ORIGINAL ARTICLE

REGADENOSON MYOCARDIAL PERFUSION SCINTIGRAPHY: A SINGLE CENTRE EXPERIENCE

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Background: Regadenoson is highly selective A2A adenosine receptors agonist used for stress myocardial perfusion scintigraphy. This study presents our initial experience utilizing Regadenoson as a myocardial perfusion stress agent, aimed to assess the safety of Regadenoson for stress myocardial perfusion scintigraphy. **Methods:** Following Institutional Ethical Review Borad approval, adult patients presenting for myocardial stress perfusion scintigraphy were included using non-probability consecutive sampling. Exclusions included second or third-degree AV block, unstable angina, recent myocardial infarction, severe hypotension, or significant heart failure. Demographic data, co-morbidities, vitals, and adverse events were recorded. **Results:** Sixty-three patients were included, predominantly male (63.5%), with a mean age of 56.81±12.95 years. Hyperlipidaemia was the most common co-morbidity (47.6%). Systolic and diastolic blood pressure decreased acutely but normalised by 60 minutes. No serious adverse effects occurred, though transient ST segment depression was noted in 8.3% of patients. The most common adverse effects were dyspnoea (23.8%) and headache (21.4%). **Conclusion:** Regadenoson is associated with transient haemodynamic changes and non-serious transient adverse effects.

Keywords: Coronary artery disease; Myocardial perfusion imaging; Regadenoson

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INTRODUCTION

Coronary artery disease (CAD) remains a predominant global health challenge, contributing to over 9 million fatalities annually, with a marked burden in low- and middle-income countries.[1] This burden is acutely felt in nations such as Pakistan, where CAD exacerbates the challenges faced by already overextended healthcare systems. CAD is a significant health issue in Pakistan, with increasing prevalence straining the healthcare system. The rise in CAD is partly due to high incidences of hypertension, diabetes, smoking, dyslipidaemia, and sedentary lifestyles. Epidemiological studies reported a CAD prevalence of 6–15%, with higher rates in urban areas, attributed to lifestyle factors like diet and physical inactivity.[2,3] The South Asian genetic predisposition to early and severe CAD further exacerbates this burden. Notably, South Asians exhibit a three to five times greater risk of myocardial infarction and tend to develop more severe forms of the disease at younger ages compared to their Caucasian counterparts, establishing South Asian ethnicity as an independent risk factor for CAD-related mortality.[4] Addressing this concern requires comprehensive strategies for prevention, early detection, and effective management of CAD.

CAD is characterised by the presence of atherosclerosis within the coronary arteries and may be asymptomatic. Early detection and intervention are crucial in mitigating its impact. However, the diagnosis of CAD remains complex, requiring a combination of clinical evaluation, non-invasive tests, and invasive procedures.[5] Invasive coronary angiography is the gold standard for visualising arterial lumens and enabling interventions. However, given its invasive nature and the need for more judicious use of this intervention, there is an increasing shift towards reserving the cardiac catheterisation laboratory for interventional procedures only after CAD has been confirmed via non-invasive imaging techniques.[6]

Myocardial perfusion scintigraphy (MPS) is a minimally-invasive technique that assesses myocardial blood flow and perfusion dynamics at rest and under stress using radiopharmaceuticals like Technetium-99m methoxyisobutylisonitrile (Tc-99m MIBI). The procedure involves intravenous Tc-99m MIBI injection, a waiting period for cardiac uptake, and subsequent imaging. Tc-99m MIBI distribution in the myocardium, visualized by a gamma camera, indicates perfusion levels and can reveal CAD.[7] Stress testing enhances myocardial oxygen demand through exercise or pharmacological agents for patients unable to exercise. Pharmacological stress is particularly suited for those with physical limitations, such as the

elderly, individuals with a history of myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), chronic obstructive pulmonary disease (COPD), severe obesity, orthopaedic restrictions, or heart rhythm disorders.[8] In stress MPS, dobutamine, a beta-1 agonist, is used which mimics exercise by increasing heart rate and myocardial contractility. Side effects include tachycardia, hypertension, and arrhythmias, such as premature ventricular contractions and atrial fibrillation. Non-selective adenosine receptor agonists, adenosine and dipyridamole are used as stress agents to induce coronary vasodilation which enhances Tc-99m MIBI uptake in normal arteries relative to stenosed ones. This effect is achieved via activation of A2A receptors. Since these agents are non-selective, they can cause bradycardia, hypotension, and sedation via A1 receptor activation. A2B receptors are associated with headache, flushing, and hypotension, while A3 receptor activation may lead to bronchoconstriction and gastrointestinal disturbances. Dobutamine and non-selective adenosine receptor agonists should be avoided in patients with asthma or COPD, severe bradycardia or AV block, hypotension, or contraindications to β-agonists due to potential serious adverse effects (AEs).[9]

