Regadenoson Stress Perfusion Cardiac Magnetic Resonance Imaging in Children With Kawasaki Disease and Coronary Artery Disease

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Coronary artery (CA) stenosis and occlusion in convalescent Kawasaki disease (KD) is progressive and may result in myocardial infarction. The use of regadenoson, a strong selective CA vasodilator with low side effect profile, for stress cardiac magnetic resonance (CMR) imaging has not been studied in children with KD. The safety, feasibility, and diagnostic utility of regadenoson stress CMR was assessed in children with KD and CA abnormalities. A retrospective review of regadenoson stress CMR in children with convalescent KD was performed. Hemodynamics changes after regadenoson administration and adverse effects were recorded. First-pass perfusion was evaluated at rest and during pharmacologic stress. The results were compared with anatomic CA imaging. Forty-one stress CMR (18 sedated examinations, 44%) were performed successfully in 32 patients. Median age was 11.2 years (range 2.2 to 18.6) and weight 41 kg (range 13 to 93.4). Heart rate increased 66 ± 25% (p <0.005) after regadenoson. Minor adverse events occurred in 6 sedated and 1 unsedated patients. Hypoperfusion during stress occurred in 16 of 41 (39%), including 5 inducible, 9 inducible and fixed, and 2 fixed lesions. Late gadolinium enhancement was present in 10 of 16 with hypoperfusion and in 1 without hypoperfusion. Stress CMR had 100% positive agreement and >90% negative and overall agreement with moderate-to-severe CA stenoses. Four patients with hypoperfusion underwent revascularization for severe CA stenoses. In conclusion, regadenoson stress CMR is hemodynamically safe and feasible in children with KD and CA disease. It has excellent agreement with CA angiography and aided decision-making to proceed with revascularization. **(Am J Cardiol 2019;124:1125−1132)**

Coronary artery (CA) aneurysm in children with Kawasaki disease (KD) evolves over time and can lead to CA thrombosis, stenosis, and occlusion.[1−3] It accounts for 5% of acute coronary syndrome in adults <40 years of age.[2] Risk stratification during periodic routine assessment of myocardial perfusion is important in the management of these patients.[2,4] Cardiac magnetic resonance (CMR) imaging using first-pass perfusion kinetics of gadolinium to detect hypoperfusion during adenosine infusion provided excellent sensitivity in patients with CA disease to risk stratify for major cardiac events.[5,6] Regadenoson has similar coronary vasodilatory effects compared with adenosine,[7] with less side effects due to its selective action on the A_{2A} adenosine receptor.[8,9] Stress perfusion CMR using regadenoson has not been studied in children with KD. We aimed to assess the safety, feasibility, and diagnostic utility of vasodilator stress perfusion CMR using regadenoson in children with KD and CA abnormalities.

Methods

We performed a retrospective cross-sectional study to evaluate the results of stress perfusion CMR utilizing regadenoson in children with KD and CA involvement. We included consecutive clinically indicated stress CMR examinations to assess for myocardial ischemia between August 2014 and December 2018 in patients with a history of KD and CA involvement at a tertiary pediatric center. The examinations were indicated as a routine surveillance or a clinical concern triggered by echocardiography with no evidence of ongoing myocardial ischemia. We studied the safety of regadenoson, the feasibility of the examination, and the diagnostic utility of the stress CMR. This study was approved by the institutional review board.

Anesthesia prescreening was performed to assess the feasibility and necessity of sedation during the examination. The CMR examinations and the use of regadenoson and gadolinium were discussed with the patients and families by a cardiologist before the tests. All patients were prepared by a pediatric nurse and examinations were performed by a CMR technologist under the supervision of a pediatric cardiologist. A pediatric cardiac anesthesiologist was present for all sedated examinations. Heart rate, respiratory rate, and pulse oximetry were monitored continuously, and a noninvasive blood pressure was cycled every 3 minutes throughout the duration of the examination. At the conclusion of the examination, patients were monitored for at least an hour and were

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assessed for major and minor events. Major events included heart block, arrhythmia, myocardial infarction, seizure, cardiac arrest, and death. Minor events were defined as nausea or vomiting, itching or rash, chest pain or chest tightness, overall discomfort, hypotension, or bronchospasm.

