

## REVIEW ARTICLE

# Regadenoson Stress in Patients with Airways Disease and Pulmonary Hypertension: A Review

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## Abstract

Regadenoson is an increasingly used pharmacological stress agent for myocardial perfusion imaging (MPI) that has an important advantage over other primary coronary vasodilators. Both adenosine and dipyridamole have a non-selective action on the adenosine receptors and can therefore induce bronchospasm in susceptible individuals. In contrast, regadenoson acts selectively on the adenosine receptor subtype responsible for the coronary vasodilator effect of these agents with little, if any, activity on adenosine receptor-mediated bronchoconstrictive pathways. This gives regadenoson an advantage over other vasodilators in the management of patients with obstructive airways disease undergoing stress MPI. There is compelling evidence for the improved tolerability of regadenoson stress in patients with a history of bronchial hyperreactivity. Moreover, regadenoson has proved to be safe in advanced forms of lung disease and is currently the preferred stress agent in these patients. Experience on the use of regadenoson in poorly controlled asthma or chronic obstructive pulmonary disease (COPD) is limited, and thus caution must be exercised when considering regadenoson stress in patients with suspected persistent or clinically manifest airway obstruction.

**Keywords:** Airways disease, MPI, Pulmonary hypertension, Regadenoson, Safety, Tolerability

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**P**harmacological stress has expanded the indications for MPI by offering an alternative form of stress to patients who cannot exercise adequately. It has also provided a practical solution to imaging protocols for which exercise is not a feasible option. All vasodilator stress agents have proved to be effective at provoking maximal or near maximal coronary hyperaemia, hence enabling the detection of flow-limiting coronary stenosis in patients with suspected or known coronary artery disease (CAD). However, the non-selective action of adenosine and dipyridamole on the ubiquitous adenosine receptors prevents their use in patients with moderate or severe airway obstruction as well as in those with advanced lung disease. Regadenoson has made it possible for these patients to undergo vasodilator stress testing safely. This review provides an overview of the basis for regadenoson use in patients with pulmonary disease undergoing stress MPI with an emphasis on the evidence to support this practice.

## Primary coronary vasodilators may cause bronchospasm

Dipyridamole, adenosine and regadenoson are currently the only commercially available vasodilator agents for stress MPI (Table 1). All three agents are highly effective stressors because of their ability to increase coronary blood flow several times its resting value independently of myocardial oxygen consumption, thereby enabling the detection of haemodynamically significant coronary stenotic lesions (1, 2). This effect is mediated by activation of the adenosine receptor subtype  $A_{2A}$  expressed on the surface of the smooth muscle cells of the coronary arterioles. Activation of this receptor subtype causes smooth muscle cell relaxation and consequently coronary vasodilation and myocardial hyperaemia (3).

In addition to the adenosine  $A_{2A}$  receptor, three other G protein-coupled receptor subtypes have been identified:  $A_1$ ,  $A_{2B}$  and  $A_3$  receptors (3). All four receptors are coupled to guanine nucleotide-binding G proteins that stimulate or inhibit

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**Table 1** Properties and protocol for all currently available pharmacological stress agents for MPI

Properties and Protocol	Primary vasodilators			Inotropic agent
	Dipyridamole	Adenosine	Regadenoson	Dobutamine
Mechanism of action	Increase in endogenous adenosine concentration by inhibition of adenosine reuptake and deamination	Direct activation of adenosine A <sub>2A</sub> receptors in coronary arteriolar smooth muscle cells	Direct activation of adenosine A <sub>2A</sub> receptors in coronary arteriolar smooth muscle cells	Secondary coronary vasodilation by increasing myocardial oxygen consumption through $\beta$ -1 receptor activation; weak $\beta$ -2 and $\beta$ -1 agonist
Half-life	Approx. 30 min	≤10 secs	Initial phase, 2.5 min; intermediate phase, 30 min; last phase, 2 hours	2 min
Administration	140 mcg/kg/min IV for 4 min	140 mcg/kg/min IV for 6 min	Single-dose of 400 mcg IV over 10 secs followed by 5mL saline flush	Escalated dosing starting at 5-10 mcg/kg/min IV and increasing by 5-10 mcg/kg/min every 3-5min to 40 mcg/kg/min
Tracer injection	3-4 min after completion of infusion	Between 3-4 min of infusion	10-20 secs after saline flush	At peak heart rate
Antidote	Aminophylline IV, 50-250 mg	Aminophylline IV, 50-250 mg	Aminophylline IV, 50-250 mg	Short-acting beta-blocker (e.g. esmolol 0.5 mg/kg over 1 min)

