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ORIGINAL PAPER

Feasibility, safety and accuracy of regadenoson–atropine (REGAT) stress echocardiography for the diagnosis of coronary artery disease: an angiographic correlative study

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Abstract Regadenoson (REG), a selective A2A receptor vasodilator, has not been widely evaluated in stress echocardiography (SE). We report results of 45 patients participating in REG + atropine (REGAT) SE protocol conducted in a single-center prospective trial. The REGAT study enrolled subjects before a clinically indicated cardiac catheterization for suspected coronary artery disease (CAD). After rest imaging, a 2 mg Atropine (AT) bolus followed by 400 mcg of REG was given. Standard stress imaging views were obtained and interpreted in blinded fashion. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated using cardiac catheterization >70 % stenosis as gold standard. Additional endpoints included major adverse cardiac events (MACE) and patient questionnaire responses. The mean duration of REGAT was 18 ± 7.2 min. There were no MACE, with only transient side-effects of dry mouth, shortness of breath, and headache. The incidence of significant CAD was 51.1 %. The sensitivity and specificity for significant stenosis was 60.9 and 86.4 %, with a PPV and NPV of 82.4 and 67.9 %. By coronary territories, the sensitivity, specificity, PPV, and NPV were: 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. The REGAT protocol is fast, safe, and well-tolerated with good specificity for CAD detection, but its low sensitivity and NPV precludes it from being an imaging modality for routine use.

Keywords Regadenoson · Stress echocardiography · Coronary disease · Atropine · Coronary angiography

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Introduction

Vasodilator use in stress echocardiography (SE) for diagnosis of coronary artery disease (CAD) has not gained popularity in North America [1, 2]. The concern is that hyperemic vasodilator stress, although sufficient to cause heterogeneity of blood flow to cause perfusion defects as in nuclear perfusion imaging, may not be sufficient to cause subendocardial ischemia, which is the integral component in causing wall motion abnormalities in SE [3–7].

Regadenoson (REG) (Lexiscan; Astellas Pharma, Northbrook, IL, USA), a new A2A selective agonist, was approved by the Food and Drug Administration (FDA) in 2008 as a pharmacologic stress vasodilator for myocardial perfusion imaging. REG has comparable accuracy and non-inferiority to adenosine in regards to detection of perfusion defects by nuclear perfusion imaging [8–10]. Given its favorable side effect profile, short half-life, and ease with single dose intravenous injection administration, REG use has steadily increased and is the vasodilator of choice in nuclear perfusion imaging in many cardiovascular centers. However, compared to the wealth of experience with adenosine (ADENOECHO) and dipyridamole as a vasodilator in SE (DIPECHO), the role of REG in SE is unclear and still evolving at the time of this study initiation [2, 11,

12]. Vasodilator stress may not always induce sufficient flow heterogeneity to cause subendocardial ischemia. Adjunctive chronotropic stress helps facilitate precipitating ischemia in settings of hyperemic stress. Hence, DIPECHO also used adjunctive atropine (AT) to achieve adequate chronotropy in addition to vasodilator stress, to enhance sensitivity for detection of CAD [13]. In this regard, REG with or without AT, has not been studied in the setting of SE. Thus, a potential advantage exists where an A2A selective agonist, REG, along with AT (REGAT) SE protocol could obviate both infusion and undesirable side effects (seen with dipyridamole and adenosine), and potentially achieve higher sensitivity for the detection of CAD. Furthermore, the entire SE protocol with REGAT can theoretically be completed in 5–10 min, thereby greatly improving turn-around time and lab efficiency. Our primary aim was to study the feasibility, safety, and accuracy for CAD detection of the REGAT SE protocol using coronary angiography (CA) as the gold standard. At the time of study inception, a target of 110 patients were slated to be enrolled, but based on interim analysis and very slow recruitment over a 2 year period, the study investigators decided to stop the study after recruitment of 45 patients. The data from the 45 patients is presented in this manuscript.

