European Heart Journal – Cardiovascular Imaging (2014) **15**, 753–760
doi:10.1093/ehjci/jet278

Safety and tolerability of regadenoson CMR

Kim-Lien Nguyen[1,2], W. Patricia Bandettini[1], Sujata Shanbhag[1], Steve W. Leung[1,3], Joel R. Wilson[1,4], and Andrew E. Arai[1]*

[1]Cardiovascular and Pulmonary Branch, National Heart, Lung and Blood Institute, National Institutes of Health, 10 Center Drive Bldg 10, Rm B1D416, MSC 1061, Bethesda, MD 20892-1061, USA; [2]Division of Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90073, USA; [3]Division of Cardiovascular Medicine, University of Kentucky, Lexington, KY 40536, USA; and [4]Division of Cardiovascular Medicine, University of California, San Diego, San Diego, CA 92103, USA

Received 5 August 2013; accepted after revision 13 December 2013; online publish-ahead-of-print 21 January 2014

Aims Knowledge of adverse events associated with regadenoson perfusion cardiac magnetic resonance (CMR) and patient tolerability has implications for patient safety and staff training. We sought to assess the safety and tolerability of regadenoson stress CMR.

Materials and methods A group of 728 consecutive patients (median age 58, 44% female) and 25 normal volunteers (median age 21, 24% female) were recruited from August 2009 to March 2012 using a prospective, cross-sectional study design. Subjects were stressed using fixed-dose regadenoson and imaged using a 1.5T MRI scanner. Symptoms and adverse events including death, myocardial infarction (MI), ventricular tachycardia (VT)/ventricular fibrillation (VF), hospitalization, arrhythmias, and haemodynamic stability were assessed.

Results There were no occurrences of death, MI, VT/VF, high-grade atrioventricular block, or stress-induced atrial fibrillation. Notable adverse events included one case of bronchospasm and one case of heart failure exacerbation resulting in hospitalization. The most common symptoms in patients were dyspnoea (30%, $n = 217$), chest discomfort (27%, $n = 200$), and headache (15%, $n = 111$). There was minimal change between baseline and peak systolic and diastolic blood pressure in both patients and volunteers ($P > 0.05$). A blunted heart rate response to regadenoson was noted in patients with body mass index (BMI) ≥ 30 kg/m^2 ($P < 0.001$), and diabetes ($P = 0.001$).

Conclusions Regadenoson CMR is well tolerated and can be performed safely with few adverse events.

Keywords Cardiovascular MRI • Perfusion imaging • Coronary artery disease • Myocardial perfusion • Vasodilator agents • Regadenoson

Introduction

Coronary vasodilators are typically used to diagnose obstructive coronary artery disease (CAD) and to risk stratify patients. Currently, three vasodilator stress agents are approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for radionuclide myocardial perfusion imaging: regadenoson, adenosine, and dipyridamole. Use of these agents in perfusion cardiac magnetic resonance (CMR) imaging is considered an off-label indication.

Vasodilator stress agents bind to adenosine receptors (A_1, A_{2A}, A_{2B}, and A_3), which are located in multiple tissue types.[1] Activation of A_{2A} results in coronary vasodilation as well as partial peripheral vasodilation; whereas, activation of A_1, A_{2B}, and A_3 results in side-effects such as bronchospasm and high-grade atrioventricular (AV) block. An ideal vasodilator stress agent is one that binds preferentially to the A_{2A} receptor to cause coronary vasodilation with minimal activation of other receptor subtypes. Regadenoson has higher selectively for A_{2A} activation while adenosine binds non-selectively to A_1, A_{2A}, A_{2B}, and A_3. Dipyridamole decreases the degradation of adenosine and thus indirectly affects all adenosine receptors.

Regadenoson has been shown to be safe, non-inferior to adenosine, and has fewer side-effects in nuclear imaging trials.[2–4] Regadenoson is also safe in patients with stage 3–4 renal failure,[5,6] end-stage liver disease,[7] post-cardiac transplant,[8] chronic obstructive pulmonary disease (COPD) and mild-to-moderate asthma.[9,10]

* Corresponding author. Tel: +1 3014963658, Fax: +1 3014022389, Email: araia@nih.gov

However, there is a paucity of data to address the safety and tolerability of regadenoson in perfusion CMR,[11,12] where ECG monitoring is less reliable due to magnetohydrodynamic effects[13] and resuscitation necessitates prompt removal of the patient from the scanner. Knowledge of the adverse events associated with regadenoson perfusion CMR has implications for patient safety and staff training. Thus, we sought to prospectively assess the safety and tolerability of regadenoson in perfusion CMR.

Methods

Subject recruitment

Patients (age $\geq$18 years) with indications for vasodilator stress testing were prospectively enrolled from August 2009 to March 2012. Exclusion criteria included active wheezing, active symptoms of myocardial ischaemia or myocardial infarction (MI) within 24 h, estimated glomerular filtration rate (eGFR) $<$30 mL/min/1.73 m^2, or contraindications for regadenoson perfusion CMR. Pregnant and lactating females who were not willing to discard their breast milk for 24 h following the CMR exam were also excluded. Twenty-five normal volunteers (defined as non-smoking subjects without chest pain within 6 months and without known risk factors for coronary disease) were recruited as a control group. The study was approved by the Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act.