MPI: myocardial perfusion imaging. Source: Reference 31.

adenylate cyclase, thus increasing or decreasing intracellular concentrations of the second messenger cAMP, respectively. Agonist binding to the A<sub>1</sub> and A<sub>3</sub> receptors inhibits adenylate cyclase while activation of the A<sub>2</sub> subtypes stimulates the activity of this enzyme. Through this signal transduction pathway, the adenosine receptors regulate several important biological functions such as inflammation and modulation of neuronal excitability and neurotransmitters availability (3). Importantly, agonist potency varies depending on receptor subtype and tissue receptor density. According to binding studies, adenosine is most potent at the A<sub>1</sub>, A<sub>3</sub> and A<sub>2A</sub> receptors in tissues where they are plentiful (4). This is particularly relevant to the coronary vasodilator effect of adenosine and related compounds; the coronary circulation is rich in A<sub>2A</sub> receptors, which helps explain the high potency of adenosine despite its modest binding affinity for the receptor (5).

At standard coronary vasodilator doses, activation of all adenosine receptor subtypes may occur after injection of adenosine and dipyridamole. This non-selective action is responsible for many of adenosine- and dipyridamole-related side effects (Fig. 1A).

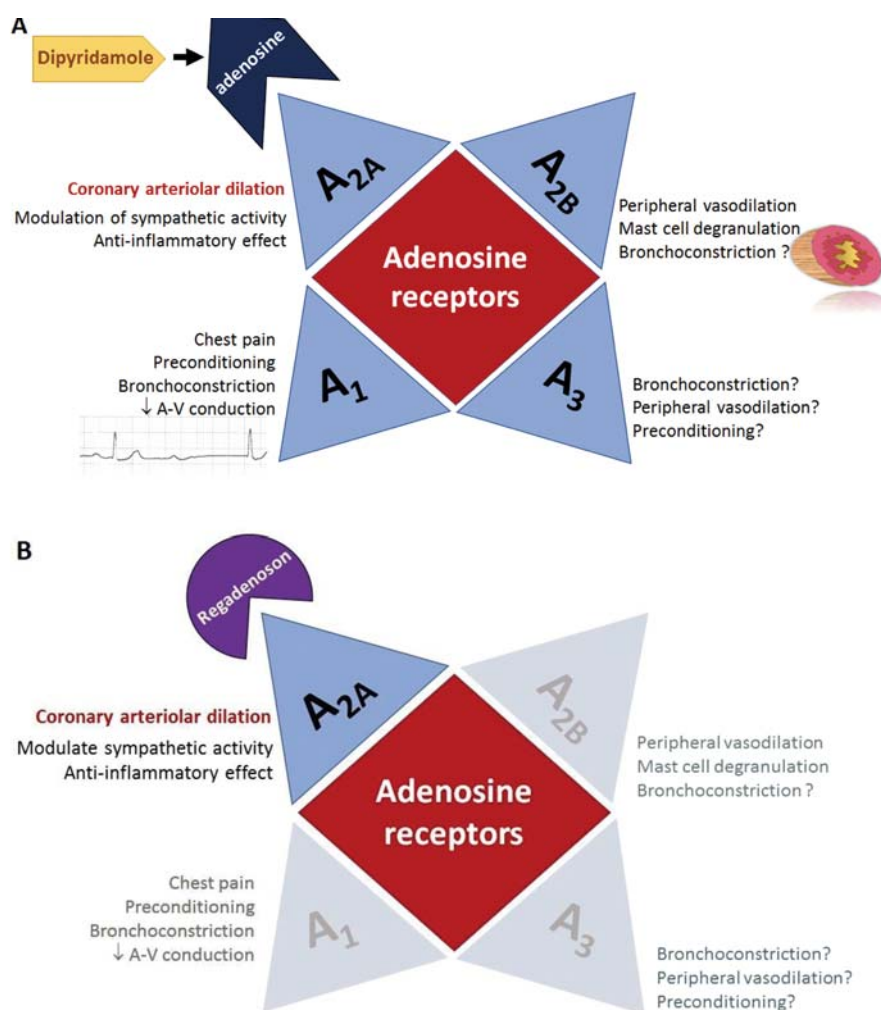
#### Adenosine receptors in the lungs and airways

