Received: 5 June 2019 | Revised: 13 August 2019 | Accepted: 29 August 2019

DOI: 10.1111/chd.12840

REVIEW ARTICLE

Congenital Heart Disease WILEY

Pharmacologic stress cardiovascular magnetic resonance in the pediatric population: A review of the literature, proposed protocol, and two examples in patients with Kawasaki disease

Munes Fares MD[1] | Paul J. Critser MD, PhD[2] | Maria J. Arruda MD[1] | Carolyn M. Wilhelm MD[1] | Mantosh S. Rattan MD[3] | Sean M. Lang MD[2,4] | Tarek Alsaied MD, MSc[2,4]

[1]Division of Pediatric Cardiology, UH Rainbow Babies & Children's Hospital, Cleveland, Ohio

[2]Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[3]Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[4]Faculty of Medicine, Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio

Correspondence
Tarek Alsaied, Faculty of Medicine, Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati, MLC 2003, 3333 Burnet Avenue, Cincinnati, OH 45229-3039.
Email: Tarek.Alsaied2@cchmc.org

Abstract

Pharmacologic stress cardiovascular magnetic resonance (PSCMR) is a well-established and reliable diagnostic tool for evaluation of coronary artery disease in the adult population. Stress imaging overall and PSCMR in particular is less utilized in the pediatric population with limited reported data. In this review, we highlight the potential use of PSCMR in specific pediatric cohorts with congenital and acquired heart disease, and we review the reported experience. A suggested protocol is presented in addition to two case examples of patients with Kawasaki disease where PSCMR aided decision making.

KEYWORDS

acquired coronary artery disease, congenital heart disease, magnetic resonance imaging, perfusion, pharmacologic stress imaging

1 | BACKGROUND

Pharmacologic stress cardiovascular magnetic resonance (PSCMR) has been well studied in adults with stable ischemic heart disease (SIHD) and has shown excellent prognostic value.[1-3] As a non-invasive imaging tool, PSCMR is helpful in guiding management, risk stratifying patients with SIHD, and it is proven to be superior compared to stress echocardiography and stress nuclear imaging.[2,4] PSCMR has multiple advantages including better safety profile, wider availability, and lower cost making, it a preferable test compared to other non-invasive imaging modalities.[5] Furthermore, myocardial perfusion utilizing PSCMR has been proven comparable to fractional flow reserve obtained by conventional angiography.[3,6,7]

Atherosclerotic coronary artery disease and congenital coronary anomalies are rare in pediatric patients. However, there is a significant portion of pediatric age patients with congenital and acquired heart disease, in whom PSCMR could be valuable in the initial and follow-up evaluation.[8,9] The feasibility and safety of PSCMR have been established in children and a number of studies have reported the important diagnostic value of PSCMR in many pediatric settings.[10]

In this article, we review the indications of PSCMR in the pediatric population, we propose a protocol and we report two cases of Kawasaki disease where PSCMR played a major role in the management approach.

Abbreviations: A2A, adenosine 2a receptor; AAOCA, Anomalous aortic origin of the coronary arteries; ALCAPA, anomalous left coronary artery from the pulmonary artery; ASO, arterial switch operation; BAV, bicuspid aortic valve; ccTGA, congenitally corrected transposition of the great arteries; CMR, cardiac magnetic resonance; CoA, coarctation of the aorta; CTA, computed tomography angiogram; D-TGA, dextro transposition of the great arteries; FPP, first pass perfusion; KD, Kawasaki disease; PSCMR, pharmacologic stress cardiac MRI; SIHD, stable ischemic heart disease; ToF, tetralogy of Fallot.

2 | INDICATIONS FOR PHARMACOLOGIC STRESS TESTING IN THE PEDIATRIC POPULATION

In pediatric age groups, there are high risk cohorts that could benefit from myocardial perfusion assessment by PSCMR (Table 1).

1. Surgical Coronary Re-implantation: A subset of patients where coronary artery re-implantation is performed include the arterial switch operation (ASO) in D- transposition of the great arteries (D-TGA), the double switch operation in the setting of congenitally corrected transposition of the great arteries (ccTGA), the Ross procedure and in anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA). As part of the arterial switch operation or the double switch approach to D-TGA and ccTGA, respectively, the coronary arteries are translocated from the aorta to the pulmonary artery which becomes the neo-aorta and it results in an increased risk of myocardial ischemia compared to the general population.[11] Periodic assessment of the coronary arteries following re-implantation becomes an integral part of the long-term follow-up.[12] Use of PSCMR for evaluation of myocardial ischemia following the ASO has been reported and it has shown excellent agreement with imaging results of the translocated coronary arteries by conventional angiography.[12,13] In the Ross procedure where the aortic root is replaced by the native pulmonary trunk and as part of the ALCAPA surgical repair, coronary artery re-implantations are performed and the role of PSCMR has been reported as well.[11,14-16]
2. Anomalous origin or course of the coronary arteries: Advanced cardiac imaging has greatly improved our knowledge of the anatomic forms of anomalous aortic origin of the coronary arteries (AAOCA) and myocardial bridges which has led to furthering our understanding of the risk of sudden death in some variants.[17,18] Provocative myocardial perfusion studies have been recommended as part of the assessment of anomalous aortic origin of the right coronary artery from the opposite sinus of Valsalva[19] where the risk of sudden cardiac death and benefit from surgical intervention are less well understood.[17] Reports of a potential role for PSCMR in this setting has been suggested.[20]
3. Acquired coronary artery disease: This group is largely represented by Kawasaki disease (KD). Patients with KD and coronary artery aneurysms including those with large and giant aneurysms require serial evaluations[21] given their increased risk of coronary occlusion acutely or years after the acute phase, due to thrombosis or myointimal proliferation.[21,22] Tsuda et al reported 36% of patients with giant aneurysms requiring coronary artery bypass graft surgery at a median interval of 7 years.[23] These findings highlight the importance of long-term follow-up and the need to consider myocardial provocative studies such as PSCMR given the coronary artery involvement.[14]
4. Systemic right ventricle: In unrepaired ccTGA or D-TGA palliated with an atrial switch operation, right ventricular dysfunction and failure are major contributors to their morbidity and mortality.[24] Early detection of right ventricular dysfunction by the assessment of myocardial reserve using PSCMR has been reported and its potential role in ccTGA patients being considered for the anatomic repair has also been suggested.[25,26]

