Chapter 1

Regadenoson — Overview of Applications in Cardiology

Gurunanthan Palani, Rebecca Baumann and Karthik Ananthasubramaniam

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/61154

Abstract

Coronary artery disease is a leading cause of morbidity and mortality in developed countries. According to a Center for Disease Control report, one out of four deaths is attributed to coronary artery disease. It costs the United States human lives, productivity, and more than 100 billion dollars each year. Due to increased incidence in both men and women and all ethnicities, risk stratification of patients at risk for developing myocardial infarction and death is of paramount importance. Various tests are available for diagnosis and prognosis in coronary heart disease such as exercise treadmill testing, coronary calcium scoring, dobutamine stress echocardiography, exercise, dipyridamole, adenosine or dobutamine stress nuclear myocardial perfusion imaging (MPI), and dobutamine or adenosine stress cardiac magnetic resonance imaging. Since 2008 a new vasodilator, regadenoson (REG), has become available and is now widely used for nuclear perfusion imaging. Pharmacologic stress testing challenges the coronary flow reserve to evaluate the hyperemic capacity of the heart, which can be impaired in significant epicardial stenosis or microvascular dysfunction. In the presence of either of these conditions, ischemia induced by hyperemia manifests as wall motion abnormalities on echocardiography or as perfusion defects in nuclear perfusion imaging.

REG is a selective adenosine A_{2A} receptor agonist, and due to its targeted coronary vasodilator properties and bolus administration of a standard dose in all patients, it has rapidly gained popularity as the preferred MPI stress agent. In this chapter we will review the basis of pharmacologic vasodilator stress imaging starting with a brief discussion of the various adenosine receptors and their function, the structure and mechanism of action of REG, and its development and approval. It will be compared with other myocardial perfusion pharmacologic stress agents like adenosine and

dipyridamole in terms of safety, efficacy, and side effect profile. We will also address the utility of REG in special situations like renal disease, chronic obstructive pulmonary disease, heart transplant, left bundle branch block, and paced rhythms. The prognostic value of REG MPI in the general population, its effectiveness with and without exercise, and the emerging applications of REG in other modalities of imaging such as positron emission tomography and stress echocardiography will be discussed.

Keywords: Regadenoson, single photon emission computed tomography, positron emission tomography, stress echocardiography, fractional flow reserve, coronary artery disease

1. Introduction

Cardiovascular disease remains a leading cause of death in the United States. According to a 2009 report by the Center for Disease Control, one out of four deaths is attributable to coronary artery disease (CAD).[1] The increased morbidity and mortality due to CAD poses a huge economic burden. In 2010, CAD alone accounted for over 100 billion dollars in combined direct and indirect (i.e., loss of productivity) costs. This is projected to more than double by 2030.[2] Hence, diagnosing and risk stratifying CAD in its early stages is vital.

Many invasive and noninvasive tests are available to identify patients at high risk of developing CAD. Functional tests include exercise stress testing, exercise or dobutamine stress echocardiography, nuclear myocardial perfusion imaging (MPI) using stress agents such as dipyridamole, adenosine, dobutamine or regadenoson (REG), and vasodilator stress magnetic resonance imaging. Coronary computed tomography angiography (CCTA) and the traditional gold standard, coronary angiography, serve as the two well-established anatomic modalities used for CAD detection. This chapter will focus on REG, the newest of the pharmacologic stress agents, and its applications in myocardial perfusion imaging. It will conclude with a brief overview of some novel applications of REG in cardiology.

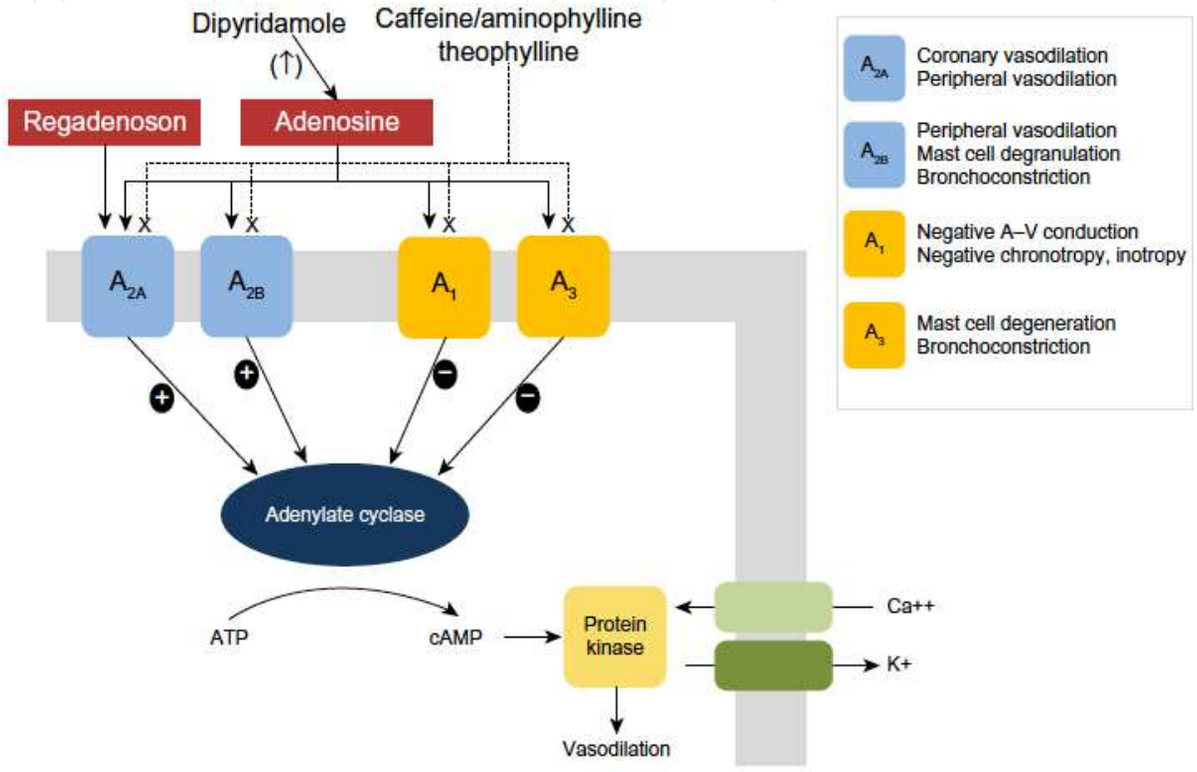
2. REG: development, pharmacology, and hemodynamic effects

2.1. Adenosine receptors

Adenosine receptors are located in the myocardium as well as in smooth muscle cells of the coronary arterioles and the bronchial tree. Various subtypes of adenosine receptors exist including A_1 receptors found in the atrioventricular node, A_{2A} receptors present in coronary arteriolar smooth muscle, and A_{2B} and A_3 receptors located in bronchial smooth muscle. The different locations and functions of these receptors have been pivotal in the development of newer pharmacologic stress agents (Figure 1). Adenosine directly and dipyridamole indirectly act on adenosine 2A (A_{2A}) G-protein-coupled receptors found on the cell membrane of coronary

http://dx.doi.org/10.5772/61154

arteriolar smooth muscle cells. However, both are nonselective and also activate the other adenosine receptor subtypes causing frequent clinically important side effects (e.g., atrioventricular block due to A_1 activation and bronchoconstriction due to A_{2B} and A_3 receptor activation) as well as other less serious but often unpleasant side effects. In contrast, REG exerts its effect selectively on A_{2A} receptors achieving the coronary dilatation necessary to perform MPI studies while keeping side effects to a minimum.



Note: Springer and *J Nucl Cardiol*, 17, 2010, 494-497, The emerging role of the selective A2A agonist in pharmacologic stress testing, Gemignani AS, Abbot BG, Figure 1. With kind permission from Springer Science and Business Media

Figure 1. Types of adenosine receptors, their functions, and activation/inhibition by various pharmacologic agents.

2.2. Development and approval of of REG

Cardiac stress testing is able to identify as well as risk stratify individuals who are at risk for CAD. Vasodilator stress testing challenges the coronary flow reserve in order to evaluate the hyperemic capacity of the heart, which can be impaired in significant epicardial stenosis or microvascular disease and lead to transient ischemia. Ischemic changes manifest either as perfusion or wall motion abnormalities depending on the imaging modality used. The currently available pharmacologic stress agents with primarily vasodilator function are dipyridamole, adenosine, and REG. While dobutamine also vasodilates, it mainly stresses the heart via its positive inotropic and chronotropic effects.

An ideal cardiac stress agent should cause short-lived but maximal coronary vasodilatation. Both of these can be achieved if the stress agent has low affinity for its receptor and the target tissue has many adenosine receptors. The coronary arterial tree has an abundance of A_{2A}

receptors of which only a fraction needs to be activated to elicit the desired coronary vasodilation and produce maximal coronary hyperemia. Given the nonspecific nature of adenosine receptor stimulation by adenosine and dipyridamole leading to undesired side effects, the need existed for the development of an A_{2A}-selective agent largely devoid of significant side effects such as bronchospasm and atrioventricular conduction block. REG (code name CVT 3146) was identified as an agent with A_{2A} selectivity yet with a low affinity for A_{2A} receptors, meaning it dissociates quickly after eliciting maximal coronary vasodilation, thus causing adequate coronary hyperemia for a short period of time. REG underwent preclinical and subsequently randomized clinical studies showing non-inferiority compared to the commonly used vasodilator adenosine. This led to its approval by the Food and Drug Administration in 2008. It is marketed by Astellas Pharma US Inc. under the trade name Lexiscan® in the United States as a cardiac stress agent for MPI studies in patients who are unable to exercise. Following REG administration, coronary hyperemia occurs for approximately 2–5 min, which is adequate for radionuclide uptake and makes it possible to perform stress testing using a single bolus injection.[3]

2.3. Pharmacology and pharmacokinetics of REG

REG is a 2-[*N*-1-(4-*N*-methylcarboxamidopyrazolyl)] adenosine derivative. It is prepared by condensing ethoxycarbonylmalondialdehyde with 2-hydrazinoadenosine in a 1:1 mixture of ethanoic acid and methanol. The resulting ester is then converted directly by aminolysis with methylamine to the amide REG (Figure 2). Alternatively, REG can be prepared from 2-chloro or 2-iodo adenosine derivatives. The amide links at the 4-position of the *N*-pyrazolyl, which has both lipophilic and hydrophilic substituents lending the drug greater affinity for the adenosine 2_A receptor than the other adenosine receptor subtypes.

