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

Romeih, Soha

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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.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.30, 31 The current guidelines recommend that a stack of slices is orientated along the RV short axis.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.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).34 Phase-encoded flow imaging measures the relative flow volume to each lung and assesses the hemodynamic significance of branch pulmonary stenosis.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.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.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.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.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.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 β-1-adrenoceptor 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. In this group impaired RV cardiac reserve can be an early sign of RV dysfunction even in asymptomatic patients.

Novel CMR techniques such as simultaneous quantification of RV pressure with MRI-compatible catheters to derive RV volume/pressure loops, and strain-encoded MRI to detect abnormal regional RV strain patterns have been developed with the aim of improving RV evaluation. 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
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. 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. 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. 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. 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.

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. 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. 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. More than 50% of the TOF patients develop a significant stenosis or regurgitation within 10 years after PVR.
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.
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

**Systemic RV**

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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}
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.
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.
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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