Patients weighing ≥40 kg received 400 μg of regadenoson (Lexiscan, Astellas Pharma, Northbrook, Illinois).[10] For patients weighing <40 kg, a dose of 8 μg/kg was adopted from the safety study by Gordi et al[11] and our own experiences.[10,12] Caffeine was avoided 24 hours before the examination. Aminophylline or caffeine was administered after stress perfusion sequences to decrease the likelihood of regadenoson-associated side effects.[13,14] Patients ≥40 kg received a 50-mg dose of aminophylline, whereas patients <40 kg received a dose of 0.25 mg/kg. A modified dose of 30-mg caffeine was used.[13]

Examinations were performed on a 1.5-T clinical CMR scanner (Achieva, Philips Medical Systems, Best, the Netherlands) using a 5-channel cardiac coil or a 16-channel XL torso coil depending on patient size, or a 3-T clinical CMR scanner (Philips Achieva) using a 32-channel cardiac coil. Cardiac synchronization and heart rate monitoring was performed with vector electrocardiographic gating. The imaging protocol remained consistent throughout the study period (Figure 1). Initial multiplanar survey imaging was performed, followed by morphologic black-blood imaging in the axial plan for a general overview of the cardiovascular anatomy. Free-breathing respiratory-triggered balanced steady-state free precession (bSSFP) pulse sequences were obtained in the 2-chamber, 4-chamber, and short-axis planes. The stress myocardial perfusion acquisition was acquired 60 seconds following administration of regadenoson, using 0.1 mmol/kg of gadolinium-based contrast agent (Gadovist, Bayer Healthcare Pharmaceuticals, Ontario, CA). Gadolinium was injected at a rate of 2.5 to 3.5 ml/s dependent on the intravenous catheter size. A single-shot (acquisition of the complete image within the same heartbeat), T_1-weighted saturation recovery gradient echo sequence with a parallel acceleration factor of 2, repetition time/echo time/flip angle = 2.5/1.2 ms/17°, voxel size 1.6 to 1.8 × 1.6 to 1.8 × 7 mm^3 (field of view 200 to 320 mm) was used for perfusion imaging at 3 short-axis slices at the basilar, mid-ventricular, and apical levels. A saturation delay of 120 milliseconds was used. Following perfusion sequences, although coronary vasodilatory effects were maintained, ventricular wall motion was assessed using cine bSSFP sequences at the same 3 ventricular short-axis levels, with a temporal resolution of approximately 20 ms/frame. Aminophylline or caffeine was administered for reversal. We then repeated the same perfusion sequence after heart rate returned to baseline. A second dose of 0.1 mmol/kg of gadolinium was given for a total gadolinium dose of 0.2 mmol/kg. A modified Look-Locker inversion time scout was done before late gadolinium enhancement (LGE) imaging using phase-sensitive inversion-recovery sequences in short-axis and 4-chamber orientation. A 3D whole heart magnetic resonance coronary angiography (MRCA) was done to assess CA anatomy.

Visual assessment of first-pass perfusion images was used to assess myocardial perfusion by 2 cardiologists (CVN and RWL) with 7 and 2 years of pediatric CMR experience. The perfusion sequences were evaluated for persistent decrease in signal intensity within the myocardium identifying hypoperfusion. Hypoperfusion during stress and not present at rest were deemed inducible and reversible. Hypoperfusion noted during stress and rest with corresponding LGE were deemed fixed and irreversible. Myocardial viability imaging was assessed based on the presence and extent of myocardial LGE. The bSSFP sequences with high-temporal resolution during rest and stress were used to assess wall motion abnormalities. Any infarct (scar) on LGE imaging was also assessed for each