All four adenosine receptors have been isolated from the lungs and airways of mammals, but their expression is not uniform (6). In the lungs of healthy humans, the adenosine A<sub>2</sub> receptor appears to be much more abundant than the other subtypes (6, 7). Moreover, all adenosine receptors have been identified in the airways of patients with asthma and COPD (6, 8). The adenosine A<sub>1</sub> receptor is expressed in bronchial

smooth muscle and epithelial cells as well as in neutrophils, eosinophils, monocytes and alveolar macrophages, while the A<sub>2A</sub> subtype has been identified not only in these but also in mast cells, alveolar epithelial cells, and endothelial cells (3, 6). Similar expression has been described for the A<sub>2B</sub> receptor. The A<sub>3</sub> subtype is relatively scarce and it has been found in interceding inflammatory cells including neutrophils, eosinophils, monocytes and macrophages (9). Following receptor activation, the final response is largely influenced by tissue receptor density, interaction with other receptor-mediated pathways, and pre-existing levels of interstitial adenosine (6, 7). Briefly, activation of the A<sub>1</sub> receptor may induce both direct and indirect bronchial smooth muscle contraction through the release of inflammatory mediators; similarly, the A<sub>2B</sub> receptor regulates bronchospastic and pro-inflammatory pathways characterised by mast cell degranulation and cytokine secretion, while activation of the A<sub>2A</sub> receptor appears to have an anti-inflammatory effect through inhibition of cell degranulation, preventing the release of leukotriene, histamine and other bronchoconstrictive mediators. Activation of neural pathways may also play a role in adenosine-induced bronchoconstriction (7). Importantly, activation of the adenosine receptors may contribute towards the pathogenesis and progression of asthma (10).

#### Adenosine receptor-mediated bronchospasm

Bronchospasm is the commonest non-cardiac adverse event during adenosine stress that occurs almost exclusively in subjects with airways disease (11). In general, adenosine-induced bronchospasm is rare (11). Patients with reversible airways disease, however, are at risk of developing broncho-

**Fig. 1**

**A :** Dipyridamole, through an increase in endogenous adenosine concentration, and exogenous adenosine act on all four adenosine receptor subtypes. Their activation mediates several biological functions including vasodilation and inflammation.

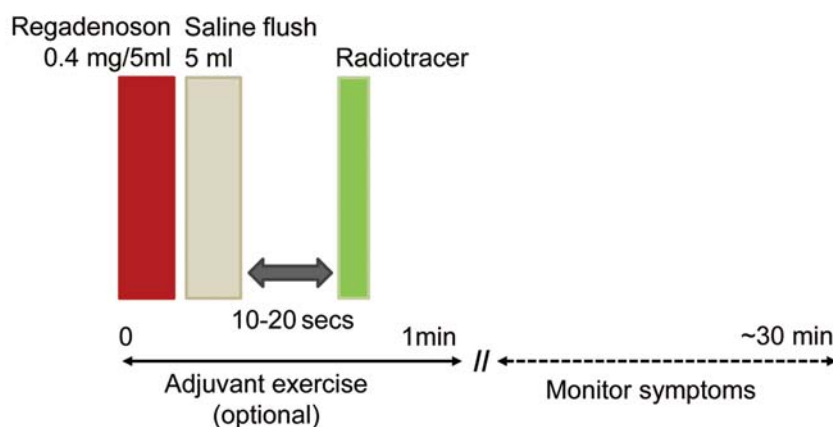
**B :** Regadenoson binds selectively to the adenosine A<sub>2A</sub> receptor and causes coronary arteriolar vasodilation. Activation of this receptor is also involved in modulation of sympathetic nerve activity and appears to have an anti-inflammatory effect. Regadenoson has shown little if any binding to adenosine A<sub>1</sub>, A<sub>2B</sub> and A<sub>3</sub> receptors.

constriction following adenosine and dipyridamole administration (12, 13). The exact mechanism is yet to be elucidated; this bronchoconstrictive response may result from an imbalance of the above-mentioned adenosine receptor-modulated pro- and anti-inflammatory pathways in susceptible individuals. In this regard, the cellular events downstream of the A<sub>1</sub> and A<sub>2B</sub> receptors appear to be key to this response. Regardless of the mechanism(s) involved, adenosine-induced bronchospasm appears to be both dose- and disease severity-dependent with patients more likely to experience bronchospasm at larger doses of adenosine, and this risk increases as disease worsens (14). This observation formed the basis for the testing and implementation of a titrated adenosine infusion protocol for patients with mild asthma/COPD undergoing stress MPI (15). The bronchospastic response to adenosine is attenuated by theophylline, a non-selective adenosine receptor

antagonist (4). Because endogenous adenosine may play an important role in the pathophysiology of airway hyperreactivity, A<sub>1</sub> and A<sub>2</sub> receptors have been targeted for the development of new drugs to treat asthma and other respiratory diseases. Antagonists against the adenosine A<sub>1</sub> and A<sub>2B</sub> receptors as well as selective agonists to the A<sub>2A</sub> subtype have been developed and tested with some success (6).

