percutaneous pulmonary valve implantation should be recommended for the comprehensive assessment of RV function recovery. In Chapter 6, the biventricular functional recovery in pulmonary embolism patients who were treated for 6 months was presented. The degree of RV recovery after 6 months of treatment for acute pulmonary embolism was dependent on the severity of RV dysfunction at the time of the acute event. Patients with more severe RV dysfunction at baseline also showed left ventricle systolic dysfunction. This indicates that restoration of LV function is dependent on the restoration of the RV, which is a manifestation of interventricular dependence.

Due to improvements in palliative cardiac surgery early in life, the number of patients with a systemic RV has increased dramatically over the past few decades. While mid-term survival is excellent, progressive RV dilatation, hypertrophy and dysfunction seems inevitable and may underlie impaired exercise tolerance, arrhythmia, progression to heart failure, or premature death. Consequently, it is essential to monitor the progression of systemic RV volumes, mass, and function closely in these patients. Current guidelines recommend that a stack of slices (should) be orientated along the subpulmonary RV short axis; however, this is not yet documented for the systemic RV. The difficulties associated with assessing systemic RV function are addressed in Chapters 7 and 8. In Chapter 7, the axial and short axis measurements of the systemic RV were compared. Measurements performed using axial slices were more reproducible than short axis slices. Consequently, it may be beneficial to measure volumes and function in the axial orientation in patients with a systemic RV. Moreover, the number of patients with a systemic RV who have a pacemaker or implantable cardioverter-defibrillator is increasing and these patients are not suitable to undergo CMR. Cardiac CT may provide an alternative for CMR in these patients. This issue was addressed in detail in Chapter 8. Cardiac CT provides a reproducible alternative for CMR for ventricular volumes and function assessment in patients with a systemic RV, although larger variability between measurements should be taken into account. Patient selection should also be based on consideration of the exposure to radiation and contrast agents.

Paediatric patients often represent a special challenge when acquiring arterial imaging using magnetic resonance angiography because children vary widely in terms of size, circulation time, and procedural compliance. The safety and accuracy of contrast
enhanced magnetic resonance angiography in children with pulmonary atresia for evaluation of pulmonary artery anatomy and blood supply are reported in Chapter 9. Finally, the pulmonary flow patterns in patients treated for a pressure overloaded RV are described in Chapters 10 and 11. The pulmonary flow profile and distensibility in patients with pulmonary embolism after 6 months of treatment was described in Chapters 10. Pulmonary flow profiles in pulmonary embolism patients treated for 6 months did not differ from those of healthy subjects, whereas the same patients with pulmonary embolism showed significantly different systolic cardiac performance compared with the healthy group, both at the time of diagnosis and before treatment was initiated. This observation may indicate the normalisation of pulmonary flow dynamics in the majority of pulmonary embolism patients after treatment.

Recently, 4D flow has gained considerable interest. This technique enables an assessment of blood flow velocities in all directions while simultaneously providing morphological information, which allows detailed insights into the local blood flow characteristics. 4D flow also allows calculation of the wall shear rate (WSR) in the vessel upstream from the valve, which is considered an important determinant for vascular remodelling. In Chapter 11, the pulmonary blood flow pattern after surgical and percutaneous pulmonary valve implantation was evaluated. 4D flow showed that pulmonary flow patterns differ significantly between patients with a surgical and percutaneously pulmonary valve implantation. Unfavourable pulmonary flow patterns with vortex formation distal from the percutaneously implanted valve lead to abnormal hemodynamics that may influence the RV function and might be a predisposing factor for a pulmonary aneurysm formation. Longer follow up studies are required to determine the implications of such knowledge for prognosis and therapy.

