Cardiovascular magnetic resonance in congenital heart disease: focus on heart failure.

Vivek Muthurangu MD (res)

Introduction

Congenital heart disease (CHD) has an incidence of 6-8 per 1000 in neonates[1]. Life expectancy of individuals with CHD has increased significantly due to improvements in diagnosis and treatment (both surgical and interventional). In the current era, the majority of children born in developed countries with CHD will survive into adulthood. This has led to an increasing prevalence of patients with CHD in the general population, most of whom will require ongoing evaluation.

Imaging is fundamental to the follow-up of CHD patients, helping to guide management decisions, evaluate interventions and guides prognosis. Echocardiography is still considered the first line imaging modality for pediatric and adult CHD assessment. This is because it is available in all institutions, portable and provides immediate anatomical and physiological information. For cooperative patients with good acoustic windows, echocardiography alone can guide the diagnosis and management of many conditions. This is particularly true in the neonatal period and early childhood. However, echocardiography is highly user-dependent, can be limited by acoustic windows and provides poor visualization of the distal vasculature. Thus, historically echocardiographic assessment has been augmented with cardiac catheterization. Cardiac catheterization not only allows high resolution delineation of vascular and intracardiac anatomy, but also provides reference standard hemodynamic information. Unfortunately, cardiac catheterization is limited by its invasive nature and exposure to ionizing radiation. In addition, conventional X-Ray fluoroscopy only provides a projection image and has limited three-dimensional (3D) capabilities.

In the last 20 years, Cardiovascular Magnetic Resonance (CMR) has become a vital part of the imaging follow-up in CHD. It provides comprehensive non-invasive evaluation of anatomy and physiology but without exposure to ionizing radiation. One the major advantages of CMR over other imaging modalities is that it provides both 3-dimensional and unrestricted 2-dimensional visualization of the cardiovascular anatomy. Thus, CMR is able to accurately delineate complex intracardiac and vascular abnormalities, irrespective of body habitus. This makes CMR particularly useful in adults with CHD, as they often have poor acoustic windows. For this reason, CMR is recommended in recent guidelines regarding multi-modality imaging and the management of adults with CHD[2-4]. Another advantage of CMR in CHD is reference standard assessment of ventricular volumes, mass, and function. This is due to the easier delineation of endocardial and epicardial borders in high contrast CMR images, as well as the ability to quantify without geometric assumptions[5-7]. The advantages of CMR are particularly valuable for right ventricular assessment, as its position and complex shape often makes it difficult to fully evaluate with echocardiography. For this reason, CMR is vital in the assessment of patients who have CHD with ventricular dysfunction. A final important general indication for CMR is assessment of blood flow. Multiple studies have shown that it provides accurate measurement of cardiac output, regurgitation fraction and the pulmonary-to-systemic flow (Qp:Qs)[8-11].

Cardiac function

Many congenital heart diseases will result in ventricular dysfunction and much of the morbidity and mortality experienced by these patients is due to ‘cardiac failure’. Thus, measuring ventricular function is a vital aspect of continuing assessment and management of these patients. Cardiac failure is often defined as an inability to produce sufficient cardiac output to supply the bodies metabolic needs. Thus, measuring cardiac output can provide important clinical information regarding cardiac failure. However, most congenital heart disease patients have normal cardiac output at baseline due to cardiac compensation (e.g. ventricular dilation, hypertrophy and increased filling pressures). In these patients, evaluation of the ventricles may provide a better correlate of symptoms.

One common ventricular manifestation of CHD is dilation, whether this be due to volume loading (e.g. valvar regurgitation or shunts) or ventricular failure. Dilation is

known to increase the risk of arrhythmia, as well as causing increased wall stress and consequent contractile failure. Thus, measuring ventricular volumes is an important part of the evaluation of congenital heart disease. Measuring ventricular volumes is also necessary for precise measurement of ejection fraction. Ejection fraction is the percentage of blood ejected from the heart with every heartbeat. It is a well-recognised measure of cardiac function and ventricular arterial coupling and an important prognostic marker in many forms of congenital heart disease[12,13]. Ventricular volumes can be estimated by 2D echocardiography, but most methods rely on significant geometric assumptions. Although these may hold true for the left ventricle (LV), they are inadequate to describe the crescentic right ventricle (RV)[14]. New 3D echocardiographic techniques do enable volumetric assessment, but still suffer from operator dependence and inadequate echocardiographic windows. As already discussed, CMR has some important advantages over echocardiography including not being limited by body habitus and unrestricted 2D imaging. Thus, CMR can image contiguous slices covering the both ventricles, enabling true 3D assessment of biventricular volumes[15]. Finally, modern steady state free precession (SSFP) techniques provide high blood pool myocardial contrast aiding segmentation and further post-processing[16]. Several studies have shown that CMR provides highly accurate and reproducible measurement of ventricular volumes, and ejection fraction data in congenital heart disease[17-19]. For these reasons cardiovascular MR should now be considered the reference standard method of measuring left and right volumetric data.