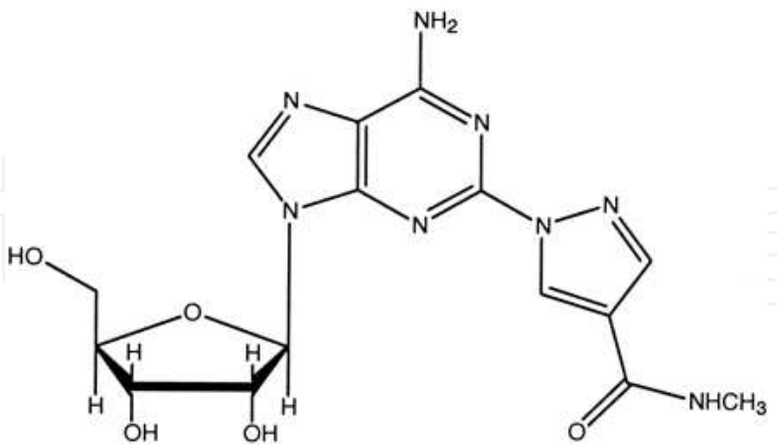


Figure 2. The molecular structure of REG (CVT-3146; (1-[9-[(4S, 2R, 3R, 5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2yl]-6aminopurin-2-yl]pyrazol-4-yl)-*N*-methylcarboxamide).

It is usually given as a single 400-μg (5 mL) intravenous bolus after which it immediately distributes throughout the body. No weight-based dose adjustment is necessary. REG then undergoes three phases of elimination. The first is the phase of maximal coronary hyperemia

lasting 2–4 min.[4] The second phase lasts 15–30 min with profound effect on heart rate and blood pressure, and the third phase, which lasts for 33–108 min, is clinically nonsignificant.[5] Much about REG's metabolism remains unknown; however, its excretion is both renal and hepatic. The kidneys remove approximately 60% via tubular secretion, while the liver excretes around 40% of the drug unmetabolized into the bile.

2.4. Hemodynamic effects of REG

As a coronary vasodilator REG is shown to cause tachycardia and changes in blood pressure (both increase and decrease).Trochu et al.[6] showed in animal studies that while adenosine increased left ventricular (LV) systolic pressure, REG did not to any significant degree, and that LV contractility measured by dP/dT increased by 39±7% with REG and 29±7% with adenosine. The ADVANCE MPI studies[7] have shown that the decrease in systolic and diastolic blood pressures (BP) was similar between REG and adenosine (systolic BP drop 14±13 mmHg vs. 13±14 mmHg, P = ns; diastolic BP drop 10±8 mmHg vs. 10±8 mmHg, P = ns). Both drugs increase the heart rate; however, REG more significantly than adenosine (25±11bpm vs. 20±10bpm, $P < 0.001$).

The increase in heart rate with REG is mainly due to direct sympathetic excitation and less so from a baroreceptor reflex induced tachycardia. Dhalla et al.[8] has also suggested that an A_{2A} receptor mediated sinus tachycardia can occur with REG. A blunted heart rate acceleration with both REG and adenosine has also been observed in studies with diabetic patients and is felt to be related to sympathetic denervation.[9]

2.5. Side effect profile of REG

Like other vasodilators, REG is associated with many minor and a few major (albeit to a lesser extent than older vasodilators) side effects of which clinicians need to be aware.[10] Transient side effects included nausea (6%), abdominal pain (5%), headache (26%), and chest tightness (13%). In the randomized studies evaluating REG prior to its FDA approval, atrioventricular (AV) block incidence was <1% with no instances of advanced AV block or asystole in the ADVANCE MPI 3 studies. However, post marketing surveillance has highlighted rare major adverse reactions related to REG such as acute myocardial infarction,[11, 12] atrioventricular block, and asystole.[13] Thus, REG, despite its A_{2A} selectivity, should not be used in patients with greater than the first-degree AV block unless they have a backup pacemaker. Furthermore, cases of syncope[14] and seizures[15] have also been reported following REG administration. Although aminophylline is used for reversal of many REG-induced side effects, it should not be used in the setting of seizures following REG injection as it lowers the seizure threshold. Instead, standard antiseizure therapy with benzodiazepines and agents such as phenytoin should be used.

2.6. Effect of caffeine on REG and clinical implications

Caffeine is an A_{2A} receptor antagonist (Figure 1). Hence, it has the potential to attenuate the hyperemic response, which occurs after vasodilator administration. This is a well-known

problem with adenosine and dipyridamole, both of which require abstinence from caffeinated products for at least 24 h prior to stress testing. However, the REG package insert specifies withholding caffeinated products for only 12 h prior to testing. Preclinical animal studies suggested that caffeine attenuated the duration of REG-induced coronary hyperemia in dogs.[16] Subsequent human studies evaluating myocardial blood flow in 41 healthy volunteers using REG with PET imaging showed that moderate caffeine consumption may not interfere with REG-induced coronary hyperemia.[17] Thus, conflicting evidence existed regarding the effect of caffeine on REG stress testing until a multicenter randomized trial on this subject was performed in 2014.

Tejani et al.[18] studied the effects of caffeine on the diagnostic accuracy of REG single proton emissions computed tomography (SPECT) MPI in 207 subjects with documented coronary artery disease on an initial rest-REG SPECT MPI sequence. A third set of SPECT images was acquired in all patients following randomization to two different caffeine doses (200 and 400 mg) or placebo. Previously noted reversible defects were attenuated in patients who consumed both doses of caffeine at least 90 min prior to REG administration, thus diminishing the diagnostic accuracy of the study. There was no difference in adverse effects between the three groups.[18] Current American Society of Nuclear Cardiology (ASNC) guidelines recommend that patients refrain from caffeine consumption for at least 12 h before REG stress testing.

Variable	Regadenoson	Adenosine	Dipyridamole
Brand name	Lexiscan®	Adenocard®/Adenoscan®	Persantine®
Indication	Pharmacologic stress agent in MPI.	Treatment of paroxysmal supraventricular tachycardia, pharmacologic stress agent in MPI	Oral—antithrombotic along with warfarin/aspirin. Intravenous—pharmacologic stress agent in MPI
Mechanism of action	Increases coronary flow reserve (CFR) via selective A_{2A} adenosine receptor agonism	Nonselective adenosine agonist on A_1, A_{2A}, A_{2B}, and A_3 receptors. Increases coronary flow reserve (CFR) via A_{2A}receptor activation.	Increases availability of adenosine by inhibiting adenosine deaminase, which prevents adenosine's breakdown
Potency	10 times more potent than adenosine	Less potent	Less potent
Distribution in body	11.5 L	Unknown	2–3 L
Metabolism	Unknown	In blood and tissue, metabolized by adenosine deaminase into inosine and then adenosine monophosphate and hypoxanthine	Hepatic
Time to peak	1–4 min	30 s	2–2.5 h

Variable	Regadenoson	Adenosine	Dipyridamole
Half-life	Triphasic First phase = 2–4 min Second phase = 15–30 min Third phase = 33–108 min	<10 s	30–45 min
Administration	Bolus	Infusion	Infusion
Dose	400 μg	140 μg/kg/min	0.14 mg/kg/min
Duration of infusion	10-20 s bolus	6 min continuous infusion	4 min continuous infusion
Excretion	57% of drug excreted unchanged in urine via tubular secretion	Cellular uptake	Conjugated by glucuronide and unchanged drug excreted in feces
Safety in pregnancy	Risk cannot be ruled out (Category C)	Risk cannot be ruled out (Category C)	No evidence of human risk in controlled studies (Category B)
Common side effects	Headache 26% , flushing 16%, dyspnea 28%, hypotension 2%	Headache 21%, flushing 35%, dyspnea 19%, hypotension 3%	Headache 12%, flushing 3.4%, dyspnea 2.6%, hypotension 5%
IV tubing	Not needed: only Hep-lock	Needed	Needed
Protocol completion time with radiotracer	Less than 1 min	4–6 min	6–8 min

Table 1. Comparison of the three commonly used vasodilator agents

Compared with the other two agents, REG is more potent, causes more selective coronary vasodilatation, can be injected in a single bolus without weight-based adjustments, and produces SPECT images comparable to adenosine and dipyridamole.

3. REG SPECT MPI in detection of coronary artery disease

3.1. Comparison to adenosine

In a multicenter phase 2 study, REG was tested in 36 patients undergoing SPECT MPI at bolus doses of 400 and 500 μg. Patients with heart transplantation, left bundle branch block, ventricular pacemaker, and low ejection fraction (14 patients) were excluded. This study showed a higher rate of detecting reversible perfusion defects with the lower dose of REG (89% for 400 μg) than with the higher dose (76% for 500 μg).[19] Subsequently, two phase 3 double-blinded, randomized, multicenter trials (ADVANCE-MPI 1 and ADVANCE-MPI 2) demonstrated non-inferiority of REG SPECT MPI to adenosine SPECT MPI. The ADVANCE-MPI 2 trial included 54 sites and 784 patients undergoing clinically indicated adenosine MPI who were blindly randomized 4 weeks later to a second MPI study with REG (n = 495) or adenosine (n = 260) in a 2:1 ratio. Study images were reported in a blinded fashion by three nuclear

cardiology experts unaware of any patient data. The primary aim of the study was to show the strength of agreement between sequential adenosine and REG images, and the non-inferiority of the adenosine-REG sequence to the adenosine-adenosine sequence for consistently detecting reversible perfusion defects. The investigators demonstrated that the overall agreement was not statistically different between sequential adenosine–adenosine images (0.64 ± 0.04) compared to adenosine–REG images (0.63 ± 0.03). Furthermore, there was no significant difference in image quality between the two stress agents, and the patient tolerability questionnaire favored REG in this study. In a subsequent quantitative analysis of the ADVANCE-MPI 2 study, investigators showed that the total perfusion defect size, ischemic perfusion defect size, ejection fraction, and LV volume estimation was similar between REG and adenosine.[20] Thus, cumulative evidence collected from over 2000 patients in these pivotal phase 3 trials demonstrated the non-inferiority of REG to adenosine in SPECT MPI, [7] as well as the effects of age, gender, obesity, and diabetes on the efficacy and safety of REG[21] leading to its approval for clinical use.

3.2. REG in special populations

3.2.1. Renal disease

The predominantly renal excretion of REG (60% of the drug) raises concern for its safety in chronic kidney disease and end stage renal disease patients, including those on dialysis. To date, two major studies and one prognostic study have shown that REG is not associated with any major adverse events in this group.

Ananthasubramaniam et al.[22] conducted a randomized, double-blinded, placebo-controlled multicenter trial to evaluate the safety and tolerability of REG in 432 patients with stage 3 (glomerular filtration rate (GFR) 30–59 mL/min/1.73 m^2) and 72 patients with stage 4 (GFR 15–29 mL/min/1.73 m^2) chronic kidney disease. There were no major adverse events within 24 h of REG injection in the intervention group. Minor adverse effects like headache, dyspnea, chest discomfort, nausea, flushing, and dizziness were more common in the REG group than in the placebo group.

Doukky et al.[23] studied 146 ESRD patients undergoing REG stress testing, which included 131 patients on hemodialysis, 12 patients on peritoneal dialysis, and two not on any dialysis. These were compared with 97 control patients with GFR ≥30 mL/min. The primary end point of the study was patient reported side effects within 24 h following REG administration. There were no statistically significant differences in adverse effects between the groups. Interestingly, end stage renal disease patients tolerated REG stress better than the control group and expressed their willingness to take the test again (117/131 (80%) vs. 63/97 (65%), P = 0.001).[23]

3.2.2. Asthma and COPD

Adenosine 2_B and 3 receptors are located in bronchial smooth muscle cells which, when activated, can lead to bronchoconstriction (Figure 1). Although REG is a selective A_{2A} receptor

agonist, there is a concern related to its use in patients with asthma and chronic obstructive pulmonary disease (COPD).

