Safety and feasibility of regadenoson use for suboptimal heart rate response during symptom-limited standard Bruce exercise stress test

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Background. **Regadenoson during exercise stress test (ETT) can provide maximal hyperemia for myocardial perfusion imaging (MPI), along with exercise information. Our aim was to study the feasibility and safety of regadenoson injection at peak ETT for submaximal heart rate (HR) response.**

Methods. **Consecutive patients who underwent SPECT MPI with standard Bruce ETT or supine-regadenoson (Supine-Reg) were analyzed. ETT patients were grouped as ETT-Max [maximal HR > 0.85 * (220 − age), N = 1,522], ETT-Submax (submaximal HR no regadenoson, N = 504), ETT-Reg (submaximal HR and regadenoson, N = 211).**

Results. **The HR during ETT was submaximal in 715 (32%) patients. Of these, 211 patients (30%) underwent ETT-Reg (mean exercise duration: 5.5 ± 2.5 minutes). ETT-Reg patients had a higher frequency of hypertension, diabetes, smoking and beta-blocker use, similar rest systolic blood pressure (SBP), but lower rest and peak HR and peak SBP compared to ETT-Max patients. There were no serious complications with regadenoson. Side effects (49% vs 6%, $P < .0001$) were fewer and aminophylline use was lower with ETT-Reg compared to Supine-Reg (0.5% vs 8.1%, $P = .001$).**

Conclusions. **Submaximal HR response to ETT is common. ETT-Reg is safe, feasible, and well-tolerated. ETT-Reg facilitates a diagnostic MPI with reporting of functional capacity, exercise ECG/hemodynamic changes and MPI at maximal hyperemia. (J Nucl Cardiol 2012;19:970–8.)**

Key Words: Exercise stress • Stress testing • Vasodilator stress • Sestamibi

INTRODUCTION

Submaximal exercise treadmill testing (ETT) reduces the diagnostic accuracy of myocardial perfusion imaging (MPI),[1-3] by reducing the size and severity of the ischemic area.[4] For patients who fail to reach target heart rate (HR) during exercise, the test is usually terminated and followed by a vasodilator stress test. However, this procedure is time and cost-inefficient since the stress laboratory personnel need to perform and monitor a full second stress test. Less commonly, atropine is injected for submaximal HR response to treadmill exercise. Although this is safe and feasible,[5,6] it is unclear whether atropine use in patients with submaximal HR is an equivalent surrogate to achieving target HR through exercise alone.

Regadenoson is a powerful adenosine A2A receptor agonist that is available as a preloaded syringe without the need for an infusion or weight-based dosing,[7,8] making it well-suited for use on short notice while the patient is on the treadmill. Thus, we hypothesize that adjunct administration of regadenoson during a standard symptom-limited Bruce ETT (ETT-Reg) would be a potentially

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useful alternative for those patients who fail to achieve target HR during exercise stress testing associated with MPI. The rapid onset of maximal hyperemia (within 1 minute of regadenoson injection) and the short-lived nature of its hyperemic response would ensure laboratory throughput without significant additional monitoring time compared to a standard ETT alone.

Prior studies have demonstrated that regadenoson in combination with low-level exercise is safe, improves symptoms, and enhances image quality compared to supine administration of regadenoson.[9,10] There are limited data evaluating the safety and the feasibility of regadenoson use during symptom-limited standard Bruce ETT.[11-14] Our objectives were (1) to determine the clinical utility of the ETT-Reg protocol in patients undergoing a symptom-limited standard Bruce ETT and (2) to assess the feasibility and the safety of ETT-Reg protocol compared to a supine-regadenoson (Supine-Reg) protocol.

METHODS

We studied 2,476 consecutive patients undergoing SPECT MPI with a standard symptom-limited Bruce ETT or Supine-Reg stress test between January 1, 2009 and September 30, 2010. We excluded patients who received regadenoson with low-level exercise. Patients with submaximal HR during ETT, who for safety or logistical reasons received vasodilator stress during recovery or later in the day in the supine position (post-exercise vasodilator stress) were not included in this analysis. Patients with relative contraindications to regadenoson such as active wheezing, LBBB, known oxygen-dependent COPD, or end stage renal disease requiring dialysis, and patients who refused pharmacological stress testing did not receive regadenoson. Also, patients undergoing supine pharmacologic stress who weighed <160 lbs received adenosine per institutional policy and were not included in this analysis. This study was approved by the Partners Human Research Committee.