Although assessment of ventricular volumes is a vital element of the CMR protocol for CHD, it does not provide a full picture of cardiac dysfunction. Increasingly, it has been recognized local myocardial motion may be a more sensitive marker of both early systolic and diastolic ventricular dysfunction. Local myocardial motion can be evaluated by several metrics such as longitudinal/radial contraction, twisting/torsion and wall thickening. Some or all of these metrics can be measured with echocardiography using tissue doppler or strain imaging. However, like all echocardiographic techniques they suffer from inadequate windows and operator dependence. Thus, CMR also plays an important role in the evaluation of local myocardial motion. Several CMR techniques can be used for this purpose and these include tissue tagging, tissue phase mapping and strain/displacement encoding[20,21].

Over the last decade these techniques have been used to better understand pathophysiology in congenital heart disease. However, significant clinical utility has not been demonstrated and most sequences are still considered research technologies. More recently, strain (and strain rate) data has been derived from conventional CMR cine data. This has allowed retrospective analysis of historical cine data and demonstration of clinical utility. Several studies have now shown that strain metrics can independently predict outcome (e.g. death or major cardiac event) and exercise tolerance in patients with congenital heart disease[22-24]. However, no large studies have demonstrated that CMR strain measures outperform conventional ventricular volumes or ejection fraction data.

There are some limitations in using CMR to measure ventricular volumes and ejection fraction in patients with CHD. In some patients, particularly children, breath holding is difficult and free breathing approaches are required. These include signal averaged gated cine acquisitions and real-time acquisitions. Real-time sequences are becoming increasingly used in paediatric imaging with new accelerated techniques now reaching the quality of conventional breath hold cines[25]. Several studies have validated real-time CMR for measurement of ventricular volumes and they are a useful alternative in patients who cannot breath hold.

Blood flow

Assessing ventricular volumes and ejection fraction remains the prime CMR method of evaluating heart failure in CHD patients. However, quantification of blood flow also plays an important role. This is because flow related lesions (e.g. shunts or valvar regurgitation) are one of the main causes of ventricular dysfunction in CHD. The reference standard method of measuring shunts in CHD is invasive oximetry with measurement of oxygen saturations (or content) in the pulmonary and systemic arterial and venous systems. From this data the pulmonary to systemic blood flow ratio (Qp:Qs) can be calculated, which is both a measure of the magnitude and direction of a shunt. However, this approach is invasive in nature and can be associated with morbidity. In addition, there are some technical problems with invasive oximetry. These include the requirement for multiple blood samples that can result in error propagation[26] and shunt quantification only being possible if sampling can be

performed distal to the shunt, which is not possible in some extracardiac lesions (i.e. systemic-pulmonary arterial collaterals).

Valvar regurgitation is usually assessed using Doppler echocardiography. The main benefit of this approach is that echocardiography is already as the first line method of evaluating anatomy and cardiac function in CHD. Unfortunately, echocardiographic evaluation of regurgitation is either qualitative or at best semi-quantitative. Thus, it is prone to inaccuracy and cannot provide accurate measures of regurgitation fraction or volumes.

CMR can be used to accurately assess blood flow using the velocity encoded phase contrast MR (PCMR) technique[8-11,27]. In PCMR, the average velocity of blood in each pixel is encoded and thus blood flow in a region of interest (e.g. a vessel) can be calculated. As PCMR is a cine acquisition the resulting flow curve can be integrated to calculate metrics such as stroke volume and cardiac output. There are a significant number of studies that have demonstrated good agreement between PCMR and both direct measurement of flow in phantom studies[11,28] and invasive oximetry in patient studies[8,11,27]. However, as well as being non-invasive, PCMR has a distinct advantage over invasive oximetry as measurement of Qp:Qs is not limited to measurement of flow in the pulmonary trunk and aorta. This can be particularly useful in situations where invasive oximetry fails, such as patients with systemic to pulmonary arterial collaterals. The ability to accurately evaluate flow throughout the cardiac cycle also means that PCMR is able to provide truly quantitative measures or pulmonary or aortic valve regurgitation. Furthermore, combing great arterial flow with ventricular volume data can also allow calculation of atrio-ventricular valve regurgitation. Thus, CMR can be used to better evaluate the important primary causes of heart failure in CHD, aiding clinical decision making in these patients.

