Safety and feasibility of adjunctive regadenoson injection at peak exercise during exercise myocardial perfusion imaging: The Both Exercise and Regadenoson Stress Test (BERST) trial

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Background. **The data existing in the literature regarding the safety of using regadenoson with symptom-limited exercise are limited, which motivated the authors to undertake this randomized study.**

Methods. **We offered patients scheduled to undergo vasodilator stress nuclear myocardial perfusion imaging the opportunity to exercise instead. Patients who failed to reach target heart rate (THR) were randomized to (1) receive regadenoson at peak exercise or (2) stop exercise and receive regadenoson at rest. Patients who reached THR received a standard Tc-99m sestamibi injection with no regadenoson.**

Results. **200 patients were included (66% male, mean age 52.5 ± 13.6). 125 patients (62%) reached THR with exercise alone. All stress protocols were well tolerated, and there were no significant adverse events. There were no statistically significant differences in the extent of perfusion abnormalities, image quality, or rate of referral to cardiac catheterization within 60 days between the groups. In fully adjusted logistic regression models, beta-blocker use and diabetes remained significant univariate predictors of failure to reach THR (OR 0.21, 95% CI 0.1-0.5, $P < .0001$, OR 0.34, 95% CI 0.2-0.7, $P = .004$, respectively).**

Conclusions. **A protocol combining regadenoson at peak exercise in patients unable to reach THR with exercise is feasible, well-tolerated, and yields comparable imaging results to a standard regadenoson injection at rest. In addition, pharmacologic stress testing may be over-ordered in current clinical practice, as patients referred for such testing were often able to exercise. (J Nucl Cardiol 2013;20:197–204.)**

Key Words: A_{2A} adenosine receptor agonists • exercise: stress testing • myocardial perfusion imaging: SPECT • pharmacologic stress

INTRODUCTION

Stress testing remains a cornerstone in the evaluation of patients for cardiovascular disease. Exercise testing is useful in eliciting and documenting exertional symptoms. Moreover, exercise is the preferred method for stress testing because exercise capacity has been shown to be a stronger predictor of mortality than established cardiovascular risk factors.[1,2] Among patients specifically referred for exercise myocardial perfusion imaging (MPI) stress testing, many are unable to achieve an adequate heart rate response. Failure to achieve adequate heart rate limits the sensitivity of exercise stress testing for the detection of coronary heart disease, resulting in a substantial number (up to 25%) of false-negative results.[3,4] The current options for such patients are to accept the potential loss of sensitivity for the detection of coronary artery disease or to reschedule the patient for a pharmacologic (i.e., adenosine or regadenoson) stress test.

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Received for publication Jun 12, 2012; final revision accepted Jan 21, 2013.

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1071-3581/$34.00

doi:10.1007/s12350-013-9679-1

Existing protocols combining adenosine infusion with exercise have been shown to be safe and feasible[5,6], and result in a greater amount of detectable ischemia while allowing for the assessment of functional capacity.[5] Greater increases in heart rate are known to occur with regadenoson compared with adenosine[7], and the safety of using regadenoson with symptom-limited exercise has not yet been completely studied outside of observational, non-randomized data.[8] We therefore hypothesized that a protocol combining a regadenoson infusion with a standard treadmill exercise protocol would be safe, well-tolerated, and improve image quality.

METHODS

We prospectively enrolled 200 patients scheduled to undergo an elective vasodilator stress nuclear MPI test. Patients who appeared to be able to ambulate without difficulty and with orders for a vasodilator nuclear stress test from their referring physician were offered the opportunity to initially undergo an exercise stress test instead. Those who agreed to exercise were randomized in a 1:1 fashion to undergo the following protocols if they did not reach target heart rate (THR) (Figure 1): (1) receive regadenoson at peak exercise [Both Exercise and Regadenoson Stress Test (BERST) group], or (2) have the exercise test stopped and receive regadenoson at rest without concomitant exercise (Regadenoson-at-Rest group). Regardless of the initial randomization, those patients who were able to reach THR with exercise received a standard Tc-99m sestamibi injection 1 minute before termination of exercise with no regadenoson administration (Exercise Only group). THR was defined as 85% of maximum predicted heart rate (MPHR) for age, which was calculated as 220—age in years. The first nine patients enrolled were not randomized in effort to preliminarily establish the procedure safety of the combined exercise plus regadenoson protocol. All patients signed informed consent forms that were approved by the Northwestern University Institutional Review Board.