Clinical Data Collection

A standardized data sheet was used to prospectively record medical history, height, and weight, as well as medications at the time of ETT. This information was verified by review of electronic medical record prior to performance of the stress study. Subjects were considered to have prior coronary artery disease (CAD) if they had a history of prior myocardial infarction based on Q waves on ECG or prior coronary revascularization.

Patient Preparation and Stress Testing Protocols

Patients were instructed to remain NPO for at least 4 hours and not consume caffeine-containing products for at least 12 hours, with-hold antianginals on the morning of the test, and theophylline-containing medications for at least 48 hours prior to the test. Diabetic patients were instructed to take half the am dose of long-acting insulin and with-hold am dose of regular insulin and oral hypoglycemic agents. All ETT patients were screened and consented a priori for the possibility of administration of pharmacological stress should a submaximal HR response occur during exercise.

ETT protocol. An ETT was performed using a standard Bruce protocol with the speed and the grade of the treadmill increasing every 3 minutes. Tests were symptom-limited except for those stopped prematurely for safety reasons or by patient choice.[15] After careful skin preparation, a standard 12-lead ECG was performed before, continuously during exercise and for at least 5 minutes into recovery or until resolution of symptoms and/or ECG changes. Blood pressure was taken manually during and following exercise. Patients were instructed to give at least a 1-minute warning prior to stopping exercise for the injection of radiotracer so that exercise could be continued for at least 1 minute following radionuclide injection at the same stage as peak exercise if tolerated by the patient. This was followed by a 1-minute cool-down at 1.7 mph/0% grade whenever feasible.

Indications for injection of radiotracer during the ETT included reaching target HR, definite ischemic symptoms or ECG changes, or refusal of pharmacological stress test. Patients with a prior history of CAD with symptoms or ECG changes concerning for possible ischemia or patients whose clinical question was ischemia at the level of exercise achieved were also not given regadenoson even if there was a failure to achieve target HR unless requested by the ordering physician. Patients with severe symptoms or comorbidities felt to restrict safe vasodilator administration on the treadmill did not receive radiotracer injection and underwent a subsequent vasodilator study later the same day whenever possible and were not included in this analysis. The ETT patients were categorized as ETT-Max if they reached target HR [>0.85 * (220 − age)] or as ETT-Submax if they did not reach target HR at the time of radiotracer injection, and did not receive regadenoson.

ETT-Reg protocol. Patients without a prior history of CAD and no contraindications for regadenoson who failed to reach target HR at the 1-minute warning period received an injection of regadenoson while continuing to exercise on the treadmill (ETT-Reg) (Figure 1). Regadenoson (400 mcg) was given intravenously over 10 seconds followed by 5 cc normal saline flush. ^{99m}Technetium (Tc) sestamibi was injected approximately 30 seconds following the start of the injection of regadenoson. The timing of the ^{99m}Tc sestamibi injection was within the recommendations for the package insert for supine regadenoson studies that suggest injecting radiotracer 10 to 20 seconds following the regadenoson injection and saline flush. Exercise was continued for at least an additional minute at the same stage or by a cool-down to 1.7 mph/0% grade whenever feasible. The ECG tracing and blood pressure was recorded for 5-10 minutes into recovery. Blood pressure was recorded at maximal ETT and approximately 2 minutes after regadenoson administration after the patient was in bed in the supine position. If patients complained of side effects with