Imaging protocol

CMR imaging was performed using a 1.5 Tesla imaging system (Siemens Medical Solution, Erlangen, Germany). First-pass stress and rest perfusion images were obtained using a steady-state-free precession sequence (SSFP) (n = 706) (TR 2.5 ms, TE 1.04 ms, flip angle 50°, voxel size 3 × 3 × 8 mm, bandwidth 1085 Hz/pixel) or a gradient spoiled echo sequence (n = 22) (TR 2.17 ms, TE 1.03 ms, flip angle 12°, voxel size 3 × 3 × 8 mm, bandwidth 651 Hz/pixel). Gadolinium (Magnevist©, Gadopentetate Dimeglumine, Bayer Healthcare, Wayne, NJ, USA) 0.05 mmol/kg body weight was given at 5 mL/s for both stress and rest image acquisition. Depending on the heart rate (HR), either three or four left ventricular short-axis slices (base, mid-ventricle, and apex) were obtained. SSFP cine images were obtained during the 20-min post-stress period (TR 2.90 ms, TE 1.19 ms, flip angle 50°, voxel size 1 × 1 × 6 mm, bandwidth 930 Hz/ pixel). Late gadolinium enhancement images were acquired using a phase sensitive inversion recovery fast gradient echo sequence (TR 8.3 ms, TE 3.25 ms, TI individualized to null the myocardium, flip angle 25°, voxel size 1 × 1 × 6 mm, bandwidth 140 Hz/ pixel) (*Figure 1*).

Stress protocol and assessment of symptoms, adverse events, and heart rate response

Patients were asked to abstain from caffeine intake and to refrain from taking anti-anginal medications including beta-blockers 24 h prior to the exam. Fixed-dose (0.4 mg) regadenoson (Astellas, Northbrook, IL, USA) was given as an iv bolus over 10 s. Within 5 min after acquisition of first-pass perfusion images, aminophylline 100 mg iv was given to reverse the effects of regadenoson (*Figure 1*). Sublingual nitroglycerine and iv metoprolol were available for severe and persistent chest pain. A 12-lead ECG was performed before and after the exam. Owing to magnetohydrodynamic effects causing ECG signal distortion, ECG tracing during examination was used only for gating purposes. Oxygen saturation, blood pressure (BP), and HR were monitored throughout the exam. Emergency medical supplies including a defibrillator were available in the immediate vicinity. One physician, one nurse, and one technologist were present during the exam.

Patients were queried about their symptoms before and after regadenoson and aminophylline administration. Stress-related adverse events including death, MI, ventricular tachycardia (VT)/ventricular fibrillation

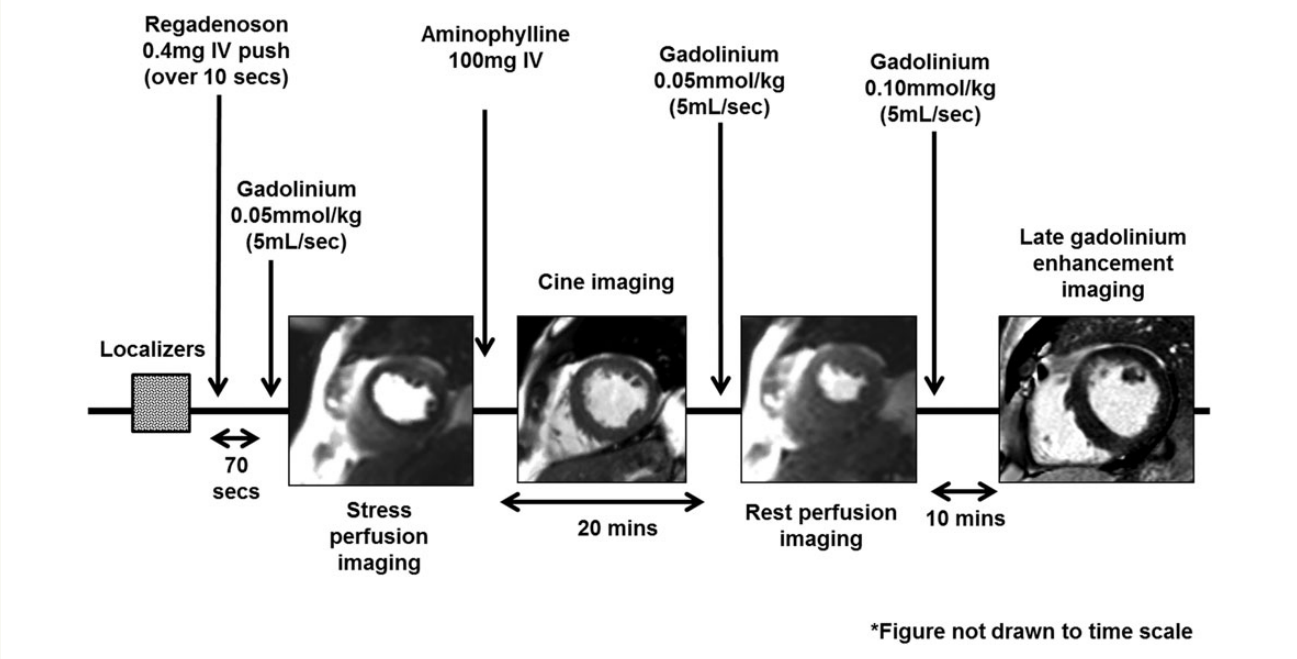
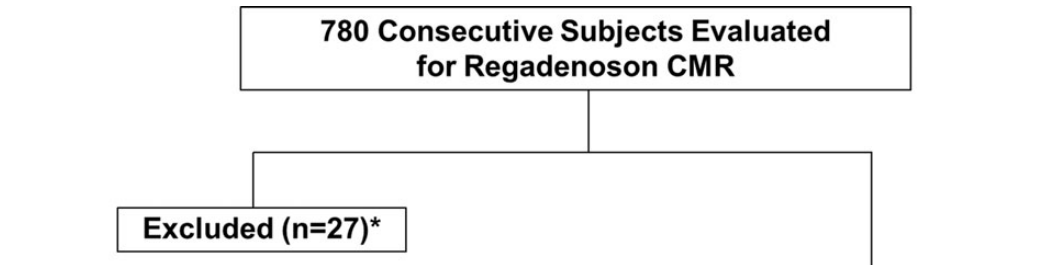


Figure 1 Regadenoson perfusion imaging protocol. sec (s), second (s); min (s), minute (s).