Exercise Protocol

All patients initially underwent a standard exercise Bruce protocol. Continuous electrocardiographic (ECG) monitoring was performed. Blood pressure and heart rate measurements were obtained during each stage of the exercise protocol and every 1 minute for at least 5 minutes during recovery until symptoms, significant hemodynamic changes, or significant ECG changes had resolved. Exercise testing was symptom limited and terminated according to ACC/AHA practice guidelines for exercise testing including, but not limited to, the patient's desire to stop, moderate-to-severe angina, dizziness, ventricular tachycardia, and ST segment elevation ($\geq$1.0 mm).[9] Exercise was not terminated solely because of the patient's ability to reach THR. Before beginning exercise, exercise physiologists or cardiology fellows instructed patients to give one- to two-minute warning before requesting to halt exercise to insure proper administration of regadenoson and/or Tc-99m sestamibi one minute before termination of exercise.

Patients assigned to the BERST group who did not achieve 85% of MPHR with exercise were given an intravenous (IV) bolus of regadenoson administered as a single 400-μg peripheral IV infusion over 10 seconds, at 1 minute before termination of exercise. This was followed immediately by a 5-mL saline solution flush, and Tc-99m sestamibi was injected 30 seconds later. During the last minute of exercise, treadmill speed and incline were not altered and a ''stage-hold'' was permissible.

Patients randomized to the Regadenoson-at-Rest group who were not able to achieve 85% of MPHR with exercise alone had the Bruce protocol terminated. After a 5-15 minute observation period, these patients underwent a resting regadenoson only stress test using a 400-μg peripheral IV bolus of regadenoson.

Patients who were able to achieve 85% of MPHR with exercise alone, regardless of initial randomization to the BERST or Regadenoson-at-Rest groups, were assigned to the Exercise Only group. In this group, Tc-99m sestamibi was injected 1 minute before the termination of exercise in a routine fashion.

Once the stress test was completed, patients were asked to rate how they felt overall during the study. A subjective four-point scale was utilized in the following manner: 1 = Comfortable, 2 = Mildly Uncomfortable, 3 = Very Uncomfortable, and 4 = Extremely Uncomfortable.

Imaging and Analysis Protocol

MPI was performed in a standard manner as established in our lab. All images were acquired on two-headed SPECT gamma cameras (Siemens e.cam, Siemens Medical Solutions, Hoffman Estates, IL). Following processing, all stress test results were reported clinically on the day of the study. Perfusion images were scored using a 20-segment model on a scale from 0 to 4, in which 0 indicated no perfusion defect, and 4 indicated absent tracer activity. Scores were summed to obtain the summed stress score (SSS). An abnormal study was defined as having SSS $>$ 0. Two readers blinded to the type of stress protocol evaluated studies for overall image quality, presence of subdiaphragmatic activity, and extent of interference from subdiaphragmatic activity. Overall image quality was scored on the following scale: 1 = poor, 2 = fair, 3 = good, and 4 = excellent. Interference from subdiaphragmatic activity was scored as follows: 1 = definite, 2 = possible, and 3 = no.

Exclusion Criteria

Patients were excluded if they were unable to complete at least 3 minutes on a standard Bruce protocol. In addition, patients with any known contraindication to regadenoson were excluded (moderate-to-severe chronic obstructive pulmonary disease or asthma, second- or third-degree AV block or sinus node disease, known hypersensitivity to regadenoson). Patients with left bundle branch block or artificial ventricular pacemaker, hemodynamic instability (defined as blood pressure >210/110 or <90/60 mmHg), decompensated congestive heart failure, use