TABLE 1 High risk pediatric patients with congenital or acquired heart diseases

1. Surgical Coronary Re-implantation
   a. D-TGA s/p ASO
   b. Aortic root replacement
   c. Aortic valve replacement (ie, Ross)
   d. ALCAPA
2. Anomalous coronary artery origin or course
   a. AAOCA
   b. Myocardial Bridge
3. Acquired coronary artery disease
   a. Kawasaki Disease
   b. Polyarteritis nodosa
4. Systemic right ventricle

Abbreviations: AAOCA, anomalous aortic origin of the coronary arteries; ALCAPA, anomalous left coronary artery from the pulmonary artery; ASO, arterial switch operation; D-TGA, dextro transposition of the great arteries; PSCMR, pharmacologic stress cardiac MRI.

3 | PHARMACOLOGIC STRESS AGENTS

Pharmacologic myocardial stress testing has been established as a reliable alternative method to mimic physical exercise testing in evaluation of myocardial ischemia.[27] Various pharmacologic agents have been approved and could be grouped into two major categories: (a) Inotropic agents (Dobutamine) and (b) Coronary vasodilator agents (Dipyridamole, Adenosine, and Regadenoson).[27] Historically, Dobutamine was the main inotropic agent used to induce myocardial ischemia by increasing myocardial oxygen demand manifested by decreased perfusion and wall motion abnormalities.[27,28] Dobutamine is better utilized, where possible dynamic coronary obstruction is suspected such as in AAOCA, and myocardial bridges.[20,29] Coronary vasodilating agents, are utilized in the assessment of myocardial ischemia by inducing maximal coronary artery vasodilation which results in perfusion deficits in the ischemic territories.[30] All coronary vasodilators achieve maximal hyperemia by stimulating Adenosine A2A receptor. Adenosine and Dipyridamole are older non-selective A2A/A1 agonists, which often result in the development of more side effects.[30-32] Regadenoson as a relatively newer and more selective agent (A2A-selective) is considered to have a better side effect profile and a very similar diagnostic, and prognostic yield compared to other vasodilator agents.[31,33-37] The ability to administer Regadenoson as a single bolus with a single IV makes it advantageous in children as opposed to all other agents which require continuous infusion.[38,39] A detailed comparison between the currently available pharmacologic agents is summarized in Table 2.

TABLE 2 Comparison of different pharmacologic agents

	Dobutamine	Adenosine	Dipyridamole	Regadenoson
Administration	IV infusion 2 PIV	IV infusion 2 PIV	IV infusion 2 PIV	IV bolus 1 PIV
Peak (min)	1-2	Immediate	7-15	1-2
Half-life (min)	2	<5 s	30-45	30
Mechanism of action	Synthetic catecholamine	Endogenous vasodilator affects A1/$A2_A$ receptors	Inhibits adenosine deaminase	A2A adenosine receptor agonist (low affinity)
Contraindications and major adverse effects	Recent ACS, electrical or hemodynamic instability[38]	Bronchospasm/asthma (relative), SSS, high degree AVB, recent ACS, hypotension[31,32]	Bronchospasm/asthma(relative), SSS, high degree AVB, recent ACS, hypotension	SSS, high degree AVB, recent ACS, hypotension[34] Bronchospasm/asthma (rare, due to A2A selectivity). Seizure is a reported side effect
Effects of caffeine intake	No effects	Reduced sensitivity	Reduced sensitivity	No effects[39]
Current use and indications	Dynamic coronary obstruction (ie, AAOCA, myocardial bridges)	Fixed coronary obstruction; Microvascular coronary disease	Fixed coronary obstruction; Microvascular coronary disease	Fixed coronary obstruction; Microvascular coronary disease

Abbreviations: A2A, adenosine 2a receptor; AAOCA, anomalous aortic origin of the coronary arteries; ACS, acute coronary syndrome; AVB, atrioventricular block; IV, intravenous; PIV, peripheral intravenous catheter; SSS, sick sinus syndrome.

4 | COMPARISON WITH OTHER MYOCARDIAL PHARMACOLOGIC STRESS TESTING MODALITIES

PSCMR's diagnostic accuracy and safety profile have been shown to be superior to other stress imaging modalities in the adult population.[40] In the pediatric age group, its use is still evolving and the limitations are multifactorial including the lack of experience and less familiarity with this modality.[41] Pharmacologic stress echocardiography is widely used in adults. Limited acoustic windows following sternotomy for surgical repair of congenital heart disease, variability in image acquisition and experience are limiting factors in the use of pharmacologic stress echocardiography in children and young adolescents.[41] Studies comparing PSCMR and pharmacologic stress echocardiography have shown higher sensitivity and accuracy detecting myocardial ischemia related to coronary artery abnormalities.[41,42] Single-photon emission computed tomography (SPECT) as another stress imaging modality that can be used in pediatric age patients,[41] has the disadvantage of radiation exposure and it has been shown to be less accurate in detecting the myocardial ischemia due to lower spatial resolution imaging compared to PSCMR in adults.[43] Stress echocardiography or SPECT should be considered in patients who cannot undergo PSCMR due to contraindications to magnetic resonance imaging such as in the setting of ferromagnetic implants, or claustrophobia.[44]