Conclusion

This thesis has addressed evaluation of RV, particularly in challenging patients with complex geometries associated with RV pressure overload. CMR has now been successfully incorporated into the management of patients with RV pressure overload. The incorporation of findings from the CMR data obtained from this group of patients into broader clinical practice will improve patient management.
Samenvatting
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Er zijn steeds meer aanwijzingen dat drukoverbelasting van de rechtventrikel (RV) leidt tot RV-dysfunctie, dit gaat gepaard met een aanzienlijk zieke- en sterftecijfer. Een juiste beoordeling van de RV is essentieel, aangezien tijdige interventie kan leiden tot het behoud van de RV functie en onherstelbare schade voorkomt. Thans is cardiovasculaire magnetische resonantie (CMR) de standaard methode voor beeldvorming bij functionele beoordeling van de RV en meting van de bloedstroom door het hart. CMR geeft een onbelemmerd zicht op het hart en maakt daardoor een gedetailleerde morfologische beoordeling mogelijk van de hele RV en de longslagaderboom in één enkel uitgebreid onderzoek. CMR biedt meerdere technische voordelen: het is niet invasief, geeft een uitstekende ruimtelijke resolutie, afbeeldingen kunnen worden weergegeven vanuit ieder gewenst gezichtspunt, er zijn geen akoestische obstakels (zoals bij echografie) en er is geen stralingsrisico. Dit proefschrift bespreekt het gebruik van CMR bij de beoordeling van de hartfunctie en hemodynamica bij kinderen en volwassenen met een drukoverbelaste RV. **Hoofdstuk 1** geeft een algemene inleiding in de implicaties en beperkingen van CMR in beoordelingen van patiënten met aangeboren overdrukbelasting van de RV, waarbij de aandacht in het bijzonder uitgaat naar de morfologie, functie en bloedstroompatronen van de RV. Na deze algemene inleiding en het bespreken van de opzet van het proefschrift, worden in **Hoofdstukken 2-4** een reeks onderzoeken besproken over de relatie tussen inspanningscapaciteit en cardiale reserves met behulp van Dobutamine Stress MRI (DS-MRI) bij asymptomatische patiënten met aangeboren drukoverbelasting van de RV. Het functieherstel van een behandele RV bij patiënten met drukoverbelasting van de RV wordt behandeld in **Hoofdstukken 5 en 6**. De moeilijkheden bij het bepalen van de systemische RV-functie komen aan de orde in **Hoofdstukken 7 en 8**. De veiligheid en nauwkeurigheid van magnetic resonance angiography MRA bij kinderen met een onderontwikkelde longslagader, ter beoordeling van de anatomie van de longslagader en de bloedtoevoer, worden besproken in **Hoofdstuk 9**. **Hoofdstukken 10 en 11** ten slotte, geven een beschrijving van de bloedstroom in de longslagader bij patiënten die worden behandeld voor drukoverbelasing van de RV. Patiënten met een drukoverbelaste RV vertonen vaak geen symptomen tijdens normale dagelijkse activiteiten totdat RV-falen optreedt. Wellicht is een geringe cardiale reserve in reactie op stress een vroege voorspeller voor inspanningscapaciteit; het correleert sterk met lichamelijke conditie en algemene gezondheidsschalen, zelfs bij asymptomatische patiënten. **Hoofdstuk 2** laat zien dat geringe cardiale reserve, gemeten met DS-MRI, het onderliggende mechanisme is voor verslechterde inspanningscapaciteit bij patiënten met onderontwikkelde longslagaders en een intact ventriculair septum (PAIVS), die behandeld zijn met univentriculaire reparatie. Daarentegen vertonen patiënten met PAIVS die biventriculaire reparaties ondergaan, een normale inspanningscapaciteit en een normale cardiale reserve. Deze mid-term follow-up resultaten ondersteunen de voorkeur voor biventriculaire reparaties boven univentriculaire reparaties.
palliatie in PAIVS-patiënten. Nu rijst echter de vraag: zijn deze bij geboorte relatief kleine en verdikte RV’s in staat om op de lange termijn een normale pompfunctie te handhaven? In Hoofdstuk 3 is aangetoond dat de inspanningscapaciteit van PAIVS-patiënten met een biventriculaire reparatie lager wordt naarmate de leeftijd stijgt. Deze resultaten worden in verband gebracht met een kleinere cardiale reserve als gevolg van een verzwarende diastolische RV-functie en verminderd vollopen van de RV tijdens stress, dit geeft aan dat de RV-functie langzaamaan verslechtert. Behandeling van patiënten met een milde vernauwing van de longslagaderklep (PS) is nog steeds controversieel en is vooral gericht op de symptomen die op latere leeftijd zouden kunnen optreden. In Hoofdstuk 4 kwam naar voren dat patiënten met milde PS geen homogene groep vormen. Patiënten met aangeboren milde PS vertonen een normale inspanningscapaciteit en cardiale reserve, terwijl patiënten met milde terugkerende PS na het behandelen van ernstige PS een verslechterde inspanningscapaciteit tonen. Dit correleert met verminderde cardiale reserve, die waarschijnlijk wordt veroorzaakt doordat de RV niet goed volloopt. De mate waarin hiervan sprake is, lijkt af te hangen van de drukgradiënt vóór interventie en de duur van de milde terugkerende vernauwing.