More than six studies have been performed to evaluate the safety of REG in this population specifically looking at respiratory symptoms, spirometry parameters, hemodynamic response, and major adverse events. The combined population of these five prospective studies and one retrospective study comprised 686 COPD patients and 695 asthmatics.[24] Respiratory parameters like FEV1, FVC, FEV1/FVC ratio, and patient-reported symptoms were monitored in most of these studies. All showed that REG is safe in COPD and asthmatics. Dyspnea was reported more frequently in COPD and asthmatics, but no significant decline in spirometry measurements occurred among these patients in two double-blinded studies.[25, 26] Of particular note, Kwon et al.[27] demonstrated that patients who underwent low-level exercise in conjunction with REG stress reported fewer respiratory symptoms than those who did not exercise following REG administration.

3.2.3. Pacemaker and left bundle branch block

In patients with left bundle branch block (LBBB), pacemaker, or intrinsic conduction disease, the increased heart rate caused by either exercise, or dobutamine can lead to false-positive septal perfusion defects. This is due to a tachycardia-induced decrease in diastolic perfusion in an already asynchronously activated septum. Multiple studies have compared adenosine and exercise stress tests in these patients. Caner et al.[28–30] showed that dobutamine stress testing is associated with higher false positives in LBBB patients, and similar results were observed in pacemaker patients as well.

The ability of REG to identify perfusion defects in this population was studied by Thomas et al.[31] In their sub-analysis of the ADVANCE MPI 1 and 2 trials, where all 2015 subjects underwent SPECT MPI with adenosine followed by SPECT MPI with either REG or adenosine, 64 patients with LBBB and 93 with pacemakers were identified. Hemodynamic changes, visually assessed summed difference scores (SDS), and quantitative perfusion defects in the LAD territory and septum were compared between REG MPI and adenosine MPI. The study showed that although REG led to a significant increase in heart rate compared with adenosine, it did not cause or exaggerate perfusion defects in the LAD or septal territories either by SDS or quantitative assessment.[31]

3.2.4. Orthotopic heart transplant patients

Orthotopic heart transplant (OHT) patients have a higher incidence of AV block due to denervation supersensitivity. Hence, OHT patients who undergo MPI studies are at increased risk for developing high-grade AV block. Few studies have evaluated the role of MPI in diagnosing cardiac allograft vasculopathy in these patients.

In a retrospective analysis, Al-Mallah et al.[32] identified 102 OHT patients who underwent adenosine MPI and compared them with 204 control patients for heart rate, blood pressure changes, and occurrence of AV block. A threefold increase in the incidence of high-grade AV block (Mobitz type II and third degree) was seen in OHT patients vs. controls. Symptomatic

bradyarrhythmias occurred in 2% of OHT patients leading to premature termination of the adenosine infusion.

OHT patients were excluded from the early trials of REG, which led to its approval, and thus the safety of REG in this population was initially unknown. The effects of REG in these patients are particularly relevant, however, given its relative A_{2A} selectivity and the decreased incidence of AV block observed with REG in other populations. Cavalcante et al.[33] identified 40 OHT patients who underwent REG MPI. These results were compared with prior adenosine MPI results in the same patients. There were five episodes of second-degree AV block (Mobitz type II) and three episodes of sinus pause in adenosine MPI compared with only one episode of sinus pause in REG MPI. No major adverse effects such as congestive heart failure or death were reported following REG administration. To reverse REG's side effects, aminophylline was given to four patients (two for severe headache and two for chest pressure). However, REG was largely well tolerated by the OHT patients with no difference in overall adverse effect profile between the two test drugs.

4. REG in positron emission tomography stress myocardial perfusion imaging

Although REG was approved in April 2008 by the U.S. Food and Drug Administration for use in single photon emission computed tomography (SPECT) radionuclide myocardial perfusion imaging (MPI) as a pharmacologic stressor in patients unable to perform exercise stress testing, it has not yet been formally approved for use in positron emission tomography (PET) MPI. Nonetheless, it is increasingly being used in PET MPI in addition to the more established vasodilators, adenosine and dipyridamole. Over the past several years, PET MPI has become more accepted into the mainstream for the diagnosis and management of coronary artery disease (CAD).[34] Furthermore, a recent consensus statement by the American Society of Nuclear Cardiology recommended PET MPI over SPECT MPI as the preferred initial pharmacologic MPI modality if available.[35] The following is a discussion of the current evidence for REG as a pharmacologic stressor in PET MPI.

4.1. Current guidelines

The 2003 ACC/AHA/ASNC Guidelines for Clinical Use of Radionuclide Imaging recommend adenosine or dipyridamole myocardial perfusion PET for diagnosis in patients with an intermediate likelihood of CAD and/or for risk stratification in patients with an intermediate or high likelihood of CAD.[36] The only class I recommendation is in "patients in whom an appropriately indicated myocardial perfusion SPECT study has been found to be equivocal for diagnostic or risk stratification purposes" (Level of Evidence B). Class IIa recommendations for vasodilator PET MPI are identification of "the extent, severity, and location of ischemia as the initial diagnostic test in patients who are unable to exercise" and in "patients who are able to exercise but have LBBB or an electronically-paced rhythm" (both Level of Evidence B). REG

is listed as an additional vasodilator in the 2009 American Society of Nuclear Cardiology Guidelines.[37]

4.2. PET vs. SPECT myocardial perfusion imaging: advantages and disadvantages

Cardiac PET imaging always includes concomitant CT acquisition for attenuation correction whereas this is still optional with SPECT. Effective radiation dose is lower with PET despite high positron emission energy due to very short half-life of rubidium-82 (Rb-82), the most commonly used PET radiotracer. Ejection fraction (EF) reserve (stress EF – rest EF) is more accurate with PET than SPECT because PET calculates the EF at peak stress rather than post stress as with SPECT. Coronary blood flow/flow reserve is possible with PET as myocardial uptake of Rb-82 bears a more linear relationship to coronary flow rates whereas the uptake of SPECT tracers plateaus at low flows. This allows for better characterization and localization of CAD. The superior image quality of PET is related to its high spatial resolution, reduced scatter, and the high positron emission energy of Rb-82 (1.52 MeV).

Advantages	Disadvantages
Higher spatial resolution (2–4 mm vs. 6–8 mm) [38-40]	Incompatible with exercise ($t_{1/2}$ of Rb-82 only 75 s)
Better count efficiency (more counts in less time) [38-40]	Insurance coverage not universal
Superior soft tissue attenuation correction [38, 39]	Less availability
Less liver/bowel uptake (less scatter) [40]	Motion artifact affects entire image (360° acquisition)
Shorter scan time (5 vs. 16 min) [40]	Claustrophobia (longer tunnel)
Less radiation (3.7 vs. 10–22 mSv) [40, 41]	
More accurate estimation of EF reserve [42]	
Ability to assess coronary blood flow/coronary flow reserve [34]	
Superior diagnostic sensitivity, specificity, and accuracy [40]	
Superior image quality [40]	
Increased confidence in interpretation [40]	

Table 2. Advantages and disadvantages of Rb-82 PET MPI vs. SPECT MPI

	Sensitivity (PET/SPECT)	Specificity (PET/SPECT)	Accuracy (PET/SPECT)
>70% stenosis	87%/82% (ns)	93%/73% ($P = 0.02$)	89%/79% ($P = 0.03$)
>50% stenosis	86%/81% (ns)	100%/66% ($P = 0.00008$)	87%/71% ($P = 0.003$)

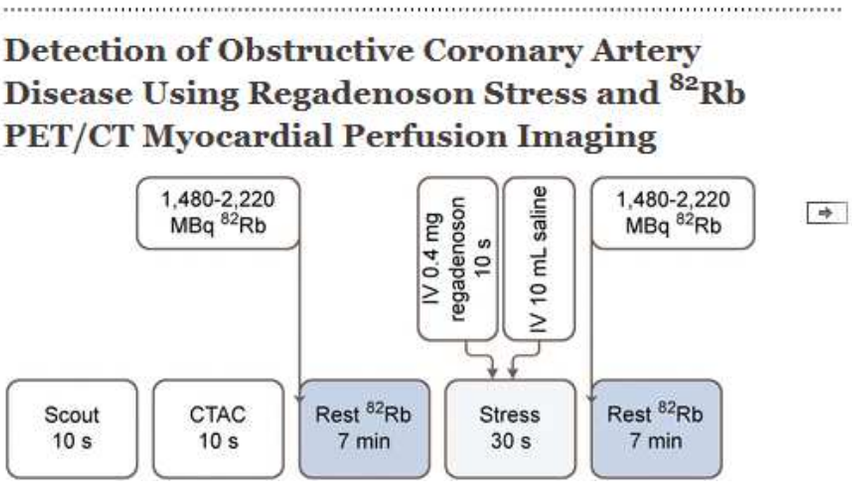
Table 3. Overall sensitivity, specificity, and diagnostic accuracy of PET vs. SPECT MPI for both moderate and severe degrees of coronary stenosis

Comparison of 112 SPECT MPI (using adenosine and Tc-99m) and 112 PET MPI (using dipyridamole and Rb-82) in populations matched for gender, BMI, and presence/extent of

CAD.[40] "Specificity" includes low-likelihood patients who did not undergo angiography in addition to angiographically normal patients. "ns" = not statistically significant.

4.3. Advantages of REG in PET MPI

The increase in coronary blood flow is over 100 times greater with REG than adenosine. Rapid onset of hyperemia (less than 1 min after injection) with peak hyperemia occurring about 2.3 min following injection[3] along with weight-independent standardized dosing make REG well suited for use with short-acting PET radiotracers such as Rb-82 ($t_{1/2}$ = 75 s). Rapid testing is thereby facilitated with the stress portion lasting less than 1 min. When using REG stress together with PET imaging, the entire test duration is only 16–18 min. Figure 3 is a flow diagram of the REG PET MPI protocol used by Hsiao et al.[43]



Reproduced with permission. Hsiao E, Ali B, Blankstein R, et al. Detection of obstructive coronary artery disease using regadenoson stress and 82Rb PET/CT myocardial perfusion imaging. J Nucl Med 2013;54:1748–54.