Methods

Study patients

Between October 2009 and January 2012, we screened patients being referred for CA for participation in our trial. Patients ≥18 years old, who were scheduled for a clinically indicated cardiac catheterization by their cardiologist with/without a prior functional stress imaging study were eligible for enrollment. Patients had to be able to stop taking their beta-blocker and/or nitrates for at least 24 h prior to the research protocol per approval of their cardiologist. The main exclusion criteria involved any history of acute myocardial infarction, unstable angina, prior percutaneous coronary intervention in last 3 months, non-sinus rhythm, left bundle branch block, electronic paced rhythm or bypass surgery. Patients with typical listed contraindications to REG and AT were also excluded [14, 15]. Patients with bronchospastic lung disease were not enrolled as literature using REG in these patients were limited at the time of the study.

After applying the above exclusion criteria, 54 patients with suspected CAD undergoing a clinically indicated CA were prospectively enrolled into the study. Nine subsequent patients were identified as screen failures (Table 1), thus a total of 45 patients completed the protocol. Overall enrollment was very slow and much lower than expected. This is, in part, due to many patients presenting to the catheterization laboratory with acute coronary syndromes as opposed to stable angina. Furthermore in the era post COURAGE trial most physicians seem to feel comfortable managing CAD with medical therapy despite positive stress test. Furthermore, there was a significant number of referring physicians who were not comfortable withholding the patient's beta-blocker therapy prior to the REGAT protocol, causing a further drop in enrollment.

All recruited patients had typical risk factor profiles for CAD, with 89 % having dyslipidemia, 69 % having hypertension, and 35.6 % having diabetes, with the majority of patients taking cardiac medications (Table 2). Of the study participants, 87 % (39) had a prior stress test, with SE being the most likely stress modality (38 %). A total of 30 patients had a positive stress test (67 % of total cohort). The study was approved by the Institutional Review Board (IRB) and registered with ClinicalTrials.gov (Identifier: NCT00894179).

REGAT protocol

All eligible patients who provided informed consent underwent REGAT SE protocol within 1 week prior to their cardiac catheterization. Standard echocardiographic imaging planes for SE per American Society of Echocardiography (ASE) guidelines were performed at rest. All patients were required to stop beta-blocker and or nitrates at least 24 h prior to the REGAT study. After exclusion of any baseline echocardiographic or hemodynamic contraindications for stress testing per our lab protocol, the REGAT protocol was initiated (Fig. 1). The first 10 patients enrolled were in a run in phase as requested by the FDA to test the safety of combined REGAT administration. AT was initially used in 0.25 mg doses cumulative to 2 mg in the first 5 patients, then changed to 0.5 mg boluses to a total of 2 mg in 4 patients to test safety, and then finally modified for the last 36 patients as 1 mg bolus × 2 (Fig. 1). Following the initial administration of 2 mg AT, a single intravenous bolus dose of 400 mcg of REG over 10 seconds was given followed by a saline flush. Thirty to 40 seconds later, standard stress echocardiographic views (apical 4, 3, 2 chamber views and parasternal long and short axis windows) were obtained for a side-by-side digital comparison to rest images. An additional set of images was obtained at 2 min post-REGAT to document any new changes not noted in initial imaging. Finally, recovery images were obtained when heart rate was around 100 beats per minute (bpm). Echocardiographic contrast was utilized as needed based on standard ASE guidelines for endocardial border visualization [16]. Since the half life of

Table 1 Patient Screening

1,596 Patients undergoing outpatient
Left Heart Catheterization for suspected CAD
Met exclusion criteria
1,542 patients
54 Patients initially enrolled
Screen failures
Severe hypertension (1)
Increased pulmonary artery pressure (1)
Tachycardia (1)
Admitted for syncope day of scan (1)
Glaucoma (2)
Withdrew consent (3)
45 Patients completing study

Table 2 Baseline patient characteristics (N = 45)

Variable	N (%) or mean ± SD
Males	26 (57.8 %)
Age (years old)	61 ± 7
BSA (m^2)	2.04 ± 0.23
Dyslipidemia	40 (88.9 %)
Hypertension	31 (68.9 %)
Diabetes	16 (35.6 %)
Family history of CAD	29 (64.4 %)
Smoker	6 (13.3 %)
History of stroke	2 (4.4 %)
History of CHF	1 (2.2 %)
Aspirin use	36 (80 %)
Statin use	31 (68.9 %)
Beta blocker use	29 (64.4 %)
Ace inhibitor or angiotensin receptor blocker use	21 (46.7 %)
Prior exercise stress echocardiogram	17 (37.8 %)
Prior pharmacologic MPI	7 (15.6 %)
Prior dobutamine stress echocardiogram	7 (15.6 %)
Prior exercise MPI	5 (11.1 %)
Prior treadmill ECG	2 (4.4 %)
Prior regadenoson PET stress	1 (2.2 %)
Total number of prior positive stress tests	30 (67 %)