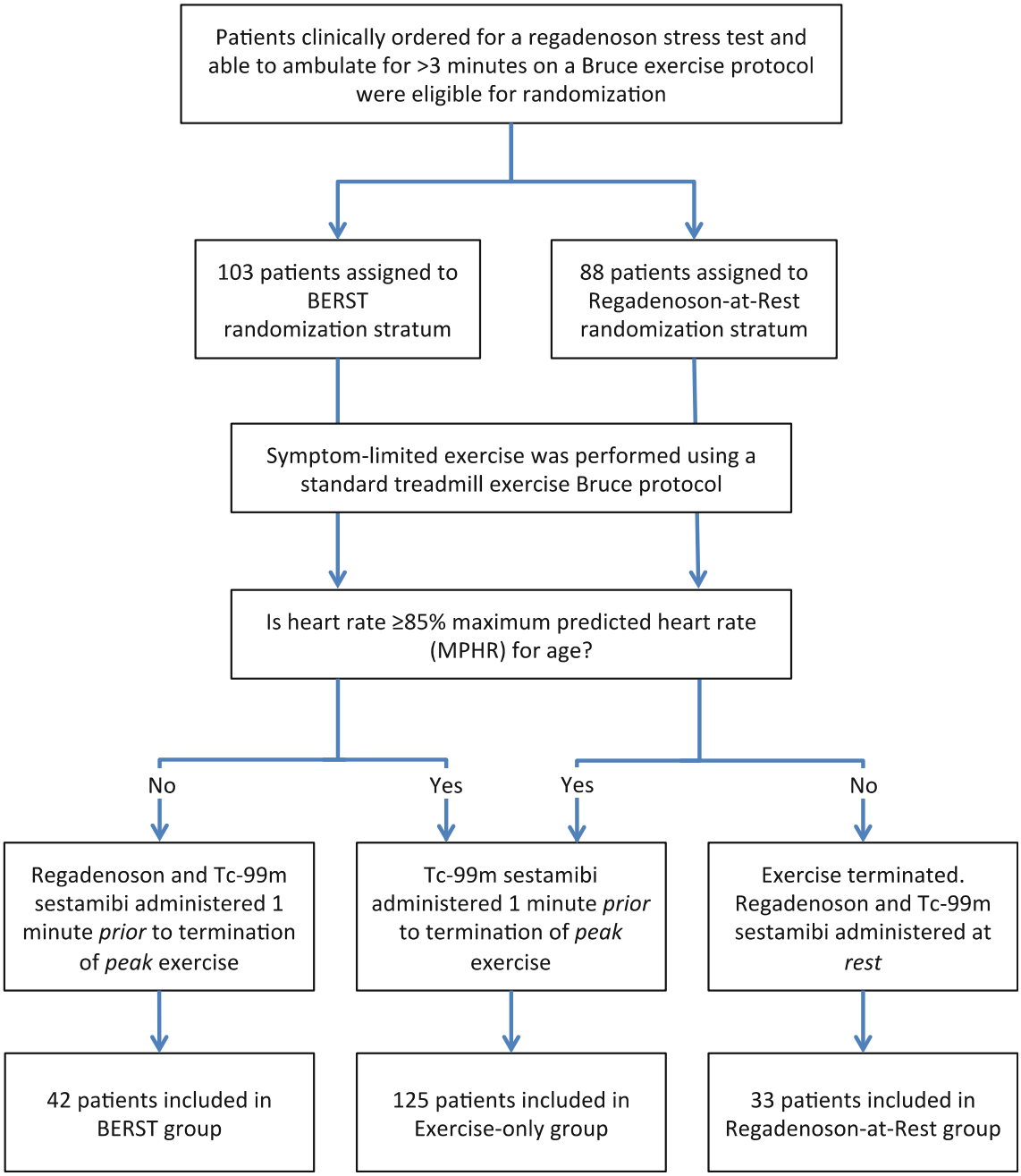

Figure 1. Study protocol.

of theophylline or dipyridamole within the preceding 48 hours, or use of caffeinated products within the preceding 12 hours were also excluded. Pregnant or nursing women were not eligible to participate.

Statistics

All continuous data are expressed as the mean ± standard deviation. Comparisons between the three stress test groups were made by one-way ANOVA tests (or Kruskal-Wallis non-parametric test when appropriate) for continuous variables and χ^2 tests (or Fisher exact test when appropriate) for categorical variables. $P \leq .05$ was considered to be statistically significant. Predictors of failure to reach 85% maximum predicted heart rate were identified using unadjusted and adjusted logistic regression models. Multivariable models were adjusted for age, sex, body mass index, and all covariates that were significant in univariate analysis at a significance of $P \leq .05$.