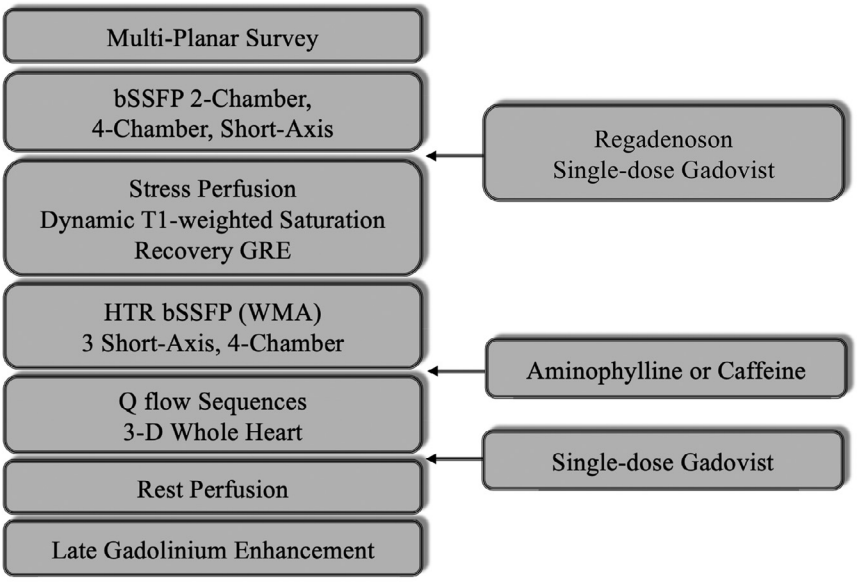

Figure 1. Flowchart shows acquisition protocol used for perfusion assessment, myocardial viability, and wall motion analysis. bSSFP = balanced steady-state free precession; GRE = gradient echo sequence; HTR = high temporal resolution; WMA = wall motion analysis.

segment. If all components were negative, the stress CMR overall result was considered negative. Anatomic location of hypoperfusion, wall motion abnormality, and LGE were recorded using the 17-segment American Heart Association/American College of Cardiology (AHA/ACC) model, excluding the apical cap segment.[15] Attempts were made to localize the affected segments to the left anterior descending, circumflex, and right CA.

The CA anatomy was assessed based on available X-ray coronary angiography (XRCA) within 12 months of stress CMR. Computerized tomographic coronary angiography (CTCA) was used if XRCA was not available, and MRCA was used if neither XRCA or CTCA was available. Moderate-to-severe CA stenoses were defined as ≥50% luminal narrowing by visual analysis. CA risk level at the time of the stress CMR was assigned using the AHA guideline.[2] CA aneurysm is considered small if the CA internal diameter z-score ≥2.5 and <5. Moderate aneurysm CA includes those with a z-score ≥5 and CA diameter <8 mm. Giant CA aneurysm is defined as an absolute CA internal diameter ≥8 mm or a z-score ≥+10.[2]

Statistical analyses were performed using STATA 14.2 software (StataCorp LLC, College Station, Texas). Comparisons of continuous variables before and after regadenoson were performed using independent sample Student's paired *t* test, and between sedated and unsedated patients using independent-sample Student's *t* test. Categorical variables were compared between sedated and unsedated group using chi-square test or Fisher's exact test. Values of $p < 0.05$ were considered statistically significant. The agreement of the first stress perfusion CMR results of each patient and visual severity of CA stenoses anatomic CA imaging was assessed by calculating positive, negative, and overall percent agreement.

Results

A total of 41 CMR examinations were performed in 32 patients (Table 1). The patient's median age at KD diagnosis was 4 years (range 3 months to 17 years). Five patients (16%) had a history of Kawasaki shock syndrome and another 4 (13%) had recurrent KD. The median age, weight, and body surface area at the time of the CMR examination were 11 years (range 2 to 19), 41 kg (range 13 to 93), and 1.3 m^2 (range 0.6 to 2.2), respectively. One patient with no history of CA involvement and 3 with mild CA dilation underwent stress CMR due to concern for exertional chest pain or dyspnea. All other patients with KD and significant CA involvement underwent stress CMR as routine surveillance.

In total, 18 (44%) sedated and 23 (56%) unsedated examinations were performed. Those required sedation were younger (9 ± 4 vs 13 ± 3 years, $p < 0.001$) with lower weight (33 ± 21 vs 56 ± 20 kg, $p = 0.001$) and body surface area (1.1 ± 0.4 vs 1.5 ± 0.4, $p < 0.001$) compared with unsedated patients. The left ventricular ejection fraction was lower in the sedated group (56 ± 5%) compared with unsedated group (60 ± 3%, $p < 0.001$). Propofol was used in all 18 (100%), inhaled volatile anesthetics (sevoflurane ± isoflurane) in 12 (67%), fentanyl in 2, midazolam in 1, ketamine in 1, and dexmedetomidine in 1 patient, in various combinations. Heart rate rose consistently in all patients after administration of regadenoson, with a percent heart rate increase of 66 ± 25% from baseline ($p < 0.001$). There was a statistically significant reduction in systolic (5 ± 10 mm Hg) and diastolic blood pressure (4 ± 9 mm Hg) with regadenoson (Table 2). Hypotension noted shortly after administration of regadenoson occurred in 5 sedated cases (28%) and 1 unsedated case (4%). Three of the 5 sedated patients were treated with a phenylephrine bolus, which promptly and adequately recovered the patient's blood pressure. One patient expressed significant agitation after the sedated stress CMR in the postanesthesia unit, requiring monitoring longer than the usual 1 hour before being discharged home in stable condition. Overall, there were 6 events (33%) in the sedated group and 1 (4%) in the unsedated group ($p = 0.03$). There was no major event (Table 3) and all were discharged home on the same day.