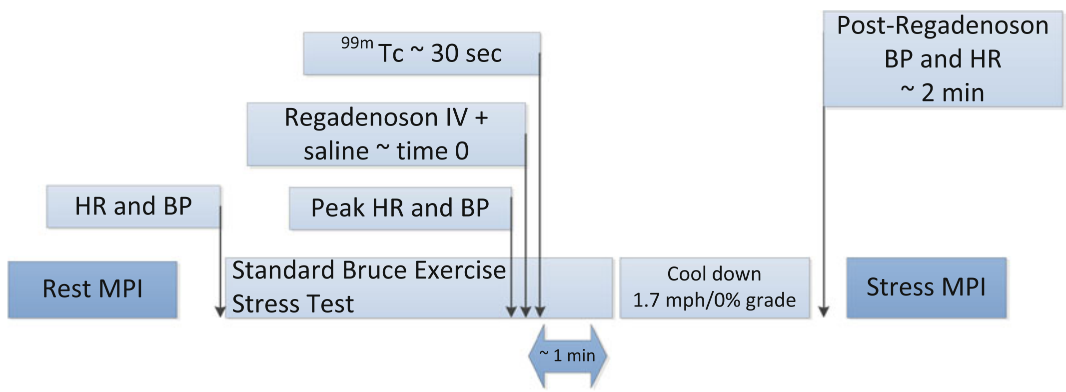

Figure 1. ETT-Reg protocol. This figure shows the steps of regadenoson injection during maximal symptom-limited standard Bruce treadmill test (ETT-Reg). *MPI*, Myocardial perfusion imaging; *HR*, heart rate; *BP*, blood pressure; *IV*, intravenous, *Tc*, ^{99m}technetium sestamibi.

regadenoson administration, the symptoms were recorded by the exercise physiologists.

Supine-Reg protocol. After patient preparation and recording of the baseline blood pressure and ECG, regadenoson (400 mcg in a 5 cc prefilled syringe) was administered intravenously over 10 seconds followed by 5 cc normal saline flush and injection of ^{99m}Tc sestamibi. Blood pressure was recorded for at least 5 minutes after injection of regadenoson.

MPI Protocol

The majority of the patients underwent rest-stress ^{99m}Tc sestamibi MPI per standard protocol, with approximately 6-10 mCi for rest and 14-40 mCi for stress. Subjects who weighed >250 lbs[16] underwent a separate day rest-stress study with approximately 15-20 mCi of ^{99m}Tc sestamibi on each day. Very few subjects (1.4%, N = 31) underwent dual isotope studies with thallium and ^{99m}Tc sestamibi. Imaging was performed 15-45 minutes after injection of radiotracer with a two-headed SPECT/CT gamma camera (model Symbia T-6, Siemen's medical Solutions, USA) or a DSPECT scanner (Spectrum Dynamics, Israel). The mode of acquisition for the conventional SPECT was a ''step-and-shoot'' mode, 32 projections over 90° arc for each head (64 projections over a 180° arc), 30 seconds per projection, and 128 × 128 matrices. Gated images were acquired using 16 frames per cardiac cycle. Transverse sections were reconstructed with a Butterworth filter (order 5 and a cutoff frequency of 0.792 cycles per pixel) for the rest and stress SPECT studies (pixel size, 6 mm). The rest and stress images were acquired on the DSPECT scanner for about 6-10 minutes and reconstructed[17] using standard manufacturer specified parameters.

All studies were assessed using the standard 17-segment model[18] and a five-point (0-4) scoring system. Global summed scores were computed for the stress (summed stress score, SSS) and rest (summed rest score, SRS) images, and their difference (summed difference score, SDS).[19] A scan with a SSS > 0 was considered abnormal. Left ventricular ejection fraction was analyzed on the post-stress images using commercially available software (Corridor 4DM, University of Michigan, Ann Arbor, MI, USA).

Statistical Analysis

Continuous variables are reported as mean ± standard deviation (SD) or median with inter-quartile ranges as appropriate. Discrete variables are reported as proportions. Differences between the study groups were assessed by one-way analysis of variance (ANOVA) for continuous variables or a χ^2 test for discrete variables. For between-group comparisons of continuous variables, an ANOVA with post hoc Bonferroni test was used. A two-tailed P value of <.05 was considered to be significant for all tests.

RESULTS

Patient Selection for ETT-Reg

A total of 715 patients (32%) had a submaximal HR response during ETT (Figure 2). Of these patients, 211 (30%) received regadenoson at maximal exercise (ETT-Reg), while 504 (70%) patients did not receive regadenoson despite submaximal HR (ETT-Submax). The predominant reasons for not administering regadenoson despite submaximal HR (ETT-Submax) included prior CAD (55%) and ischemic symptoms limiting the test (16%). By laboratory protocol, vasodilator was not routinely administered to patients with known CAD if the clinical question was ischemia at workload achieved; however, a significant number of patients with known CAD were given regadenoson with 22% of the ETT-Reg patients having a prior diagnosis of CAD. The rest of the patients in the ETT-Submax group (29%) did not receive regadenoson due to patient refusal, active wheezing, symptoms thought to preclude the administration of regadenoson or because the decision was made to give regadenoson during the recovery period rather than at peak exercise.