BSA body surface area, *CAD* coronary artery disease, *CHF* congestive heart failure, *MPI* myocardial perfusion imaging, *PET* positron emission tomography

REG is short and imaging is usually commenced in less than 1 min after REG to coincide with its peak hyperemic effect, REG was administered after AT bolus. The choice to initiate stress imaging within 1 min of REG injection was to enhance the opportunity to detect ischemia due to the combined hyperemia AND augmentation of heart rate provided by both REG injection and atropine. As there is continued hyperemia effect of REG that persists 2–3 min after injection, a second set of images was captured 2 min post-REGAT to ensure that wall motion abnormalities were not missed in the first few minutes post stress. This was felt the best way to allow for assessment of both hyperemic effect and chronotropic effect of this protocol.

Echocardiographic analysis

All echocardiograms were performed by using a commercially available imaging system (Acuson Sequia C512, Siemens Medical Solutions, Malvern, PA, USA). A directed 2-dimensional (2D) echocardiogram was obtained with standard pre-stress and post-stress views in all patients. The SE's were interpreted off-line on a digital workstation (Syngo Dynamics, Siemens Medical Solution, Malvern, PA, USA) and independently by two board certified adult echocardiography ASE Level III readers (KA and MA), who were blinded to clinical and angiographic data. In cases of any discordance, both readers reviewed the study together and reached a consensus (occurred in 2 patients). There was no discordance between the two readers at time of study completion. A standard 16-segment ASE model was used for left ventricular wall motion and wall motion score index [17]. A positive stress study was defined as demonstration of a new or worsening wall motion abnormality seen in 2 or more adjacent myocardial segments with stress.

Patient monitoring

After baseline hemodynamics were recorded, patients were placed on continuous 12-lead electrocardiogram monitoring with blood pressure measurements at 2 min intervals. Patients were questioned by supervising nurses regarding any symptoms they experienced during the REGAT protocol. After completion of the stress protocol, patients were monitored for a minimum of 15 min. Routine use of antidote therapy with aminophylline was not used, given the relatively short half-

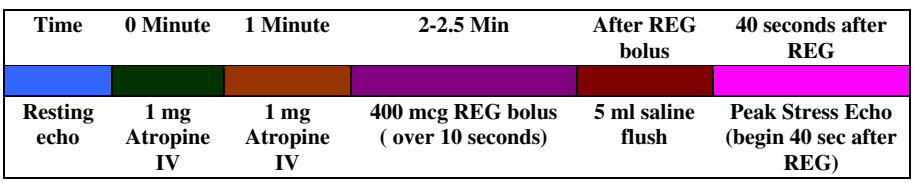

Fig. 1 REGAT protocol. *IV* intravenous, *REG* regadenoson

life of REG and its one time intravenous bolus technique (compared to longer infusion times of both adenosine and dipyridamole). If aminophylline was used, patients were monitored for an additional 15 minutes prior to discharge from the echocardiographic laboratory. Criteria for protocol termination prior to REG injection included progressive and severe angina accompanied by marked ST segment changes, symptomatic hypo/hypertension (decrease in systolic blood pressure of >20 mmHg or blood pressure >220/110 mmHg, respectively), severe electrocardiogram rhythm or conduction disturbance, other intolerable symptoms or a patients' request to terminate the exam. All patients were administered a satisfaction questionnaire at completion of testing asking them to rate their level of comfort with the REGAT protocol and compare it to other stress modalities they have underwent (if applicable).

