

Cardiovascular Magnetic Resonance in Pediatric and Congenital Heart Disease: An Update on Recent Developments

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Abstract Cardiovascular magnetic resonance (CMR) plays an important role in the evaluation of children and adults with congenital heart disease. It provides complementary information to echocardiography and cardiac catheterization, and has unique diagnostic capabilities. Accordingly, data from CMR are increasingly being incorporated into disease management algorithms. This article critically reviews recently published reports related to pediatric and congenital CMR with sections on new techniques, congenital heart disease lesions, and cardiomyopathy.

Keywords Cardiac magnetic resonance imaging · Congenital heart disease · Pediatric cardiology · Three-dimensional phase contrast · Diffuse myocardial fibrosis · Postmortem magnetic resonance imaging

Introduction

Cardiovascular magnetic resonance imaging (CMR) plays an important role in the evaluation of children and adults with congenital heart disease. Earlier work in this field was

primarily focused on the anatomic characterization of congenital heart defects and functional assessment of the ventricles and valves. More recent efforts have sought to apply new CMR technical developments to pediatric and congenital heart disease, and investigate the value of CMR for disease management. This article will critically review recently published reports in the field of pediatric and congenital CMR. It is not intended to be exhaustive and space restrictions have no doubt led to the exclusion of some important work. Reports are categorized under techniques, congenital heart disease lesions, and cardiomyopathy.

CMR Techniques

CMR studies in infants and children unable to hold still are often performed using deep sedation or general anesthesia to avoid motion artifact. Concerns about the hemodynamic and neurologic adverse effects of anesthesia, and the increased resources it requires, pose a barrier to CMR use in this population. To address this issue, Shariat et al. performed a prospective dual-center study to assess the feasibility of a “feed-and-sleep” technique in 60 patients <6 months old undergoing CMR for the evaluation of congenital heart disease [1]. Infants fasted for 4 h prior to the scan, and then were swaddled with sheets, placed in a vacuum immobilizer, fed, and soothed with extra milk or sucrose solution if necessary. Most scans were performed for borderline left heart structures (17/60) or suspected vascular ring (20/60), and the mean scan duration was 45 ± 21 min. The investigators found that the clinical question was answered in all subjects. Thus, this approach seems reasonable for infants with less complex lesions in which the assessment of ventricular size and function, and anatomic evaluation of great arteries are sufficient. Though

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not examined in the report, it is likely that the image quality with this technique is not as good as when breath-holding is employed.

Another practical challenge to performing CMR in young children is respiratory motion artifact. In older patients, this can be addressed by having them to hold their breath on command; however, this is not possible in children too young to cooperate or those who are asleep or sedated. In these circumstances, motion artifact can be mitigated by acquiring multiple signal averages or using real-time imaging, both of which yield inferior image quality to breath-held acquisitions. To address this shortcoming, two recent studies reported results with novel respiratory-gated steady-state free precession 2-dimensional (2D) cine CMR techniques. Moghari et al.'s approach [2] used three respiratory navigator beam acquisitions over each cardiac cycle to track the diaphragm position and accept data only from cardiac cycles that occurred completely in end-expiration. Start-up pulses were used in the preceding cardiac cycle to preserve the equilibrium state of the net magnetization vector and avoid flash artifact. In a prospective study of ten un sedated patients, they demonstrated that the image quality with their technique was equivalent to breath-hold images and superior to free-breathing acquisitions performed with three signal averages. Moreover, there were no significant differences between their new technique and breath-hold images for calculations of ventricular volumes and mass. The mean scan time to complete a short-axis stack was 100 s longer than for breath-hold imaging. Further validation in a larger group which includes younger children is still needed. Krishnamurthy et al. [3] independently developed a similar approach to free-breathing, 2D cine CMR. With their technique, data acquisition was confined to either inspiration or expiration based on respiratory triggering, and start-up pulses were initiated on the preceding beat. The operator defined a patient-specific respiratory trigger point, trigger delay, and minimum duration for start-up excitations. The sequence was prospectively tested on a group of 20 consecutive children with congenital heart disease, 18 of whom received intravenous sedation and 2 of whom were un sedated. Compared to a free-breathing scan using four signal averages, their technique had a slightly shorter scan duration, as well as improved endocardial border definition. Limitations of this approach include the need for operator input to adjust the trigger delay based on respiratory rate, as well as motion blurring in situations of higher respiratory rates if the acquisition spilled over into the next inspiratory cycle.