RESULTS

The demographic data of the 200 patients in this trial are shown in Table 1. Exercise testing was terminated in the majority of patients because of fatigue and the patient's desire to stop (95%). Chest pain was noted in the remaining patients: three patients in the BERST group, two patients in the Regadenoson-at-Rest group and six patients in the Exercise Only group. Exercise was not terminated because of arrhythmias, hypotension, or ECG changes. A total of 42 patients (21%) were assigned to the BERST group, 33 patients (16%) were assigned to the Regadenoson-at-Rest group, and 125 patients (63%) were assigned to the Exercise Only group. The mean age was 52 years old (age range 25-89 years). The majority of subjects were male with typical risk factors for coronary artery disease. There was significantly less known coronary artery disease, prior history of myocardial infarction, diabetes, and beta blocker use at baseline in the Exercise Only group compared with the combined group of patients who received regadenoson (BERST group and Regadenoson-at-Rest group; $P = .02$, $P = .01$, $P = .01$, $P < .0001$, respectively).

The stress testing data are presented in Table 2. Mean Bruce protocol times differed significantly between the groups (BERST group 6.9 ± 2.5 minutes, Regadenoson-at-Rest group 7.5 ± 2.5 minutes, Exercise Only group 8.3 ± 2.4 minutes; $P = .003$). Likewise, the mean percent maximum predicted heart rate was significantly higher in the Exercise Only group compared with the BERST and Regadenoson-at-Rest groups (93% ± 7%, 75% ± 9%, 66% ± 10%, respectively; $P < .0001$). In the Exercise Only group, the median and range [minimum-maximum] exercise time and METS achieved were 8.5 [3.0-14.0] minutes and 10.1 [3.6-17.1] METS. All stress protocols were well tolerated, and there were no adverse events such as significant hypotension, excessive hypertension, heart block, or respiratory distress. Specifically, no patients in the study experienced a change in blood pressure greater than 20 mmHg following regadenoson injection, and no patients developed symptoms attributed to a change in blood pressure. There was no significant difference in a subjective, patient-reported four-point symptom scale between the three groups (BERST group 2.0 ± 0.9, Regadenoson-at-Rest group 1.9 ± 0.9, Exercise Only group 1.7 ± 0.9; $P = .16$).

There were no significant differences in the incidence of ECG evidence of ischemia (BERST group 10% of patients, Regadenoson-at-Rest group 3%, Exercise Only group 13%; $P = .52$). Similarly, the incidence of abnormal perfusion results (BERST group 43%, Regadenoson-at-Rest group 39%, Exercise Only group 34%; $P = .52$) did not differ between the groups. There were no statistically significant differences in the extent of perfusion abnormalities as assessed by SSS and summed difference score (SDS). Overall image quality, subdiaphragmatic interference, and rate of referral to cardiac catheterization within 60 days were similar between the groups (Table 3).

Table 1. Patient characteristics

	Overall (n = 200)	BERST (n = 42)	Regadenoson-at-Rest (n = 33)	Exercise Only (n = 125)	*P* value*
Age (years)	52.5 ± 13.6	54.8 ± 10.6	50.9 ± 12.1	52.3 ± 14.7	.41
Male	132 (66)	29 (69)	26 (79)	77 (62)	.16
Body mass index	28.9 ± 6.5	29.7 ± 5.4	27.7 ± 7.0	28.9 ± 6.7	.40
Prior diagnosis of CAD	33 (17)	9 (21)	10 (30)	14 (11)	.02
Diabetes	52 (26)	16 (38)	13 (39)	23 (18)	.01
Hypertension	154 (77)	34 (81)	30 (91)	90 (72)	.06
Hyperlipidemia	101 (51)	23 (55)	20 (61)	58 (46)	.29
Prior myocardial infarction	16 (8)	5 (12)	6 (18)	5 (4)	.01†
Current tobacco use	11 (6)	4 (10)	3 (9)	4 (3)	.12†
Calcium channel blocker use	68 (34)	13 (31)	14 (42)	41 (33)	.52
Beta blocker use	112 (56)	31 (74)	29 (88)	52 (42)	<.0001

Values expressed as mean ± S.D. or number (percent).
CAD, Coronary artery disease.
* *P* value between groups receiving regadenoson (either BERST or Regadenoson-at-Rest) compared with Exercise Only.
†Fisher exact test.