Coronary angiography (CA) analysis

All patients underwent a selective CA within 7 days of the REGAT protocol. In cases where REGAT was followed by CA on the same day, both studies were separated by a minimum period of 1 hour to ensure patient stability and full recovery after the REGAT protocol prior to catheterization. Multiple standard views were obtained of both the right and left coronary arteries and their branches. Catheterization images were assessed by an experienced interventional angiographer (AK) blinded to clinical and echo data with each individual coronary tree scored by qualitative analysis. A significant lesion on catheterization was defined as >70 % luminal stenosis in any coronary vessel or >50 % left main stenosis.

Statistical analysis

Categorical variables are presented as frequency and percentage of occurrence. Continuous variables are presented in the form of the average and standard deviation. Sensitivity, specificity, positive and negative predictive values (PPV, NPV), and accuracy were calculated using standard definitions on a patient and vessel level. The correlation between the REGAT SE and angiogram results were tested using Spearman correlation coefficients.

Sample size justification

A sample size of 100 patients was calculated to have an 82 % power to detect a correlation coefficient of $\rho = 0.683$, with null hypothesis value of $\rho = 0.50$. For a sensitivity of 75 % and 100 patients, there would be a 95 % binomial confidence interval ranging from 66.4 to 83.5 %. If the sensitivity is 90 %, the 95 % confidence interval would be 84.4–95.9 %. This level of precision was felt to be sufficient for this study. Per FDA recommendation, a run-in phase of 10 patients was first performed to evaluate the safety of combination of REG + AT as this has not been previously investigated. A total of 110 patients were planned to be enrolled; however, the study was terminated after 54 patients were enrolled due to slow recruitment and after interim analysis was reviewed.

Table 3 REGAT protocol data (N = 45)

Variable	Rest	Stress	*P* value
SBP (mmHg)	141 ± 16.1	139 ± 22	0.624
DBP (mmHg)	82 ± 9.2	77 ± 9.4	0.0125
HR (bpm)	70 ± 13.9	123 ± 16.7	0.001
WMSI	1.06 ± 0.18	1.15 ± 0.22	0.0365
Image acquisition (min)	12.9 ± 5.9	1.5 ± 0.8	0.001
MPHR (%)	n/a	77.4 ± 10.3	n/a
Achieved 85 % MPHR	n/a	13(28.9 %)	n/a
Double-product (bpm mmHg)	n/a	17,221 ± 4,196	n/a
Protocol time (baseline through stress images) (min)	n/a	17.8 ± 7.2	n/a
Total lab time (arrival to discharge) (min)	n/a	70.7 ± 29.2	n/a
REGAT scans positive for ischemia	n/a	17 (37.8 %)	n/a

N (%), Mean ± SD

P value calculated 2-tailed unpaired *t* test

DBP diastolic blood pressure, *HR* heart rate, *MPHR* percent of maximal heart rate, *WMSI* wall motion score index

Results

All 45 patients completed the protocol. Hemodynamic data and protocol times were collected for all enrolled patients (Table 3). Patients were mildly hypertensive (141 ± 16/82 ± 9 mmHg) with normal heart rates (70 ± 14 bpm) at baseline. Only 29 % of the patients achieved >85 % maximal predicted heart rate (MPHR), with an average MPHR of 77.4 ± 10.3 %. The double-product (peak systolic blood pressure × peak heart rate) was 17,221 ± 4,196.

Baseline and stress images were acquired in 12.9 ± 5.9 min and 1.5 ± 0.8 min respectively. Echocardiography contrast agent (Definity, Lantheus Medical Imaging; N. Billerica, MA, USA) was used in 62 % of the patients. All 17 segments were available for interpretation on each patient's echocardiogram. We followed standard guidelines for contrast imaging using lack of visualization of 2 or more contiguous segments as a criteria for using contrast. Thus the remainder of the patients had adequate

Table 4 Sensitivity analysis on a per patient and CAT basis using a 70 % stenosis angiographic cutoff by angiography

	Sensitivity	Specificity	PPV	NPV	Accuracy
Per patient	60.9 (43–79)	86.4 (66–95)	82.4(60–94)	67.9 (49–82)	73.3 (60–84)
By CAT					
LAD	58.8 (38–80)	92.9 (77–98)	83.3 (57–95)	78.8 (62–89)	80 (67–89)
LCX	6.7 (2–30)	93.3 (79–98)	33.3 (7–80)	66.7 (52–80)	64.4 (51–77)
RCA	16.7 (5–45)	93.9 (81–98)	50 (15–85)	75.6 (61–86)	73.3 (60–84)