Han et al. also aimed to improve the image quality and exam efficiency in pediatric patients without requiring breath-holding, by developing a cardiac and respiratory-gated high-resolution 3-dimensional (3D) magnetic resonance angiography technique [4]. Electrocardiogram-gating

was used to generate multiple 3D angiography data sets across the cardiac cycle with a temporal resolution of 65–95 ms, isotropic spatial resolution of 0.6–0.9 mm, and scan time of 3.5–8 min. All subjects were mechanically ventilated allowing respiratory-gating to be achieved by tracking the air pressure signal in the respiratory circuit. Importantly, this approach was facilitated by the intravenous administration of ferumoxytol which served as a high T1 relaxivity intravascular contrast agent. In eight patients, age 3 days to 5 years, this technique provided sharper images and better definition of the coronary arteries, aortic root, myocardium, and pulmonary trunk than standard breath-held, first-pass ferumoxytol-enhanced magnetic resonance angiography. Moreover, the ventricular volume measurements had good agreement with those generated from standard 2D cine CMR images. As the authors note, other strategies for respiratory motion compensation will need to be developed for patients who are not mechanically ventilated. Also, because ferumoxytol has a higher reported incidence of anaphylactoid and other hypersensitivity reactions than gadolinium-based contrast agents, a careful risk–benefit assessment must be performed.

3D cine phase contrast velocity sequences [also referred to as “4-dimensional (4D) flow”] have been a topic of investigation for many years. Compared to conventional 2D cine acquisitions, they offer a number of advantages including measurement of all three directional components of blood velocity and simplified exam planning. Nevertheless, concerns regarding accuracy, scan time, and post-processing ease have limited the penetration of 4D flow into clinical practice. Gabbour et al. recently investigated the validity of 4D flow for quantification of aortic and pulmonary flow by comparing it to measurements from 2D flow CMR and Doppler echocardiography [5]. They retrospectively identified 50 subjects (mean age 13.1 ± 6.4 years) who underwent a clinically indicated CMR study with 2D phase contrast MRI and 4D flow during the same examination. To minimize breathing motion related artifacts, the 4D flow acquisition was respiratory-gated using adaptive diaphragm navigator gating and a fixed acceptance window. The mean acquisition time was 12.6 ± 5.1 min with an acceleration factor of 2, and 6.6 ± 3 min with an acceleration factor of 5. The spatial resolution of the 4D flow acquisition was $2.7\text{--}4.1 \times 2\text{--}2.7 \times 2\text{--}3.5$ mm, compared with $1.0\text{--}1.9 \times 1.0\text{--}1.9 \times 5\text{--}6$ mm for 2D cine phase contrast, and the number of reconstructed cardiac time frames was 9–24 compared with 30 for 2D phase contrast. There was good agreement for net flow measurements and regurgitation fractions between the two techniques. 2D flow significantly underestimated aortic and main pulmonary artery peak velocities compared to Doppler echocardiography, while 4D flow yielded higher aortic and similar main pulmonary artery peak velocities relative to Doppler echocardiography. The

authors attribute the higher peak velocities with 4D flow acquisitions to being able to assess velocity data along the entire vessel rather than just at a narrow location as with 2D flow. Moreover, they point out that although 4D flow scan time is longer, it may save time in situations that would require multiple 2D cine phase contrast sequences. Additional development goals for 4D flow should include further acceleration to allow better spatial and temporal resolution without increasing scan time, implementation of retrospective rather than prospective ECG-gating, so that the entire cardiac cycle can be sampled, and more efficient tools for 4D flow data post-processing.

4D flow CMR also holds promise for improved noninvasive measurement of hemodynamics in children with congenital heart disease. From the velocity data, dynamic pressure differences along the course of a vessel can be computed by solving the pressure-Poisson equation. The accuracy of this approach was studied by Riesenkampff et al. in 13 consecutive patients with coarctation of the aorta who underwent 4D flow CMR followed by cardiac catheterization [6]. The CMR-based dynamic pressure fields only slightly underestimated the peak-to-peak catheterization gradients (mean difference 1.5 ± 4.6 mmHg). These encouraging results could be strengthened in subsequent studies by simultaneously acquiring the pressure and velocity data, and by using manometer-tipped rather than fluid-filled catheters. More generally, it is worth noting that without invasive pressure measurement calibration, blood flow velocities can be used to calculate only relative local pressure differences over the cardiac cycle (i.e., gradients) rather than absolute pressures. Nevertheless, this approach has the potential to expand the clinical role of CMR in congenital heart disease and decrease the need for invasive procedures.