*Reasons for Exclusions	
IV access difficulty	n=1
Unverifiable prosthesis	n=1
Acute renal failure	n=1
Decompensated heart failure prior to MRI	n=1
Intake of dipyridamole	n=1
Acute asthma exacerbation prior to MRI	n=1
2° AV block	n=1
Afib with rapid ventricular response	n=1
Scanner malfunction prior to regadenoson administration	n=2
Claustrophobia	n=17 (2%)

Figure 2 Recruitment of subjects. AV, atrioventricular; CMR, cardiac magnetic resonance imaging.

(VF), hospitalization, bronchospasm, and non-life-threatening arrhythmias were noted. Other adverse events, including nephrogenic systemic fibrosis, contrast extravasation, reaction to gadolinium, and thrombophlebitis, were also assessed.

Baseline HR and BP were obtained at rest prior to stress exam in the supine position. Peak HR was defined as the highest HR during the stress perfusion scan and prior to administration of aminophylline. Peak BP was defined as the BP prior to reversal with aminophylline. Heart rate response (HRR) and blood pressure response (BPR) were calculated as previously described[14] (HR response = $[(HR_{peak} - HR_{baseline})/HR_{baseline}] \times 100$; BP response = $[(BP_{peak} - BP_{baseline})/BP_{baseline}] \times 100$).

Statistical analysis

Continuous variables are reported as median [inter-quartile range (IQR)] and compared using the Mann–Whitney *U* test. Categorical data are reported as discrete values and percentages and compared using the Chi square test. Nine variables [age $\geq$64 years, BMI $\geq$30 kg/m^2, diabetes (DM), left ventricular ejection fraction (LVEF) $\leq$40%, abnormal perfusion, eGFR 30–44.9 mL/min/1.73 cm^2, eGFR 45–60 mL/min/1.73 cm^2, eGFR >60 mL/min/1.73 cm^2, and beta-blocker use) were chosen based on their potential association with cardiac autonomic function and HRR and evaluated using univariable logistic regression analysis. Significant predictors were then entered into a multivariable logistic regression model to predict HRR in the lowest quartile. Interactions among significant predictors were assessed and adjusted in the best-fit model. Model sensitivity and specificity were assessed via area under the curve (ROC) analysis and goodness of fit was assessed by the Hosmer–Lemeshow test. Two-tailed *P*-values were used for all statistical assessment and a *P*-value <0.05 was considered significant. Analyses were performed using MedCalc Version 12.0.1.0 (Mariakerke, Belgium).

Results

Study population

Seven hundred and eighty consecutive subjects were evaluated over a period of 2.6 years, but 27 patients were excluded because they did not receive regadenoson for various reasons (*Figure 2*). Thus, a total of 753 subjects [728 patients (median age 58 (IQR: 49–64, range 19–86), 44% female, 33% BMI $\geq$30 kg/m^2, 20% DM and 25 normal volunteers (median age 21 (IQR: 20–23, range 18–48), 24% female)] were included in the final analysis. Two per cent of subjects (17 of 780) developed claustrophobia during the initial stages of the CMR exam and did not receive regadenoson nor complete the CMR exam—thereby accounting for 63% (17 of 27) of those excluded from the final analysis. Patient characteristics are summarized in *Table 1*.

Adverse events

Overall, there were few adverse events (*Table 2*). There were no deaths, MIs, VT/VF, high-grade AV block, regadenoson-induced atrial fibrillation, or nephrogenic systemic fibrosis. There was one hospitalization related to acute exacerbation of chronic heart failure and one episode of bronchospasm requiring observation in the emergency department despite reversal with aminophylline. Six per cent (46 of 728) of patients had minor stress-induced dysrhythmias (premature atrial and/or ventricular contractions). Two patients experienced transient symptomatic hypotension (one was secondary to transient bigeminy; one was secondary to transient narrow complex bradycardia with difficult to distinguish *P*-wave morphology). Two patients had contrast extravasation. Rash or hives

Table 1 Baseline patient characteristics

	Patient group (n = 728)
Age, y	58 (49–64)
Female	322 (44%)
BMI (kg/m^2)	28 (25–31)
Creatinine	0.90 (0.80–1.1)
eGFR >60 mL/min/1.73 cm^2	647 (89%)
eGFR 45–60 mL/min/1.73 cm^2	72 (10%)
eGFR 30–44.9 mL/min/1.73 cm^2	9 (1%)
Ethnicity (%)	
Hispanic	82 (11)
White	76 (92)
Non-Hispanic	646 (89)
White	365 (57)
Black	124 (19)
Asian	147 (23)
Other	10 (2)
Medications (%)	
ACE inhibitors	232 (32)
ARB	69 (9)
Aspirin	394 (54)
Beta-blocker	337 (46)
CCB	108 (15)
Clopidogrel/prasugrel	82 (11)
Statin	384 (53)
CAD risk factors (%)	
Family history of CAD	164 (23)
HTN	410 (56)
Dyslipidaemia	381 (52)
Smoking	201 (28)
CAD equivalent (%)	
Diabetes	147 (20)
Known CAD	175 (24)
Prior MI	93 (13)
Prior PCI	91 (13)
CABG	46 (6)
Atrial fibrillation	8 (1)
CVA/TIA	24 (3)
COPD/asthma	10 (1)
MRI LV function and morphology	n = 684[a]
LV EF, %	63 (57–68)
LV ESVI, mL/m^2	28 (23–36)
LV EDVI, mL/m^2	77 (67–88)
LV mass index, g/m^2	49 (42–57)
LV SVI, mL/m^2	47 (42–52)

*Continuous variables are reported as median (IQR) and compared using the Mann–Whitney U test. Categorical variables are reported as absolute values and percentages and compared using the Chi square test.
[a]Forty-four studies had real-time cine images and thus volumetric measurements were not calculated.
ACE, angiotensin; ARB, angiotensin receptor blocker; ASA, aspirin; BMI, body mass index; CAD, coronary artery disease; CABG, coronary artery bypass graft; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; EF, ejection fraction; eGFR, glomerular filtration index; HTN, hypertension; LV ESVI, left ventricular end-systolic volume index; LV EDVI, left ventricular end-diastolic volume index; LV SVI, left ventricular stroke volume index; MI, myocardial infarction; PCI, percutaneous intervention; TIA, transient ischaemic attack; y, year (s).