Regadenoson offers significant advantages as a pharmacological stress agent.[10] Due to its selective action on A2A adenosine receptors it reduces the risk of bronchospasm in patients with asthma or COPD and minimizes symptom exacerbation in those with severe bradycardia or AV block. It provides a controlled hypotensive response, making it suitable for patients with hypotension, while avoiding complications associated with dobutamine in individuals with contraindications to β-agonists. Regadenoson rapidly increases intracoronary blood flow to at least 2.5 times the baseline level within 1 to 4 minutes, with this effect sustained for approximately 2.3 minutes before decreasing to less than twice the baseline level within 10 minutes. Administered as a fixed-dose intravenous bolus, Regadenoson simplifies clinical use due to its rapid plasma concentration decline (2–4 minutes) as it distributes to the highly perfused central compartment. A further decline occurs over 30 minutes due to tissue redistribution, with elimination completed in approximately 2 hours. Regadenoson is minimally metabolized and is primarily excreted unchanged in the urine. It has common mild and transient side effects including headache, flushing, and dizziness. By inducing coronary vasodilation similar to exercise with fewer side effects, Regadenoson provides a safer, more convenient alternative for myocardial perfusion imaging, particularly for those who cannot tolerate other agents due to hypersensitivity or intolerable side effects. Furthermore, its ease of administration enhances the reliability of myocardial perfusion assessments.

This study aimed to evaluate the incidence and severity of AEs associated with Regadenoson administration, alongside its hemodynamic impact and overall patient tolerability during MPS. By examining these parameters, the research sought to determine the suitability of Regadenoson use in our patient populations. The findings are intended to enhance the understanding of Regadenoson risk-benefit profile within the context of nuclear medicine practice in Pakistan, ultimately informing clinical decision-making and patient management strategies.

MATERIAL AND METHODS

This analytical cross-sectional study was conducted at the Nuclear Medical Centre, Armed Forces Institute of Pathology Rawalpindi, from April 2022 to April 2023. Using non-probability consecutive sampling technique, we enrolled consecutive adult patients of either gender who were referred to our centre for a clinically indicated pharmacological stress MPS. Individuals with any contraindication to Regadenoson administration were excluded from the study. These included hypersensitivity to the active pharmacological ingredient or its excipients; second- or third-degree AV block or sinus node dysfunction without a functioning artificial pacemaker; unstable angina not stabilised with medical therapy; severe hypotension; and decompensated heart failure. Pregnant or breastfeeding women were also excluded. The study protocols were approved by institutional review board before start of study (IRB certificate no. FC-NMC21-11/READ-IRB/22/1453

After informed consent, demographic and clinical data, including major comorbid conditions, were collected. The standard one-day testing protocol for MPS using Tc-99m MIBI with Regadenoson stress was employed. Patients fasted for at least 4 hours before the test and withheld medications such as beta-blockers, calcium channel blockers, and nitrates as per physician instructions. They also avoided caffeine and theophylline-containing medications for 12–24 hours prior. The protocol began with an intravenous dose of Tc-99m MIBI (8–12 mCi) for rest imaging, followed by resting imaging after 45 minutes. After a 1-2 hour wait to clear the initial tracer, patients received an intravenous dose of 0.4 mg Regadenoson, followed by a 5 mL saline flush and a second, higher dose of Tc-99m MIBI (20–30 mCi) after 10–20 seconds.

Stress images were acquired 45 minutes later. A nuclear medicine specialist or resident was present throughout the procedure, with trained staff and cardiac resuscitation equipment readily available. Aminophylline was also on hand for reversal if needed. Heart rate (HR), blood pressure (BP), and ECG were continuously monitored. HR and BP measurements at baseline (immediately before Regadenoson administration) and at 1 minute, 4 minutes, 15 minutes, and 60 minutes post-injection were noted for study data analysis. All patient-reported or observed AEs were recorded, with particular attention to significant hypotension, sustained arrhythmias, bronchoconstriction, angina, ST segment depression, and anaphylaxis.