Congenital Heart Disease

Despite significant advances in the treatment of tetralogy of Fallot (TOF) in childhood, residual hemodynamic and electrophysiological abnormalities contribute to increasing morbidity and mortality rates beginning in the third decade of life [7]. CMR has been useful in characterizing residual lesions and identifying candidates for pulmonary valve replacement [8]. Its value for risk stratification, particularly in comparison to other parameters, is less certain. The International Multicenter TOF Registry (INDICATOR), which enrolls the contemporarily managed patients from four large congenital heart centers in the United States, Canada, and Europe, was established to promote risk stratification based on clinical, ECG, exercise test, echocardiographic, and CMR data. In 2014, they reported results for a cohort of 873 patients with repaired TOF who

were a median age of 24.4 years at the time of CMR [9••]. Over a median post-CMR follow-up of 4.2 years, 32 (3.7 %) patients reached the primary outcomes of death ($n = 28$) or sustained ventricular tachycardia ($n = 4$). Cox proportional hazards regression identified right ventricular hypertrophy (defined as mass: volume ratio ≥ 0.3 g/mL), and decreased left and right ventricular ejection fraction measured by CMR, as well as a history of atrial tachyarrhythmias as outcome predictors. The presence of multiple risk factors was a stronger predictor than isolated risk factors (Fig. 1). The authors speculate that therapeutic interventions designed to prevent or lessen the identified risk factors may lead to improved clinical outcomes. A notable study limitation was that the cohort was restricted to subjects who had undergone CMR and, as a result, patients with pacemakers or defibrillators implanted before CMR were excluded.

Another developing area of investigation in TOF is myocardial fibrosis. In a variety of conditions, myocardial fibrosis, with an increase of collagen in the interstitium, has been associated with impaired systolic and diastolic ventricular function, arrhythmia, and increased mortality. The CMR late gadolinium enhancement (LGE) technique detects focal fibrosis, and multiple studies using it have previously shown an increased right ventricular scar burden in adults with repaired TOF. The LGE technique, however, is not sensitive to diffuse, homogeneously distributed fibrosis. For this purpose, T1 measurement techniques have been employed as myocardium with increased extracellular space (such as diffuse fibrosis) will contain a higher concentration of gadolinium-based contrast agent, and thus will have a shorter T1 relaxation time constant. In order to investigate the prevalence of diffuse myocardial fibrosis in children with

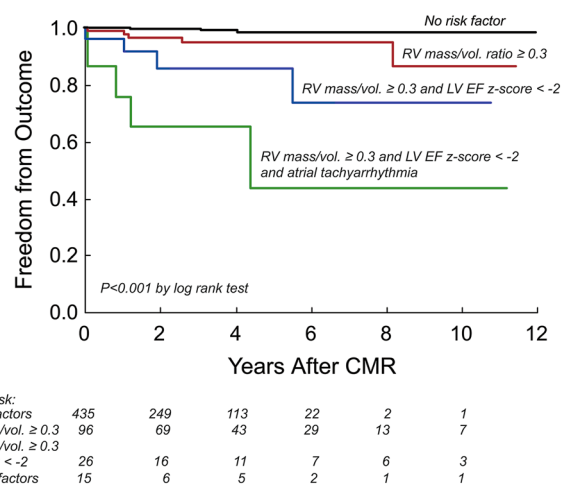


Fig. 1 Kaplan–Meier curves for the outcome (death and sustained VT) in patients with repaired tetralogy of Fallot according to risk factors. Reprinted from Valente et al. [9••]