Figure 3. Rest-stress regadenoson [82]Rb PET/CT protocol. After scout CT acquisition (120 kVp, 10 mA), CT transmission scan (CTAC) (140 kVp, 10 mA, pitch of 1.35) was acquired. Patients received 1,480-2,220 MBq of [82]Rb intravenously at rest, and emission images were acquired in 2-dimensional list mode. After rest imaging, patients remained in scanner gantry for stress imaging. Stress was induced with 0.4 mcg of regadenoson given intravenously over 10 s followed by 10-mL flush with normal saline. Immediately after saline flush, second dose of 1,480-2,220 MBq of [82]Rb was administered intravenously approximately 30 s after regadenoson injection and emission images were acquired as previously described. Ordered-subsets expectation maximization (30 iterations and 2 subsets) and 3-dimensional PET filtering (Butterworth filter, cutoff frequency of 10, order of 5) were used for reconstruction of images.[43]

4.4. Coronary flow reserve using PET

The ability to quantitatively assess coronary blood flow (CBF) and coronary flow reserve (CFR) on angiography was discovered by Gould in animal experiments during the mid 1970s.[44] Because PET image acquisition occurs during peak stress, calculation of CFR (peak flow ÷ rest flow) is one of the unique features of PET as opposed to other noninvasive imaging modalities. A "normal range" has proved difficult to define given the disparity between coronary flows in asymptomatic patients. Based on pooled data from nearly 15,000 patients in 252 studies using three different PET isotopes, CFR in patients without CAD is 3.55 ± 1.36. In patients with established coronary disease, this drops to 2.02 ± 0.70.[45] Table 4 displays the range of values

for absolute coronary flow and CFR in the presence of CAD risk factors and other forms of cardiac disease. One of the larger studies in the literature, however, identified a CFR of 1.74 as the cutoff for "definite ischemia" below which patients manifest anginal symptoms and/or ischemic ECG changes during vasodilator stress testing matched by a significant perfusion defect on PET imaging.[46]

Population	n	Rest Flow (cc/min/g)	Stress Flow (cc/min/g)	CFR
Normal controls	3,484	0.82 ± 0.06	2.86 ± 1.29	3.55 ± 1.36
Risk factors only	3,592	0.85 ± 0.08	2.25 ± 1.07	2.80 ± 1.39
Established coronary artery disease	1,650	0.83 ± 0.10	1.71 ± 0.71	2.02 ± 0.70
Mixed (risk factors and/or known coronary artery disease)	4,765	0.97 ± 0.10	1.86 ± 0.58	1.93 ± 0.48
Cardiomyopathy	594	0.73 ± 0.07	1.47 ± 0.56	2.02 ± 0.67
Hypertrophic cardiomyopathy	345	0.90 ± 0.10	1.57 ± 0.33	1.84 ± 0.36
Syndrome X	348	1.06 ± 0.11	2.65 ± 1.31	2.54 ± 1.31
After cardiac transplant	184	1.14 ± 0.18	2.44 ± 1.34	2.29 ± 0.86

N = 14,962 from 252 unique publications. N-13 ammonia = 5,541; O-15 water = 3,161; Rb-82 = 6,175.

Reproduced with permission. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am CollCardiol2013;62:1639–53.

Table 4. Graded Absolute Flow and Coronary Flow Reserve Across Spectrum of Disease : n=14,962[45]

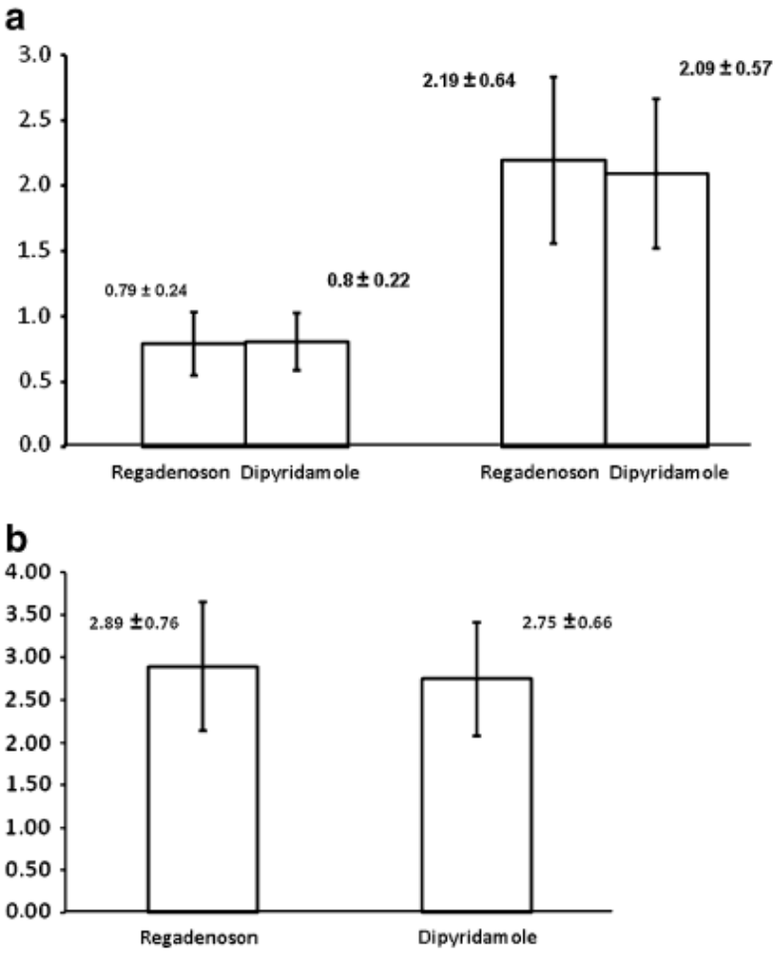
Not until recently was the clinical utility of PET-derived CFR fully appreciated. A study of 205 patients (using REG in half of these) demonstrated that with a negative predictive value of 97%, normal global CFR virtually assures the absence of high-risk CAD, despite any coexistent abnormal perfusion.[47] However, as a reduced CFR can occur in three different conditions (diffuse non-obstructive atherosclerosis, significant epicardial coronary stenosis, and micro-vascular disease), it can be somewhat helpful but is not specific for selecting patients likely to have high-risk CAD on angiography. A very recent study of PET-derived CFR further illustrated that low CFR can be seen in patients with systolic cardiomyopathy (EF ≤ 45%) of both ischemic and non-ischemic etiologies.[48] Murthy et al.[49] studied 2783 patients with known or suspected CAD referred for rest/stress PET MPI and then followed over a median of 1.4 years. Those in the lowest CFR tertile (<1.5) had a 16-fold increase in risk of cardiac death versus those in the highest tertile (>2.0). The middle tertile had a 5.7-fold increase in risk compared to the highest tertile. The addition of CFR to clinical and standard MPI factors led to the correct re-categorization of 34.9% of patients in the intermediate-risk group. Patients in this study received one of four different vasodilators (adenosine, dipyridamole, dobutamine, or REG). As resting CBF was similar between all three tertiles, the reduction in CFR was primarily driven by lower CBF with stress suggesting impaired coronary vasodilator function as an etiology. No difference was drawn between the various vasodilators used, however.

Very little has been published on the specific use of REG to assess CFR in Rb-82 PET MPI. Van Tosh et al.[50] used REG alone to show that CFR corresponded with LV dysfunction (LVD) during stress and that regional reductions in CFR were more often present in patients with

LVD than those without, indicating that the phenomenon of coronary steal may be involved in the genesis of LVD.

4.5. REG PET MPI vs. dipyridamole PET MPI

There exist scant data comparing REG and dipyridamole in PET MPI. A recent study retrospectively assessed CBF and CFR using Rb-82 perfusion PET/CT in 104 matched patients with normal stress tests, half with dipyridamole and half with REG. No significant difference in stress CBF and CFR was found between the two vasodilators (Figure 4). Further supporting REG's usefulness as a stress agent was the lack of any correlation between stress CBF or CFR and patient weight or BMI.[51]



Reproduced with permission. Goudarzi B, Fukushima K, Bravo P, Merrill J, Bengel FM. Comparison of the myocardial blood flow response to regadenoson and dipyridamole: a quantitative analysis in patients referred for clinical 82Rb myocardial perfusion PET. Eur J Nucl Med Mol Imaging2011;38:1908–16.

Figure 4. Myocardial blood flow (MBF) and myocardial flow reserve (MFR) in subjects undergoing pharmacological stress with regadenoson versus dipyridamole. **a** No significant difference in MBF between groups at rest (*left*, p=0.77) or during stress (*right*, p=0.39). **b** No significant difference in MFR (p=0.31).[51]

A very recent study by Johnson and Gould compared CFR in patients undergoing two sequential PET MPIs, either both with dipyridamole (n = 50) or with dipyridamole and REG

http://dx.doi.org/10.5772/61154

(*n* = 126).[52] In the latter group, various timings between REG administration and activation of the Rb-82 generator were used. It was demonstrated that using the timing recommended in the REG package insert (10–20 s between REG injection and radioisotope injection), the stress CBF and CFR with REG were only 80% of the hyperemia attained with dipyridamole. By increasing this interval to 55 ms, this percentage was increased to 90%. These findings suggest that with the current timing recommendation, REG remains inferior to diypirdamole in detecting stress CBF and CFR.

The shorter duration of peak hyperemia with REG (2.3 min) than dipyridamole has raised some concern as to whether Rb-82 uptake by the myocardium would be sufficient to register perfusion defects or changes in cardiac function with the newer vasodilator. Cullom et al.[53] studied 32 patients, all of whom underwent both REG and dipyridamole PET MPI, and compared summed stress and difference scores, total perfusion deficit, LVEF, LV volumes, and change in stress-rest function. They determined that REG and dipyridamole yielded equivalent measures of cardiac perfusion and function.

To date, there are no published investigations of REG vs. adenosine in PET myocardial perfusion imaging.

4.6. Diagnostic accuracy of REG PET MPI

Studies comparing vasodilator stress SPECT and PET MPI have repeatedly demonstrated slightly higher sensitivity in PET (90%) than SPECT (80–84%) but far greater specificity in PET (89%) than SPECT (53–76%).[34, 38, 39] Table 5 summarizes the results of all published literature on the diagnostic accuracy of PET through 2007. Most of these studies used Rb-82 as a tracer and dipyridamole ± handgrip for stress. One included dipyridamole, adenosine, and dobutamine stress, and one used exercise stress with ammonia-N13 PET imaging.

Reference	No. of patients	Women	Prior CAD	PET radiotracer	Sensitivity	Specificity	PPV	NPV	Accuracy
Sampson et al. (*22*)*	102	0.42	0	^{82}Rb	0.93	0.83	0.80	0.94	0.87
Bateman et al. (*21*)	112	0.46	0.25	^{82}Rb	0.87	0.93	0.95	0.81	0.89
Marwick et al. (*23*)	74	0.19	0.49	^{82}Rb	0.90	1	1	0.36	0.91
Grover-McKay et al. (*24*)	31	0.01	0.13	^{82}Rb	1	0.73	0.80	1	0.87
Stewart et al. (*20*)	81	0.36	0.42	^{82}Rb	0.83	0.86	0.94	0.64	0.84
Go et al. (*19*)	202	NR	0.47	^{82}Rb	0.93	78	0.93	0.80	0.90
Demer et al. (*25*)	193	0.26	0.34	^{82}Rb /^{13}N-ammonia	83	0.95	0.98	0.60	0.85
Tamaki et al. (*26*)	51	NR	0.75	^{13}N-ammonia	0.98	1	1	0.75	0.98
Gould et al. (*27*)	31	NR	NR	^{82}Rb /^{13}N-ammonia	0.95	1	1	0.90	0.97
Weighted summary	877	0.29	0.35		0.90	0.89	0.94	0.73	0.90

*Study using PET/CT (in which CT was used for attenuation correction only).

PPV= positive predictive value; NPV= negative predictive value; NR= not reported. (Reprinted with permission of (28).)