While this review article is focused on pharmacologic stress testing modalities, it is worth mentioning that exercise cardiac magnetic resonance was studied and found to be feasible for pediatric patients with congenital heart disease.[45] This modality could offer a new form of stress CMR and add to our understanding of exercise physiology in patients with variant congenital heart diseases.[46]

5 | SUGGESTED PROTOCOL

5.1 | Pharmacologic agents

1. *Dobutamine* is administered as an infusion. Dobutamine is administered as an infusion. The typical initial dose is 5-10 μg/kg/min with an increase every 3 minutes to a maximum dose of 40 μg/kg/min in order to achieve a target heart rate of 85% of the maximal heart rate for age.
2. *Adenosine* is administered as an infusion with a starting dose of 140 μg/kg/min. If after 2-3 minutes, the heart rate does not increase by 10 bpm and/or blood pressure does not drop by >10 mm Hg, the infusion rate may be increased up to a maximal dose of 210 μg/kg/min depending on institutional and local norms.[33]
3. *Regadenoson* is administered as a single injection of 0.4 mg for patients with weight greater than 40 kg. It requires only a single peripheral IV. For patients less than 40 kg, a dose of 10 μg/kg/dose is used.

Table 3 summarizes the reported pediatric experience with PSCMR with variant pharmacologic agents.

Dobutamine use for pediatric patients is reported and well described in the pediatric literature.[10] Regadenoson use, however, has been increasingly used in the pediatric population and is not as well described. Here we report our institutional protocol. A conceptual framework for this protocol is shown (Figure 1).

TABLE 3 Summary of published literature on the use of Pharmacologic Stress Cardiovascular Magnetic Resonance (PSCMR) in the pediatric population and adults with congenital heart disease

First Author, Year, Country, (Ref. #), N, Median/Mean Age	Diagnoses	Agent used	Findings	Major adverse events	Comments
Noel et al., 2018, USA, ([12]), *N* = 36, 15 y	ASO	Regadenoson	Perfusion defects were noted in 30.5% of the cases	None	39% of cases underwent catheterization coronary angiography with excellent agreement with PSCMR results
Raimondi el al., 2018, France, ([13]), *N* = 132, 17 y	ASO	Dipyridamole	Perfusion defects were noted in 12%	Not reported	A subgroup of patients who underwent anteriorly re-implanted left CA were noted to have a higher probability for perfusion defects
Noel et al., 2017, USA, ([14]), *N* = 31, 15.8 y	ASO (36%) KD (29%) Aortic root replacement (19%) AAOCA (9.6%) Others (6.4%)	Regadenoson	Perfusion defects were noted in 23% of cases with FPP. None with LGE. 5/7 had concomitant wall motion abnormality	None	One patient with autism spectrum disorder was unable to complete the stress perfusion portion of the examination
Vijarnsorn et al., 2016, Canada,Thailand, ([49]), *N* = 48, 10.9 y	KD (39%) ASO (12.5%) Post Heart Transplantation (12.5%) Post AAOCA Repair (11%) Chest Pain (11%) Myocarditis (3%) Post coronary revascularization (3%) Other (8%)	Adenosine (92%) Dipyridamole (8%)	Perfusion defects were noted in 28%. 6 % with LGE without perfusion defect	None	Compared to catheterization coronary angiography, stress perfusion CMR had PPV of 89%, and NPV of 88%
Ntsinjana et al., 2016, UK, ([50]), *N* = 58, 14.1 y	ASO (60%) KD (14%) ALCAPA post coronary re-implantation (9%) Others (17%)	Adenosine	Perfusion defects were noted in 21%	Two aborted exams due to chest discomfort in one, and atrial tachycardia in another	Compared to catheterization coronary angiography and CTA, adenosine stress perfusion CMR: sensitivity 100% (95% confidence interval, CI: 71.6-100%), specificity 98% (95% CI: 86.7-99.9%), PPV 92.9% (95% CI: 64.2-99.6%), and NPV 100% (95% CI: 89.9-100%)
Schmitt et al., 2014, Germany, ([16]), *N* = 21, 2.8 y	ALCAPA post repair	Dobutamine	Wall motion abnormalities were noted in 67%. Perfusion defects were noted in 28%	Not reported	PSCMR identified perfusion defects and wall motion abnormalities that were not detected at rest.

(Continues)

TABLE 3 (Continued)

First Author, Year, Country, (Ref. #), N, Median/Mean Age	Diagnoses	Agent used	Findings	Major adverse events	Comments
Campbell et al., 2012, USA, ([51]), *N* = 51, 25.6 y	KD (20%) ToF s/p repair (12%) Hypertrophic Cardiomyopathy (8%) ALCAPA post coronary re-implantation (6%) AAOCA (left) post repair (6%) Aortic Stenosis post Ross procedure (5%) CoA post repair (5%) AAOCA (right) post repair (5%) Others (33%)	Adenosine	Perfusion defects were noted in 21.5%	Not reported	100% agreement in five patients who underwent catheterization coronary angiography
Buechel et al., 2009, Switzerland, ([8]), *N* = 47, 12 y	KD (32%) ASO (21%) AS post Ross procedure (19%) Cardiomyopathies, Myocarditis (13%) Others (16%)	Adenosine	Perfusion defects in 28.5%	Not reported	Compared to catheterization coronary angiography, stress perfusion CMR showed a sensitivity of 87% and a specificity of 95%
Strigl et al., 2009, USA, ([10]), N= 28, 7.3 y	KD 47% ASO 14% Post heart transplant 11% AAOCA (right) post repair 7% ALCAPA post coronary re-implantation 3.5% Others 17.5%	Dobutamine	One patient had an inducible wall motion abnormality (3.5%)	None	Interobserver agreement was 100% for test positivity and 92% for wall motion scores
Oosterhof et al., 2005, The Netherlands, ([52]), N= 39, 24 y	D-TGA patients post Mustard or Senning	Dobutamine physical exercise		Not reported	The study describes exercise stress response of D-TGA patients following atrial surgical baffling compared to healthy controls
Prakash et al., 2004, USA, ([53]), *N* = 30, 13 y	Tetralogy of Fallot post repair (16.6%) Left ventricular fibroma (10%) Hypertrophic Cardiomyopathy (10%) Dilated cardiomyopathy (3.3%) Post AAOCA (left) (6.6 %) Others (55%)	Adenosine (57%) Dipyridamole (29%) Dobutamine (14%)		Not reported	Good agreement was found between CMR evaluation of myocardial perfusion and viability and analysis of segmental wall motion with catheterization coronary angiography, and single photon emission computed tomography