Values are percent (95 % CI)

CAT coronary artery territory, *NPV* negative predictive value, *PPV* positive predictive value, *CI* confidence interval, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery

baseline visualization of endocardial borders which not requiring contrast during rest and stress. The REGAT protocol time was completed in 17.8 ± 7.2 min, with total time spent in the non-invasive laboratory (arrival to discharge) lasting 70.7 ± 29.2 min. (Note: Total laboratory time included consenting the patient and a mandatory 15 min post-monitoring period; total 40–45 min.)

Angiographic data

The overall incidence of angiographic significant CAD (defined as >70 % stenosis in any epicardial coronary vessel) was 51.1 % (23 patients). There was a relatively similar incidence of left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA) stenosis (37.8 % (17 patients), 33.3 % (15 patients), and 26.7 % (12 patients) respectively). Twenty percent of patients had significant two-vessel CAD and 15.6 % (7 patients) had three-vessel/left main disease.

Detection of significant CAD on a per patient and coronary artery territory basis

A total of 17 REGAT echocardiograms (37.8 %) were considered positive for ischemia with the majority of scans showing ischemia in the LAD territory (70.5 % of positive scans). The overall sensitivity and specificity for diagnosing significant CAD was 60.9 and 86.4 % respectively, with an accuracy of 73.3 % (Table 4). The PPV and NPV were 82.4 and 67.9 %, respectively. The sensitivity, specificity, accuracy, PPV and NPV for detection of significant stenosis in the LAD were 58.8, 92.9, 80, 83.3 and 78.8 %, respectively. There was a significant drop in sensitivity in the detection of LCX and RCA stenosis. For the LCX, the sensitivity, specificity, accuracy, PPV and NPV were 6.7, 93.3, 64.4, 33.3 and 66.7 %, respectively. For the RCA, the sensitivity, specificity, accuracy, PPV and NPV were 16.7, 93.9, 73.3, 50 and 75.6 %, respectively. There was no change in the analysis results when a >50 % stenosis angiographic cut-off was used.

Table 5 Safety analysis

Adverse reaction/event	N (%)
Dry mouth	28 (62.2 %)
Shortness of breath	27 (60 %)
Headache	20 (44.4 %)
Dizziness	18 (40 %)
Chest pain	13 (28.9 %)
Flushing	9 (20 %)
Blurry vision	2 (4.4 %)
Aminophylline use	9 (20 %)
Arrhythmia	0 (0 %)
MI/death	0 (0 %)

MI myocardial infarction

Table 6 Patient post-procedure satisfaction survey

Question	N (%)
Feel very comfortable	12 (26.7 %)
Feel comfortable	29 (64.4 %)
Feel neutral	2 (4.4 %)
Feel uncomfortable	2 (4.4 %)
Feel very uncomfortable	0 (0 %)
REGAT is MUCH better than prior stress test	21 (46.7 %)
Better than prior stress test	14 (31.1 %)
Same as prior stress test	7 (15.6 %)
Worse than prior stress test	3 (6.7 %)
MUCH worse than prior stress test	0 (0 %)
I would do this stress test again	37 (82.2 %)
I would NOT do this test again	8 (17.8 %)

Safety and feasibility

The most common side effects were dry mouth, shortness of breath, and headache (62.2, 60 and 44.4 % respectively) (Table 5). There were no serious adverse events requiring hospitalization, malignant arrhythmias, myocardial infarctions, or death. The vast majority of patients felt comfortable during the examination (>90 %, Table 6).

Furthermore, 78 % of patients felt the REGAT protocol was more tolerable than their prior stress test. If further stress testing was indicated in their future, 82.2 % of patients said they would prefer the REGAT protocol to another stress test.

Discussion

The REGAT protocol is safe, has minimal side-effects, and is much faster than standard exercise and dobutamine based SE protocols used in clinical practice. The sensitivity (and NPV) of detection of CAD (defined as ≥70 % stenosis by angiography) is <70 %. Sensitivity is highest for detection of LAD disease and lowest for detection of RCA/LCX disease. The specificity (and PPV) is highest in the LAD distribution, and overall comparable to most current stress modalities.