CMR is een reproduceerbare beeldvormingsmethode om de RV-functie te beoordelen, die niet uitgaat van geometrische aannames. In Hoofdstuk 5 is nader ingegaan op het herstel van de systolische en diastolische functie van de RV na behandeling van de RVOT-obstructie met percutaan implanteren van een longslagaderklep. De systolische functie van de RV blijkt snel te normaliseren, binnen enkele weken na implantatie van een longslagaderklep. Verbetering van de diastolische functie en afname van de RV-massa daarentegen, treedt minder snel op. De resultaten tonen aan dat langdurige follow-up geïndiceerd is in patiënten die een percutane implantatie van een longslagaderklep hebben ondergaan, om zo een duidelijk beeld te krijgen van het functieherstel van de RV. In Hoofdstuk 6 werd het biventriculaire functieherstel besproken van patiënten met een longembolie die gedurende zes maanden waren behandeld. De mate van herstel van de RV bij deze patiënten hing samen met de ernst van de RV-dysfunctie ten tijde van de acute aanval. Patiënten met een ernstigere RV-dysfunctie vertoonden bij de uitgangsmeting ook systolische dysfunctie van de linkervertrikel (LV). Dit wijst erop dat herstel van de LV-functie samenhangt met het herstel van de RV en dat er dus sprake is van interventriculaire afhankelijkheid. Als gevolg van de vooruitgang op het gebied van hartchirurgie op jonge leeftijd is het aantal patiënten met een systemische RV in de laatste decennia sterk toegenomen. Terwijl de levensverwachting uitstekend is, lijken progressieve RV-verwijding, -verdikking en -dysfunctie onvermijdelijk, en liggen mogelijk ten grondslag aan verslechterde inspanningstolerantie, ritmestoornissen, hartfalen of vroegtijdige sterfte. Daarom is het van groot belang om de toename van RV-volume, -massa en -functie bij deze patiënten in het oog te houden. De huidige richtlijnen raden aan om een aantal opnames te maken langs de korte as van de subpulmonaire RV. Dit is echter nog niet vastgesteld voor de systemische
RV. In Hoofdstuk 7 werden de horizontale metingen en metingen langs de korte as van de systemische RV met elkaar vergeleken. De metingen op basis van horizontale opnames bleken beter reproduceerbaar dan die op basis van de opnames langs de korte as. Daarom verdient het wellicht de voorkeur om bij patiënten met een systemische RV, het volume en de functie te meten in horizontale richting. Bovendien stijgt het aantal patiënten met een systemische RV die een pacemaker of *implantable cardioverter-defibrillator* dragen. CMR is niet mogelijk voor deze patiënten en cardiale CT biedt in dit geval wellicht een alternatief. Dit onderwerp is uitgebreid aan bod gekomen in Hoofdstuk 8. Uit onderzoek blijkt dat cardiale CT een reproduceerbaar alternatief is voor CMR bij het beoordelen van ventrikelvolume en –functie van patiënten met een systemische RV, hoewel er rekening gehouden dient te worden met een grotere variabiliteit tussen metingen. Bij het selecteren van patiënten dient ook de blootstelling aan straling en contrastvloeistoffen in ogenschouw genomen worden.

Kinderen vormen een bijzondere uitdaging wanneer beeldvorming van de slagaderen geschiedt met gebruik van magnetic resonance angiography (MRA), vanwege grote verschillen in omvang en de bereidheid om mee te werken. In Hoofdstuk 9 werden de nauwkeurigheid en veiligheid getoond van MRA bij het beoordelen van de anatomie van de longslagader en bloedtoevoer bij kinderen met onderontwikkelde longslagaders, in vergelijking met de meer ingrijpende meetmethoden.

De bloedstroom in het hart kan kwalitatief en kwantitatief worden onderzocht door middel van MRI. In Hoofdstuk 10 werd het profiel van de bloedstroom in en de rekbaarheid van de longslagader beschreven bij patiënten met een longembolie na een behandeling van zes maanden. Deze verschilde niet van die bij gezonde personen, terwijl dezelfde patiënten significant afwijkende systolische hartfunctie vertoonden in vergelijking met de gezonde groep, zowel ten tijde van de diagnose als voor het begin van de behandeling. Deze vaststelling wijst er wellicht op dat de bloedstroom in de longslagader bij de meerderheid van de patiënten met longembolie na de behandeling normaliseert.

Recentelijk is er een groeiende interesse voor *4D MRI flow*. Deze techniek maakt het onderzoeken van bloedstroomsnelheden in alle richtingen mogelijk, terwijl ook morfológische informatie kan worden verkregen. Dit biedt gedetailleerd inzicht in de lokale kenmerken van de bloedstroom. 4D flow maakt ook berekeningen mogelijk van de *wall shear rate* (WSR) in het bloedvat; deze wordt beschouwd als een belangrijke determinant voor de conditie van de vaten. In Hoofdstuk 11 werd het stroompatroon van de longslagader na chirurgische en percutane implantaat of een longslagaderklep besproken. *4D MRI flow* heeft in beeld gebracht dat de stroompatronen van de longslagader duidelijk verschillen van die na chirurgische implantaat. Ongunstige longslagader bloedstromen met wervelingen distaal van de percutaan ingebrachte klep, leiden tot abnormale hemodynamiek die de RV functie kan beïnvloeden. Dit vergroot voor deze groep mogelijk het risico op nadelige effecten in de toekomst. Langere follow-up
studies zijn nodig om te bepalen wat de implicaties hiervan zijn voor de prognose en behandeling.

**Conclusie:** Dit proefschrift onderzocht de beoordeling van de RV, vooral in patiënten met een complexe geometrie die verband houdt met drukoverbelasting van de RV. CMR wordt nu succesvol ingezet bij de behandeling van patiënten met drukoverbelaste RV’s. Het toepassen van de kennis die is verkregen uit dit onderzoek in de bredere klinische praktijk, zal leiden tot een betere behandeling van patiënten.