Table 2. Stress test results

	Overall	BERST	Regadenoson-at-Rest	Exercise Only	*P* value
Bruce protocol time (minutes)	7.9 ± 2.5	6.9 ± 2.5	7.5 ± 2.5	8.3 ± 2.4	.003
% Maximum predicted heart rate reached	85 ± 14	75 ± 9	66 ± 10	93 ± 7	<.0001
METS	9.5 ± 2.7	8.5 ± 2.5	9.2 ± 2.5	10 ± 2.6	.003
ECG consistent with ischemia	18 (9)	4 (10)	1 (3)	13 (10)	.52*
Symptom score, range 1-4	1.8 ± 0.9	2.0 ± 0.9	1.9 ± 0.9	1.7 ± 0.9	.16

Numbers express as mean ± SD or number (percent).
METS, Metabolic equivalents.
* Fisher exact test.

Table 3. Imaging results

	BERST	Regadenoson-at-Rest	Exercise Only	*P* value
Summed stress score	2.7 ± 4.6	3.7 ± 9.3	2.0 ± 4.8	.35*
Summed rest score	0.6 ± 1.7	2.1 ± 8.8	0.8 ± 3.7	.40*
Summed difference score	2.1 ± 3.3	1.6 ± 3.1	1.2 ± 2.7	.25*
Overall image quality score	2.8 ± 0.7	2.7 ± 0.8	3.0 ± 0.6	.12
Significant subdiaphragmatic activity	2.9 ± 0.8	2.8 ± 0.8	3.0 ± 0.7	.39
Significant subdiaphragmatic interference	2.7 ± 0.6	2.6 ± 0.5	2.8 ± 0.5	.12
Cardiac catheterization within 60 days	7 (17)	4 (12)	9 (7)	.18†
Abnormal myocardial perfusion imaging (defined as SSS > 0)	18 (43)	13 (39)	42 (34)	.52

Values expressed as mean ± SD or number (percent).
SSS, Summed stress score.
* Kruskal-Wallis non-parametric test.
†Fisher exact test.

Safety

There were no significant adverse reactions to regadenoson such as instances of AV block, hemodynamic instability, or respiratory distress requiring intervention. There were no tracer spills or deviations from the study protocols. All studies were performed within protocol, and all patients who received regadenoson (at rest or with exercise) were injected with the stress dose tracer within 40 seconds of initiating the regadenoson bolus.

Subanalysis of Patients Who Failed to Reach THR

Although all were originally ordered for pharmacologic testing, 125 patients (62%) reached THR with exercise alone. We therefore performed an analysis of the subset of patients who failed to reach THR. There was more diabetes (39% vs 18%), previous diagnosis of coronary disease (25% vs 11%), previous myocardial infarction (15% vs 4%), hypertension (85% vs 72%), and beta-blocker use (80% vs 42%) in the group that did not reach THR compared with the group that reached THR ($P = .002$, $P = .009$, $P = .007$, $P = .03$, $P < .0001$, respectively). Primary care physicians, as opposed to surgeons or cardiologists, referred more patients for pharmacologic stress testing who were able to reach THR with exercise alone ($P = .008$). There was no significant difference in the rate of cardiac catheterization within 60 days among the patients who reached THR compared with those who did not ($P = .18$). Age, sex, body mass index, tobacco use, hyperlipidemia, and calcium channel blocker use were not significant predictors of failure to reach THR in univariate analysis. In fully adjusted logistic regression models, beta blocker use and diabetes remained significant univariate predictors of failure to reach THR (Table 4).

Table 4. Logistic regression analysis: predictors of failure to reach THR

Predictors of reaching THR	Unadjusted odds ratio	Unadjusted *P* value	Multivariate-adjusted odds ratio	Multivariate-adjusted *P* value
Age	1.0 (0.97-1.0)	.48	1.0 (0.98-1.0)	.55
Body mass index	1.0 (0.96-1.1)	.79	1.0 (0.95-1.1)	.99
Prior diagnosis of CAD	0.37 (0.17-0.80)	.01	1.3 (0.40-4.2)	.66
Prior myocardial infarction	0.24 (0.08-0.73)	.01	0.31 (0.07-1.4)	.13
Diabetes	0.40 (0.21-0.76)	.005	0.36 (0.17-0.74)	.005
Hypertension	0.44 (0.21-0.94)	.03	1.3 (0.50-3.2)	.61
Beta blocker use	0.14 (0.07-0.28)	<.0001	0.21 (0.09-0.46)	<.0001
Referring provider PCP	2.40 (1.1-5.3)	.03	2.6 (1.0-6.7)	.05

* Multivariable models were adjusted for age, sex, body mass index, and all covariates that were significant in univariate analysis at a significance of $P \leq .05$

DISCUSSION

We have demonstrated in this prospective, randomized study that a protocol combining a regadenoson infusion with symptom-limited exercise is feasible, and allows for the assessment of functional capacity in patients who are unable to reach a THR with maximal exertional exercise alone.