repaired TOF, Kozak et al. retrospectively identified 18 repaired TOF patients (mean age 13.41 ± 2.75 years) and 12 control patients (mean age 12.72 ± 2.24 years) who had all undergone post-contrast myocardial T1 measurements [10]. The T1 measurements were acquired using a modified Look-Locker inversion (MOLLI) acquisition at a single mid-ventricular position in short-axis, 12 min after contrast agent administration. They found that post-contrast T1 values of the left ventricular lateral wall and right ventricular anterior wall in the TOF group were significantly shorter than those of controls, whereas post-contrast T1 values of the ventricular septum and of the right ventricular inferior wall were not significantly different. Thus, portions of the myocardium of both ventricles in TOF patients had shorter T1 values, a surrogate for increased fibrosis. The authors speculate that various processes may result in increased fibrosis, including preoperative hypoxemia, exposure to cardiopulmonary bypass and ventriculotomy, right ventricular pressure overload caused by outflow tract obstruction, and volume overload from pulmonary regurgitation. Notable limitations of the study include the lack of validation of the T1 measurement technique in the thin-walled right ventricle, and the absence of pre-contrast T1 measurements and hematocrit values to allow for calculation of the extracellular volume fraction (ECV), which is a more valid measure of myocardial fibrosis.

In addition to TOF, the utility of CMR for risk stratification has also recently been explored for patients with a functional single ventricle. Rathod et al. retrospectively evaluated 215 patients with a Fontan circulation who underwent CMR at a mean age of 18.3 years [11•]. In addition to CMR data, they collected a variety of clinical parameters such as a history of arrhythmias, thrombus, liver disease, congestive heart failure, and exercise test results. Over a median follow-up of 4.1 years after CMR, 24 patients (11 %) reached the endpoint of death, transplant, or transplant listing. The investigators found that a higher CMR-derived ventricular end-diastolic volume index and the presence of protein losing enteropathy were both independent predictors of shorter transplant-free survival. In a multivariable Cox proportional hazards model to predict the likelihood of death or transplant, the addition of CMR-derived ventricular end-diastolic volume index significantly strengthened the model compared to clinical parameters alone. An end-diastolic volume index cutoff value of $>125 \text{ mL/BSA}^{1.3}$ was found to be most discriminative between those who survived free of transplant and those who did not. Based on these results, the authors speculate that therapies aimed at reducing ventricular dilatation, such as aggressively treating valve regurgitation and aortopulmonary collateral vessels, may be warranted. As with the TOF risk-stratification study described above, there may be a selection bias as patients with pacemakers,

and defibrillators were not included. Moreover, the importance of end-diastolic volume should be validated in cohorts from other centers as well.

One of the most challenging clinical dilemmas in pediatric cardiology is whether to pursue a univentricular or biventricular approach in patients with borderline small left heart structures. As the preceding discussion highlights, patients with a univentricular palliation and a Fontan circulation have a guarded long-term prognosis. Nevertheless, aggressively pursuing a biventricular repair in suboptimal candidates can lead to short-term morbidity and mortality. Accordingly, Banka et al. sought to identify CMR parameters associated with successful univentricular to biventricular conversion surgery in patients with small left hearts [12•]. The cohort in this retrospective study was composed of two anatomic groups: 22 with borderline hypoplastic left heart syndrome (HLHS) and 10 with right-dominant atrioventricular canal defects. In the borderline HLHS group, 40 % had undergone in utero aortic valvuloplasty and 77 % had a prior procedure to augment blood flow to the left ventricle. A pre-operative CMR was performed at a median age of 39 months, and was then followed by surgery for biventricular conversion a median of 3 days afterward. Sixteen patients (73 %) survived with a biventricular circulation at a median follow-up time of 40 months. Survival was associated with a larger CMR left ventricular end-diastolic volume, higher left ventricular-to-right ventricular stroke volume ratio, and higher mitral-to-tricuspid inflow ratio. The right-dominant atrioventricular canal defect group had a median age at CMR of 6 months, and had all undergone some type of cardiac surgery to limit pulmonary blood flow. Nine patients (90 %) survived the biventricular conversion surgery at a median follow-up time of 29 months. The high success rate precluded discriminant analysis; nevertheless, the range of CMR-derived ventricular parameters that were compatible with biventricular conversion was reported. Overall, these data will facilitate interpretation of CMR measurements in patients being considered for biventricular conversion and assist with risk stratification. One must keep in mind, however, that this was a small study from a single center in a selected patient population (e.g., many had undergone prior procedures to help recruit the left heart), and thus, the findings may not be generalizable.

The focus of treatment in congenital aortic valve stenosis is on relief of valve obstruction in order to prevent the development of ventricular systolic dysfunction or symptoms. Nevertheless, despite adequate gradient relief, some patients develop diastolic dysfunction and exercise intolerance [13, 14]. One possible contributing factor may be myocardial fibrosis and CMR techniques are well-suited to investigate this concern. Focal fibrosis can be assessed with the LGE technique, and diffuse fibrosis by calculating the ECV with T1 relaxation time measurements.