(Continues)

TABLE 3 (Continued)

First Author, Year, Country, (Ref. #), N, Median/Mean Age	Diagnoses	Agent used	Findings	Major adverse events	Comments
Zedde et al., 2004, The Netherlands, ([54]), N= 41, 29 y	ccTGA (31%) D-TGA post Intraatrial surgical repair with Senning or Mustard (42%) Healthy controls (27%)	Dobutamine		Not reported	The study compares segmental and global right ventricular function at rest and during stress in patients having a systemic morphologically right ventricle
Dodge-Khatami et al., 2002, The Netherlands, ([27]), *N* = 24, 28 y	Unoperated and physiologically repaired ccTGA (54%) Healthy control (46%)	Dobutamine		Not reported	Compared to healthy controls, both patient groups had larger systemic RV volumes, diminished ejection fraction, but an appropriate response to dobutamine stress. Values of unoperated ccTGA patients are closer to normal than physiologically repaired patients
Tulevski et al., 2002, The Netherlands, ([55]), *N* = 58, 25 y	ccTGA (14%) Atrial Switch (27%) Subpulmonic RV (40%) Controls (19%)	Dobutamine		Not reported	Impaired filling in surgically corrected TGA and decreased contractility in patients with chronic pressure overloaded subpulmonic right ventricles. Dobutamine stress MRI may facilitate follow-up of RV dysfunction in patients with chronic RV pressure overload due to congenital heart disease
Tulevski et al, 2000, The Netherlands, ([26]), *N* = 21, 22.8 y	D-TGA post intra-atrial repair with Senning or Mustard (57%) Healthy controls (43%)	Dobutamine		Not reported	The study examined the role of dobutamine stress in the early detection of RV dysfunction in patients with TGA using CMR. The study showed inadequate RV filling possibly due to rigid atrial baffles, and compromised atrial function or decreased RV compliance

Abbreviations: AAOCA, anomalous aortic origin of the coronary arteries; ALCAPA, anomalous left coronary artery from the pulmonary artery; AS, aortic stenosis; ASO, arterial switch operation; BAV, bicuspid aortic valve; CA, coronary artery; ccTGA, congenitally corrected transposition of the great arteries; CoA, coarctation of the aorta; CMR, cardiac magnetic resonance; CTA, computed tomography angiogram; D-TGA, dextroposition of the great arteries; DCM, dilated cardiomyopathy; FPP, first pass perfusion; KD, Kawasaki disease; LGE, late gadolinium enhancement; LMS, left main stem; NPV, negative predictive value; PPV, positive predictive value; RV, right ventricle; ToF, tetralogy of Fallot.