Table 2 Frequency of adverse events associated with regadenoson CMR

Adverse events	Patient cohort (n = 728)
Death	0
VT/VF	0
Myocardial infarction	0
Hospitalization	1
Bronchospasm	1
High-grade AV block	0
Stress-induced atrial fibrillation	0
Nephrogenic systemic fibrosis	0
Stress-induced ectopies (PACs/PVCs)	46 (6%)
Bigeminy	2 (<1%)
Symptomatic hypotension	2 (<1%)
Contrast extravasation	2 (<1%)
Minor reaction to gadolinium (rash/hives)	1 (<1%)
Thrombophlebitis	0
Chest pain requiring NTG	9 (1%)
Chest pain requiring iv metoprolol	6 (<1%)

AV, atrioventricular; iv, intravenous; NTG, nitroglycerine; PACs, premature atrial contractions; PVCs, premature ventricular contractions; VF, ventricular fibrillation; VT, ventricular tachycardia.

occurred in one subject and may be related to gadolinium or regadenoson. Nine patients required sublingual nitroglycerine for chest pain; whereas six patients required additional iv metoprolol for symptom resolution.

Frequency of symptoms

Dyspnoea, chest pain, and headache were the three symptoms most frequently reported by patients (*Figure 3*). More normal volunteers experienced palpitations when compared with the patient cohort (60 vs. 8%; $P = 0.652$), while dyspnoea was experienced at a similar frequency ($P = 0.525$).

Haemodynamic response to regadenoson

Systolic and diastolic BPR among patient subgroups and normal volunteers was not statistically significant ($P > 0.05$, *Figure 4*). In the patient cohort, median systolic and diastolic BPR were −2% (IQR: −10 to 5) and −5% (IQR: −14 to 3), respectively. In normal volunteers, median systolic and diastolic BPR were −3% (IQR: −6 to 6) and −10% (IQR: −17 to 1), respectively. Despite relatively similar baseline median HR between normal volunteers [65 bpm (IQR: 53–71)] and patient cohort [66 bpm (IQR: 58–76), $P = 0.066$], normal volunteers had a higher median HRR [71% (IQR: 58–97)] when compared with the patient cohort [48% (IQR: 35–63), $P < 0.001$] (*Figure 4*). The higher HRR by normal volunteers likely represent a robust sympathetic response as one would expect in a younger cohort of normal healthy volunteers. A statistically significant blunted HRR was noted in those with BMI ≥30 kg/m^2 and DM (*Figure 5*). Patients with BMI ≥30 kg/m^2 had a higher median baseline HR [68 bpm (IQR: 62–77)] when compared with those

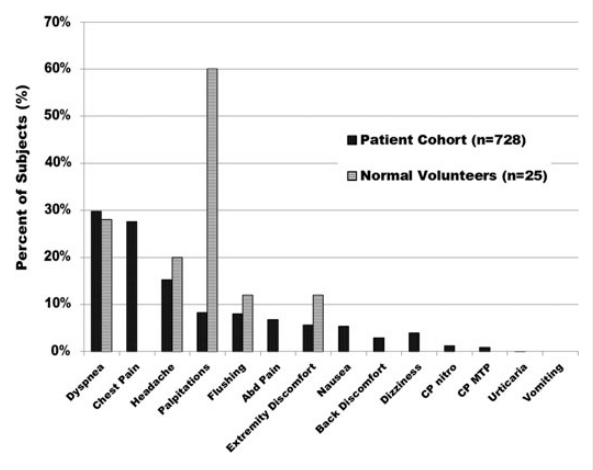


Figure 3 Frequency of symptoms reported by patients and normal volunteers. Abd, abdominal; CP nitro, chest pain requiring nitroglycerine; CP MTP, chest pain requiring metoprolol.

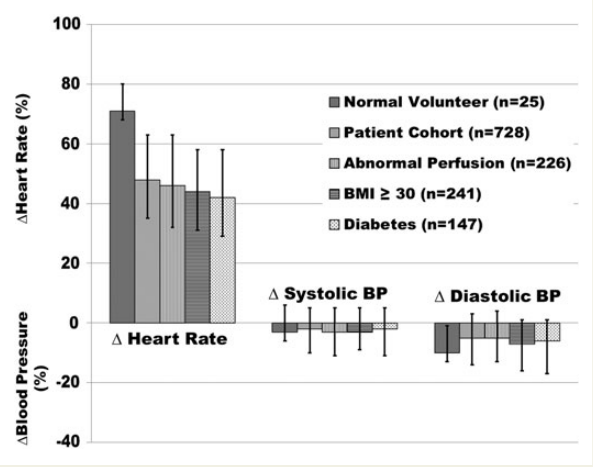


Figure 4 Haemodynamic response with regadenoson. Values reported are medians. Error bars represent the inter-quartile range. Systolic and diastolic BP response among patient subgroups was not statistically significant ($P > 0.05$). BMI, body mass index; BP, blood pressure.

with BMI <30 kg/m^2 [64 bpm (IQR: 57–65 bpm), $P = 0.001$]. A higher resting HR was also present in patients with DM [69 bpm (IQR: 62–80)] compared with those without DM [65 bpm (IQR: 58–75), $P = 0.001$].

Using a multivariable logistic regression model, the following variables predicted the lowest quartile of HRR (Hosmer–Lemeshow test for goodness of fit $\chi^2 = 8$, $P = 0.37$): age $\geq$64, BMI $\geq$30 kg/m^2, DM, LVEF $\leq$40%, and abnormal perfusion (*Table 3*). Of the significant predictors of HRR in the lowest quartile, abnormal perfusion was the weakest ($P = 0.042$). Interactions were found between age*BMI*DM ($P = 0.023$) and abnormal perfusion*DM ($P = 0.037$).