The acquired images were analysed to compare myocardial perfusion between rest and stress conditions, identifying areas of reversible ischemia or infarction. Two independent observers evaluated the images, and in cases of disagreement, a third observer resolved conflicts by consensus. Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 23.0. Descriptive statistics, including frequencies and percentages, were computed for categorical variables. Means and standard deviations (SD) were presented for normally distributed continuous variables, while medians and interquartile ranges (IQR) were reported for continuous variables that did not meet the criteria for normality. Demographic and clinical characteristics were assessed for associations with the incidence of AEs using the chi-square test. To compare means with the baseline measurement, paired t-tests were conducted for normally distributed data, while Wilcoxon signed-rank tests were employed for data that did not meet normality assumptions. A confidence interval of 95% was used, and a p-value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 63 patients were included in the study. Among these, 40 patients (63.5%) were male. Age was found to be normally distributed and the mean age of the participants was 56.81±12.95 years, with an age range spanning from 33 to 89 years. Age was not found to be associated with presence of an AE (p=0.352). 16 (25.4%) patients were smokers, all of them male. Percutaneous Coronary Intervention (PCI) had been performed in 23 (36.5%) patients. The most common co-morbid condition was hyperlipidaemia which was present in 30 (47.6%) patients. None of the baseline characteristics were found to be significantly associated with occurrence of an AE (Table-1).

At baseline, mean HR was 86.22±13.64 beats per minute (bpm). It significantly increased to 101.59±14.94 bpm at 1 minute after Regadenoson injection (p<0.001) and remained elevated at 4 minutes (99.60±14.39 bpm, p<0.001) and 15 minutes (98.24±22.34 bpm, p=0.001), returning to baseline at 60 minutes (87.57±9.63 bpm, p=0.553). The systolic and diastolic blood pressure (SBP and DBP, respectively) measurements revealed distinct trends. The median SBP decreased significantly from a baseline of 130 mmHg (IQR 21.00) to 111 mmHg (IQR 24.00) at 1 minute (p<0.001) and gradually increased over time, reaching 128 mmHg (IQR 13.00) at 60 minutes, where the difference from baseline was not statistically significant (p=0.356). Similarly, the median DBP showed a significant reduction from a baseline of 76.00 mmHg (IQR 19.00) to 67.00 mmHg (IQR 23.00) at 1 minute (p=0.001), with values progressively returning towards baseline by 60 minutes (72.00 mmHg, IQR 16.00), also without a significant difference from baseline (p=0.167). These findings indicated an acute, transient drop in blood pressure following Regadenoson administration, with recovery by 60 minutes.

None of the patients experienced serious AEs such as significant hypotension, sustained arrhythmias, bronchoconstriction, angina, or anaphylaxis. ST segment depression (≥ 0.5mm) on the ECG was noted in 7 (8.3%) patients which was transient in nature. None of these patients displayed significant chest pain or other acute coronary syndrome symptoms, and acute management measures, halting the test, or initiating emergency protocols were not required. 18 (28.6%) patients did not experience any AE while 10 (15.9%) experienced more than 2 (Figure-1). The most common AE was dyspnoea (n=20 [23.8%]), followed by headache (n=18 [21.4%]) (Table-3).

Table-1: Baseline characteristics and their association with presence of an adverse Effect (n=63)

Baseline Characteristic	n (%)	*p*-value
Gender		
Male	40 (63.5)	0.781
Female	23 (36.5)	
History		
Smoker	16 (25.4)	0.360
Percutaneous Coronary Intervention	23 (36.5)	0.246
Coronary Artery Bypass Grafting	8 (12.7)	0.678
Co-morbid Conditions		
Hyperlipidaemia	30 (47.6)	0.787
Diabetes Mellitus	26 (41.3)	0.573
Hypertension	25 (39.7)	0.579
Chronic Obstructive Pulmonary Disease	23 (36.5)	0.563
Congestive Heart Failure	20 (31.7)	0.551
Chronic Kidney Disease	29 (31.7)	0.770
Myocardial Infarction	17 (27.0)	0.536

Table-2: Changes in heart rate and blood pressure over time (n=63)