#### Adenosine-induced dyspnoea

Unlike bronchospasm, dyspnoea is a common side effect during vasodilator stress that is usually well-tolerated (11). A few studies have already demonstrated that this side effect bears no relationship to changes in respiratory resistance, thus ruling out bronchoconstriction as the underlying mechanism (16). The precise cellular pathway by which adenosine causes dyspnoea remains uncertain; some evidence suggests that this



Monitor heart rate, blood pressure & ECG

Aminophylline readily available for the management of severe symptoms or complications

**Fig. 2** Regadenoson stress protocol for myocardial perfusion imaging. A single-dose of 400 µg of regadenoson is injected IV over 10 seconds, followed by a 5 mL-saline flush. The tracer is administered 10-20 seconds after the saline injection. Regadenoson administration can be combined with exercise if possible.

symptom is probably mediated by stimulation of pulmonary vagal afferent C-fibres via the adenosine  $A_1$  and  $A_{2A}$  receptor subtypes (17). Regardless of the mechanism involved, dyspnoea during vasodilator stress may be associated with an increase in respiratory and ventilation rates, and this is often preceded by an enhanced perception of respiratory effort or “an urge for breathing” (16). Consequently, patients with pulmonary disease not only report dyspnoea more frequently, but also perceive it as more troublesome (15). In patients with an understandable fear of breathlessness, this response may cause significant distress, which may prompt discontinuation of the test and administration of the antidote aminophylline.

#### Selective adenosine $A_{2A}$ receptor agonism improves vasodilator stress tolerability

As mentioned previously, most of adenosine and dipyridamole undesirable effects are attributed to their non-selective action on the adenosine receptors. Thus, regadenoson, a selective adenosine  $A_{2A}$  receptor agonist, may improve tolerability to vasodilator stress (Fig. 1B).

Regadenoson is a low-affinity ( $K_i \approx 1.3 \mu\text{M}$ ), highly selective agonist to the adenosine  $A_{2A}$  receptor and, unlike adenosine, it has a much lower affinity for the  $A_1$  receptor ( $K_i > 16.5 \mu\text{M}$ ) and minimal, if any, affinity for the  $A_{2B}$  and  $A_3$  receptors (2, 18). Accordingly, early in-vivo studies showed that the coronary hyperaemic response to regadenoson was associated with a few and transient systemic effects (19). However, subsequent clinical studies demonstrated that, at the recommended dose of 400 µg, regadenoson injection was not exempted from symptoms (20). A plausible explanation for

this finding is that side effects that were initially attributed to adenosine receptors other than the  $A_{2A}$  might be modulated by this receptor subtype.

In order of frequency, the commonest side effects during regadenoson stress are dyspnoea, chest discomfort, headache and light-headedness, gastrointestinal symptoms and flushing (20, 21). Despite an incidence of approx. 73%, most of regadenoson-related symptoms are short-lived and resolve spontaneously within a few minutes, except for headache and gastrointestinal symptoms, which may last up to 30 minutes post-injection.

Clinical trials comparing regadenoson and adenosine stress MPI suggested that test tolerability improves with regadenoson, with patients preferring this agent over adenosine (20, 22). Furthermore, a more favourable side effect profile was observed among the elderly, women and obese patients compared with adenosine (22). In general, regadenoson stress is a well-tolerated and safe test; no major cardiac events or life-threatening complications were reported in large clinical studies (20-22). An important advantage of regadenoson over other stress agents is its ease of use. Unlike adenosine and dipyridamole, regadenoson is given intravenously as a single-dose injection of 400 µg over 10 seconds with completion of the stress test in less than one minute (Fig. 2). Like many patients with comorbidities that limit their tolerability of medical interventions, patients with advanced lung disease may benefit from this abbreviated form of stress.