Dusenbery et al. assessed LGE and ECV in 35 congenital aortic stenosis patients <30 years of age and compared the results to 27 control patients [15•]. In the aortic stenosis patients, LGE was present in 24 % and ECV was elevated in 37 %. Moreover, higher ECV correlated with echocardiographic indices of diastolic dysfunction (higher mitral valve Doppler E-wave, lower tissue Doppler e' , higher E/e' , and higher left atrial volume). These results highlight that congenital aortic stenosis is a disease of both the valve and myocardium, and that there is a need for therapies directed at reducing or preventing myocardial fibrosis. Further work is needed to confirm these findings in a broader population to address any referral bias, and to examine the longitudinal course of fibrosis.

A newer and perhaps not widely appreciated role for CMR is the postmortem identification of heart disease. Fetal and pediatric cardiac autopsies have a crucial role in counseling parents with regard to both the cause of death and future pregnancies, as well as for quality assurance of pre-morbid diagnostic procedures. Autopsy rates have declined in recent decades, and postmortem imaging may be more widely accepted by families. A landmark study published by the Magnetic Resonance Imaging Autopsy Study Collaborative Group in the United Kingdom was compared the diagnostic accuracy of postmortem CMR with conventional autopsy and histopathology assessment [16••]. Postmortem magnetic resonance imaging was performed in an unselected population of 400 fetuses and children. Imaging was carried out on a 1.5T scanner using the following non-contrast techniques: (1) 3D T2-weighted turbo spin echo, (2) 3D T1-weighted volumetric interpolated breath-hold examination, and (3) 3D constructive interference in the steady state. Forty-four cardiac abnormalities were detected at autopsy. Thirty-eight CMR data sets (10 %) were nondiagnostic (37 in fetuses ≤ 24 weeks, 1 in a fetus >24 weeks). Compared to autopsy, CMR had an overall sensitivity of 73 %, specificity of 96 %, positive predictive value of 73 %, and negative predictive values of 96 % for the detection of congenital heart disease. The CMR data were particularly useful in fetuses ≥ 24 weeks gestation and children with major congenital heart disease, and performed less well for fetuses <24 weeks gestation (presumably due to worse image quality) and in cases of myocarditis. Thus, it appears that postmortem CMR may become a clinically useful diagnostic technique with more widespread acceptance than conventional autopsy.

Cardiomyopathy

Pediatric cardiomyopathies affect about 1.13 per 100,000 children per year, and encompass a broad range of etiologies and phenotypes [17]. Although echocardiography has

been the most commonly used modality in evaluating patients, the utility of CMR in children with cardiomyopathy is evolving. Occasionally, patients may have sub-optimal echocardiographic windows in which case CMR can provide accurate and reproducible measurements of left and right ventricular function. Perhaps more importantly, CMR has an unparalleled ability to visualize myocardial tissue characteristic such as fibrosis and edema. The diagnostic and prognostic significance of such findings is an active area of research, and recent developments have spurred increased CMR utilization.

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by a mutation in the dystrophin gene. It is associated with cardiac myocyte death, myocardial inflammation, and ultimately dilated cardiomyopathy. Ongoing drug trials aimed at slowing the progression of the disease have heightened interest in identifying biomarkers for risk stratification and surrogate outcomes. Recent CMR investigations have attempted to characterize the myocardial pathology in these patients and determine its prognostic significance. For example, Menon et al. retrospectively analyzed the CMR findings and outcomes in 32 boys (median age 13.8 years) with DMD [18]. Their mean left ventricular ejection fraction was 52 ± 14 % and LGE was present in 25 (78 %). In addition to advancing age, LGE, left ventricular enlargement and dysfunction, and ventricular tachycardia were all predictive of mortality. Another recent study compared post-contrast myocardial T1 measurements, an indirect measure of diffuse fibrosis, in a cohort of 21 DMD subjects to those in 11 controls [19]. The investigators performed a Look-Locker sequence at a consistent time after administering a standardized dose of gadolinium contrast, and measured post-contrast T1 ratios (myocardial T1/blood pool T1). They found that patients with DMD had a shorter mean T1 ratio (consistent with increased myocardial fibrosis) than controls, even in DMD patients with otherwise normal CMR studies. Thus, they speculate that myocardial T1 measurements may serve as a pre-clinical marker of myocardial deterioration, and serve to identify patients who are candidates for aggressive or novel therapy. Future studies along these lines will benefit from utilizing more valid CMR measures of fibrosis such as ECV, and longitudinal follow-up.