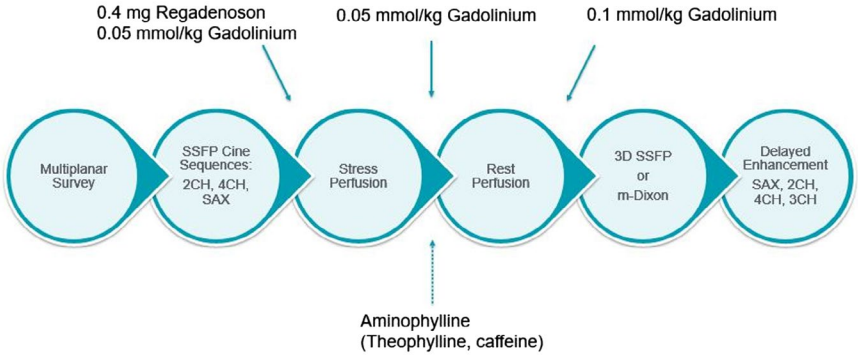

FIGURE 1 Conceptual framework for Regadenoson imaging protocol

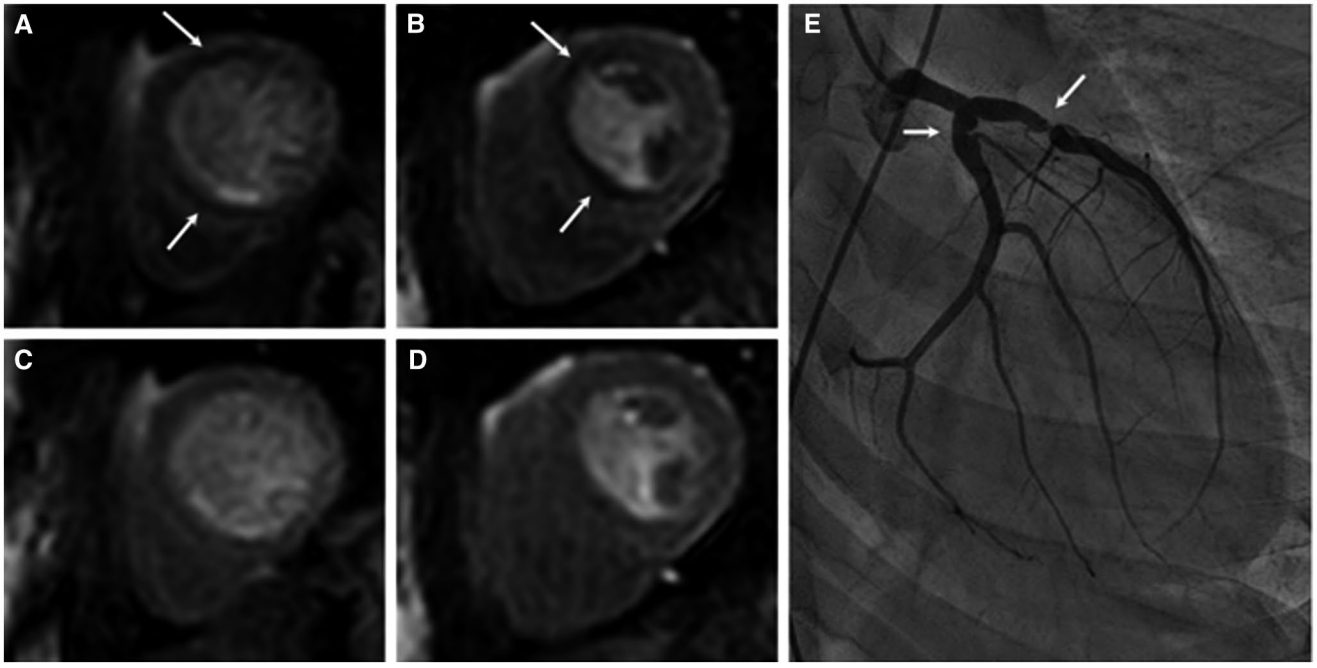

FIGURE 2 Stress (A, B) and rest (C, D) first pass perfusion imaging showing reversible subendocardial perfusion defects (arrows) at mid and apical inferoseptal and anteroseptal segments. E, Selective left coronary angiogram in RAO 20, CAU 30 orientation demonstrating good sized left main and LAD, with diffuse ectasia of the left system. There is a discrete stenosis of the LAD (arrow) and a second discrete area of stenosis of the circumflex (arrow), just proximal to an obtuse marginal branch

5.2 | Regadenoson imaging protocol

Survey imaging is performed followed by respiratory and vector gated axial stack steady state free precession (SSFP) imaging. Two chamber, four chamber, and short axis cines are obtained to evaluate ventricular volumes and function. Regadenoson is administered and stress myocardial first pass imaging is performed after administering the first dose of gadolinium at 0.05 mmol/kg injected at a rate of 3.5 mL/h or the highest rate the peripheral IV will allow in smaller children. Three slices in ventricular short axis are obtained with a voxel size of 2-2.5 × 2-2.5 × 7 mm. Slice thickness can be decreased in smaller patients to 4-5 mm. Repeat short axis cine imaging is performed to assess for ventricular wall motion abnormalities. Once the heart rate approaches the baseline, we proceed with resting perfusion imaging following a second dose of gadolinium at 0.05 mmol/kg. Another 0.1 mmol/kg of gadolinium is administered for late gadolinium enhancement imaging. 3-D SSFP or three point Dixon (m-Dixon) respiratory navigator sequence is then obtained to evaluate the proximal coronary arteries. In cases where susceptibility artifact is an issue, M-Dixon is institutionally preferred as it better compensates for magnetic field heterogeneity.[47] Approximately 6-8 minutes after the last dose of gadolinium, myocardial viability is assessed using a phase sensitive inversion recovery sequence in short axis, two chamber, four chamber, and three chamber orientations.[14] Aminophyllin is available as a single dose of 50 mg should side effects of Regadenoson develop. Given recurrent national shortages of Aminophylline, Theophylline and Caffeine can be considered as a substitute reversal agent.[48] Similar principles apply to dobutamine stress testing however resting perfusion sequence is done before dobutamine administration and cine