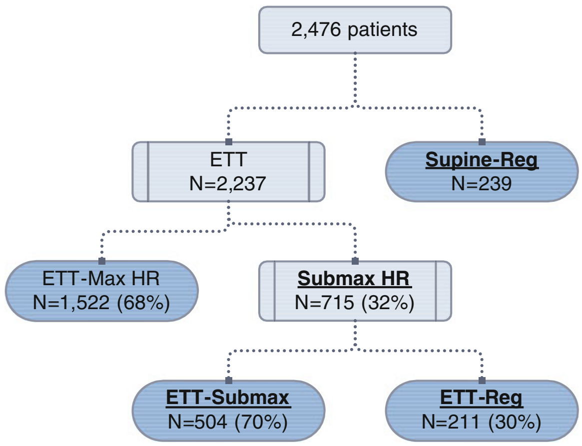

Figure 2. The selection of patients for the ETT-Reg protocol. All patients were Supine-Reg (unable to exercise) or ETT (able to exercise on a standard Bruce protocol). Among patients who underwent an ETT, those who attained >85% of the age-predicted maximum HR (220-age) received radiotracer and the test was considered completed (ETT-Max HR). Among the patients who did not attain maximal HR (Submax HR), and did not have known coronary artery disease or definite ischemic signs or symptoms, regadenoson was injected while the patient was still exercising on the treadmill (ETT-Reg). The rest of the patients received radiotracer injection irrespective of HR (ETT-Submax).

Baseline Characteristics

The baseline characteristics of the study cohort undergoing the stress protocols of ETT-Max, ETT-Submax, ETT-Reg, and Supine-Reg are described in Table 1. The mean age of the ETT-Reg patients was 63 ± 11 years. The ETT-Reg patients had an intermediate prevalence of hypertension, dyslipidemia, and chronic obstructive lung disease compared to ETT-Max or ETT-Submax groups. ETT-Reg patients had the highest prevalence of smoking. ETT-Reg and ETT-Submax patients also had a higher frequency of beta-blocker use. ETT-Max patients appeared to be the healthiest patients with the least amount of comorbidities, while the Supine-Reg group was older with a greater prevalence of comorbidities. ETT-Submax patients had the highest prevalence of prior CAD and Q wave MI on ECG.

Exercise and Hemodynamic Information

ETT-Reg patients exercised for a shorter duration and, therefore, achieved a lower MET level compared to the ETT-Max patients (Table 2). Although ETT-Reg patients had the lowest exercise capacity, they attained a significant workload of 7.3 METS. The majority (96%) of the ETT-Reg patients attained <80% of the age-

Table 1. Baseline characteristics

Characteristic	ETT-Max N = 1,522	ETT-Submax N = 504	ETT-Reg N = 211	Supine-Reg N = 239	ANOVA *P* value
Age (years)	61 ± 11	62 ± 11	63 ± 11*	66 ± 12	NS
Female, N (%)	659 (43)	170 (34)	90 (43)	120 (50)	.001
Body mass index (kg/m^2)	28 ± 5	29 ± 5	30 ± 6*	34 ± 8	NS
Historical data					
Hypertension, N (%)	934 (61)	408 (81)	166 (79)*	215 (90)	<.0001
Dyslipidemia, N (%)	963 (63)	395 (78)	143 (68)	173 (72)	<.0001
Diabetes, N (%)	270 (18)	109 (22)	63 (30)*	95 (41)	<.0001
Smoking, N (%)	158 (10)	83 (17)	42 (20)*	37 (16)	<.0001
COPD, N (%)	16 (1)	18 (4)	5 (2)	14 (6)	.001
Prior CAD, N (%)	343 (23)	275(55)	47(22)	67 (28)	<.0001
Prior PVD, N (%)	9 (0.6)	14 (2.8)	10 (4.7)*	15 (6.3)	<.0001
Beta-blocker use, N (%)	537 (35)	373 (74)	152 (72)*	158 (66)	<.001
Rest ECG					
Atrial fibrillation, N (%)	54 (3.5)	13 (2.6)	8 (3.8)	22 (9.2)	<.0001
Normal, N (%)	267 (17.5)	49 (9.7)	13 (6.2)*	37 (15.5)	<.0001
Q wave MI, N (%)	64 (4.2)	51 (10.1)	7 (3.3)	12 (5.0)	<.0001