Nine examinations (22%) were performed on the 3.0-T and 32 (78%) on the 1.5-T scanner. All images were deemed of diagnostic quality for interpretation. The time between the stress and rest sequence was 23 ± 7 minutes. In Figure 2, hypoperfusion was noted in 16 of 41 (39%). Of

Table 1
Patient population and demographics at the time of the CMR

Total number of patients (n = 32)	
Age at onset of KD (years)	
<1	12 (38%)
1 − 5	9 (28%)
>5	11 (34%)
Male	20 (62%)
Female	12 (38%)
White	9 (28%)
Black	10 (31%)
Hispanic	9 (28%)
Other/Asian	4 (13%)
Dominant coronary artery	
Right	21 (65.6)
Left	1 (3.1)
Co-	1 (3.1)
Unknown	9 (28.1)
AHA risk level at the time of the 41 CMR examinations	
1: No coronary artery involvement	1 (2%)
2: Coronary artery dilation only	3 (7%)
3.1: Small aneurysm	5 (12%)
3.2: Small aneurysm regressed	2 (5%)
4.1: Persistent medium aneurysm	5 (12%)
4.2: Medium aneurysm regressed to small aneurysm	1 (2%)
4.3: Medium aneurysm regressed	0
5.1: Persistent large/giant aneurysm	19 (46%)
5.2: Large aneurysm regressed to medium	3 (7%)
5.3: Large aneurysm regressed to small	2 (5%)
5.4: Large aneurysm regressed	0

AHA = American Heart Association; CMR = cardiac magnetic resonance imaging; KD = Kawasaki disease.

Table 2
Hemodynamics changes with regadenoson

Parameters	Before	After	Difference	p
Heart rate (beats per minute)	77.5 ± 15.1	125.8 ± 16.0	48.3 ± 13.0	<0.001
Systolic blood pressure (mm Hg)	104.4 ± 10.6	99.0 ± 14.6	5.4 ± 9.6	<0.001
Diastolic blood pressure (mm Hg)	57.2 ± 12.5	53.5 ± 14.4	3.7 ± 9.0	0.01

Table 3
Potential side effects of regadenoson and events during all examinations

	Sedated (18)	Unsedated (23)
Major events		
Heart block	0	0
Arrhythmia	0	0
Myocardial infarction	0	0
Arrest	0	0
Death	0	0
Minor events		
Hypotension	5 (28%)	1 (4%)
Nausea or vomiting	0	0
Itching or rash	0	0
Chest pain/tightness	0	0
Overall discomfort	1 (6%)	0
Bronchospasm	0	0
Hospitalization	0	0
Total events	6 (33%)	1 (4%)

the 9 inducible and fixed hypoperfusion, 1 (2%) did not have LGE initially but was positive for LGE on the follow-up examination. Interestingly, of the 25 (61%) with normal myocardial perfusion, 1 (2%) had evidence of LGE in the inferior septum but no hypoperfusion. This patient was noted to have nonocclusive RCA thrombus on the MRCA that led to escalation of anticoagulation at that time. The patient developed occlusive RCA thrombus and ST-elevation myocardial infarction 5 months later. A repeat perfusion CMR showed extensive hypoperfusion and significant increase in the area of myocardial infarction and evidence of myocardial edema.

All balanced SSFP sequences during rest and stress were of diagnostic quality. Wall motion abnormalities at rest were noted on 7 examinations and were corresponding to perfusion defects and LGE. New areas of hypokinesia on the stress sequences were noted in 5 cases in which inducible hypoperfusion of the corresponding wall segments were also noted.