#### Is regadenoson safe in obstructive airways disease?

By avoiding stimulation of the pro-inflammatory and

bronchoconstrictive A<sub>1</sub>, A<sub>2B</sub> and A<sub>3</sub> receptor pathways, regadenoson may be safe in patients with airways disease. Indeed, the results of an early randomised, placebo-controlled study showed that regadenoson injection was well-tolerated in patients with mild or moderate asthma (23). Importantly, all 48 patients were responsive to nebulised adenosine monophosphate (AMP), a marker of airway reactivity and inflammation. There were no significant changes in FEV<sub>1</sub> in the two hours that followed regadenoson administration and, importantly, FEV<sub>1</sub> values were not lower than those observed after placebo. In a similar study of 49 patients with moderate to severe COPD (FEV<sub>1</sub> > 30% and < 80%), regadenoson caused no major airflow limitation (24). There were no significant differences across several lung function parameters including FEV<sub>1</sub>, forced vital capacity, respiratory rate and oxygen saturation between regadenoson and placebo injection. Twice the number of patients (n=6) experienced a >15% reduction in FEV<sub>1</sub> following regadenoson compared with placebo, but there was no need for medical intervention. These observations suggested that changes in airflow might occur during regadenoson injection, but they did not appear to be clinically important. Despite these encouraging findings, the safety profile of regadenoson in patients with more severe forms of airways disease remained unknown. Further research provided an insight into the safety of regadenoson in these patients.

In a large prospective study, 999 patients with asthma or COPD of various severities were randomly assigned to regadenoson or placebo (25). Criteria for enrolment included well-controlled asthma and no history of disease exacerbation in the 30 days prior to drug administration. The proportion of patients who experienced a >15% reduction in FEV<sub>1</sub> from baseline to two and 24 hours post-injection was similar between the regadenoson and placebo groups (2.6% vs. 4.0%, and 3.8% vs. 3.6%, respectively), and this was independent of disease type or severity. No symptomatic bronchoconstriction was reported after regadenoson, and aminophylline was given to one patient with COPD to treat dyspnoea. Indeed, dyspnoea was among the commonest side effects, and was significantly more frequent after regadenoson than placebo. These observations supported earlier evidence and suggested that regadenoson was safe in more severe forms of airways disease.

An observational study designed to reflect routine clinical practice showed that regadenoson combined with low-level exercise on a treadmill was safe and well-tolerated in patients with asthma and COPD who did not have a history of severe disease or active bronchoconstriction at the time of test (26). Symptoms were common with fatigue, dyspnoea and dizziness among the commonest side effects. In general, the frequency of side effects was greater in patients with asthma (94%) than

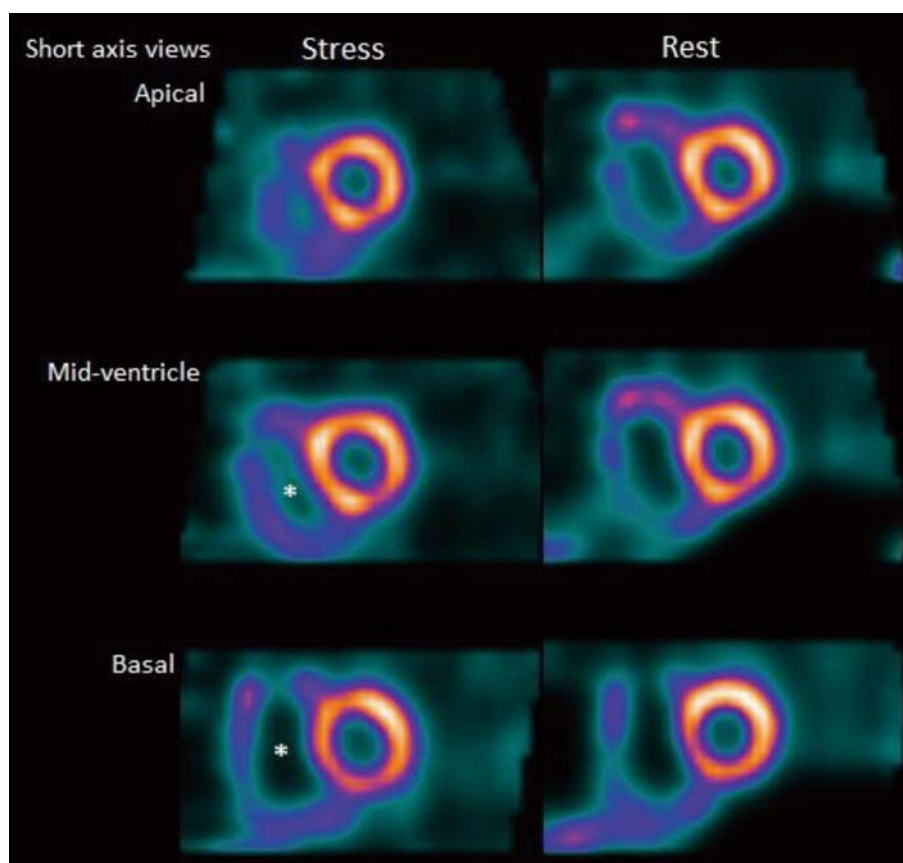
COPD (78%). There were also differences in side effect profile with dyspnoea being more frequent among COPD patients while headache and a hot feeling were more common in patients with asthma. This response might reflect differences in disease status and exercise tolerance in the case of dyspnoea, but there was no single confounding factor to explain the greater risk of regadenoson-induced headache in asthma patients. The haemodynamic response to regadenoson was similar between the groups. Importantly, the great majority of side effects were self-limiting, with only 3 of 116 patients receiving theophylline to treat persistent dyspnoea. As in previous clinical trials, none of the patients developed clinically manifest bronchospasm.