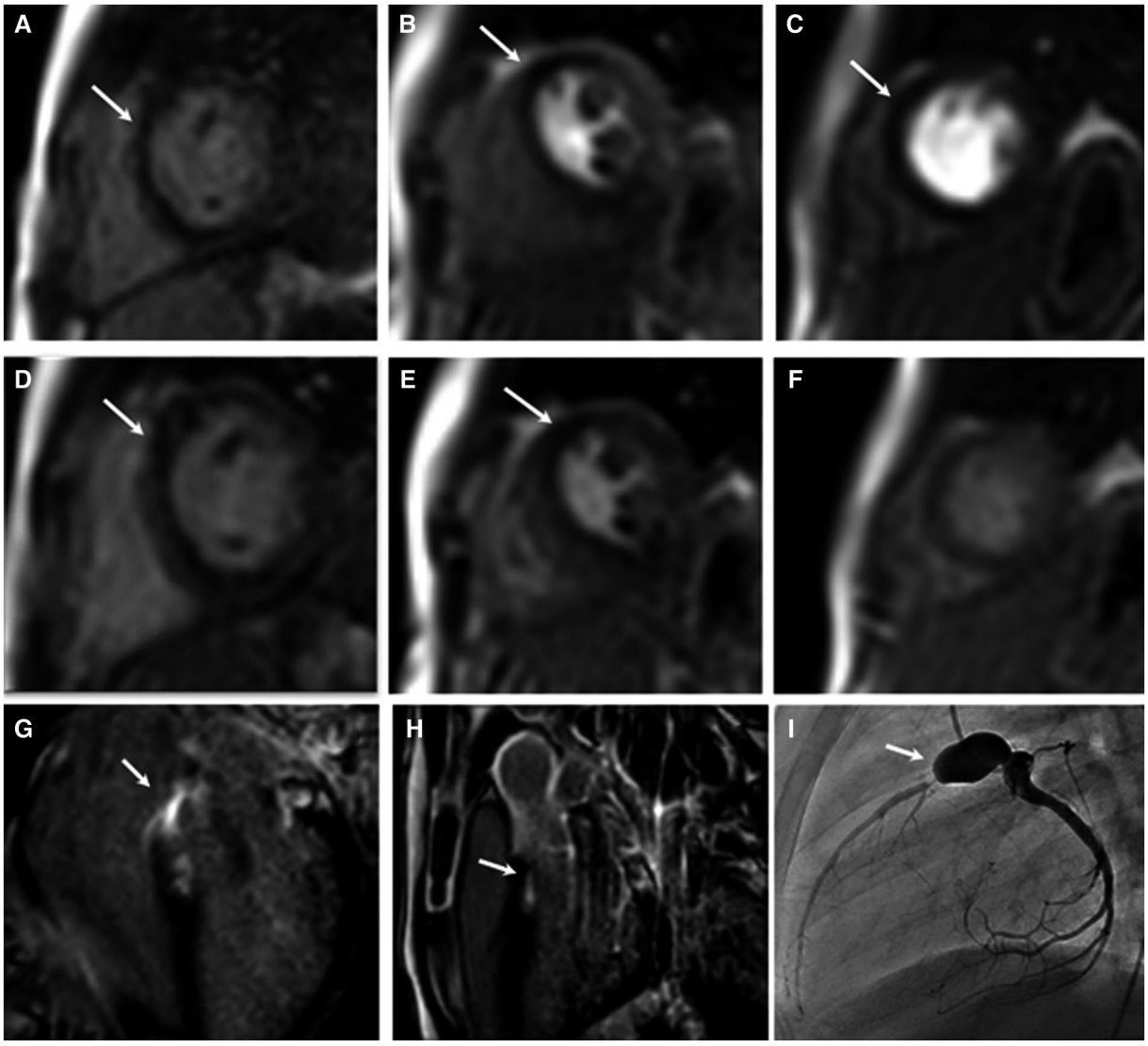

FIGURE 3 Stress (A-C) and rest (D-F) first pass perfusion imaging demonstrating fixed defect in basal (A,D) and mid anteroseptal (B, E, arrows) and reversible defect in the apical septal segment (C, F, arrows). G and H, Four chamber and three chamber view showing transmural LGE of basal anteroseptal segment (arrow). I, Selective left coronary angiogram in LAO 90, CRA 0 orientation demonstrating near total occlusion of LADartery and giant aneurysm with potential thrombus (arrow)

imaging is done during dobutamine infusion to evaluate for work motion abnormalities.

5.3 | Utility of PSCMR in two cases of Kawasaki disease

5.3.1 | Case 1

A 15-year-old female with KD diagnosed at 3 years of age developed giant aneurysms of right and left coronary artery systems. Overtime, there was regression of the aneurysms with resolution on right and persistently small aneurysms on the left coronary artery. She remained clinically asymptomatic on aspirin therapy. Surveillance treadmill exercise stress test demonstrated normal exercise capacity, no symptoms and no electrocardiographic abnormalities.

Stable mild residual fusiform dilation of the distal left main coronary artery, proximal left anterior descending (LAD), and circumflex coronary arteries were seen by CMR. Stress first pass perfusion showed subendocardial perfusion defects in the distribution of the LAD not noticed at rest perfusion. Subsequent cardiac catheterization showed a focal area of stenosis in the proximal LAD and circumflex coronary arteries and fractional flow reserve in the left coronary system was abnormal corroborating the myocardial perfusion findings (Figure 2). The patient ultimately underwent catheterization-based rotational atherectomy and cutting balloon dilation.

5.3.2 | Case 2

A 4-year-old male diagnosed with KD at 2 years of age, developed giant aneurysms of the left main, LAD artery, and right coronary arteries.

CMR evaluation was notable for giant aneurysms of the left coronary system, hyopkinesis of the basal anteroseptal segment in the LAD distribution, and the global left ventricular systolic function was normal. Myocardial perfusion imaging demonstrated a fixed perfusion defect in the basal and mid anteroseptal walls, and a reversible defect in the apical septal segment. In addition, there was transmural late gadolinium hyperenhancement of the basal anteroseptal segment. Subsequent cardiac catheterization showed near total occlusion of LAD and a giant aneurysm with a questionable thrombus (Figure 3). The patient underwent coronary artery bypass graft of the LAD and posterior descending coronary arteries.

6 | SUMMARY AND CONCLUSIONS

The role and utilization of PSCMR continue to evolve in the evaluation of pediatric age patients with congenital and acquired heart disease at high risk for myocardial ischemia.

Additional studies will hopefully add to our understanding of the indications, benefits, and pitfalls of this robust non-invasive imaging tool and its potential impact in management and prognostication.

AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript.
Conception and design of study: TA and MF
Drafting the manuscript: All authors
Revision of manuscript: All authors