Discussion

Our study demonstrates that regadenoson perfusion CMR can be performed in a clinical setting with few adverse events and that regadenoson is well tolerated. There were no occurrences of death, MI, VT/VF, high-grade AV block, or stress-induced atrial fibrillation. A blunted HRR was noted in patients with a BMI $\geq$30 kg/m^2 and diabetes.

Several studies have reported on the safety and tolerability of adenosine and dobutamine stress CMR.[15–18] Large-scale trials have also established the safety of regadenoson stress testing with single photon emission computed tomography (SPECT).[2–4,19] However, there are no published large-scale, prospective studies assessing the safety and tolerability of regadenoson perfusion CMR. The CMR environment represents a confined space with a strong magnetic field, where the ECG signalsmay be distorted,[13] and resuscitation requires prompt patient removal. Thus, knowledge of adverse events relating to the safety and tolerability of regadenoson CMR is important for patient safety and for staff training.

The EMA defines adverse events as 'any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment' while the United States FDA defines adverse events as 'an undesirable experience associated with the use of a medical product or device'. Both define serious events as those resulting in death, life-threatening conditions, hospitalization, disability or permanent damage, or congenital anomaly or birth defect. Based on the above definition, two adverse events in our study merit further discussion.

Event #1 involved regadenoson-induced bronchospasm in a patient with known CAD but no history of COPD or asthma. He developed bronchospasm with active wheezing following regadenoson injection. After reversal with aminophylline, albuterol, and methylprednisolone were administered. He was admitted to the emergency department for further monitoring. No intubation or hospitalization was required. According to the package inserts, bronchoconstrictive or bronchospastic conditions such as asthma are contraindications for adenosine.[20,21] However, these conditions are not listed as contraindications for regadenoson.[22,23] The regadenoson package insert contains a warning for potential bronchoconstriction and suggests that bronchodilator therapy and resuscitative measures be available. However, multiple studies evaluated the specific safety of regadenoson in patients with COPD and asthma and found no increase in acute COPD or asthma exacerbation.[9,10,24]

Event #2 involved exacerbation of chronic heart failure requiring hospitalization. The patient had known multivessel CAD and declined bypass surgery 2 years prior to his presentation. Because of recurrent heart failure, he was referred for assessment of his ischaemia and scar burden. On presentation, he reported stable dyspnoea and lower extremity oedema. He was haemodynamically stable before, during, and after the perfusion CMR. However, his exam showed multiple moderate to severe perfusion defects with viable myocardium. After discharge, he had worsening of dyspnoea and presented to the hospital where he did not have ischaemic ECG changes, but did have a troponin-I of 0.15 μg/L and a pro-BNP of 2550 pg/mL. He was admitted for three-vessel revascularization and heart failure management. In reviewing the case, we