An earlier retrospective study investigating the safety of regadenoson stress MPI in an unselected population with chronic lung disease (n=228) demonstrated good tolerability with no respiratory complications following regadenoson with low-level exercise (27). Importantly, there were no adverse events at 24-hour and 7-day follow-up, and the overall response to stress was comparable to that of a control group. Two other observational studies produced similar results (21, 28). No bronchospasm was reported in a cohort of 325 patients with various stages of COPD and asthma who received regadenoson combined with dynamic exercise. Patients with a history of severe airways disease were excluded, and in one study they received dobutamine stress instead (21). The authors argued that this cautionary approach reflected early experience with regadenoson stress and concluded that this agent was a safe alternative in patients with airways disease (21).

A recent small study aimed at investigating the safety of regadenoson in patients with severe COPD (n=12; GOLD stage III) reported no bronchospasm or any other adverse event during regadenoson stress (29). Side effect profile was comparable to that of patients with milder forms of airways disease; symptoms were self-limiting and reverted within 5-8 minutes after regadenoson injection. Moreover, the presence of inducible ischaemia on MPI bore no relationship to stress tolerability in these patients.

All these studies have consistently shown that regadenoson is generally safe and well-tolerated in patients with asthma and COPD. Although symptoms are frequent, they are mostly short-lasting and immediate reversal with aminophylline is seldom required. What these studies have also in common is that enrolled patients had reasonably well-controlled disease and were stable at the time of regadenoson administration. Until more safety data becomes available, caution must be exercised when considering the administration of regadenoson in patients in whom the clinical history and/or the physical exam indicate active bronchoconstriction, or in whom the severity of their condition cannot be established with certainty.





**Fig. 3** A 75-year-old man with a history of heavy smoking and emphysema is being investigated for worsening breathlessness. A transthoracic echocardiogram performed a couple of years earlier showed a normal left ventricular (LV) function, and no other contributory finding. A repeat echocardiogram was requested, as well as stress myocardial perfusion imaging to exclude obstructive coronary artery disease. Regadenoson combined with low-level exercise on a bicycle ergometer was followed by image acquisition on a solid-state gamma camera. The stress test was well-tolerated. The tomograms (above) show normal myocardial perfusion in the LV myocardium. The RV appears severely dilated (\*) with increased myocardial tracer uptake indicating RV hypertrophy. There is also septal flattening. The appearances are compatible with RV pressure overload. The concurrent echocardiogram also showed signs of elevated pulmonary artery pressure, and subsequent right heart catheterisation revealed a mean pulmonary artery pressure of 74 mmHg confirming the diagnosis of pulmonary hypertension.

In this regard, the presence of concurrent pulmonary hypertension may affect test safety and tolerability, and the overall performance of the stress procedure. None of the above-mentioned studies examined the effect of pulmonary hypertension on the safety and tolerability of regadenoson stress.

#### **Is regadenoson safe in pulmonary hypertension?**

The safety profile of regadenoson stress in pulmonary hypertension was documented in a recently published study. This included 67 patients with a diagnosis of primary or secondary pulmonary hypertension who received regadenoson alone or combined with low-level treadmill exercise for clinically indicated stress MPI (30). The average mean pulmonary artery pressure was 44 mmHg, and a previous echocardiogram revealed right ventricular involvement in the form of dilatation or contractile dysfunction in most patients.