Another area PCMR can be used is assessment of diastolic function. Diastolic dysfunction is often overlooked as a cause of symptoms in congenital heart disease. The traditional method of assessing diastolic function is echocardiographic assessment of AV valve inflow. Specifically, the ratio of early to late inflow velocities (E/A ratio) is an important indicator of ventricular diastolic dysfunction. The E/A ratio

can also be measured using PCMR and some studies have demonstrated clinical utility[29].

Specific lesions

Not all congenital heart diseases result in heart failure and many patients have minimal symptoms after successful repair in the infant period. However, there are 4 instances in which ventricular dysfunction and accompanying symptoms are common and these will be discussed in more detail in the next section.

Shunt lesions

Many shunt lesions are identified in early life, particularly ventricular septal defects (VSD) and patent ductus arteriosus (PDA). In younger children, both VSDs and PDAs can be easily identified and assessed using echocardiography. However, children with complex or multiple VSDs[30] or difficult to visualize ducts may benefit from CMR for full 3D evaluation. In addition, CMR measurement of the Qp:Qs ratio and left ventricular volume may be important in determining management in older children and adults[2].

Consequently, the most common indication for CMR in patients with shunts is assessment of older children and adults with unrepaired atrial septal defects (ASD). Atrial septal defects are an anatomically heterogeneous group of lesions and the natural history and management of this disease depends on the specific type. Ostium secundum defects are the most common lesions and are located in the fossa ovalis Ostium primum defects on the other hand are a type atrioventricular septal defect (AVSD) and associated with some degree of atrioventricular valve abnormality. Sinus venosus defects are found at the junction of the right atrium and either one of the caval veins and are often associated with partial anomalous pulmonary venous drainage. The final type of ASD is an unroofed coronary sinus, which is not strictly a defect in the atrial septum but is associated with similar physiology. The majority of isolated ASDs result in left to right shunts and right volume overload due to the fact that the shunt occurs before the atrio-ventricular valves.

The use of CMR in patients with ASDs falls into 2 main categories i) comprehensive assessment of anatomy and ii) evaluation of physiology. In terms of anatomical assessment, definitive diagnosis and evaluation of possible sinus venosus defects and

anomalous pulmonary venous connection is one of the most important CMR indications[31,32]. This is because these lesions are often difficult to image with echocardiography, particularly in adults where they can easily be missed. This is also true for patients with unroofed coronary sinus, which are often difficult to visualize with transthoracic echocardiography. Although secundum defects can usually be identified with transthoracic echocardiography, CMR can be used determine suitability for transcatheter or surgical closure[33-35], providing a non-invasive alternative to transesophageal echocardiography with better sensitivity for anomalous pulmonary venous connections.

The other aspect of CMR assessment in these patients is quantification of the magnitude of the shunt through calculation of Qp:Qs and measurement of right ventricular volumes and function. This provides important information for clinical decision making particularly in borderline lesions.

Tetralogy of Fallot

Another group of patients with right ventricular volume overload are those with repaired tetralogy of Fallot and pulmonary regurgitation. Tetralogy of Fallot (ToF) is the most common cyanotic congenital heart defect with an incidence of approximately 420 per million live births[1]. It is caused by malalignment of the infundibular septum, which leads to right ventricular outflow (RVOT) obstruction, a sub-aortic VSD with aortic override, and right ventricular hypertrophy. Current management consists of early single stage reconstructive surgery[36], although staged procedures are necessary in more complex cases. This procedure has the benefit of leaving the patient acyanotic and has good survival rates[37]. As symptom appear in early life in most patients, echocardiography is usually sufficient for initial diagnosis and assessment[38]. Prior to the initial repair CMR is rarely needed but it may have a role in assessing the pulmonary arteries in more complex cases[39-41].