		Mean±SD	*p*-value
Heart Rate (beats/minute)	Baseline	86.22±13.64	
	1 minute	101.59±14.94	<0.001
	4 minutes	99.60±14.39	<0.001
	15 minutes	98.24±22.34	0.001
	60 minutes	87.57±9.63	0.553
		Median (IQR)	***p*-value**
Systolic Blood Pressure (mmHg)	Baseline	130 (21.00)	
	1 minute	111 (24.00)	<0.001
	4 minutes	116 (24.00)	<0.001
	15 minutes	121 (19.00)	0.001
	60 minutes	128 (13.00)	0.356
Diastolic Blood Pressure (mmHg)	Baseline	76.00 (19.00)	
	1 minute	67.00 (23.00)	0.001
	4 minutes	73.00 (18.00)	0.026
	15 minutes	72.00 (13.00)	0.288
	60 minutes	72.00 (16.00)	0.167

Table-3: Incidence of each adverse effect (n=63)

Adverse effect	n (%)
Dyspnoea	20 (23.8%)
Headache	18 (21.4%
Chest Pain or Discomfort	16 (19.0%)
Flushing	11 (13.1%)
ST Depression on ECG	7 (8.3%)
Dizziness	3 (3.6%)
Nausea	2 (2.4%)
Epigastric Pain	1 (1.2%)
Abdominal Discomfort	1 (1.2%)

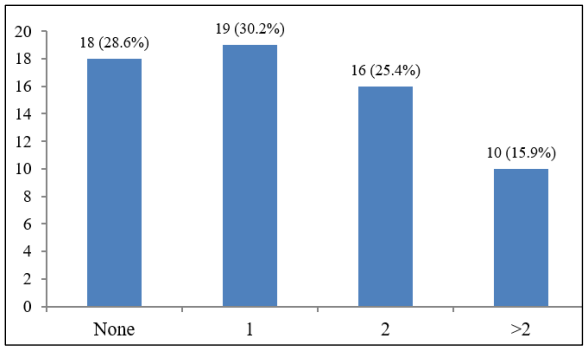

Figure-1: Distribution of Patients by Number of Adverse effects (n=63).

DISCUSSION

Clinical trials establishing the efficacy and safety of Regadenoson, leading to its approval by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), included 1,651 patients with a median age of 66 years, predominantly male (70%) and Caucasian (76%).[11] In phase 3 studies, the most common adverse events were dyspnoea (28%), headache (26%), and flushing (16%). Chest discomfort and angina or ST segment depression occurred in 13% and 12% of patients, respectively, while dizziness, chest pain, nausea, and abdominal discomfort were reported in 8% or less. In our study, dyspnoea was observed in 23.8%, headache in 21.4%, and chest pain or discomfort in 19.0%. Flushing occurred in 13.1%, and ST segment depression in 8.3%. Our findings indicate a higher incidence of chest pain or discomfort and a lower incidence of dizziness compared to phase 3 trials. A study, conducted in Athens, Greece, between December 2016 and July 2017, involved 96 patients (mean age 70.35 years) undergoing MPS using Regadenoson for pharmacological stress.[12] One patient experienced severe dyspnoea requiring treatment, while ischemic ECG changes occurred in 8 (8.3%). None of the patients in our study experienced severe dyspnoea, and ST depression on ECG was observed in 7 (8.3%). Dyspnoea was more common in the previous study (30.21%) than in our study (23.8%). Overall, these findings are consistent with our results in terms of the type and nature of AEs observed, though the incidence rates varied, with our study showing a lower incidence of dyspnoea. In the previous study, HR increased after Regadenoson administration, peaking within six minutes, but data beyond this period were not provided. Our study extended the observation period, showing that HR remained elevated after peaking at one minute and gradually returned to near-baseline levels by 60 minutes. Similarly, the previous study reported significant drops in SBP and DBP within the first six minutes. In contrast, our study showed that after an initial drop, both SBP and DBP gradually returned to near-baseline by 60 minutes, providing a more detailed understanding of Regadenoson hemodynamic effects over time. Another study evaluated Regadenoson safety and tolerability in a Danish population undergoing MPS.[13] Conducted in a clinical setting with 232 participants, the study followed a standard protocol for Regadenoson administration, focusing on AEs, HR, BP, and patient tolerability. The most reported AE was dyspnoea (64%), followed by headache (19%), chest pain (17%), and flushing (15%). No severe AEs occurred, and most were transient, resolving without intervention. These findings align with our results regarding AEs, although the incidence of dyspnoea was lower in our study. HR and BP were monitored post-administration, showing a significant HR increase, peaking one to two minutes after Regadenoson, consistent with our findings. SBP decreased by 10 to 15 mmHg, while changes in DBP were minimal. In our study, both SBP and DBP showed significant initial decreases, with SBP rebounding more sharply and DBP gradually returning to baseline levels. A retrospective review of 51 medical files conducted from January 2018 to December 2019 at a tertiary academic hospital in Gauteng, South Africa, evaluated Regadenoson administration parameters, co-morbidities, and AEs.[14]

AEs occurred in 41.2% of patients, with dizziness the most common side effect (55.6%) and headache at 7.4%. Additionally, 31.4% of patients experienced over a 50% increase in heart rate after Regadenoson injection. These findings support existing literature on the transient and benign profile of AEs associated with Regadenoson and the temporary HR elevation.