The agreement between the distribution of hypoperfusion and the presence of moderate-to-severe CA stenoses on XRCA (7 patients, 22%), CTCA (9 patients, 28%), or MRCA (14 patients, 44%) was assessed. Two patients (6%) were excluded from this analysis because XRCA and CTCA were not available and MRCA images were not interpretable due to motion artifact. Neither patient had hypoperfusion, LGE, or wall motion abnormalities. Six of the 7 who underwent XRCA were found to have moderate-to-severe stenoses of at least 1 major CA branch. One patient had positive stress CMR but only mild CA stenosis on XRCA. Subsequently, 1 patient underwent an elective coronary stent revascularization of the RCA, and 3 had successful surgical revascularization. CTCA revealed moderate-severe stenoses in 2 and no significant obstruction in 7 patients. MRCA was of adequate quality for interpretation in the remaining 14 patients who did not have significant CA stenoses. Figure 3 demonstrated the distribution of abnormal stress perfusion CMR and the severity of major CA branch stenoses by anatomic CA imaging. Hypoperfusion was present in all patients with moderate-to-severe left CA stenoses and moderate-to-severe right CA stenoses. The overall agreement between stress CMR and moderate-to-severe left anterior descending and right CA stenoses

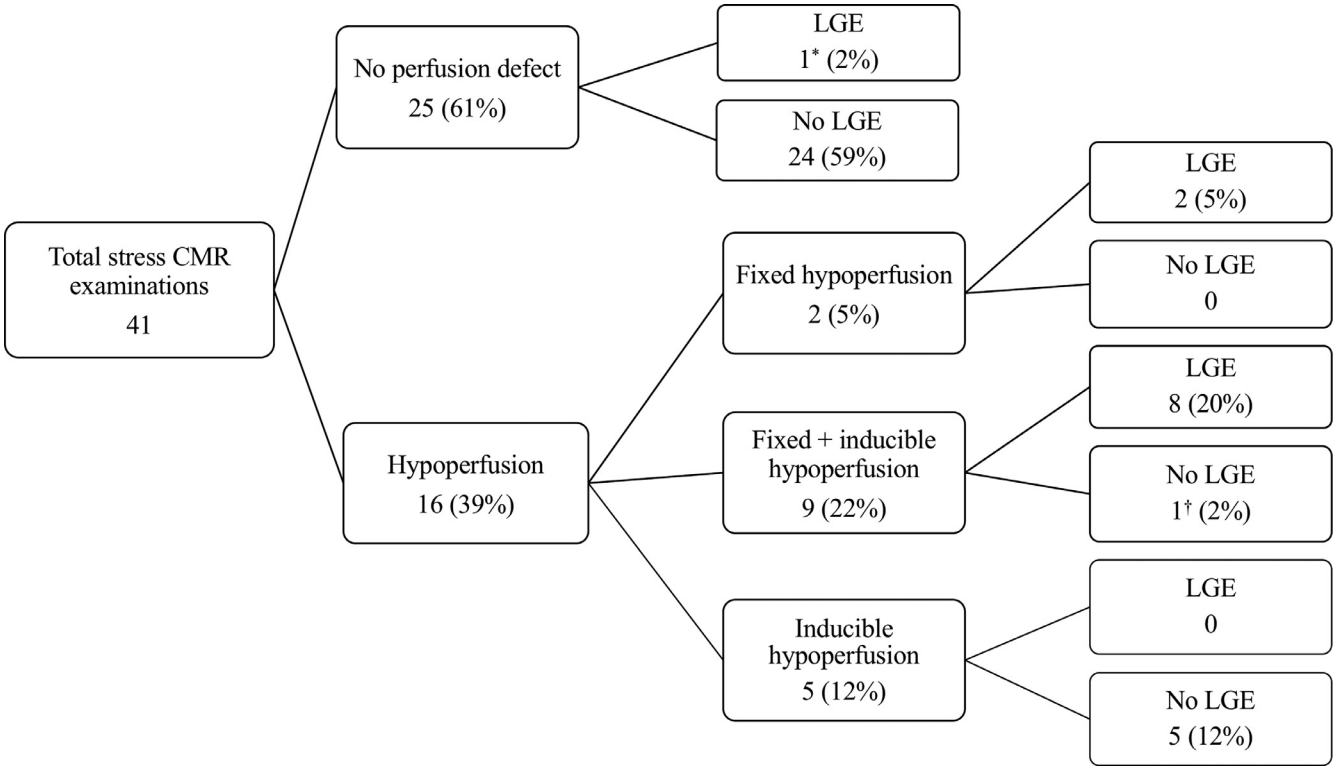

Figure 2. Distribution of stress perfusion CMR results. CMR = cardiac magnetic resonance imaging; LGE = late gadolinium enhancement. *This patient had ST-elevation myocardial infarction from RCA occlusion 5 months later. †LGE was present on the follow-up stress CMR.