Reproduced with permission. Di Carli MF, Dorbala S, Meserve J, El Fakhri G, Sitek A, Moore SC. Clinical myocardial perfusion PET/CT. J Nucl Med2007;48:783–93.

Table 5. Summary of Published Literature with Regard to Diagnostic Accuracy of PET[34]

Hsiao et al.[43] performed the first and so far only published study to evaluate the diagnostic accuracy of REG in PET MPI. In a relatively small cohort of 134 patients in 98 of whom angiographic data were also available, its accuracy was found to be similar to that of PET MPI using other vasodilators. Sensitivity for obstructive CAD was 92%, and overall specificity was 77% (53% in patients with high likelihood of CAD but no angiographic evidence of obstructive disease and 93% in low likelihood patients who did not go on to angiography [normalcy rate]). The area under the receiver–operator curve was 0.847, comparable to the high accuracy rates of PET in previous studies.

The high sensitivity of PET MPI for detection of obstructive CAD can be further increased by PET's ability to quantify blood flow/flow reserve and to calculate LVEF reserve using peak-stress LVEF.

4.7. Prognostic value of REG PET MPI

It has been shown that the prognostic value of REG is comparable to that of adenosine in patients with normal SPECT myocardial perfusion tests.[54] There are no published data on the prognostic value of REG in PET MPI, nor of REG MPI in patients with abnormal results using either PET or SPECT. Recent studies, however, offer insight as to the prognostic value of LVEF reserve in vasodilator stress PET.

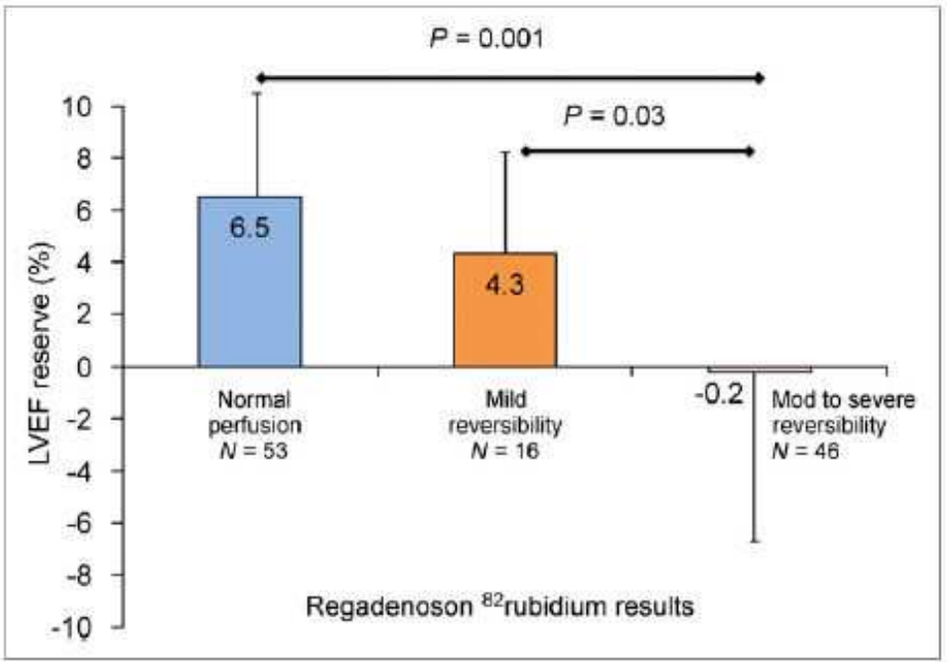
Dorbala et al.[42] established that LVEF reserve (stress LVEF – rest LVEF) is independently predictive of the extent of at-risk myocardium on Rb-82 PET MPI and the extent of CAD on invasive angiography. Based on these results, LVEF reserve >5% essentially rules out severe 3-vessel or left main disease with a negative predictive value of 97%. In 985 patients with gated vasodilator stress Rb-82 PET MPI, nearly half of whom were at intermediate risk for CAD consistent with contemporary practice, the same group of investigators showed that during a mean follow-up period of 1.7 years, the frequency of cardiac events and all-cause death was higher in patients with LVEF reserve <0 than in those with LVEF which either remained the same or augmented with stress.[55] The prognostic value of LVEF reserve was found to be independent of, and incremental to, clinical variables and rest LVEF. These studies, however, included only patients who had received either dipyridamole or adenosine.

Hsiao's was the first group to investigate LVEF reserve using REG PET MPI, albeit in a much smaller cohort of 115 patients. Here, LVEF reserve with REG was inversely related to the severity of reversible perfusion defect (summed difference score) as well as jeopardized myocardium on coronary angiography (Duke Jeopardy Score)[43] (Figures 5 and 6). This suggests that REG may be as useful as dipyridamole or adenosine in determining LVEF reserve; however, further studies are still needed to evaluate its prognostic value.

4.8. Future directions for REG PET MPI

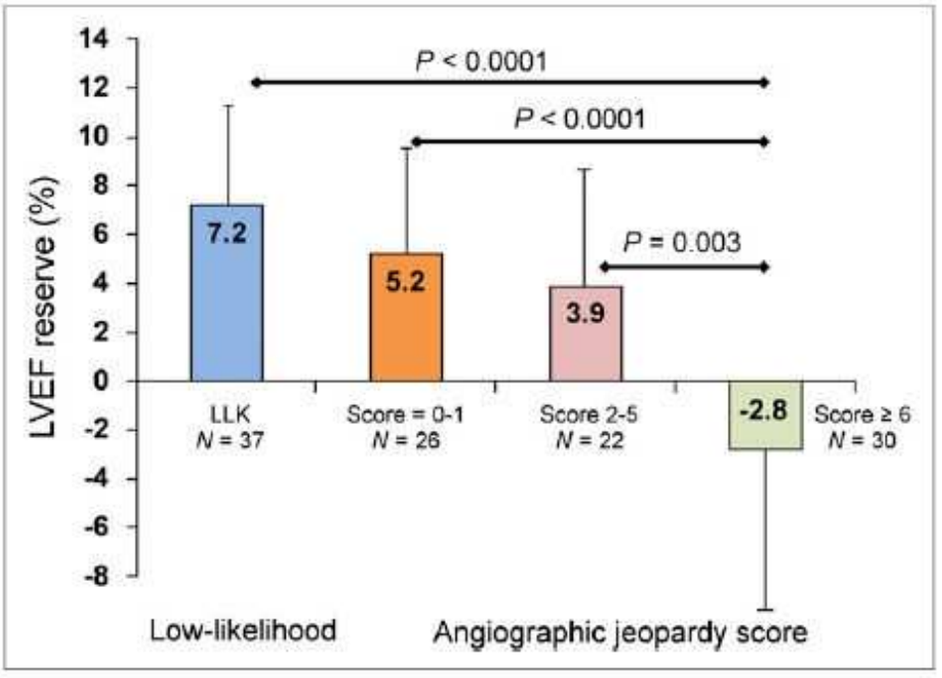
The IDEALPET (Integrated Dual Exercise and Lexiscan PET) study is currently underway and will compare Lexiscan© alone with Lexiscan© plus exercise ("Lexercise") with regards to safety, tolerability, myocardial perfusion image quality, and assessment of relative and absolute myocardial perfusion.[56]

http://dx.doi.org/10.5772/61154



Reproduced with permission. Hsiao E, Ali B, Blankstein R, et al. Detection of obstructive coronary artery disease using regadenoson stress and 82Rb PET/CT myocardial perfusion imaging. J Nucl Med2013;54:1748–54.

Figure 5. Regadenoson LVEF reserve as function of relative MPI results. Mod=moderate.[43]



Reproduced with permission. Hsiao E, Ali B, Blankstein R, et al. Detection of obstructive coronary artery disease using regadenoson stress and 82Rb PET/CT myocardial perfusion imaging. J Nucl Med2013;54:1748–54.

Figure 6. Regadenoson LVEF reserve as function of Duke Jeopardy Score. LLK= low likelihood.[43]

As of February 2011 REG was being used in 68% of all pharmacologic stress MPI studies in the United States.[54] Given its already widespread use and favorable profile as a stress agent plus the advantages inherent in Rb-82 PET perfusion imaging (superior image quality, shorter scan time, lower radiation dose to patient, quantitation of myocardial blood flow, measurement of peak LVEF, additional prognostic information), REG PET MPI has the capacity to become the pharmacologic stress test of choice over the next several years.

5. Novel applications of REG

5.1. Adjunct to exercise MPI

Exercise-based testing has been convincingly shown to provide powerful prognostic data and remains the preferred mode of stress testing if patients are capable of exercising.[57, 58] However, about 25% of exercise-based testing may be non-diagnostic due to inability to achieve target heart rates. Two alternatives for these patients have been evaluated in the past: either rescheduling for pharmacologic stress or immediately attempting adjunctive vasodilator stress with agents such as adenosine and dipyridamole.[59, 60] The combination of simultaneous adjunctive low-level exercise with adenosine or dipyridamole helps both to lessen side effects and improve image quality.[61, 62] However, trying to add on adenosine or dipyridamole when exercise testing is submaximal poses major challenges as both are given as an infusion over a few minutes, need to be adjusted for weight or delivered via pump (as in the case of adenosine), and thus are not immediately feasible. In these instances, patients are usually rescheduled for a pharmacologic stress test when exercise testing is submaximal. With the advent of rapid-acting, weight-independent, single-bolus dosing of REG, its use as an adjunct to exercise seemed logistically feasible and potentially convenient. Its administration could result in quick conversion of an otherwise non-diagnostic nuclear exercise stress study due to submaximal heart rate to a diagnostic one. Early data support such a practice.

Thomas et al.[63] evaluated the safety of REG during exercise in a double blind study of 60 patients focusing on image quality, patient acceptance, and detection of perfusion defects. Patients undergoing a clinically indicated adenosine supine MPI were subsequently randomized in a 2:1 fashion to REG with low-level exercise (RegEx) or placebo with low-level exercise (PlcEx). This small study showed no significant differences in blood pressure response between the RegEx and PlcEx groups, although a smaller increase in heart rate was noted in the RegEx than in the PlcEx group. The image quality was better with REGEx compared to the adenosine supine MPI images. Patient tolerability was also reported to be better with RegEx compared to adenosine supine MPI. No significant adverse events, including high-grade AV block, were reported in the RegEx group.

In a subsequent study, Kwon et al.[27] published their retrospective experience with 1263 patients undergoing REG MPI with either adjunctive low-level treadmill exercise (n = 596) or as a standard supine REG stress test (n = 667). Among all participants an asymptomatic drop in systolic blood pressure > 10 mmHg occurred in 51% and > 30 mmHg in 9%. A pressure drop was observed more often in those randomized to REG plus low-level treadmill exercise (56%) than in those undergoing supine REG (47%). In their COPD/asthma patients

http://dx.doi.org/10.5772/61154

(16%), REG with low-level exercise was well tolerated, and they also reported lower incidence of nausea, shortness of breath, transient heart block, palpitations, and dizziness overall in those who underwent low-level exercise.