The main role of MR in patients with ToF is assessment of post-operative complications. Operative repair of ToF consists of VSD closure and relief of RVOT obstruction, often with placement of a transannular patch. This compromises pulmonary valve integrity, resulting pulmonary regurgitation. Pulmonary regurgitation results in right ventricular volume overload and ultimately RV dysfunction. In some

patients, either as part of the initial repair or subsequent pulmonary valve replacement (PVR), a right ventricular to pulmonary artery conduit is placed. In conduits the main mode of failure is mixed dysfunction with some degree of both RVOT obstruction and pulmonary regurgitation. Due to this RVOT dysfunction, the majority of patients will require pulmonary valve replacement (PVR). CMR is useful in these patients for determining both the timing of PVR and the type of PVR performed(e.g. surgical or catheter based).

Accurate quantification of regurgitation and/or stenosis is important in deciding the type and timing of procedures. Phase contrast MR has been shown to accurately quantify pulmonary regurgitation and has been internally validated against MR ventricular volumetry in patients with ToF[42]. Phase contrast MR can also accurately assess differential regurgitation in the branch pulmonary arteries (Kang et al. 2003). This is important in patients with pulmonary valve replacement with metallic components (e.g. Hancock valve), as artefact may prevent accurate flow mapping in the pulmonary trunk. Although regurgitation can be qualitatively assessed using transthoracic or transoesophageal echocardiography, the ability of MR to accurately quantify regurgitant fraction and volume makes it a superior technique. Phase contrast MR can also be used to measure peak velocities at the level RVOT obstruction. However, it should be noted that conventional PCMR will underestimate peak velocity[43] and Doppler echocardiography should still be considered the reference standard method of measuring peak velocities. CMR is also useful in delineating anatomical abnormalities of RVOT, which is important for planning surgical or interventional valve replacement.

The result of RVOT dysfunction is volume and or pressure loading, which results in RV failure, as well as LV dysfunction due to ventricular interdependence. As morbidity and mortality in these patients is ultimately related to ventricular dysfunction, volumetric evaluation is a vital aspect of the follow-up in ToF patients. Measuring ventricular volumes function is also important when evaluating the effect of any invasive procedure[44-46]. It has been shown that, using a combination of MR ventricular volumetry and tricuspid and pulmonary flow maps, precise information about global and diastolic ventricular function can be assessed in patients with repaired ToF[47]. Importantly, CMR-derived parameters inform risk-stratification [13,48-50] and referral for

pulmonary valve replacement [44,51,52], and figure prominently in published clinical management guidelines [2,4,53,54]. The presence of localized ventricular scarring or fibrosis has also been associated with arrhythmia and ventricular dysfunction in patients following repair of tetralogy of Fallot[55]. Thus, late gadolinium enhancement is an important component of assessing older patients with repaired ToF.

Systemic Right ventricle

Ventricular dysfunction due to volume overload (e.g. shunts or valvar regurgitation) is common in congenital heart disease. However, pressure overload is also an important cause of ventricular dysfunction in some CHD patients. This is particularly true in patients with systemic right ventricles. This group include patients born with transposition of the great arteries (TGA) who have undergone an atrial switch procedure and congenitally corrected TGA. Transposition of the great arteries is the second commonest cyanotic congenital heart disease[1] and is defined as ventriculo-arterial discordance with an anterior aorta arising from the RV, and the pulmonary artery arising from the LV. Surgical therapy for this condition was revolutionised with the introduction of the Senning procedure in which an intra-atrial baffle was used to divert blood from the right atrium to the left ventricle, and the left atrium to the right ventricle[56]. A further variation was the Mustard procedure in which a pericardial patch was used to construct the intra-atrial baffle[57]. Both procedures produced a physiologically normal but an anatomically abnormal circulation (systemic venous return to the left atrium, LV and then pulmonary artery; pulmonary venous return to the right atrium, RV and then aorta). Although the intra-atrial repair has been superseded by the arterial switch operation, there is a sizeable population of adults who have undergone either a Senning or Mustard operation. The most common complications of intra-atrial repair are baffle obstruction or leak, arrhythmias, and RV dysfunction. Baffle obstruction is more common in the Mustard operation [58] probably due to calcification and poor growth of the pericardial tissue used to construct the baffle. The venous pathways have a complex 3D structure and are difficult to accurately assess with transthoracic echocardiography. Thus, 3D MR imaging is extremely useful in demonstrate the anatomy of the Senning/ Mustard anatomy and has been shown to be able to detect baffle narrowing [59]. Obstruction of either the superior venocaval or inferior veno-caval limb of the intra-atrial baffles can be corroborated from MR angiographic by identifying venous collaterals, which divert

blood from the obstructed venous system. Phase contrast MR can also be useful in identifying baffle obstruction, with in-plane PCMR visualizing flow turbulence at the site of baffle narrowing, and through-plane PCMR confirming loss of the typical, phasic, venous flow profile. Baffle leaks can be difficult to visualize even with CMR cine imaging. However, they will result in a shunt and can easily be detected measuring Qp:Qs using PCMR .