Hypertrophic cardiomyopathy (HCM) in children is a heterogeneous group of disorders characterized by myocardial disarray, hypertrophy, and fibrosis. It is associated with symptoms related to outflow tract obstruction and diastolic dysfunction, as well as an increased risk of sudden cardiac death. There is mounting evidence in adults with the sarcomeric form of HCM that the presence and perhaps extent of LGE is associated with arrhythmia and sudden cardiac death [20, 21]. Data in pediatric age

patients with HCM are just beginning to emerge. One single center study retrospectively evaluated 30 children with HCM (age range 7–19 years) who underwent CMR [22]. Patients with genotype positive, phenotype negative HCM (i.e., no left ventricular hypertrophy) were included, whereas patients with associated congenital heart disease and syndromic HCM were excluded. LGE was present in 57 % of patients, was highly associated with hypertrophy, and was found only in patients with phenotypic hypertrophy. The seven patients who had adverse outcomes (five with ventricular tachycardia, one with appropriate implantable cardioverter-defibrillator discharge, and one cardiac death) over a median follow-up of 27 months had more segments of LGE than those without adverse outcomes. The small study size did not allow the authors to determine whether LGE offered additional predictive power over established risk factors. Moreover, inclusion of only patients referred for CMR may have imposed a selection bias favoring more severe disease.

Diffuse rather than focal myocardial fibrosis in HCM was the subject of a retrospective study by Hussain et al. [23]. Pre- and post-contrast myocardial T1 measurements were used to calculate the partition coefficients in 28 children with HCM and 12 healthy control patients. The partition coefficient for both septal and lateral walls was increased in patients compared with controls indicating greater diffuse fibrosis. Significantly higher lateral wall partition coefficients were found in patients who were symptomatic, those with an elevated brain natriuretic peptide (BNP) level, and those with traditional risk factors for sudden death. The clinical utility of such diffuse fibrosis measurements in children with HCM requires further exploration including the potential for identification of gene positive, phenotype negative (i.e., no hypertrophy) patients. More broadly, given the relatively low adverse event rates in children with HCM, a multicenter collaborative approach will likely be needed to ascertain the value of CMR fibrosis measurements for risk stratification.

Viral myocarditis is an important cause of morbidity and mortality in children, and may manifest as acute heart failure, dilated cardiomyopathy, and sudden cardiac death. Obtaining an accurate diagnosis can be challenging because the clinical symptoms and severity are quite variable. Over the past decade, CMR has emerged as an important noninvasive tool for the diagnosis of myocarditis in adults [24, 25]. Myocardial tissue characterization techniques can assess for inflammatory changes such as edema, hyperemia, capillary leak, and myocyte necrosis. More recently, CMR findings have been linked to prognosis [26]. In the pediatric population, however, data are considerably more scarce. A recent single center retrospective study by Sachdeva et al. sought to identify predictors of adverse outcomes in 58 children with myocarditis [27]. In the 34 patient subgroup who had CMR

examinations, LGE was found in 17 (50 %), most commonly in the posterior and lateral walls of the left ventricle. Poor outcomes, defined as the need for mechanical support, heart transplantation or death, occurred in six patients. On multivariate analysis, independent risk factors for poor outcomes were peak BNP >10,000 ng/L, left ventricular ejection fraction <30 %, and the presence of LGE. As with the pediatric HCM studies, the small number of outcomes demonstrates the need for larger multicenter studies to better understand the role of CMR in pediatric myocarditis.

Conclusion

Over the last year or so, there have been multiple advances in pediatric and congenital CMR related to new techniques, congenital heart defects, and myocardial disorders. The developments in techniques illustrate the need to make CMR easier to perform in younger children as well as the desire to expand the use of CMR as an alternative to diagnostic catheterization. In congenital heart disease, studies have demonstrated the important role of CMR for decision making and risk stratification. By comparison, the investigations focused on myocardial disorders have been smaller and carried less impact; nevertheless, their results should stimulate the developments of larger, likely multicenter, studies which have sufficient power to answer important clinical questions.

Compliance with Ethics Guidelines

Disclosure Rebecca Beroukhim and Andrew J. Powell declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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