Over 70% of patients had a World Health Organisation functional class III-IV. Unsurprisingly, most patients were unable to perform low-level exercise. Those who did exercise were more likely to complain of fatigue but not more likely to experience dyspnoea. Overall, the frequency of side effects was similar to that of previous studies in patients with lung disease, despite routine administration of aminophylline (75 mg) after tracer injection. This is not surprising since most regadenoson-induced side effects occur soon after injection and revert spontaneously within a few minutes. Importantly, the overall haemodynamic response was not different from that observed in larger cohorts of patients undergoing regadenoson stress, which is characterised by an average increase in heart rate of 25 bpm and a modest change in blood pressure (20). A few patients experienced a significant reduction in blood pressure (>10 mmHg) but there were no episodes of syncope or symptomatic hypotension. These

findings are reassuring, considering that the pathophysiology of pulmonary hypertension and the action of drugs used to ameliorate symptoms may influence the response to regadenoson. Regarding the latter, 56 of 67 patients were on first-line single or combination therapy with a prostacyclin, phosphodiesterase inhibitor and/or endothelin receptor antagonist. No relation was found between regadenoson effects and anti-hypertensive medication. Importantly, no serious adverse events or complications were documented in this study. Anecdotal experience supports these findings (Fig. 3), but it is important to bear in mind that these are highly selected patients who may not represent the larger pulmonary hypertension patient population.

### Conclusion

Primary coronary vasodilators are potent stress agents widely used for the detection of flow-limiting coronary artery disease with MPI. Unlike non-selective adenosine receptor agonists, regadenoson is safe and well-tolerated in patients with well-controlled airways disease regardless of its severity. Safety data in high-risk patients with advanced lung disease and active airflow obstruction is scarce and thus, until more evidence becomes available, the suitability of regadenoson in these patients must be decided on a case by case basis, ideally after a thorough evaluation of their respiratory status. A conscientious approach would be recommended whereby the risks are balanced against the prospective benefit, and the possibility of an alternative test is kept in mind. Future research may contribute more safety and tolerability data in high-risk patients, and may provide valuable insights into the complex pathways that govern the respiratory response to adenosine receptor agonists in health and disease.

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### Conflicts of interest

None.

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## References

1. Wilson RF, Wyche K, Christensen BV, et al. Effects of adenosine on human coronary arterial circulation. *Circulation* 1990; 82: 1595-606.
2. Gao Z, Li Z, Baker SP, et al. Novel short-acting A<sub>2A</sub> adenosine receptor agonists for coronary vasodilation: inverse relationship between affinity and duration of action of A<sub>2A</sub> agonists. *J Pharmacol Exp Ther* 2001; 298: 209-18.
3. Fredholm BB, IJzerman AP, Jacobson KA, et al. International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. *Pharmacol Rev* 2001; 53: 527-52.
4. Fredholm BB, Irenius E, Kull B, et al. Comparison of the potency of adenosine as an agonist at human adenosine receptors expressed in Chinese hamster ovary cells. *Biochem Pharmacol* 2001; 61: 443-48.
5. Shryock JC, Snowdy S, Baraldi PG, et al. A<sub>2A</sub>-Adenosine Receptor Reserve for Coronary Vasodilation. *Circulation* 1998; 98: 711-8.
6. Brown RA, Spina D, Page CP. Adenosine receptors and asthma. *Br J Pharmacol* 2008; 153 Suppl 1: S446-S56.
7. Polosa R, Rorke S, Holgate ST. Evolving concepts on the value of adenosine hyperresponsiveness in asthma and chronic obstructive pulmonary disease. *Thorax* 2002; 57: 649-54.
8. Varani K, Caramori G, Vincenzi F, et al. Alteration of adenosine receptors in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 398-406.
9. Baraldi PG, Cacciari B, Romagnoli R, et al. A<sub>3</sub> adenosine receptor ligands: history and perspectives. *Med Res Rev* 2000; 20: 103-28.
10. Polosa R, Holgate ST. Adenosine receptors as promising therapeutic targets for drug development in chronic airway inflammation. *Curr Drug Targets* 2006; 7: 699-706.
11. Cerqueira MD, Verani MS, Schwaiger M, et al. Safety profile of adenosine stress perfusion imaging: results from the Adenoscan Multicenter Trial Registry. *J Am Coll Cardiol* 1994; 23: 384-89.
12. Thurnheer R, Laube I, Kaufmann PA, et al. Practicability and safety of dipyridamole cardiac imaging in patients with severe chronic obstructive pulmonary disease. *Eur J Nucl Med* 1999; 26: 812-7.
13. Cushley MJ, Tattersfield AE, Holgate ST. Inhaled adenosine and guanosine on airway resistance in normal and asthmatic subjects. 1983. *Br J Clin Pharmacol* 2004; 58: S751-5.
14. Larsson K, Sollevi A. Influence of infused adenosine on bronchial tone and bronchial reactivity in asthma. *Chest* 1988; 93: 280-4.
15. Reyes E, Loong CY, Wechalekar K, et al. Side effect profile and tolerability of adenosine myocardial perfusion scintigraphy in patients with mild asthma or chronic obstructive pulmonary disease. *J Nucl Cardiol* 2007; 14: 827-34.
16. Fricke E, Esdorn E, Kammeier A, et al. Respiratory resistance of patients during cardiac stress testing with adenosine: is dyspnea a sign of bronchospasm? *J Nucl Cardiol* 2008; 15: 94-9.
17. Chuaychoo B, Lee MG, Kollarik M, et al. Evidence for both adenosine A<sub>1</sub> and A<sub>2A</sub> receptors activating single vagal sensory C-fibres in guinea pig lungs. *J Physiol* 2006; 575: 481-90.