Our own experience comparing REG MPI (n = 887) to REGWALK MPI (n = 485) (REG with adjunctive low-level exercise) was published as a retrospective series. We showed that REGWALK studies demonstrated higher stress heart rate response, higher heart rate reserve, and higher systolic blood pressure with stress. There was less use of aminophylline for reversal of REG side effects in the REGWALK compared to the REG group. No major adverse events were reported in this series.

No data exist showing improved detection of ischemia/prognosis by combining REG with exercise. A few randomized studies have assessed the safety and efficacy of REG when used as an adjunct to maximal exercise when target heart rate is not achieved. Ross et al.[64] randomized 200 patients undergoing exercise MPI to either adjunctive REG if target heart rate was not achieved at peak exercise or to the discontinuation of exercise with conversion to a standard supine REG stress test. They showed that both approaches were well tolerated without any adverse events. There were no differences in ischemia detection, image quality or referral to cardiac catheterization in either group. Another small randomized study (n = 140) also showed that augmenting submaximal exercise with REG as needed was safe in patients.[65] In an effort to finalize the evaluation of REG's safety as an adjunct to exercise, a large randomized trial has just been completed by Astellas.[66] Results of this study will conclusively address not only the safety of REG with exercise but also the detection of ischemia when compared to REG alone.

5.2. Fractional Flow Reserve (FFR)

The concept of reactive hyperemia is particularly useful in guiding percutaneous coronary intervention (PCI) when intermediate coronary lesions of unclear hemodynamic significance are present on invasive angiography.[67, 68] More recently, seminal studies have firmly established that FFR-guided decision making for coronary lesions of unclear significance is associated with a favorable outcome with PCI being deferred or performed based on FFR values.[69] Most catheterization labs use either intracoronary or intravenous adenosine for assessment of hyperemic response.[70, 71] However recent studies have now shown that REG may be a viable alternative to adenosine with its weight independent bolus and rapid achievement of hyperemia in 33–40 s, thus shortening the entire time needed for FFR assessment.[72, 73] In a study of 25 patients undergoing catheterization, Nair et al.[72] compared the ability of IV adenosine and IV REG to induce coronary hyperemia in assessment of coronary stenosis significance. They found excellent linear correlation for measurement of FFR between the two agents (r = 0.985, P = 0.001). Furthermore, none of the hemodynamically significant lesions (FFR <0.8, 52% of patients) identified by adenosine were reclassified by REG. There were no significant adverse reactions to either drug and REG was overall better tolerated than adenosine.[72] In a more recent study by Prasad et al.,[74] the authors compared 57 patients (60 lesions) undergoing FFR measurements first with adenosine followed by a 10 min washout phase and then with REG. They showed high correlation in hyperemic response between the two drugs (R^2 = 0.93) (Figure 7) and substantially shorter time to peak hyperemia with REG

than adenosine as well as a trend to a better side effect profile with REG. One issue of concern raised by these authors has been the potential cost of a single vial of REG (around 250 dollars) compared to a 3-min adenosine infusion (80 dollars). However, such cost differences could be made up by shorter duration of REG administration, no need for infusion pumps and less nursing time for set up. A recent randomized study of 100 patients has also shown that REG is equivalent to central venous infusion of adenosine to induce maximal hyperemia for FFR determination.[75]

In summary, the data accumulated on REG in FFR suggest that it could very well be the preferred agent in the catheterization lab given its ease of use and proven efficacy and comparability to adenosine.

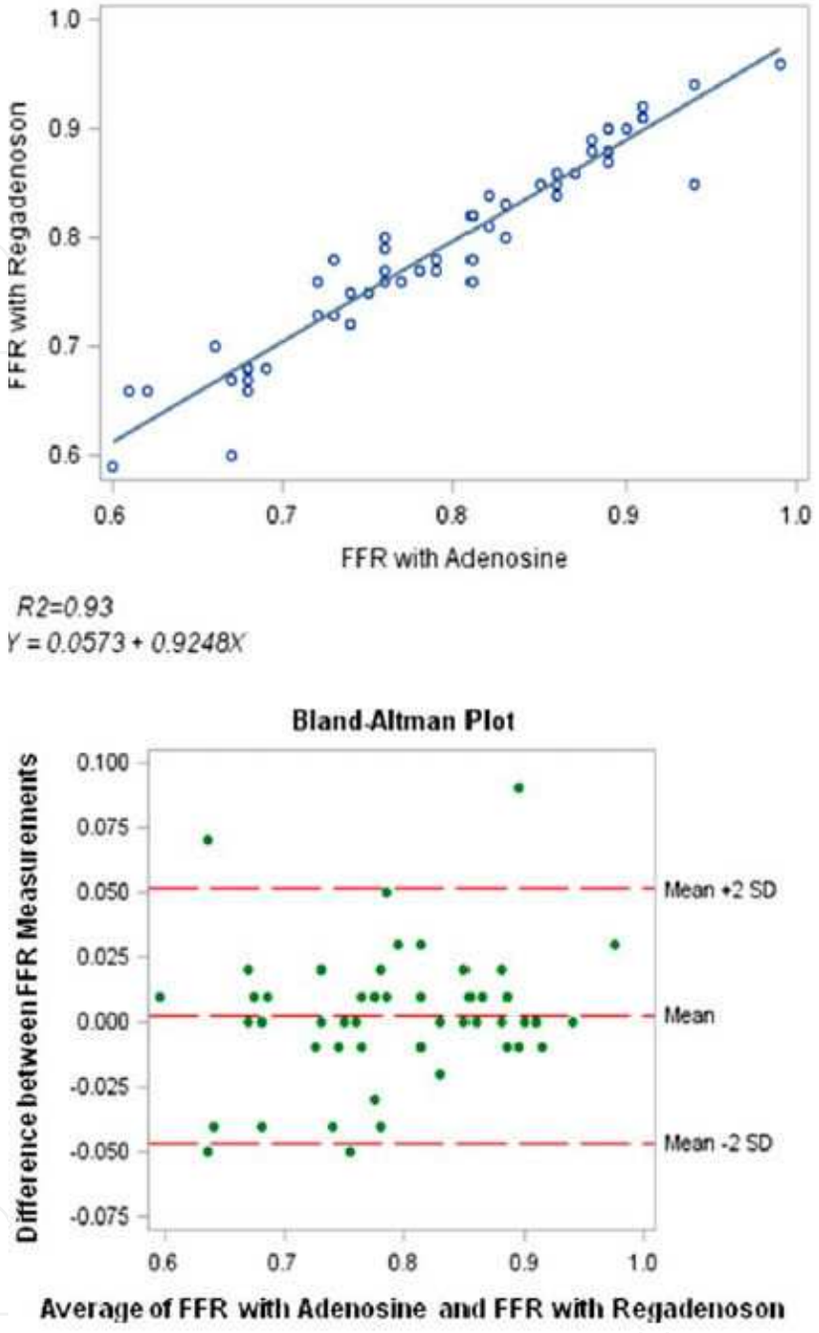
5.3. Stress echocardiography

The detection of CAD using stress echocardiography (SE) is based on the physiologic principle of stress-induced subendocardial ischemia causing wall motion abnormalities in the territory subtended by stenosis. Exercise and dobutamine (DSE) are the main methods of SE in North America,[76] whereas high-dose dipyridamole supplemented with atropine has been the mainstay pharmacologic stressor in Europe.[76, 77]

It is well known that wall motion can be completely normal with DSE despite mild to moderate stenosis and corresponding abnormalities in hyperemic blood flow.[78] Using a newer technique of myocardial contrast echocardiography (MCE), contrast imaging during induced hyperemia allows for the detection of milder degrees of coronary stenosis. Similar to nuclear perfusion imaging, MCE is able to pick up small perfusion abnormalities, which occur prior to ischemic changes in wall motion, in keeping with the "ischemic cascade." Prior studies using adenosine, dobutamine, and exercise with MCE have shown that myocardial contrast perfusion enables detection of moderate stenosis when added to wall motion.[79–81]

Given its ease of use, there has been interest in using REG as a vasodilator to induce hyperemic stress during MCE. In a study of 100 patients undergoing quantitative coronary angiography, Porter et al.[82] performed real-time MCE with Definity 3% infusion at baseline and then at 2-min intervals for up to 6 min after a REG bolus. This study showed that MCE with REG can detect noncritical coronary stenosis (>50% diameter) with sensitivity, specificity, and accuracy of 80%, 74%, and 75%, respectively, which was better than wall motion analysis alone (60%, 70%, and 66%, respectively ($P < 0.001$ for sensitivity)). Furthermore, the authors concluded that the sensitivity was highest when imaging was performed 4–6 min after REG administration.[82] In a recent study performed in 10 dogs with mild to moderate non flow limiting CAD, Le et al.[83] used REG (5 μg/kg, 10-s bolus) along with MCE and assessed myocardial blood volume, flow velocity, and total regional myocardial flow before and after REG administration. REG induced an increase in coronary blood flow for 30 min. This decreased proportionally to stenosis severity, and perfusion defects were visible for up to 10 min after REG bolus. They noted that the optimal time for imaging myocardial perfusion in stress echo with REG was between 3 and 10 min after REG bolus.[83]

http://dx.doi.org/10.5772/61154



Prasad et al.: CCI; 2014;83;365–74 [74]
Reproduced with permission Prasad A, Zareh M, Doherty R, et al. Use of regadenoson for measurement of fractional flow reserve. Catheter CardiovascInterv2014;83:369–74.

Figure 7. Average of FFR with Adenosine and FFR with Regadenoson[74]

Our group recently reported on 44 patients undergoing diagnostic angiography based on prior abnormal stress testing who also underwent a novel protocol called REGAT (REG + atropine) SE to assess feasibility, safety, and diagnostic accuracy of CAD detection. The testing sequence began with administration of 2 × 1 mg boluses of atropine to induce chronotro-

py followed by a 400-μg bolus of REG, and then echo imaging at peak stress starting 20 s after the REG bolus. The protocol was found to be safe and well tolerated with no serious adverse effects. The mean duration of REGAT SE was 18 ± 7 min. Significant CAD (≥70% stenosis) by angiography was present in 51.1%. Sensitivity, specificity, and positive and negative predictive values for REGAT SE were 60.9%, 80.4%, 82.4%, and 67.9%, respectively. By coronary territories, the sensitivity, specificity, PPV, and NPV were as follows: left anterior descending artery, 58.8%, 92.9%, 83.3%, and 78.8%; left circumflex artery, 6.7%, 93.3%, 33.3%, and 67.7%; and right coronary artery, 16.7%, 93.9%, 50%, and 75.6%. Over 90% of subjects reported feeling comfortable, with 83% preferring REGAT as a future stress modality. We concluded that although the REGAT protocol was fast, safe, and well-tolerated with good specificity for CAD detection, its low sensitivity and NPV preclude it from routine use. Importantly, contrast was not utilized in our study as we were testing the feasibility of a combination of REG and atropine. Overall evidence indicates that REG in SE may be feasible and safe and, but larger studies are needed in this area as concern still exits that echocardiographic imaging may not detect ischemia induced by vasodilator stress.