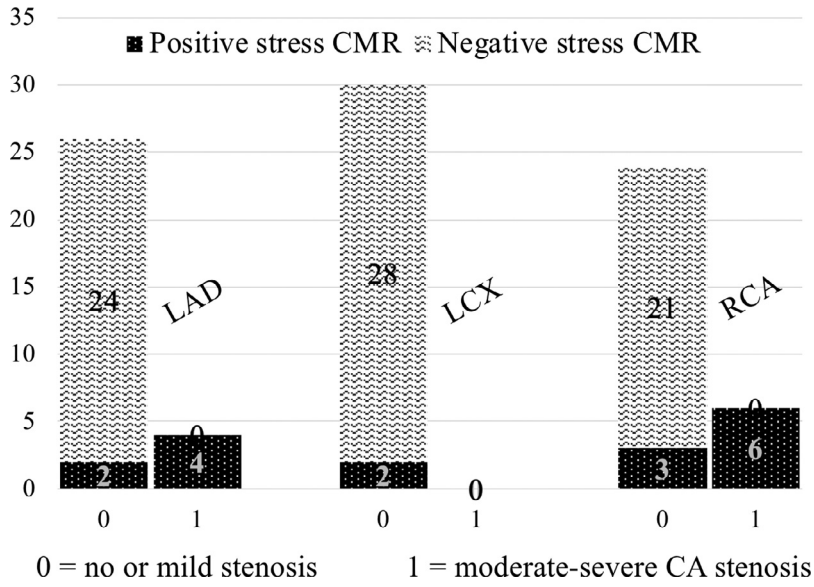

Figure 3. Distribution of stress perfusion CMR results and severity of each major CA branch stenoses (n = 30 patients). CA = coronary artery; CMR = cardiac magnetic resonance imaging; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery.

were 93% and 90%, respectively. The positive percent agreement was 100% for both left anterior descending and right CA stenoses, and the negative percent agreements were 92% and 88%, respectively.

CA revascularization was indicated in 4 patients with significant inducible hypoperfusion on regadenoson stress CMR and severe CA stenoses (Table 4). Figure 4 and Supplementary Videos 1 to 3 showed an example of patient 2 who was diagnosed with KD as an infant, had giant right and left anterior descending CA aneurysm which became stenotic. There was dyskinesia of the inferior wall corresponding to a previous right CA myocardial infarction, and extensive inducible hypoperfusion. XRCA showed right CA occlusion with reconstituted collateral formation and severe (90%) proximal left anterior descending CA stenosis. The patient underwent a bypass graft surgery between the left internal mammary artery and left anterior descending CA. A routine follow-up regadenoson stress perfusion CMR was performed 20 months after the bypass graft and showed marked improvement in myocardial perfusion and similar LGE pattern.

Discussion

To our knowledge, this is the first study to evaluate the safety, feasibility, and diagnostic utility of regadenoson as a coronary vasodilator for CMR to assess myocardial perfusion in children with convalescent KD. There were no major adverse events. Transient hypotension was the most commonly seen minor event in the sedated patients. All examinations were complete, and images were of diagnostic quality. The stress CMR results were highly agreeable with anatomic CA assessment and contributed to the complex decision-making process for revascularization of the most severe form of CA diseases in our experience. Vasodilator stress CMR was considered by KD experts as a promising noninvasive and radiation-free imaging modality with good diagnostic value.[2] It has been used in routine surveillance of children who had history of KD with and without persistent CA abnormalities.[10,16–18]

Regadenoson is well tolerated and safe with few adverse events during stress CMR in adults,[8] as well as in children.[10,12] Comparing with adenosine, regadenoson has similar to stronger vasodilatory effects,[7] and does not stimulate A_1 receptor that causes negative chronotropic and dromotropic effects, or A_3 receptor which is associated with mast cell degranulation and bronchospasm.[19] It was the first selective A_{2A} agonist approved by the US Food and Drug Administration.[19] In this study, more sedated children experienced hypotension; however, this number did not reach a statistical significance ($p = 0.07$). In adults whose stress

Table 4
Characteristics of patients who underwent revascularization

Patient	Age*	KD onset to intervention†	Inducible hypoperfusion	WMA	LGE	Interventions
1	10.1	9.9	+	+	+	RIMA − RCA; LIMA − LAD
2	2.3	1.7	+	+	+	LIMA − LAD
3	9.5	8.3	+	+	0	RCA stent
4	5.1	4.9	+	0	0	LIMA − LAD

KD = Kawasaki disease; LGE = late gadolinium enhancement; LIMA − LAD = graft from the left internal mammary artery to the left anterior descending coronary artery; RIMA − RCA = graft from the right internal mammary artery to the right coronary artery; RCA = right coronary artery; WMA = wall motion abnormalities.