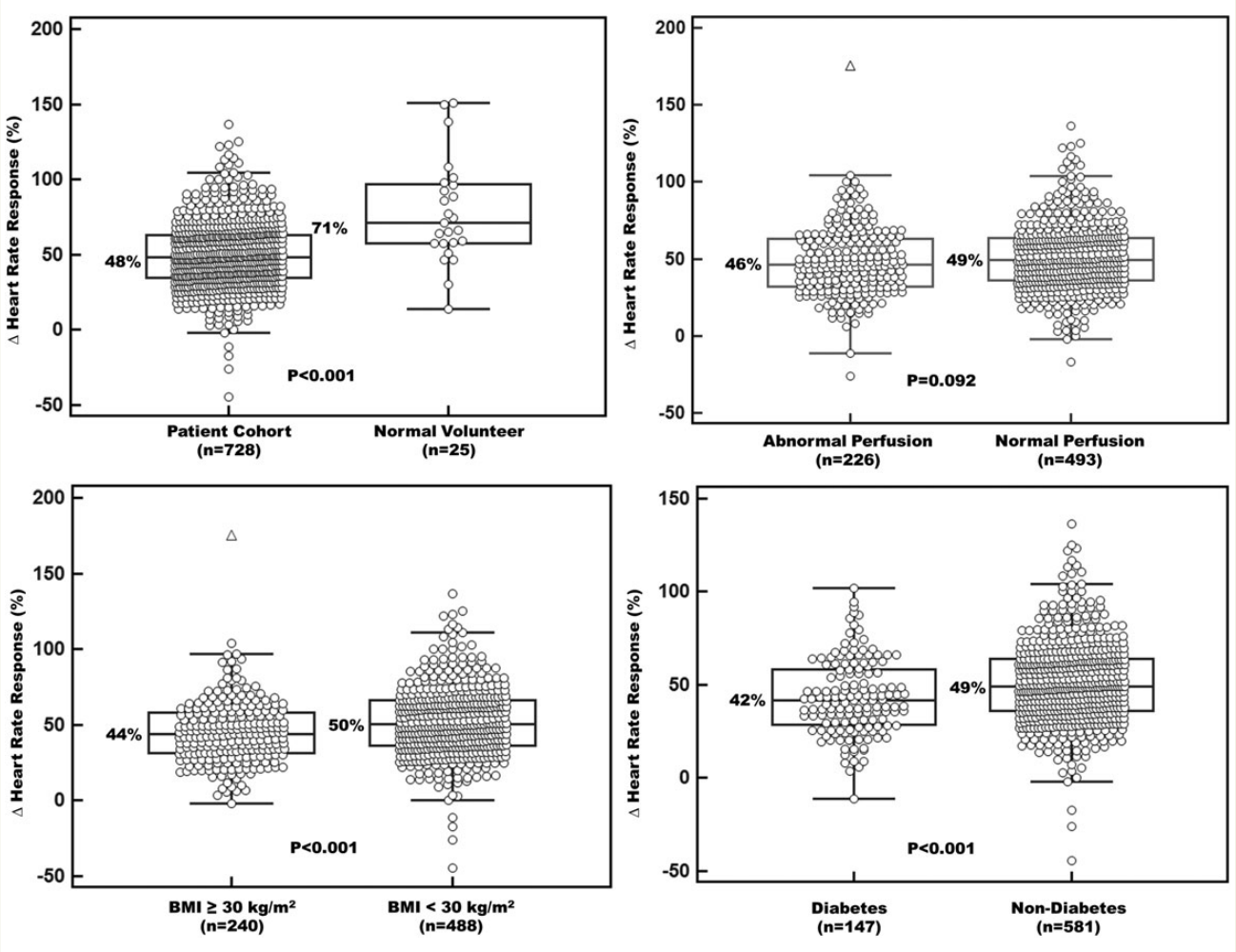


Figure 5 Box-and-Whisker plot of median heart rate response in patient subgroups. Differences between patient subgroups were evaluated using the Mann–Whitney *U* test. The height of the box represents the inter-quartile range. The middle horizontal line in the box represents the median. Whiskers (error bars) extending from the box represent minimum–maximum values. Circles represent data points. BMI, body mass index.

could not delineate whether exacerbation of his symptoms was secondary to a stress-induced increase in left ventricular end-diastolic and wedge pressure[25] or whether this was a natural progression of his disease. Although his heart failure medications were held the morning of the exam, a 3- to 4-h lapse in the usual timing of his medications would unlikely lead to his decompensation. To our knowledge, there are no reports of regadenoson- or aminophylline-induced heart failure in the literature or on the package insert.

The mechanism of adenosine-induced tachycardia has been attributed to a baroreflex-mediated activation of the sympathetic nervous system.[26] However, a recent study using regadenoson suggests that activation of the A_{2A} receptor causes direct activation of the sympathetic nervous system.[27] Because regadenoson has greater selectivity for the A_{2A} receptor, the effect of regadenoson-mediated tachycardia is exaggerated. Abidov *et al.*[28] first reported on the prognostic significance of HRR following adenosine infusion in 2003, thereby spurring an interest in HRR in vasodilator testing. Recently, Hage *et al.*[29] hypothesized that a blunted HRR may reflect the health of the sympathetic system and therefore, be prognostically useful. In their recent work, they demonstrated that a blunted HRR in both regadenoson and adenosine perfusion SPECT is an independent predictor of poor outcome.[30,31] A blunted HRR in regadenoson SPECT was noted in those with DM[14] and metabolic syndrome.[32] In this study, we report a blunted HRR in those with BMI $\geq$30 kg/m^2 and DM. Further, DiBella *et al.*[12] found that fixed-dose regadenoson was sufficient in obese subjects. Taken together, these data suggest that blunted HRR observed in our obese subjects is unlikely due to a simple dose effect, but additional studies are warranted. Interestingly, analysis of individual absolute HRR via Box–Whisker plots showed great overlap between-patient subgroups thereby suggesting that individual data points have limited diagnostic value in individual patients.

Perfusion CMR imaging has progressed in recent years.[33,34] Despite its superiority to SPECT in the diagnosis of CAD,[35] its high sensitivity and specificity,[35,36] potential overall cost reduction in diagnosing chest pain,[37] and lack of radiation, the incorporation of perfusion CMR into daily clinical routine has been slow.

Table 3 Univariable and multivariable logistic analysis of predictors for the lowest quartile of heart rate response

Variables	Coefficient (β)	Standard error	*P*-value	Odds ratio	95% CI
Multivariable analysis[a]					
Age ≥64 years	1.010 (0.884)	0.310 (0.204)	0.001 (<0.001)	2.745 (2.421)	1.495–5.040 (1.623–3.611)
BMI ≥30 kg/m^2	0.784 (0.737)	0.212 (0.192)	0.001 (0.001)	2.190 (2.089)	1.445–3.320 (1.433–3.045)
Diabetes	1.009 (0.552)	0.277 (0.212)	0.001 (0.009)	2.743 (1.736)	1.595–4.718 (1.146–2.631)
LVEF ≤40%	0.944 (0.945)	0.391 (0.391)	0.016 (0.016)	2.569 (2.573)	1.195–5.522 (1.195–5.537)
Abnormal perfusion	0.472 (0.264)	0.232 (0.203)	0.042 (0.194)	1.603 (1.302)	1.018–2.524 (0.875–1.937)
Univariable analysis					
Age ≥64 years	0.783	0.184	<0.001	2.189	1.527–3.138
BMI ≥30 kg/m^2	0.494	0.173	0.004	1.639	1.168–2.301
Diabetes	0.624	0.197	0.002	1.867	1.269–2.746
LVEF ≤40%	0.987	0.371	0.008	2.683	1.298–5.547
Abnormal perfusion	0.371	0.176	0.035	1.449	1.027–2.044
eGFR 30–44.9	1.209	0.676	0.074	3.348	0.890–12.600
eGFR 45–60	−0.307	0.289	0.288	0.736	0.418–1.296
eGFR >60	0.096	0.263	0.716	1.100	0.657–1.843
Gender	0.053	0.168	0.753	1.054	0.759–1.465
Beta-blocker use	0.436	0.168	0.010	1.547	1.113–2.149

BMI, body mass index; CI, confidence interval; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate (mL/min/1.73 cm^2).
[a]Beta-blocker use was removed from the best-fit multivariable model for $P > 0.05$ after entry into the model. The best-fit model was also adjusted for interactions between age*BMI*DM ($P = 0.023$) and abnormal perfusion*DM ($P = 0.037$). Values without adjustment for interactions are in parentheses. Goodness of fit for the best-fit model using the Hosmer–Lemeshow test: model adjusted for interactions $\chi^2 = 8$, $P = 0.374$, area under ROC curve 0.694 (95% CI: 0.658–0.729); Model unadjusted for interactions $\chi^2 = 17$, $P = 0.020$, area under ROC curve 0.686 (95% CI: 0.650–0.721).

Requirements for MRI compatible infusion pumps and weight-based vasodilator infusions complicate the workflow. Regadenoson can simplify current stress protocols in perfusion CMR. Fixed-dose bolus administration obviates the need for infusion pumps and shortens exam time.