The aetiology of RV dysfunction in patients with intra-atrial baffles is complex. Deranged atrio-ventricular coupling as a result of the baffles maybe important [60]. Studies have shown that atrial baffle function limits RV filling rates during exercise or pharmacological stress, despite appropriate responses in load-independent indices of RV contraction and relaxation [61]. However, RV dysfunction may be present without abnormal coupling and it is likely that the RV is also inherently unprepared to pump against systemic afterload RV systolic function has been assessed in patients with intra-atrial repair of TGA using CMR and has been shown to be lower than in matched controls [60]. Studies have also demonstrated areas of focal myocardial fibrosis using late gadolinium enhancement techniques in adults late after atrial baffle repair of TGA [62 63]. These studies demonstrated that the presence of fibrosis was associated with RV systolic dysfunction, poor exercise tolerance, arrhythmia and progressive clinical deterioration.

Congenitally corrected transposition (CCTGA) is a rare disorder characterised by atrio-ventricular and ventricle-arterial discordance (right atrium to left ventricle to pulmonary artery and left atrium to right ventricle to aorta). Thus, these patients also have a systemic RV. Congenitally corrected transposition may be asymptomatic and in some patients an incidental finding. However, the majority of patients with CCTGA have associated cardiac lesions, which often the source of cardiac problems. The most common associated lesions are ventricular septal defects, pulmonary stenosis and tricuspid valve abnormalities (i.e. Ebstein abnormality) [64]. Even without associated abnormalities, the majority of patients with CCTGA develop systemic ventricular failure over time. The main role of MR is in evaluation of associated lesions, quantification of ventricular function and assessment of post-operative complications. RV function has been assessed in patients with CCTGA using CMR [60] and has been shown to be reduced both at baseline and in response to dobutamine stress [60].

Single ventricle

The final example of patients with CHD and ventricular dysfunction are those born with a functionally single ventricle. As most patients present in the newborn period, echocardiography is the primary imaging tool during initial evaluation. However, in some cases, CMR may be used to determine whether a one versus two-ventricle repair should be pursued [65,66]. CMR can also be useful in more complex forms of heterotaxy syndrome [67,68], as it provides reliable three dimensional visualization of intracardiac and vascular anatomy. Nevertheless, the common use of CMR in these in infancts and younger children is as a non-invasive alternative to cardiac catheterization during staged palliation towards a Fontan circulation. Multiple studies have shown CMR outperforms echocardiography and can substitute routine diagnostic catheterization in selected patients prior to the bidirectional cavopulmonary connection (Glenn shunt or a hemi-Fontan procedure) [69-72], and total cavopulmonary connection (Fontan procedure)[73-75]. In addition, CMR measurements of systemic-to-pulmonary artery collateral flow predict post-operative outcomes such as hospital length of stay [76-78] and can be used for optimization of hospital resources. Following the Fontan procedure, patients remain at risk for numerous complications including ventricular and valve dysfunction, Fontan baffle obstruction, pulmonary artery stenosis, aortic coarctation, systemic-to-pulmonary venous collateral formation, and intracardiac thrombus formation. CMR has a key role in surveillance for these complications as echocardiography alone is often inadequate [79,80]. Finally, CMR-derived parameters such as ventricular volume and myocardial fibrosis have been shown to be associated with adverse outcomes [81,82].

Conclusion

Over the last decade, CMR has become a mainstream non-invasive imaging tool for assessment of adult and paediatric patients with congenital heart disease. It provides comprehensive anatomic and hemodynamic information that echocardiography and catheterization alone do not provide. Extracardiac anatomy can be delineated with high spatial resolution, intracardiac anatomy can be imaged in multiple planes, and functional assessment can be made accurately and with high reproducibility. In patient with heart failure, CMR not only provides reference standard evaluation of ventricular volumes and function, but also information about the possible causes of dysfunction

(e.g. shunts and valvar regurgitation). It should therefore be considered a vital part of the follow-up in this group of patients.

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