5.4. Coronary CT Angiography (CCTA) and stress perfusion

It is now well established that CCTA performs with high diagnostic sensitivity and has excellent negative predictive value for the noninvasive evaluation of CAD[84, 85] However the specificity and positive predictive value have been shown to be less than desired with overestimation of stenosis severity in published studies[86, 87]. When compared to fractional flow reserve or SPECT even apparent high grade stenosis diagnosed on CCTA has not be consistently associated with ischemia[87]. This has raised some concerns that CCTA as a noninvasive modality for CAD may lead to higher false positives and downstream testing. CCTA stenosis detection requires additional physiologic information to correctly identify physiologic significant lesions. Until recently evidence for ischemia evaluation with CCTA has been very limited. The concept of combining stress perfusion with CT (CTP) has been tested and found to be accomplished in many single center studies mainly using adenosine or adenosine triphosphate. This has raised the possibility that a comprehensive anatomic and physiologically CAD assessment could be feasible by CCTA+CTP. [88-90]

Most recently a multicenter study sponsored by Astellas was completed and published evaluating the non-inferiority of REG CTP to REG SPECT. Patients (men > 45 years; women > 50 years) with known or suspected coronary artery disease (n=124) were randomized to 1 of 2 diagnostic sequences: rest/REG SPECT MPI on day 1, then REG/rest CTP on day 2, or REG/rest CTP on day 1 followed by rest/REG SPECT MPI on day 2. CCTA was also performed during the same acquisition as the CTP in both groups. Scanning platforms included 64-, 128-, 256-, and 320-slice systems. The primary analysis examined the agreement rate between CTP and SPECT for detecting or excluding reversible ischemia in 2 myocardial segments as assessed by independent blinded readers. Across the 110 patients included in the final analysis REG CTP was non-inferior to SPECT for detecting or excluding reversible ischemia with an agreement rate of 0.87 (95% confidence interval [CI], 0.77-0.97) and sensitivity and specificity of 0.90 (95% CI, 0.71-1.00) and 0.84 (95% CI, 0.77-0.91), respectively. The agreement rate for

detecting or excluding fixed defects by REG CTP and SPECT was 0.86 (95% CI, 0.74e0.98). With SPECT as the reference standard, the diagnostic accuracies for detecting or excluding ischemia by REG CTP and CTA alone were 0.85 (95% CI, 0.78-0.91) and 0.69 (95% CI, 0.60-0.77), respectively. The authors concluded that REG CTP is non-inferior to SPECT. Thus, CT vasodilator stress perfusion imaging either with REG or adenosine appears to have a promising role in providing physiologic information to clarify anatomic stenosis. Further studies are awaited to establish this modality in clinical practice.

6. Conclusion

We have aimed to provide the reader in this chapter a detailed overview of REG and its current status in cardiac stress testing and other emerging cardiac applications. The role of REG remains to be better defined in cardiac MRI and CT.

Acknowledgements

We thank Stephanie Stebens MLIS AHIP, Sladen Library, Henry Ford Hospital, for her expert assistance in the preparation of this manuscript.

Author details

Gurunanthan Palani[1], Rebecca Baumann[2] and Karthik Ananthasubramaniam[2*]

*Address all correspondence to: kananth1@hfhs.org

1 Department of Internal Medicine, McLaren Regional Medical Center, Michigan State University, Flint, MI, USA

2 Heart and Vascular Institute, Henry Ford Hospital, Detroit MI, USA

Dr. Palani and Dr. Baumann have no disclosures. Dr. Ananthasubramaniam has received research grants from Astellas Pharma US Inc.

References

[1] Kochanek KD, Xu J, Murphy SL, Minino AM, Kung HC. Deaths: final data for 2009. *Natl Vital Stat Rep.* 2011;60(3):1–116.

[2] Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation.* 2011;123(8):933–944.

[3] Lieu HD, Shryock JC, von Mering GO, et al. Regadenoson, a selective A2A adenosine receptor agonist, causes dose-dependent increases in coronary blood flow velocity in humans. *J Nucl Cardiol.* 2007;14(4):514–520.

[4] Laighold S, Druz R. Initial clinical experience with a selective A2A receptor agonist, regadenoson, in a patient with end-stage renal disease on hemodialysis. *J Nucl Cardiol.* 2009;16(3):478–480.

[5] Gordi T, Frohna P, Sun HL, Wolff A, Belardinelli L, Lieu H. A population pharmacokinetic/pharmacodynamic analysis of regadenoson, an adenosine A2A-receptor agonist, in healthy male volunteers. *Clin Pharmacokinet.* 2006;45(12):1201–1212.

[6] Trochu JN, Zhao G, Post H, et al. Selective A2A adenosine receptor agonist as a coronary vasodilator in conscious dogs: potential for use in myocardial perfusion imaging. *J Cardiovasc Pharmacol.* 2003;41(1):132–139.

[7] 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(5):645–658.

[8] 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(2):695–702.

[9] Hage FG, Heo J, Franks B, et al. Differences in heart rate response to adenosine and regadenoson in patients with and without diabetes mellitus. *Am Heart J.* 2009;157(4): 771–776.

[10] Lexiscan (Regadenoson) [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; 2014.

[11] Shah S, Parra D, Rosenstein RS. Acute myocardial infarction during regadenoson myocardial perfusion imaging. *Pharmacotherapy.* 2013;33(6):e90–95.

[12] Hsi DH, Marreddy R, Moshiyakhov M, Luft U. Regadenoson induced acute ST-segment elevation myocardial infarction and multivessel coronary thrombosis. *J Nucl Cardiol.* 2013;20(3):481–484.

[13] Rosenblatt J, Mooney D, Dunn T, Cohen M. Asystole following regadenoson infusion in stable outpatients. *J Nucl Cardiol.* 2014;21(5):862–868.

[14] Agarwal V, DePuey EG. Advanced heart block and unresponsiveness after regadenoson administration during myocardial SPECT study. *Int J Cardiol.* 2014;176(2):e49–51.

[15] Page RL, 2nd, Spurck P, Bainbridge JL, Michalek J, Quaife RA. Seizures associated with regadenoson: a case series. *J Nucl Cardiol.* 2012;19(2):389–391.

[16] Zhao G, Messina E, Xu X, et al. Caffeine attenuates the duration of coronary vasodilation and changes in hemodynamics induced by regadenoson (CVT-3146), a novel adenosine A2A receptor agonist. *J Cardiovasc Pharmacol.* 2007;49(6):369–375.

[17] Gaemperli O, Schepis T, Koepfli P, et al. Interaction of caffeine with regadenoson-induced hyperemic myocardial blood flow as measured by positron emission tomography: a randomized, double-blind, placebo-controlled crossover trial. *J Am Coll Cardiol.* 2008;51(3):328–329.

[18] Tejani FH, Thompson RC, Kristy R, Bukofzer S. Effect of caffeine on SPECT myocardial perfusion imaging during regadenoson pharmacologic stress: a prospective, randomized, multicenter study. *Int J Cardiovasc Imaging.* 2014;30(5):979–989.

[19] Hendel RC, Bateman TM, Cerqueira MD, 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(11):2069–2075.

[20] Mahmarian JJ, Cerqueira MD, Iskandrian AE, et al. Regadenoson induces comparable left ventricular perfusion defects as adenosine: a quantitative analysis from the ADVANCE MPI 2 trial. *JACC Cardiovasc Imaging.* 2009;2(8):959–968.

[21] 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(3):307–316.

[22] 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(2):319–329.

[23] Doukky R, Rangel MO, Wassouf M, Dick R, Alqaid A, Morales Demori R. The safety and tolerability of regadenoson in patients with end-stage renal disease: the first prospective evaluation. *J Nucl Cardiol.* 2013;20(2):205–213.

[24] Golzar Y, Doukky R. Regadenoson use in patients with chronic obstructive pulmonary disease: the state of current knowledge. *Int J Chron Obstruct Pulmon Dis.* 2014;9:129–137.

[25] 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(4):681–692.

[26] Thomas GS, Tammelin BR, Schiffman GL, 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(3):319–328.

[27] Kwon DH, Cerqueira MD, Young R, et al. Lessons from regadenoson and low-level treadmill/regadenoson myocardial perfusion imaging: initial clinical experience in 1263 patients. *J Nucl Cardiol.* 2010;17(5):853–857.

[28] Caner B, Rezaghi C, Uysal U, et al. Dobutamine thallium-201 myocardial SPECT in patients with left bundle branch block and normal coronary arteries. *J Nucl Med.* 1997;38(3):424–427.

[29] O'Keefe JH, Jr., Bateman TM, Barnhart CS. Adenosine thallium-201 is superior to exercise thallium-201 for detecting coronary artery disease in patients with left bundle branch block. *J Am Coll Cardiol.* 1993;21(6):1332–1338.

[30] Lakkis NM, He ZX, Verani MS. Diagnosis of coronary artery disease by exercise thallium-201 tomography in patients with a right ventricular pacemaker. *J Am Coll Cardiol.* 1997;29(6):1221–1225.

[31] Thomas GS, Kinser CR, Kristy R, Xu J, Mahmarian JJ. Is regadenoson an appropriate stressor for MPI in patients with left bundle branch block or pacemakers? *J Nucl Cardiol.* 2013;20(6):1076–1085.

[32] Al-Mallah MH, Arida M, Garcia-Sayan E, et al. Safety of adenosine pharmacologic stress myocardial perfusion imaging in orthotopic cardiac transplant recipients: a single center experience of 102 transplant patients. *Int J Cardiovasc Imaging.* 2011;27(7):1105–1111.

[33] 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(4):628–633.

[34] Di Carli MF, Dorbala S, Meserve J, El Fakhri G, Sitek A, Moore SC. Clinical myocardial perfusion PET/CT. *J Nucl Med.* 2007;48(5):783–793.

[35] Cerqueira MD, Allman KC, Ficaro EP, et al. Recommendations for reducing radiation exposure in myocardial perfusion imaging. *J Nucl Cardiol.* 2010;17(4):709–718.

[36] Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *Circulation.* 2003;108(11):1404–1418.

[37] Henzlova MJ, Cerqueira MD, Hansen CL, Taillefer R, Yao S-S. ASNC imaging guidelines for nuclear cardiology procedures, stress protocols and tracers. *J Nucl Cardiol.* 2009;16(2):331.

[38] Stewart RE, Schwaiger M, Molina E, et al. Comparison of rubidium-82 positron emission tomography and thallium-201 SPECT imaging for detection of coronary artery disease. *Am J Cardiol.* 1991;67(16):1303–1310.

[39] Go RT, Marwick TH, MacIntyre WJ, et al. A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in the diagnosis of coronary artery disease. *J Nucl Med.* 1990;31(12): 1899–1905.

[40] Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. *J Nucl Cardiol.* 2006;13(1):24–33.

[41] Gerber TC, Carr JJ, Arai AE, et al. Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. *Circulation.* 2009;119(7):1056–1065.

[42] Dorbala S, Vangala D, Sampson U, Limaye A, Kwong R, Di Carli MF. Value of vasodilator left ventricular ejection fraction reserve in evaluating the magnitude of myocardium at risk and the extent of angiographic coronary artery disease: a 82Rb PET/CT study. *J Nucl Med.* 2007;48(3):349–358.