Regadenoson has been studied in high-risk patients as the demand for pharmacological stress tests rises. While adenosine is commonly used for MPS, it poses risks for patients with COPD or asthma due to potential bronchospasm. In contrast, Regadenoson, a selective A2A receptor agonist, was developed to reduce these risks. In a prospective study involving 780 patients with COPD or bronchial asthma, Regadenoson was administered with close monitoring of BP, HR, and AEs.[15] Results showed a significant increase in HR and a decrease in SBP, consistent with Regadenoson pharmacodynamics. All AEs were non-severe and self-limiting, including dyspnoea, headache, and dizziness. Only one patient experienced a notable drop in BP and transient dyspnoea, which resolved without complications. There were no cases of bronchospasm or severe pulmonary side effects. A smaller study of 14 patients with severe COPD assessed Regadenoson safety during MPS, excluding those with active wheezing or on corticosteroids.[16] Regadenoson was given as a bolus, followed by saline flush and 99mTc-MIBI injection. Oxygen saturation remained stable, with dyspnoea as the most reported AE, along with fatigue, chest pain, headache, and gastrointestinal discomfort. All AEs were self-limiting, with significant increases in HR and decreases in SBP post-stress. In our study of 23 patients with COPD, no association between COPD and AEs was found. While our findings align with previous studies, our sample size was small, and our cohort was younger, with a mean age of 56.81 ± 12.95 years. We did not document the severity or remission status of COPD. Overall, the AE profile was similar, with comparable haemodynamic effects. The safety of Regadenoson in patients with renal disease is important due to its renal excretion. A multicentre, double-blind, randomized, placebo-controlled study assessed the safety and tolerability of Regadenoson in 432 subjects with chronic kidney disease (CKD) aged 18 years or older with known or suspected CAD.[17] Participants received a 10-second intravenous injection of Regadenoson or placebo, with the primary outcome being the incidence of serious AEs post-dose. No serious AEs or deaths occurred during the 24-hour follow-up. However, the incidence of AEs was significantly higher in the Regadenoson group compared to placebo (62.6% vs. 21.2%; $p<0.001$). Common AEs associated with Regadenoson included headache (24.9%), dyspnoea (19.2%), chest discomfort (14.7%), nausea (14.7%), flushing (12.0%), and dizziness (9.6%). Regadenoson was found to be safe and well tolerated in CKD patients. Our findings align with this study, as no serious AEs were observed in our study of 29 CKD patients, and AEs were transient. Another study aimed to assess the safety of Regadenoson administration in patients failing to reach target HR during standard exercise treadmill testing, particularly among those with known CAD.[18] The analysis included 514 patients, with prospective collection of hemodynamic data, side effects, and adverse events. Results showed that 12% of patients experienced a significant drop in SBP (≥30 mmHg) following Regadenoson administration, and 2% had SBP below 100 mmHg. Common side effects included dyspnoea, chest pain or discomfort, and dizziness. The study concluded that Regadenoson is safe, even in patients with CAD, and does not lead to major AEs. In our study, 31 (49.21%) patients had a known history of CAD, but the incidence of AEs in this subgroup was not significantly different. Notably, Regadenoson was administered at rest in our study.

Limitations of the study

The primary limitations of our study include a small sample size and the fact that it was conducted at a single centre. These factors may limit the generalizability of the findings, as the results might not fully represent broader populations or different clinical settings. Further multi-centre studies with larger sample sizes are needed to validate these findings.

CONCLUSION

These results indicate Regadenoson is associated with transient haemodynamic changes and non-serious transient AEs in our patients.

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AUTHORS' CONTRIBUTION

MA: Write-up, data collection. ZSD: Literature review, proof reading. SK: Data analysis, interpretation. FH: Proof reading, concept & study protocols. AM: Data collection, write-up. HS: Data collection, literature review.

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