* Age at the time of interventions (years).

† Timing from KD diagnosis to intervention (years).

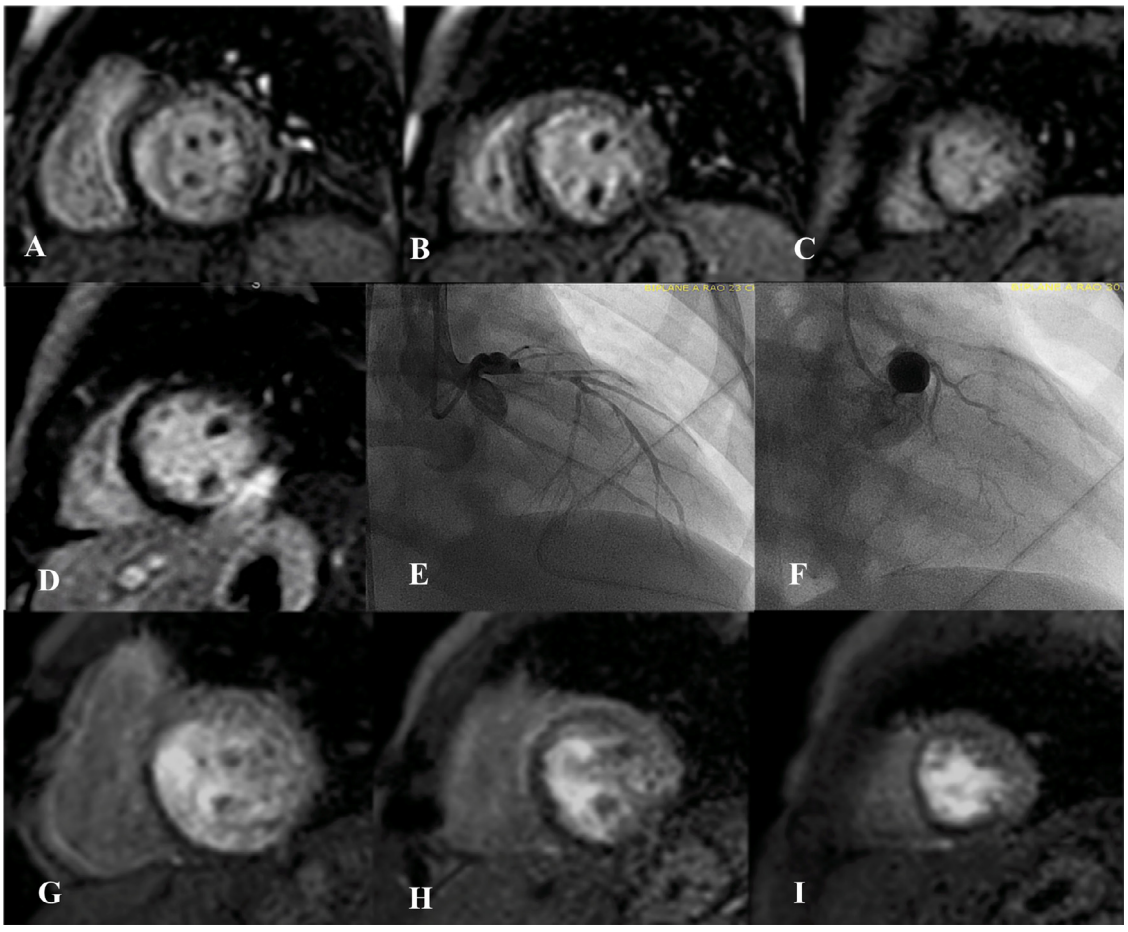

Figure 4. Stress CMR and XRCA in a 2-year-old patient (13 kg) with right dominant CA. Hypoperfusion (Supplementary Video 3) was seen in the anteroseptal, inferoseptal, and inferior segments of the basal *(A)* and mid-ventricular *(B)* region as well as the septal and inferior apical segments (*C*). Small transmural LGE was apparent in the inferior wall *(D)*. XRCA demonstrated moderate left CA aneurysm with severe LAD stenosis (*E*, Supplementary Video 1), and giant RCA aneurysm with severe stenosis with reconstituted collateral formation (*F*, Supplementary Video 2). A follow-up regadenoson stress perfusion CMR 20 months after LIMA-LAD graft showed hypoperfusion in the endocardial region of the anterior septum and small hypoperfusion in the inferior septum (*G* to *I*, Supplementary Video 4). CA = coronary artery; CMR = cardiac magnetic resonance imaging; LAD = left anterior descending coronary artery; LGE = late gadolinium enhancement; LIMA = left internal mammary artery; RCA = right coronary artery; XRCA = X-ray coronary angiography.