Several limitations in our study merit discussion. Our sample size is modest compared with prior clinical trials evaluating the safety of regadenoson SPECT. Secondly, our study reflects a single-centre experience, but the patient demographics are representative of the general population being referred for stress testing. We note that the prevalence of patients with COPD/asthma is low. Many referred patients have been pre-screened by other cardiologists followed by a second round of screening by our nursing staff. Additionally, we excluded one patient with acute exacerbation of asthma, which may represent a potential limitation of this study. Thirdly, because of ECG distortion by a strong magnetic field, the diagnosis of heart block is limited. With regadenoson, the fixed rapid bolus administration does not allow for dose-modification based on ECG findings and thus is one reason why our study primarily focused on haemodynamically significant adverse events, which were infrequent. Despite recent work to reduce ECG signal distortion during stress testing, ECG monitoring during stress CMR perfusion exams remains suboptimal. Lastly, recent work by Bhave *et al.*[38] demonstrated partial reversal of regadenoson-induced hyperaemia despite aminophylline. This finding has implications for the quantification of myocardial perfusion reserve and diagnostic accuracy. Although these issues are of clinical significance, they are beyond the scope of this study.

In conclusion, our findings demonstrate that regadenoson perfusion CMR is safe and the frequency of adverse events is low. Regadenoson perfusion CMR is well-tolerated and symptoms are comparable with those reported in the nuclear literature.

Acknowledgements

The authors thank Dr Xin Tian, PhD (Office of Biostatistics Division, NHLBI) for her statistical guidance on logistic regression modelling. The authors also thank all patients, referring physicians, research coordinators (particularly Tracy Lowrey and Luis Rosario), clinical fellows within the Advanced Cardiovascular Imaging Fellowship Program, and technologists at NHLBI for their assistance.

Conflict of interest: A.E.A. is the principal investigator on a U.S. Government Cooperative Research and Development Agreement (CRADA) with Siemens.

Funding

This research was supported by the Division of Intramural Research of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (1ZIAHL004607, 1ZIAHL006137, 1ZIEHL006139, 1ZIDHL006140). Funding to pay the Open Access publication charges for this article was provided by the Division of Intramural Research of the National Heart, Lung and Blood Institute, National Institutes of Health.

References

1. Zoghbi GJ, Iskandrian AE. Selective adenosine agonists and myocardial perfusion imaging. *J Nucl Cardiol* 2012;**19**:126–41.