Although the use of an 85% MPHR cut-off has frequently been defined as the minimum level of exercise a patient needs to perform to test cardiac reserve, current ACC/AHA guidelines do not support the use of heart rate as an appropriate endpoint for exercising. Jain et al[10] have recently shown how terminating exercise at 85% of MPHR can significantly underestimate the amount of ischemia. However, certain conditions such as orthopedic, peripheral vascular, psychologic, or treadmill unfamiliarity can prevent achieving adequate heart rate responses despite an elevated perceived level of exertion. Therefore, our protocol required at least a 3-minute exercise period along with an 85% MPHR minimal level to indicate a condition when a patient should be converted from an exercise stress test to a pharmacologic stress test.

Regadenoson is a selective adenosine (A_{2A}) receptor agonist producing primarily coronary and systemic vasodilation, and it may be utilized as an alternative ''stress'' agent to treadmill exercise.[7] Regadenoson has substantially enhanced affinity for the adenosine A_{2A} receptor compared with adenosine, resulting in fewer side effects.[7] One particular advantage of regadenoson over adenosine is the ability to administer a single bolus dose without the need to hook-up extension tubing and an infusion pump. In addition, the dose of regadenoson is the same for all patients. Therefore, a potential application of regadenoson is in patients who undergo exercise stress testing and are unable to reach adequate heart rates. In this situation, regadenoson may be immediately infused during exercise to obtain diagnostic MPI images without terminating the prognostically important exercise protocol. However, it should be noted that there are potential logistical complications that might occur while administering a bolus of medication during peak exercise. For one, a nurse must be available to administer and flush the regadenoson injection. Immediately following, the nurse must safely move away while the nuclear medicine technologist administers the radiotracer. All must be performed while the patient is exercising at maximal exertion without misadministration or tracer spill.

Despite the adenosine A_{2A} receptor selectivity, side effects are common during routine regadenoson stress testing. It is important to note that compared with adenosine, regadenoson results in a greater overall increase in heart rate and similar decrease in blood pressure.[7] In the present study, there were no significant side effects or adverse reactions attributed to the regadenoson infusion; for example, there were no instances of advanced AV block. There was no significant difference in a subjective four-point symptom score between the three study groups. Although there are inherent limitations in this method of assessment, the findings suggest that the combined exercise and regadenoson (BERST) protocol was tolerated at least as well as the Exercise Only and Regadenoson-at-Rest protocols. A prior study by Thomas et al[11] demonstrated no significant difference in safety or side effects when regadenoson was combined with low level exercise; our study adds to recent observational data[8] and now extends this finding to subjects undergoing symptom-limited exercise testing.

Our lab previously pioneered a protocol combining 4 minutes of adenosine infusion with a symptom-limited exercise stress test to address the needs of patients who are able to exercise, but could not reach adequate heart rates. This combined exercise and adenosine protocol proved to be safe and feasible, and resulted in a greater amount of detectable ischemia while allowing for the assessment of functional capacity.[5,6] However, in the present study, there was no significant difference in the extent of ischemia as assessed by the SDS among the groups. A likely explanation for this finding is the difference in protocol between the studies. By design, the prior study compared symptom-limited exercise without adenosine against symptom-limited exercise with adenosine in the same patients who often did not reach THR. In the present study, regadenoson with symptom-limited exercise was compared with regadenoson at rest and with maximal symptom-limited exercise alone. The greater amount of ischemia detected by the combined stress group in the prior study likely reflected the fact that maximal vasodilation was achieved in more patients with the additional adenosine. This conclusion could be made because patients in the prior study served as their own control. In the present study, a similar extent of vasodilation was likely achieved among different groups of patients.