ORCID

Munes Fares https://orcid.org/0000-0003-4516-2815

REFERENCES

1. Kato S, Saito N, Nakachi T, et al. Stress perfusion coronary flow reserve versus cardiac magnetic resonance for known or suspected CAD. *J Am Coll Cardiol*. 2017;70(7):869-879.
2. Buckert D, Witzel S, Steinacker JM, Rottbauer W, Bernhardt P. Comparing cardiac magnetic resonance-guided versus angiography-guided treatment of patients with stable coronary artery disease: results from a prospective randomized controlled trial. *JACC Cardiovasc Imaging*. 2018;11(7):987-996.
3. Vincenti G, Masci PG, Monney P, et al. Stress perfusion CMR in patients with known and suspected CAD: prognostic value and optimal ischemic threshold for revascularization. *JACC Cardiovasc Imaging*. 2017;10(5):526-537.
4. Manka R, Wissmann L, Gebker R, et al. Multicenter evaluation of dynamic three-dimensional magnetic resonance myocardial perfusion imaging for the detection of coronary artery disease defined by fractional flow reserve. *Circ Cardiovasc Imaging*. 2015;8(5): pii: e003061. https://doi.org/10.1161/CIRCIMAGING.114.003061
5. Stillman AE, Oudkerk M, Bluemke DA, et al. Imaging the myocardial ischemic cascade. *Int J Cardiovasc Imaging*. 2018;34(8):1249-1263.
6. Nagel E, Greenwood JP, McCann GP, et al. MR-INFORM Investigators. *N Engl J Med*. 2019;380(25):2418-2428. https://doi.org/10.1056/NEJMoa1716734.
7. Berry C, Mangion K, Corcoran D. Magnetic resonance perfusion imaging to guide management of patients with stable ischemic heart disease. *JACC Cardiovasc Imaging*. 2018;11(7):997-999.
8. Buechel ER, Balmer C, Bauersfeld U, Kellenberger CJ, Schwitter J. Feasibility of perfusion cardiovascular magnetic resonance in paediatric patients. *J Cardiovasc Magn Reson*. 2009;11:51.
9. Partington SL, Valente AM, Landzberg M, Grant F, Di Carli MF, Dorbala S. Clinical applications of radionuclide imaging in the evaluation and management of patients with congenital heart disease. *J Nucl Cardiol*. 2016;23(1):45-63.
10. Strigl S, Beroukhim R, Valente AM, et al. Feasibility of dobutamine stress cardiovascular magnetic resonance imaging in children. *J Magn Reson Imaging*. 2009;29(2):313-319.
11. Hauser M, Bengel FM, Kuhn A, et al. Myocardial blood flow and flow reserve after coronary reimplantation in patients after arterial switch and ross operation. *Circulation*. 2001;103(14):1875-1880.
12. Noel CV, Krishnamurthy R, Masand P, et al. Myocardial stress perfusion MRI: experience in pediatric and young-adult patients following arterial switch operation utilizing regadenoson. *Pediatr Cardiol*. 2018;39(6):1249-1257.
13. Raimondi F, Aquaro GD, De Marchi D, et al. Cardiac magnetic resonance myocardial perfusion after arterial switch for transposition of great arteries. *JACC Cardiovasc Imaging*. 2018;11(5):778-779.
14. Noel CV, Krishnamurthy R, Moffett B, Krishnamurthy R. Myocardial stress perfusion magnetic resonance: initial experience in a pediatric and young adult population using regadenoson. *Pediatr Radiol*. 2017;47(3):280-289.
15. Alsoufi B, Fadel B, Bulbul Z, et al. Cardiac reoperations following the Ross procedure in children: spectrum of surgery and reoperation results. *Eur J Cardiothorac Surg*. 2012;42(1):25-30; discussion 30–21.
16. Schmitt B, Bauer S, Kutty S, et al. Myocardial perfusion, scarring, and function in anomalous left coronary artery from the pulmonary artery syndrome: a long-term analysis using magnetic resonance imaging. *Ann Thorac Surg*. 2014;98(4):1425-1436.
17. Mery CM, Lawrence SM, Krishnamurthy R, et al. Anomalous aortic origin of a coronary artery: toward a standardized approach. *Semin Thorac Cardiovasc Surg*. 2014;26(2):110-122.
18. Uebleis C, Groebner M, von Ziegler F, et al. Combined anatomical and functional imaging using coronary CT angiography and myocardial perfusion SPECT in symptomatic adults with abnormal origin of a coronary artery. *Int J Cardiovasc Imaging*. 2012;28(7):1763-1774.
19. Cremer PC, Mentias A, Koneru S, et al. Risk stratification with exercise N(13)-ammonia PET in adults with anomalous right coronary arteries. *Open Heart*. 2016;3(2):e000490.
20. Noel C. Cardiac stress MRI evaluation of anomalous aortic origin of a coronary artery. *Congenit Heart Dis*. 2017;12(5):627-629.
21. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927-e999.
22. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, et al. Coronary artery aneurysms in Kawasaki disease: risk factors for progressive disease and adverse cardiac events in the US population. *J Am Heart Assoc*. 2016;5(9): pii: e003289. https://doi.org/10.1161/JAHA.116.003289
23. Tsuda E, Hamaoka K, Suzuki H, et al. A survey of the 3-decade outcome for patients with giant aneurysms caused by Kawasaki disease. *Am Heart J*. 2014;167(2):249-258.
24. Graham TP Jr, Bernard YD, Mellen BG, et al. Long-term outcome in congenitally corrected transposition of the great arteries: a multiinstitutional study. *J Am Coll Cardiol*. 2000;36(1):255-261.
25. Dodge-Khatami A, Tulevski II, Bennink GB, et al. Comparable systemic ventricular function in healthy adults and patients with unoperated congenitally corrected transposition using MRI dobutamine stress testing. *Ann Thorac Surg*. 2002;73(6):1759-1764.