ETT = symptom-limited standard Bruce treadmill test; ETT-Max = attained 85% age-predicted maximal HR during ETT, ETT-Reg = Regadenoson during ETT for submaximal HR.
COPD, Chronic obstructive pulmonary disease; *CAD*, coronary artery disease; *PVD*, peripheral vascular disease; *MI*, myocardial infarction.
* *P* < .01 versus ETT-Max.

Table 2. Exercise capacity among the ETT patients

Variable	ETT-Max N = 1,522	ETT-Submax N = 504	ETT-Reg N = 211	ANOVA *P* value
Exercise time (minutes)	8.4 ± 2.9	7.4 ± 2.5	5.5 ± 2.5	<.0001
METS achieved	10.1 ± 5.5	8.9 ± 2.6	7.3 ± 2.3	<.0001
Rate pressure product	26.164 ± 4.644	19.657 ± 4.603	16.674 ± 4.279	<.0001

ETT = symptom-limited standard Bruce treadmill test; ETT-Max = attained 85% age-predicted maximal HR during ETT, ETT-Reg = Regadenoson during ETT for submaximal HR. Continuous variables are shown as mean ± SD. Frequencies are shown as percentages.

predicted maximal HR, with only 4% of patients reaching a peak HR between 80% and 85% of the age-predicted maximal HR. In contrast, 56% of the ETT-Submax patients attained <80% of the age-predicted maximal HR, with 44% of patients reaching a peak HR between 80% and 85% of the age-predicted maximal HR.

The rest systolic blood pressure (SBP) was similar across the groups, but the peak SBP was higher in the ETT-Max group versus the ETT-Submax and the ETT-Reg groups ($P < .0001$ for each comparison, post hoc test). The rest HR and peak exercise HR were higher in the ETT-Max group versus the ETT-Submax and the ETT-Reg groups ($P < .0001$ for each comparison, post hoc test) (Figure 3). As expected, there was a stepwise decline in peak stress HR and blood pressure from ETT-Max, to ETT-Submax to ETT-Reg groups.

Hemodynamic Changes After Injection of Regadenoson

Within the ETT-Reg group, 208 patients had complete post-exercise hemodynamic data. The majority of patients had insignificant changes in SBP (≤10 mm Hg) (33%) or a decrease in SBP by >10 mm Hg (55%) between peak exercise and 2 minutes after regadenoson administration. Three patients developed a peak SBP of <100 mm Hg following exercise and regadenoson. A small proportion of patients (12%) increased their SBP by >10 mm Hg following regadenoson injection after maximal exercise. Four patients developed a peak SBP > 190 mm Hg following regadenoson and all these patients had elevated SBP at peak exercise prior to receiving regadenoson.

In the Supine-Reg group, the SBP decreased by 1.5 ± 21.2 mm Hg and HR increased by 20.2 ± 11.6 bpm following regadenoson injection.

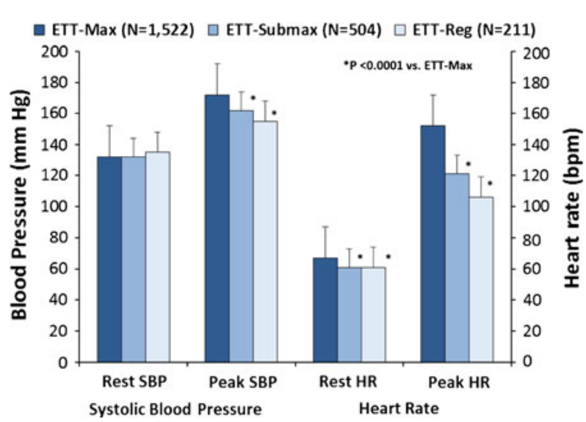

Figure 3. The rest and peak stress heart rate (HR) and blood pressure in patients undergoing an ETT-Max, ETT-Submax and ETT-Reg protocols. The peak stress HR and blood pressure were significantly different between each of the groups (ANOVA with post hoc tests $P < .0001$ for each comparison vs ETT-Max).