[43] Hsiao E, Ali B, Blankstein R, et al. Detection of obstructive coronary artery disease using regadenoson stress and 82Rb PET/CT myocardial perfusion imaging. *J Nucl Med.* 2013;54(10):1748–1754.

[44] Gould KL. Coronary flow reserve and pharmacologic stress perfusion imaging: beginnings and evolution. *JACC Cardiovasc Imaging.* 2009;2(5):664–669.

[45] Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol.* 2013;62(18):1639–1653.

[46] Johnson NP, Gould KL. Physiological basis for angina and ST-segment change PET-verified thresholds of quantitative stress myocardial perfusion and coronary flow reserve. *JACC Cardiovasc Imaging.* 2011;4(9):990–998.

[47] Naya M, Murthy VL, Taqueti VR, et al. Preserved coronary flow reserve effectively excludes high-risk coronary artery disease on angiography. *J Nucl Med.* 2014;55(2): 248–255.

[48] Majmudar MD, Murthy VL, Shah RV, et al. Quantification of coronary flow reserve in patients with ischaemic and non-ischaemic cardiomyopathy and its association with clinical outcomes. *Eur Heart J Cardiovasc Imaging.* 2015.

[49] Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation.* 2011;124(20):2215–2224.

[50] Van Tosh A, Votaw JR, Reichek N, Palestro CJ, Nichols KJ. The relationship between ischemia-induced left ventricular dysfunction, coronary flow reserve, and coronary steal on regadenoson stress-gated (82)Rb PET myocardial perfusion imaging. *J Nucl Cardiol.* 2013;20(6):1060–1068.

[51] Goudarzi B, Fukushima K, Bravo P, Merrill J, Bengel FM. Comparison of the myocardial blood flow response to regadenoson and dipyridamole: a quantitative analysis in patients referred for clinical 82Rb myocardial perfusion PET. *Eur J Nucl Med Mol Imaging.* 2011;38(10):1908–1916.

[52] Johnson NP, Gould KL. Regadenoson versus dipyridamole hyperemia for cardiac PET imaging. *JACC Cardiovasc Imaging.* 2015.

[53] Cullom SJ, Case JA, Courter SA, McGhie AI, Bateman TM. Regadenoson pharmacologic rubidium-82 PET: a comparison of quantitative perfusion and function to dipyridamole. *J Nucl Cardiol.* 2013;20(1):76–83.

[54] Iqbal FM, Hage FG, Ahmed A, et al. Comparison of the prognostic value of normal regadenoson with normal adenosine myocardial perfusion imaging with propensity score matching. *JACC Cardiovasc Imaging.* 2012;5(10):1014–1021.

[55] Dorbala S, Hachamovitch R, Curillova Z, et al. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. *JACC Cardiovasc Imaging.* 2009;2(7):846–854.

[56] Brigham and Women's Hospital. Integrated Dual Exercise and Lexiscan Positron Emission Tomography: IDEALPET. *ClinicalTrials.gov*. Bethesda, MD: National Library of Medicine; 2010: http://clinicaltrials.gov/show/NCT01109992.

[57] Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med.* 2002;346(11): 793–801.

[58] Johnson NP, Wu E, Bonow RO, Holly TA. Relation of exercise capacity and body mass index to mortality in patients with intermediate to high risk of coronary artery disease. *Am J Cardiol.* 2008;102(8):1028–1033.

[59] Casale PN, Guiney TE, Strauss HW, Boucher CA. Simultaneous low level treadmill exercise and intravenous dipyridamole stress thallium imaging. *Am J Cardiol.* 1988;62(10 Pt 1):799–802.

[60] Ignaszewski AP, McCormick LX, Heslip PG, McEwan AJ, Humen DP. Safety and clinical utility of combined intravenous dipyridamole/symptom-limited exercise stress test with thallium-201 imaging in patients with known or suspected coronary artery disease. *J Nucl Med.* 1993;34(12):2053–2061.

[61] Holly TA, Satran A, Bromet DS, et al. The impact of adjunctive adenosine infusion during exercise myocardial perfusion imaging: results of the Both Exercise and Adenosine Stress Test (BEAST) trial. *J Nucl Cardiol.* 2003;10(3):291–296.

[62] Elliott MD, Holly TA, Leonard SM, Hendel RC. Impact of an abbreviated adenosine protocol incorporating adjunctive treadmill exercise on adverse effects and image quality in patients undergoing stress myocardial perfusion imaging. *J Nucl Cardiol.* 2000;7(6):584–589.

[63] Thomas GS, Thompson RC, Miyamoto MI, et al. The RegEx trial: a randomized, double-blind, placebo- and active-controlled pilot study combining regadenoson, a selective A(2A) adenosine agonist, with low-level exercise, in patients undergoing myocardial perfusion imaging. *J Nucl Cardiol.* 2009;16(1):63–72.

[64] Ross MI, Wu E, Wilkins JT, et al. Safety and feasibility of adjunctive regadenoson injection at peak exercise during exercise myocardial perfusion imaging: the Both Exercise and Regadenoson Stress Test (BERST) trial. *J Nucl Cardiol.* 2013;20(2):197–204.

[65] Parker MW, Morales DC, Slim HB, et al. A strategy of symptom-limited exercise with regadenoson-as-needed for stress myocardial perfusion imaging: a randomized controlled trial. *J Nucl Cardiol.* 2013;20(2):185–196.

[66] Astellas Pharma Global Development Inc. A Study to Assess Regadenoson Administration following an Inadequate Exercise Stress Test as Compared to Regadenoson Alone for Myocardial Perfusion Imaging (MPI) Using Single Photon Emission Computed Tomography (SPECT). *ClinicalTrials.gov*. Bethesda, MD: National Library of Medicine; 2012: https://clinicaltrials.gov/ct2/show/NCT01618669.

[67] Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol.* 2007;49(21):2105–2111.

[68] Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360(3):213–224.

[69] De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* 2012;367(11):991–1001.

[70] Jeremias A, Whitbourn RJ, Filardo SD, et al. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. *Am Heart J.* 2000;140(4):651–657.

[71] Seo MK, Koo BK, Kim JH, et al. Comparison of hyperemic efficacy between central and peripheral venous adenosine infusion for fractional flow reserve measurement. *Circ Cardiovasc Interv.* 2012;5(3):401–405.

[72] Nair PK, Marroquin OC, Mulukutla SR, et al. Clinical utility of regadenoson for assessing fractional flow reserve. *JACC Cardiovasc Interv.* 2011;4(10):1085–1092.

[73] Arumugham P, Figueredo VM, Patel PB, Morris DL. Comparison of intravenous adenosine and intravenous regadenoson for the measurement of pressure-derived coronary fractional flow reserve. *EuroIntervention.* 2013;8(10):1166–1171.

[74] Prasad A, Zareh M, Doherty R, et al. Use of regadenoson for measurement of fractional flow reserve. *Catheter Cardiovasc Interv.* 2014;83(3):369–374.

[75] van Nunen LX, Lenders G, Schampaert S, et al. TCT-619 single bolus regadenoson injection versus central venous infusion of adenosine to induce maximum coronary hyperemia for measurement of FFR. *J Am Coll Cardiol.* 2013;62(18 Suppl 1):B188.

[76] Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr.* 2007;20(9):1021–1041.

[77] Picano E, Molinaro S, Pasanisi E. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. *Cardiovasc Ultrasound.* 2008;6:30.

[78] Leong-Poi H, Coggins MP, Sklenar J, Jayaweera AR, Wang XQ, Kaul S. Role of collateral blood flow in the apparent disparity between the extent of abnormal wall thickening and perfusion defect size during acute myocardial infarction and demand ischemia. *J Am Coll Cardiol.* 2005;45(4):565–572.

[79] Elhendy A, O'Leary EL, Xie F, McGrain AC, Anderson JR, Porter TR. Comparative accuracy of real-time myocardial contrast perfusion imaging and wall motion analysis during dobutamine stress echocardiography for the diagnosis of coronary artery disease. *J Am Coll Cardiol.* 2004;44(11):2185–2191.

[80] Tsutsui JM, Elhendy A, Anderson JR, Xie F, McGrain AC, Porter TR. Prognostic value of dobutamine stress myocardial contrast perfusion echocardiography. *Circulation.* 2005;112(10):1444–1450.

[81] Miszalski-Jamka T, Kuntz-Hehner S, Schmidt H, et al. Myocardial contrast echocardiography enhances long-term prognostic value of supine bicycle stress two-dimensional echocardiography. *J Am Soc Echocardiogr.* 2009;22(11):1220–1227.

[82] Porter TR, Adolphson M, High RR, et al. Rapid detection of coronary artery stenoses with real-time perfusion echocardiography during regadenoson stress. *Circ Cardiovasc Imaging.* 2011;4(6):628–635.

[83] Le DE, Bragadeesh T, Zhao Y, Wang YG, Zha D, Kaul S. Detection of coronary stenosis with myocardial contrast echocardiography using regadenoson, a selective adenosine A2A receptor agonist. *Eur Heart J Cardiovasc Imaging.* 2012;13(4):298–308.

[84] Meijboom WB, Meijs MF, Chujif JD, et al. Diagnostic accuracy of 64 slice computed tomography coronary angiography ; a prospective multicenter multivendor trial. J Am Coll Cardiol 2008;52;2135-44

[85] Raff GL, Gallagher MJ, O''Neill WW, Goldstein JA. Diagnostic accuracy of noninvasive coronary angiography using 64 slice spiral computed tomography. J Am Coll Cardiol 2005;45;552-57

[86] DiCarli MF, Dorbala S, Currilova Z et al. Relationship between CT coronary angiography and stress perfusion imaging in patients with suspected ischemic heart disease assessed by integrated PET-CT imaging J Nucl Cardjol 2007;14; 799-809

[87] Schujjf JD, Wijns W, Jukema JW, et al. Relationship between noninvasive coronary angiography with multislice computed tomography and myocardial perfusion imaging J Amer Coll Cardiol 2006;48; 2508-2514

[88] George RT, Arbab-Zadeh A, Miller JM ET al. Adenosine stress 64 and 256 row detector computed tomography angiography and perfusion imaging : a pilot study evaluating the transmural extent of perfusion abnormalities to predict atherosclerosis causing myocardial ischemia.Circ Cardiovasc Imaging ;2;174-182

[89] George RT, Arbab-Zadeh A, Miller JM ET al. Computed tomography myocardial perfusion imaging with 320 row computed tomography accurately detects myocardial ischemia in patients with obstructive coronary disease..Circ Cardiovasc Imaging 2012;5;333-340

[90] Kurata A, Mochizuki T, Koyama Y et al. Myocardial perfusion imaging using adenosine triphosphate stress mutltislice spiral computed tomography; alternative to stress myocardial perfusion scintigraphy. Circ J 2005;69;550-557

[91] Cury RC, Kitt TM, Feaheny K et al. A randomized mutlicenter mutlivendor study of myocardial perfusion imaging with regadenoson CT perfusion vs single photon emission CT. J Cardiovasc Comput Tomogr. 2015 Mar-Apr;9(2):103-12

IntechOpen