26. Tulevski II, Lee PL, Groenink M, et al. Dobutamine-induced increase of right ventricular contractility without increased stroke volume in adolescent patients with transposition of the great arteries: evaluation with magnetic resonance imaging. *Int J Card Imaging*. 2000;16(6):471-478.
27. Leppo JA. Comparison of pharmacologic stress agents. *J Nucl Cardiol*. 1996;3(6 Pt 2):S22-S26.
28. Paetsch I, Jahnke C, Wahl A, et al. Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance perfusion. *Circulation*. 2004;110(7):835-842.
29. Paetsch I, Jahnke C, Fleck E, Nagel E. Current clinical applications of stress wall motion analysis with cardiac magnetic resonance imaging. *Eur J Echocardiogr*. 2005;6(5):317-326.
30. Lim WH, Koo BK, Nam CW, et al. Variability of fractional flow reserve according to the methods of hyperemia induction. *Catheter Cardiovasc Interv*. 2015;85(6):970-976.
31. Eltzschig HK. Adenosine: an old drug newly discovered. *Anesthesiology*. 2009;111(4):904-915.
32. Karamitsos TD, Arnold JR, Pegg TJ, et al. Tolerance and safety of adenosine stress perfusion cardiovascular magnetic resonance imaging in patients with severe coronary artery disease. *Int J Cardiovasc Imaging*. 2009;25(3):277-283.
33. Brink HL, Dickerson JA, Stephens JA, Pickworth KK. Comparison of the safety of adenosine and regadenoson in patients undergoing outpatient cardiac stress testing. *Pharmacotherapy*. 2015;35(12):1117-1123.
34. Mahmarian JJ, Peterson LE, Xu J, et al. Regadenoson provides perfusion results comparable to adenosine in heterogeneous patient populations: a quantitative analysis from the ADVANCE MPI trials. *J Nucl Cardiol*. 2015;22(2):248-261.
35. Farzaneh-Far A, Shaw LK, Dunning A, Oldan JD, O'Connor CM, Borges-Neto S. Comparison of the prognostic value of regadenoson and adenosine myocardial perfusion imaging. *J Nucl Cardiol*. 2015;22(4):600-607.
36. Hojjati MR, Muthupillai R, Wilson JM, Preventza OA, Cheong BY. Assessment of perfusion and wall-motion abnormalities and transient ischemic dilation in regadenoson stress cardiac magnetic resonance perfusion imaging. *Int J Cardiovasc Imaging*. 2014;30(5):949-957.
37. Iskandrian AE, Bateman TM, Belardinelli L, et al. Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. *J Nucl Cardiol*. 2007;14(5):645-658.
38. Wahl A, Paetsch I, Gollesch A, et al. Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases. *Eur Heart J*. 2004;25(14):1230-1236.
39. van Dijk R, Kuijpers D, Kaandorp T, et al. Effects of caffeine intake prior to stress cardiac magnetic resonance perfusion imaging on regadenoson- versus adenosine-induced hyperemia as measured by T1 mapping. *Int J Cardiovasc Imaging*. 2017;33(11):1753-1759.
40. Greenwood JP, Motwani M, Maredia N, et al. Comparison of cardiovascular magnetic resonance and single-photon emission computed tomography in women with suspected coronary artery disease from the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) Trial. *Circulation*. 2014;129(10):1129-1138.
41. Robbers-Visser D, Luijnenburg SE, van den Berg J, Moelker A, Helbing WA. Stress imaging in congenital cardiac disease. *Cardiol Young*. 2009;19(6):552-562.
42. Heitner JF, Klem I, Rasheed D, et al. Stress cardiac MR imaging compared with stress echocardiography in the early evaluation of patients who present to the emergency department with intermediate-risk chest pain. *Radiology*. 2014;271(1):56-64.
43. Smith-Bindman R, Miglioretti DL, Johnson E, et al. Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996–2010. *J Am Med Assoc*. 2012;307(22):2400-2409.
44. Shah R, Heydari B, Coelho-Filho O, et al. Stress cardiac magnetic resonance imaging provides effective cardiac risk reclassification in patients with known or suspected stable coronary artery disease. *Circulation*. 2013;128(6):605-614.
45. Barber NJ, Ako EO, Kowalik GT, et al. Magnetic resonance-augmented cardiopulmonary exercise testing: comprehensively assessing exercise intolerance in children with cardiovascular disease. *Circ Cardiovasc Imaging*. 2016;9(12): pii: e005282.
46. Claessen G, La Gerche A, Van De Bruaene A, et al. Heart rate reserve in fontan patients: chronotropic incompetence or hemodynamic limitation? *J Am Heart Assoc*. 2019;8(9):e012008.
47. Nezafat M, Henningsson M, Ripley DP, et al. Coronary MR angiography at 3T: fat suppression versus water-fat separation. *Magma*. 2016;29(5):733-738.
48. Abidov A, Dilsizian V, Doukky R, et al. Aminophylline shortage and current recommendations for reversal of vasodilator stress: an ASNC information statement endorsed by SCMR. *J Cardiovasc Magn Reson*. 2018;20(1):87.
49. Vijarnsorn C, Noga M, Schantz D, Pepelassis D, Tham EB. Stress perfusion magnetic resonance imaging to detect coronary artery lesions in children. *Int J Cardiovasc Imaging*. 2017;33(5):699-709.
50. Ntsinjana HN, Tann O, Hughes M, et al. Utility of adenosine stress perfusion CMR to assess paediatric coronary artery disease. *Eur Heart J Cardiovasc Imaging*. 2017;18(8):898-905.
51. Campbell MJ, Barker P, Darty S, Kim RJ. Adenosine stress perfusion CMR in young children: assessment of optimal imaging parameters. *J Cardiovasc Magn Reson*. 2013;15(1):P298.
52. Oosterhof T, Tulevski I, Roest A, et al. Disparity between dobutamine stress and physical exercise magnetic resonance imaging in patients with an intra-atrial correction for transposition of the great arteries. *J Cardiovasc Magn Reson*. 2005;7(2):383-389.
53. Prakash A, Powell AJ, Krishnamurthy R, Geva T. Magnetic resonance imaging evaluation of myocardial perfusion and viability in congenital and acquired pediatric heart disease. *Am J Cardiol*. 2004;93(5):657-661.
54. van der Zedde J, Oosterhof T, Tulevski II, Vliegen HW, Mulder BJ. Comparison of segmental and global systemic ventricular function at rest and during dobutamine stress between patients with transposition and congenitally corrected transposition. *Cardiol Young*. 2005;15(2):148-153.
55. 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):1077-1081.

How to cite this article: Fares M, Critser PJ, Arruda MJ, et al. Pharmacologic stress cardiovascular magnetic resonance in the pediatric population: A review of the literature, proposed protocol and two examples in patients with Kawasaki disease. *Congenital Heart Disease*. 2019;14:1166–1175. https://doi.org/10.1111/chd.12840