Tolerability of ETT-Reg Protocol

The ETT-Reg protocol was well tolerated. There were no major complications of myocardial infarction, ST-segment elevations, or marked or prolonged ST-segment depressions. The symptoms observed with ETT-Max, ETT-Submax, ETT-Reg, and Supine-Reg protocols are shown in Figure 4. Symptoms of chest pain and dyspnea were more frequent with ETT-Reg compared to the Supine-Reg protocol. However, the typical symptoms associated with regadenoson including flushing, dizziness, light-headedness, or gastrointestinal symptoms were 8 times more common in the Supine-Reg patients compared to ETT-Reg patients (49% vs 6%, $P < .0001$). Aminophylline was used much less frequently in the ETT-Reg patients compared to the Supine-Reg patients (0.5% vs 8.1%, $P = .001$).

SPECT MPI Results

The scan results in the study groups are shown in Table 3. The ETT-Reg patients had 28% abnormal scans. The frequency of abnormal scans in the ETT-Reg group was higher than in the ETT-Max group but lower than in the Supine-Reg group, suggesting that ETT-Reg patients are intermediate in risk between the functionally active patients (ETT-Max) and the patients unable to exercise (Supine-Reg). The frequency of abnormal scans

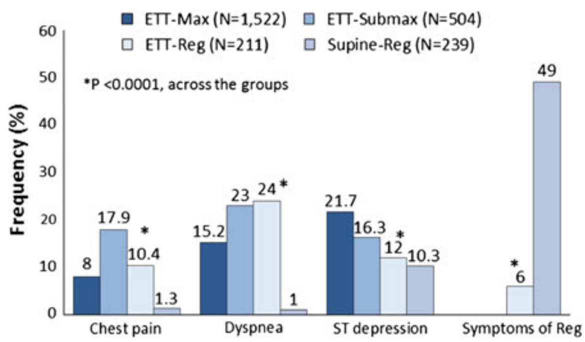

Figure 4. Tolerability and ST-segment changes with regadenoson demonstrating the frequency of chest pain, dyspnea, ST-segment depression, and symptoms consistent with regadenoson (flushing, dizziness, gastrointestinal symptoms, or headache), in the ETT-Max, ETT-Submax, ETT-Reg, and Supine-Reg groups. Symptoms consistent with regadenoson use were most frequent in the Supine-Reg group.

was highest in the ETT-Submax group, consistent with this group having the highest prevalence of Q wave MI and prior coronary revascularization (Table 1).

DISCUSSION

Submaximal HR response during ETT is a common clinical concern during exercise MPI studies. In our study, about a third of the patients referred for ETT had submaximal HR response to exercise, and a third of these patients were administered regadenoson at peak exercise. Our data demonstrate that supplementing a symptom-limited ETT with regadenoson at peak exercise in patients who are unable to obtain target HR is feasible, well-tolerated, and results in no major complications. Notably, the use of ETT-Reg was associated with a significantly lower requirement for aminophylline compared to the Supine-Reg protocol. The combined ETT-Reg protocol ensured radiotracer uptake during maximal hyperemia and allowed for the assessment of important diagnostic and prognostic indicators such as functional capacity[20-22] and exercise hemodynamics,[23] which cannot be obtained with vasodilator alone or vasodilator with low-level exercise protocols.

Comparison to Prior Studies of Combined Vasodilator Stress and Exercise MPI

Several prior studies have evaluated the role of symptom-limited exercise with adenosine,[24] low-level exercise with adenosine,[25,26] and low-level exercise with regadenoson.[9,10] Our data are consistent with early research by Thomas et al[10] investigating 39 patients undergoing pharmacologic stress randomized to low-level exercise with regadenoson or resting adenosine. They demonstrated no serious complications with regadenoson accompanied by low-level exercise. They also reported fewer side effects and better myocardial-to-liver ratio of ^{99m}Tc sestamibi with low-level exercise combined with regadenoson compared to resting adenosine stress.

