Safety and tolerability of regadenoson CMR

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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 (A1, A2A, A2B, and A3), which are located in multiple tissue types. Activation of A2A results in coronary vasodilation as well as partial peripheral vasodilation; whereas, activation of A1, A2B, and A3 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 A2A receptor to cause coronary vasodilation with minimal activation of other receptor subtypes. Regadenoson has higher selectivity for A2A activation while adenosine binds non-selectively to A1, A2A, A2B, and A3. 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

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/m2 (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

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However, there is a paucity of data to address the safety and tolerability of regadenoson in perfusion CMR,\textsuperscript{11,12} where ECG monitoring is less reliable due to magnetohydrodynamic effects\textsuperscript{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) $\leq 30$ 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 $3 \times 3 \times 8$ mm, bandwidth 651 Hz/pixel). Gadolinium (Magnevist$^\text{\textregistered}$, 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 $1 \times 1 \times 6$ 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 $1 \times 1 \times 6$ 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
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

\[
HRR = \left( \frac{HR_{\text{peak}} - HR_{\text{baseline}}}{HR_{\text{baseline}}} \right) \times 100;
\]

\[
BPR = \left( \frac{BP_{\text{peak}} - BP_{\text{baseline}}}{BP_{\text{baseline}}} \right) \times 100.
\]

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/m², diabetes (DM), left ventricular ejection fraction (LVEF) $\leq$ 40%, abnormal perfusion, eGFR 30–44.9 mL/min/1.73 cm², eGFR 45–60 mL/min/1.73 cm², eGFR $>60 mL/min/1.73 cm²$, 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/m², 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
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 $2\%$ (IQR: $2$ to $6$) and $2\%$ (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 $\geq 30$ kg/m$^2$ and DM (Figure 5). Patients with BMI $\geq 30$ kg/m$^2$ had a higher median baseline HR [68 bpm (IQR: $62$–$77$)] when compared with those

### 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 $n = 684^*$ |   |
| 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.

$^*$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.
with BMI ≥30 kg/m² [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 χ² = 8, P = 0.37): age ≥64, BMI ≥30 kg/m², DM, LVEF ≤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 ≥30 kg/m² 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 signals may 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
could not delineate whether exacerbation of his symptoms was secondary to a stress-induced increase in left ventricular end-diastolic and wedge pressure 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. However, a recent study using regadenoson suggests that activation of the A2A receptor causes direct activation of the sympathetic nervous system. Because regadenoson has greater selectivity for the A2A receptor, the effect of regadenoson-mediated tachycardia is exaggerated. Abidov et al. 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. 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. A blunted HRR in regadenoson SPECT was noted in those with DM and metabolic syndrome. In this study, we report a blunted HRR in those with BMI ≥ 30 kg/m² and DM. Further, DiBella et al. 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. Despite its superiority to SPECT in the diagnosis of CAD, its high sensitivity and specificity, potential overall cost reduction in diagnosing chest pain, and lack of radiation, the incorporation of perfusion CMR into daily clinical routine has been slow.

**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.
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.

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