Likewise, there was no significant difference in image quality between the groups. We postulate that one potential explanation for this finding is the allowance of varied time from termination of exercise and/or injection of regadenoson to imaging. In effort to avoid interference from clinical studies ongoing in our nuclear laboratory, a specified time to imaging was not established in our protocol. Subjects who underwent any form of exercise (i.e., the BERST or Exercise Only groups) proceeded to SPECT imaging without delay. Moreover, even though regadenoson was only injected at rest in patients randomized to the Regadenoson-at-Rest protocol, splanchnic flow may still be reduced because of a relative short wait time (5-15 minutes) between termination of exercise and injection of regadenoson. Therefore, the potential effects of exercise combined with regadenoson in reducing splanchnic activity may have been blunted compared with regadenoson at rest.

Interestingly, 125 patients (62%) in this cohort referred for clinically indicated pharmacologic nuclear perfusion stress testing reached THR with exercise alone. We note that although the use of 85% of MPHR as an endpoint for exercise is widely practiced, this is not recommended by the ACC/AHA guidelines or what was performed in this study. In fact, the patients who exercised alone far exceeded THR reaching an average of 93% ± 7% of MPHR. This unexpected observation prompted further analysis of the subgroup of patients able to exercise to target. It should be noted that patients who could clearly ambulate despite orders for a pharmacologic stress study were approached to participate. Although the mean age of the entire cohort is significantly younger than patients typically referred for pharmacologic stress testing, the age of the patient was not predictive of whether the patient reached THR or not. The findings suggest that many physicians, particularly referring primary care providers, may underestimate the ability of their patients to reach THR on exercise testing alone. Interestingly, the patients that received regadenoson, either with peak exercise or at rest, tended to be ''sicker'' with more CAD, MI, hypertension, and diabetes. However, in fully adjusted logistic regression models, beta-blocker use appeared to be the strongest predictor of failure to reach the THR, a principle that has been demonstrated in prior studies.[12]

Patient selection for exercise vs pharmacologic stress testing can be challenging because of difficulty in predicting which patients will reach THR. While we did monitor for moderate-to-severe dyspnea or angina, specific ECG changes, and abnormal blood pressure responses, we did not record perceived exertion according to the Borg scale. In addition, the Duke Activity Status Index (DASI) is a 12-item questionnaire that utilizes self-reported physical work capacity to estimate peak metabolic equivalents (METs) and has been shown to be a valid measurement of functional capacity.[13] While we did not incorporate either method into our protocol, future studies may consider integrating this questionnaire in effort to determine which patients are likely to fail to reach the THR with exercise alone; such methodology could facilitate the selection of those patients who may benefit from a combined exercise plus regadenoson protocol.

LIMITATIONS

More patients than expected who were enrolled in the study reached THR with exercise. Specifically, 62% of our cohort of patients ordered for routine pharmacologic stress testing was able to achieve the THR with exercise alone. This unexpected shift lead to fewer patients in the BERST and Regadenon-at-Rest groups resulting in a loss of power to detect potential differences such as the degree of ischemia or image quality. In addition, after randomization, patients were not blinded to the assigned protocol; patients only underwent one clinically indicated protocol and therefore did not serve as their own controls.

Our lab does not mandate that patients hold antiischemic and other cardioactive medications before nuclear stress testing. As there were more patients with known myocardial infarction and coronary artery

disease in the groups that received regadenoson, it is possible that less ischemia was provoked in the context of ongoing background medical therapy. Specifically, our inability to detect a difference in SSS between the BERST and Exercise Only groups may be a result of this potential limitation. Furthermore, it is noted that the majority of patients demonstrated normal MPI (defined as SSS = 0) in the present study.

CONCLUSIONS

In this prospective, randomized study, a protocol combining a regadenoson injection at peak exercise in those patients unable to reach THR with a standard Bruce treadmill exercise protocol is feasible, well-tolerated, and yields comparable imaging results to a standard regadenoson injection at rest. It is possible to obtain diagnostic MPI images without terminating the prognostically important exercise protocol and without increased incidence of adverse events. In addition, pharmacologic stress testing may be over-ordered in current clinical practice, as patients referred for such testing were often able to exercise.

This trial adds further evidence supporting the concomitant use of regadenoson injection at maximal exertion in patients who fail to reach THR with exercise alone. While the utilization of a combined protocol has been limited to patients scheduled for a pharmacologic nuclear perfusion study, it may be reasonable to expand this approach to all patients referred for stress MPI without being unduly concerned about its safety.

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