2. Hendel RC, Bateman TM, Cerqueira MD, Iskandrian AE, Leppo JA, Blackburn B *et al.* Initial clinical experience with regadenoson, a novel selective A2A agonist for pharmacologic stress single-photon emission computed tomography myocardial perfusion imaging. *J Am Coll Cardiol* 2005;**46**:2069–75.
3. Iskandrian AE, Bateman TM, Belardinelli L, Blackburn B, Cerqueira MD, Hendel RC *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**:645–58.
4. Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE. Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A2A agonist regadenoson versus adenosine in myocardial perfusion imaging integrated ADVANCE-MPI trial results. *JACC Cardiovasc Imaging* 2008;**1**:307–16.
5. Palani G, Husain Z, Salinas RC, Karthikeyan V, Karthikeyan AS, Ananthasubramaniam K. Safety of regadenoson as a pharmacologic stress agent for myocardial perfusion imaging in chronic kidney disease patients not on hemodialysis. *J Nucl Cardiol* 2011; **18**:605–11.
6. Ananthasubramaniam K, Weiss R, McNutt B, Klauke B, Feaheny K, Bukofzer S. A randomized, double-blind, placebo-controlled study of the safety and tolerance of regadenoson in subjects with stage 3 or 4 chronic kidney disease. *J Nucl Cardiol* 2012;**19**: 319–29.
7. Aljaroudi W, Iqbal F, Koneru J, Bhambhvani P, Heo J, Iskandrian AE. Safety of regadenoson in patients with end-stage liver disease. *J Nucl Cardiol* 2011;**18**:90–5.
8. Cavalcante JL, Barboza J, Ananthasubramaniam K. Regadenoson is a safe and well-tolerated pharmacological stress agent for myocardial perfusion imaging in post-heart transplant patients. *J Nucl Cardiol* 2011;**18**:628–33.
9. Husain Z, Palani G, Cabrera R, Karthikeyan AS, Dhanalakota S, Pathmanathan S *et al.* Hemodynamic response, arrhythmic risk, and overall safety of Regadenoson as a pharmacologic stress agent for myocardial perfusion imaging in chronic obstructive pulmonary disease and bronchial asthma patients. *Int J Cardiovasc Imaging* 2012;**28**: 1841–9.
10. Prenner BM, Bukofzer S, Behm S, Feaheny K, McNutt BE. A randomized, double-blind, placebo-controlled study assessing the safety and tolerability of regadenoson in subjects with asthma or chronic obstructive pulmonary disease. *J Nucl Cardiol* 2012;**19**:681–92.
11. Tarroni G, Corsi C, Antkowiak PF, Veronesi F, Kramer CM, Epstein FH *et al.* Myocardial perfusion: near-automated evaluation from contrast-enhanced mr images obtained at rest and during vasodilator stress. *Radiology* 2012;**265**:576–83.
12. Dibella EV, Fluckiger JU, Chen L, Kim TH, Pack NA, Matthews B *et al.* The effect of obesity on regadenoson-induced myocardial hyperemia: a quantitative magnetic resonance imaging study. *Int J Cardiovasc Imaging* 2012;**28**:1435–44.
13. Jekic M, Ding Y, Dzwonczyk R, Burns P, Raman SV, Simonetti OP. Magnetic field threshold for accurate electrocardiography in the MRI environment. *Magn Reson Med* 2010;**64**:1586–91.
14. Hage FG, Heo J, Franks B, Belardinelli L, Blackburn B, Wang W *et al.* Differences in heart rate response to adenosine and regadenoson in patients with and without diabetes mellitus. *Am Heart J* 2009;**157**:771–6.
15. Bernhardt P, Levenson B, Engels T, Strohm O. Contrast-enhanced adenosine-stress magnetic resonance imaging—feasibility and practicability of a protocol for detection or exclusion of ischemic heart disease in an outpatient setting. *Clin Res Cardiol* 2006;**95**:461–7.
16. Khoo JP, Grundy BJ, Steadman CD, Sonnex EP, Coulden RA, McCann GP. Stress cardiovascular magnetic resonance in routine clinical practice: referral patterns, accuracy, tolerance, safety and incidental findings. *Br J Radiol* 2012;**85**:e851–7.
17. Karamitsos TD, Arnold JR, Pegg TJ, Cheng AS, van Gaal WJ, Francis JM *et al.* Tolerance and safety of adenosine stress perfusion cardiovascular magnetic resonance imaging in patients with severe coronary artery disease. *J Cardiovasc Imaging* 2009; **25**:277–83.
18. Karamitsos TD, Ntusi NA, Francis JM, Holloway CJ, Myerson SG, Neubauer S. Feasibility and safety of high-dose adenosine perfusion cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2010;**12**:66.
19. Reyes E, Staehr P, Olmsted A, Zeng D, Blackburn B, Cerqueira MD *et al.* Effect of body mass index on the efficacy, side effect profile, and plasma concentration of fixed-dose regadenoson for myocardial perfusion imaging. *J Nucl Cardiol* 2011;**18**: 620–7.
20. *Adenoscan [Package Insert]*. Northbrook, IL: Astellas Pharma US, Inc.
21. *Adenosine 30 mg/10 mL Solution for Infusion [Package Insert]*. LL13 9UF, UK: Wockhardt UK Ltd.
22. *Lexiscan [Package Insert]*. Northbrook, IL: Astellas Pharma US, Inc.
23. *Rapiscan [Package Insert]*. London, UK: Pharma Solutions EU Ltd.
24. Thomas GS, Tammelin BR, Schiffman GL, Marquez R, Rice DL, Milikien D *et al.* Safety of regadenoson, a selective adenosine A2A agonist, in patients with chronic obstructive pulmonary disease: A randomized, double-blind, placebo-controlled trial (RegCOPD trial). *J Nucl Cardiol* 2008;**15**:319–28.
25. Beleslin BD, Ostojic M, Djordjevic-Dikic A, Nedeljkovic M, Stankovic G, Stojkovic S *et al.* Coronary vasodilation without myocardial erection. Simultaneous haemodynamic, echocardiographic and arteriographic findings during adenosine and dipyridamole infusion. *Eur Heart J* 1997;**18**:1166–74.
26. Alberti C, Monopoli A, Casati C, Forlani A, Sala C, Nador B *et al.* Mechanism and pressor relevance of the short-term cardiovascular and renin excitatory actions of the selective A2A-adenosine receptor agonists. *J Cardiovasc Pharmacol* 1997;**30**: 320–4.
27. Dhalla AK, Wong MY, Wang WQ, Biaggioni I, Belardinelli L. Tachycardia caused by A2A adenosine receptor agonists is mediated by direct sympathoexcitation in awake rats. *J Pharmacol Exp Ther* 2006;**316**:695–702.
28. Abidov A, Hachamovitch R, Hayes SW, Ng CK, Cohen I, Friedman JD *et al.* Prognostic impact of hemodynamic response to adenosine in patients older than age 55 years undergoing vasodilator stress myocardial perfusion study. *Circulation* 2003;**107**: 2894–9.
29. Hage FG, Iskandrian AE. Heart rate response during vasodilator stress myocardial perfusion imaging: mechanisms and implications. *J Nucl Cardiol* 2010;**17**:536–9.
30. Hage FG, Dean P, Iqbal F, Heo J, Iskandrian AE. A blunted heart rate response to regadenoson is an independent prognostic indicator in patients undergoing myocardial perfusion imaging. *J Nucl Cardiol* 2011;**18**:1086–94.
31. Iqbal FM, Al Jaroudi W, Sanam K, Sweeney A, Heo J, Iskandrian AE *et al.* Reclassification of cardiovascular risk in patients with normal myocardial perfusion imaging using heart rate response to vasodilator stress. *Am J Cardiol* 2013;**111**:190–5.
32. Hage FG, Perry G, Heo J, Iskandrian AE. Blunting of the heart rate response to adenosine and regadenoson in relation to hyperglycemia and the metabolic syndrome. *Am J Cardiol* 2010;**105**:839–43.
33. Gerber BL, Raman SV, Nayak K, Epstein FH, Ferreira P, Axel L *et al.* Myocardial first-pass perfusion cardiovascular magnetic resonance: history, theory, and current state of the art. *J Cardiovasc Magn Reson* 2008;**10**:18.
34. Cheng AS, Pegg TJ, Karamitsos TD, Searle N, Jerosch-Herold M, Choudhury RP *et al.* Cardiovascular magnetic resonance perfusion imaging at 3-tesla for the detection of coronary artery disease: a comparison with 1.5-tesla. *J Am Coll Cardiol* 2007;**49**: 2440–9.
35. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC *et al.* Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet* 2012; **379**:453–60.
36. Hamon M, Fau G, Nee G, Ehtisham J, Morello R. Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease. *J Cardiovasc Magn Reson* 2010;**12**:29.
37. Miller CD, Hwang W, Case D, Hoekstra JW, Lefebvre C, Blumstein H *et al.* Stress CMR imaging observation unit in the emergency department reduces 1-year medical care costs in patients with acute chest pain: a randomized study for comparison with inpatient care. *JACC Cardiovasc Imaging* 2011;**4**:862–70.
38. Bhave NM, Freed BH, Yodwut C, Kolanczyk D, Dill K, Lang RM *et al.* Considerations when measuring myocardial perfusion reserve by cardiovascular magnetic resonance using regadenoson. *J Cardiovasc Magn Reson* 2012;**14**:89.