These data were confirmed by a larger study by Kwon et al[9] who compared their clinical experience with low-level exercise combined with regadenoson compared to resting regadenoson. They determined that regadenoson combined with low-level exercise was safe and that regadenoson was also well-tolerated in their large number of patients with COPD or asthma. Contrary to our findings, they found that regadenoson with low-level exercise resulted in more patients experiencing a drop in SBP by >10 and >30 mm Hg. Our results demonstrated that patients increased their SBP by 21 mm Hg from rest to peak stress with ETT-Reg likely reflecting the fact that our patients exercised to their maximum capacity increasing their blood pressure prior to the administration of regadenoson. From peak exercise to following regadenoson administration, the majority of patients had no significant change or a drop in SBP with only 3 patients showing a SBP of <100 mg Hg following regadenoson.

Combined vasodilator and symptom-limited treadmill exercise was studied in 35 patients in a multicenter study by Holly et al.[24] All patients underwent both an exercise MPI and a symptom-limited exercise stress test with adenosine infusion with MPI on a separate day. The exercise vasodilator protocol included a 4-minute adenosine infusion with radiotracer injected at 2 minutes and continuation of symptom-limited exercise stress test after radiotracer was injected. The perfusion images likely reflected maximal vasodilator-induced hyperemic myocardial blood flow and the ETT provided functional capacity and hemodynamic information. Combined symptom-limited exercise and adenosine stress was safe and demonstrated a greater amount of scan abnormality on the MPI than exercise alone (SSS 10.0 vs 8.6, $P = .02$, and SDS 4.9 vs 3.3, $P = .002$). In contrast, in the current study, regadenoson was injected at the end of the exercise stress, allowing for a maximal ETT followed by regadenoson use only if needed, potentially resulting in more cost savings. Also, mechanistically, myocardial blood flow in the ETT-Reg group likely reflects combined endothelial-dependent and endothelial-independent flow abnormalities.[27]

Chronotropic Incompetence and MPI

From our data, the higher frequency of beta-blocker use in the ETT-Reg and the ETT-Submax groups, suggests that beta adrenergic antagonism may be a possible mechanism for failure to reach target HR in at

Table 3. Scan results among the study groups

Variable	ETT-Max N = 1,522	ETT-Submax N = 504	ETT-Reg N = 211	Supine-Reg N = 239	ANOVA *P* value
Abnormal scan, N (%)	353 (23)	198 (39)	58 (28)	87 (36)	<.0001
SSS	1.4 ± 4.1	3.3 ± 5.9	1.8 ± 4.2	2.7 ± 5.5	<.0001
SDS	0.5 ± 2.3	1.0 ± 2.6	0.8 ± 2.2	1.0 ± 2.4	<.0001
SRS	0.9 ± 3.1	2.3 ± 5.1	1.0 ± 3.3	1.7 ± 4.7	<.0001
SDS in patients SDS > 0*	4.1 ± 5.1	4.6 ± 3.8	4.2 ± 3.4	4.5 ± 3.2	NS
Post-stress LVEF (%)	66 ± 11	61 ± 13	64 ± 12	63 ± 14	<.0001

ETT = symptom-limited standard Bruce treadmill test; ETT-Max = attained 85% age-predicted maximal HR during ETT, ETT-Reg = Regadenoson during ETT for submaximal HR.
Continuous variables are shown as mean ± SD. Frequencies are shown as percentages.
SSS, summed stress score; *SDS*, summed difference score; *SRS*, summed rest score; *LVEF*, left ventricular ejection fraction
* Only patients with SDS > 0 were included in this row (ETT-Max, N = 203, ETT-Submax, N = 112, ETT-Reg, N = 41, Supine-Reg, N = 51).

least some of the ETT patients. Lauer et al[28] found that the predictors of chronotropic incompetence included older age, smoking, hypertension, diabetes, and known CAD reflecting that patients with chronotropic incompetence represent a sicker group of patients. This finding was confirmed in our study with a higher proportion of abnormal scans in the ETT-Submax and the ETT-Reg groups compared to the ETT-Max group. A higher frequency of abnormal MPI in these groups also reflects the fact that patients with a known diagnosis of CAD and a submaximal HR response to ETT, by laboratory protocol, were not routinely changed to vasodilator stress unless thought to be clinically indicated. Patients with known CAD are generally referred to assess the adequacy of medical management or to determine if symptoms are likely to be from an ischemic origin, therefore, this assessment can generally be made with symptom-limited exercise stress test.