CMR were performed without sedation, symptomatic hypotension occurred in <1% and was associated with dysrhythmia.[8] No arrhythmia was observed in our study or series of children reported by Noel et al.[10,12] Hypotension among sedated cases may be explained by the augmented vasodilatory effects of anesthetics and dehydration from preprocedural fasting in younger patients. Although all incidences of hypotension were transient, the tendency to have hypotension in the sedated patients led to a recent modified approach in our practice to administer intravenous fluid bolus before administration of regadenoson in the sedated patients. In addition, 1 sedated patient became agitated in the postanesthesia recovery unit and was suspected to have postanesthesia delirium. This patient was given midazolam to allow time for a full recovery. Overall, sedation was associated with a higher rate of having minor events in our study ($p = 0.03$). However, patients recovered from all events and were discharged home the same day in stable conditions.

Similar to our previous experiences,[10,12] regadenoson stress CMR has been demonstrated in this series as a feasible diagnostic test for the assessment of myocardial perfusion in children with KD and CA disease. Heart rate increased in all cases and there was a small decrease in blood pressure, suggestive of adequate coronary vasodilatory effects in normal CA and potentially unmasking myocardial hypoperfusion in diseased territories. After administration of aminophylline and caffeine, heart rate and blood pressure recovered to the previously acceptable ranges. Although a dedicated line is required for a continuous adenosine infusion, regadenoson is administered as a single intravenous bolus, which allowed the CMR examination to be performed with a single intravenous access. Its onset peaks at 60 to 90 seconds, with vasodilatory effect lasting up to 6 minutes allowing for additional wall motion analysis in all of our patients.[10] All CMR examinations were completed within 45 to 60 minutes. Perfusion during stress and at rest, wall motion analysis, and LGE sequences were obtained successfully and of diagnostic quality. All of these features, in addition to the selective A_{2A} effects, make regadenoson an ideal coronary vasodilator for perfusion stress CMR.

Importantly, our results demonstrated vasodilator stress perfusion CMR using regadenoson having excellent agreement

with the anatomic assessment of CA by XRCA, CTCA, or MRCA. Stress CMR was recognized as a very sensitive test with moderate specificity in adults.[6] Although this study was not designed to examine the sensitivity of the test, stress CMR was positive in all cases with moderate-to-severe stenoses (100% positive agreement). The hypoperfusion seen in those without significant CA stenoses may be false-positive results or represent abnormal myocardial perfusion observed in all children with history of KD, as reported by Bratis et al using quantitative perfusion CMR.[17] There was no false-negative perfusion result during the time of the study. In addition, stress perfusion CMR using regadenoson can be helpful and allows for comparison following intervention such as the case depicted in Figure 4, similar to other studies in adults.[20,21]

Although limited by the nature of a retrospective design from a single center with small sample size, the study reported the novel use of regadenoson to assess myocardial perfusion in children with KD and significant CA disease. The use of anesthetics was variable among the sedated examinations and may have an impact on hemodynamics changes, especially hypotension.

In conclusion, vasodilator stress CMR examinations using regadenoson were feasible, diagnostic, and had excellent agreement with visual assessment of the CA by coronary angiography. Regadenoson was safe in older patients and hypotension may occur more commonly in the sedated patients, who may require additional interventions with intravenous fluid and/or medications. Our results suggest that stress CMR using regadenoson is a reasonable tool to assess myocardial perfusion and myocardial viability, which can provide useful information in the management of this challenging population.

Author Contributions

TTD was responsible for study design, data collection and analysis, and manuscript formation and revision. JCW participated in study design, data analysis, and manuscript formation and revision. RWL participated in study design, supervised the stress CMR, interpreted the images, and participated in manuscript formation and revision. AP participated in study design, was responsible for performance of CMR sequence, and participated in manuscript formation and revision. PM participated in study design, and manuscript formation and revision. CVN was responsible for study design, supervised the stress CMR, interpreted the images, and participated in manuscript formation and revision.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.06.033.

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