18. Zablocki J, Palle V, Blackburn B, et al. 2-substituted pi system derivatives of adenosine that are coronary vasodilators acting via the A<sub>2A</sub> adenosine receptor. *Nucleosides Nucleotides Nucleic Acids* 2001; 20: 343-60.
19. Trochu JN, Zhao G, Post H, et al. Selective A<sub>2A</sub> adenosine receptor agonist as a coronary vasodilator in conscious dogs: potential for use in myocardial perfusion imaging. *J Cardiovasc Pharmacol* 2003; 41: 132-9.
20. Iskandrian AE, Bateman TM, Belardinelli L, et al. Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. *J Nucl Cardiol* 2007; 14: 645-58.
21. Brinkert M, Reyes E, Walker S, et al. Regadenoson in Europe: first-year experience of regadenoson stress combined with submaximal exercise in patients undergoing myocardial perfusion scintigraphy. *Eur J Nucl Med Mol Imaging* 2014; 41: 511-21.
22. Cerqueira MD, Nguyen P, Staehr P, et al. ADVANCE-MPI Trial Investigators. Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A<sub>2A</sub> agonist regadenoson versus adenosine in myocardial perfusion imaging integrated ADVANCE-MPI trial results. *JACC Cardiovasc Imaging* 2008; 1: 307-16.
23. Leaker BR, O'Connor B, Hansel TT, et al. Safety of regadenoson, an adenosine A<sub>2A</sub> receptor agonist for myocardial perfusion imaging, in mild asthma and moderate asthma patients: a randomized, double-blind, placebo-controlled trial. *J Nucl Cardiol* 2008; 15: 329-36.
24. Thomas GS, Tammelin BR, Schiffman GL, et al. Safety of regadenoson, a selective adenosine A<sub>2A</sub> 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. Prenner BM, Bukofzer S, Behm S, et al. 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.
26. Garcia CS, Heffernan AJ, Sanchez de ME, et al. Comparative study of the safety of regadenoson between patients with mild/moderate chronic obstructive pulmonary disease and asthma. *Eur J Nucl Med Mol Imaging* 2014; 41: 119-25.
27. Husain Z, Palani G, Cabrera R, 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.
28. AlJaroudi WA, Alraies MC, Cerquiera MD, et al. Safety and tolerability of regadenoson in 514 SPECT MPI patients with and without coronary artery disease and submaximal exercise heart rate response. *Eur J Nucl Med Mol Imaging* 2013; 40: 341-8.
29. Salgado-Garcia C, Jimenez-Heffernan A, Ramos-Font C, et al. Safety of regadenoson in patients with severe chronic obstructive pulmonary disease. *Rev Esp Med Nucl Imagen Mol* 2016; 35: 283-6.
30. Moles VM, Cascino T, Saleh A, et al. Safety of regadenoson stress testing in patients with pulmonary hypertension. *J Nucl Cardiol* 2018; 25: 820-7.
31. Henzlova MJ, Duvall WL, Einstein AJ, et al. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. *J Nucl Cardiol* 2016; 23: 606-39.