Reasons to Consider Regadenoson During Symptom-Limited Maximal ETT

Several logistic and mechanistic reasons lead one to consider the administration of regadenoson during maximal ETT. MPI has diagnostic limitations in patients with suboptimal HR response due to failure to detect all flow-limiting ischemia.[1-4] ETT-Reg protocol ensures maximal hyperemia despite submaximal HR and allows for assessment of functional capacity. Although 85% of the maximal predicted HR represents an accepted measure of adequacy of stress testing, it is an arbitrary value and not based on hyperemic response.[29] Hence, most laboratories perform a symptom-limited ETT, rather than an ETT based on attaining 85% of the age-predicted maximal HR. The ETT-Reg protocol also streamlines the laboratory processes and allows for rapid laboratory throughput. Variations of ETT-Reg protocol are increasingly being used in present day clinical practice and there are published abstracts on this topic, but to the best of our knowledge this is the first paper to provide evidence that the administration of regadenoson during maximal exercise is feasible, safe, and well tolerated.

Mechanistically, exercise stress testing provokes predominantly endothelium-dependent hyperemic flow,[30] while vasodilator stress provokes predominantly endothelium-independent hyperemic flow.[27,30] Likewise, cold-pressor testing causes sympathetic stimulation[31-34] (similar to exercise) and is more sensitive for detecting endothelial dysfunction than pharmacologic vasodilator stress. Endothelial dysfunction occurs early in the course of atherosclerotic vascular dysfunction. For example, endothelial dysfunction is detected in insulin-resistant states with cold-pressor stress, while impairment of vasodilator function is not detected until the patient is frankly diabetic with pharmacologic vasodilator stress testing.[31] Therefore, we propose that combined exercise and vasodilator stress can be a powerful tool to assess the both endothelium-dependent and endothelium-independent abnormalities in myocardial blood flow. Since atherosclerotic coronary arteries vasoconstrict with exercise and non-diseased arteries vasodilate maximally with vasodilator stress, it is intriguing to postulate that the combined protocol may theoretically improve defect contrast and allow for the detection of greater degrees of ischemia. A larger study directly comparing MPI results of ETT-Submax to an ETT-Reg protocol within the same patient is warranted to evaluate if this translates clinically into a superior diagnostic accuracy for this technique.

Also, the pharmacologic vasodilatory effects of dipyridamole and adenosine vary widely between individuals.[35] There may be non-responders to vasodilator stress agents[35,36] that may be due to either intrinsic causes or to inadvertent caffeine intake. Allowing for more endothelial-dependent vasodilation with exercise may help equalize these findings.

Limitations

This is a single-center study with patients selected for ETT-Reg as per local protocols. The results are hence most applicable to similar patient cohorts. These data cannot be extrapolated to all patients who fail to reach target HR with maximal exercise; because regadenoson was not given to 70% of patients with a suboptimal HR response, including patients with ischemic symptoms limiting the test and patients with a known diagnosis of CAD whose clinical question was ischemia at the level of exercise achieved. Not all the patients with prior CAD may have been identified, since, Q wave MI on ECG or prior coronary revascularization was used to define these patients. The number of patients undergoing ETT-Reg in this study is somewhat limited and larger studies may be warranted to confirm these findings. A detailed symptom questionnaire was not obtained from the patients to provide a comparison graded severity of symptoms with Supine-Reg versus ETT-Reg. Likewise comparisons of image quality (liver to heart ratio) were not made. However it is well known from prior literature that use of vasodilator stress during ETT improves symptoms and image quality.[25,26]

CONCLUSIONS

Submaximal HR is observed frequently in patients undergoing exercise MPI studies. In these patients, symptom-limited ETT supplemented with regadenoson during peak exercise is feasible and safe. This protocol not only ensures maximal hyperemic MPI but also allows for reporting of functional capacity and exercise-induced hemodynamic and ECG changes. Routine supplementation of regadenoson during exercise should be considered in patients not reaching target HR and requiring a maximal hyperemic MPI.

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Disclosures

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