When using vasodilators, the most important challenge is for the agent to cause sufficient hyperemia and induce subendocardial ischemia in the region subtended by a coronary stenosis. In contrast, adequate chronotropic stimulation with exercise along with concomitant inotropic stimulation as seen with dobutamine, and augmenting myocardial oxygen consumption has been shown to reliably elicit ischemic wall motion abnormalities by echocardiography with acceptable sensitivity and specificities and excellent negative predictive values for prediction of cardiac events, making them current standard methodologies in North America for SE [17–19]. However, when one considers agents such as adenosine and dipyridamole which increase coronary blood flow 4–5 times normal, such degree of hyperemia along with chronotropic stress from adjunctive AT could precipitate sufficient flow mismatch between diseased and normal regions to cause subendocardial ischemia [20–22]. This may explain the comparable published sensitivities and specificities of DIPECHO of 72 and 95 % for detection of CAD [23]. Furthermore, its excellent prognostic value has also been shown to be comparable to dobutamine SE [24, 25].

However, when REG was combined with AT in our study to try to reproduce a combination of vasodilator stress and chronotropic challenge, although heart rate did increase with AT, it generally did not reach the typical >85 % MPHR that is used in traditional exercise protocols or dobutamine echocardiography [26–31]. Although 100 % of our patients by protocol received AT, only approximately 30 % of patients achieved ≥85 % predicted maximal heart rate (PMHR), which further hampered detection of ischemia. This occurred despite patients holding beta-blockers for at least 24 h. Thus, despite maximum dose REG + 2 mg cumulative dose of AT, poor sensitivity for CAD detection is likely due to the fact REG has a lower degree of induced hyperemia compared to adenosine/dipyridamole (2–3 times baseline versus 4–5 times baseline), which may pose challenges for precipitating subendocardial ischemia. The peak effect of REG is in 30–40 s with most of the drug metabolized by 2–3 min, where as adenosine/dipyridamole both are constant infusions for anywhere between 4 and 18 min depending on the specific protocol [19–32].

Table 7 False negative REGAT scans

Pt no.	Extent of CAD	sWMSI	Cor Terr
#8	Small 90–99 % D1 and 70–80 % mid RCA	1	none
#12	80–89 % mid LAD and 80–90 % mid LCX	1	none
#13	Small 90–99 % ramus and 90–99 % non-dominant proximal RCA	1	none
#15	90–99 % D1 and small 90–99 % OM2	1	none
#18	80–89 % mid LAD and 80–89 % mid OM2	1	none
#19	80–90 % PAV	1.25	RCA (present on rest and stress)
#21	70–80 % OM2	1	none
#39	100 % distal RCA	1	none
#41	70–80 % D1 and 70–80 % PDA	1	none

CAD coronary artery disease, *Cor Terr* abnormal coronary territory on REGAT scan, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery disease, *LM* left main coronary artery, *D* diagonal artery, *OM* obtuse marginal artery, *PDA* posterior descending artery, *PAV* posterior atrio-ventricular groove artery, *sWMSI* stress wall motion score index

In this context, our study's findings suggests that REG, at its maximum recommended dose of 400 mcg, in conjunction with AT has substantial limitations in detection of CAD, particularly in the RCA and LCX distributions when compared to published data from DIPECHO. While REGAT proved to be fast, safe, and the preferred stress modality by patients, its ability to diagnose CAD was less than adequate to recommend it as modality for evaluation of suspected CAD. Although REGAT was able to demonstrate comparable specificity and PPV compared to other imaging modalities (including DIPECHO), the sensitivity and NPV are insufficient to allow for routine clinical use.

Prior Literature with REGECHO

It is important however to note the overall sensitivity observed in the REGAT protocol is comparable to the sensitivities from prior vasodilator echocardiographic studies *not* utilizing adjunctive AT or handgrip maneuvers [1, 2, 11, 12]. Additionally, recently published studies

using REG for SE combined with myocardial contrast perfusion imaging, showed similar sensitivities to REGAT when looking *only at wall motion*, without incorporation of AT use [33]. Sensitivity, specificity and overall accuracy for wall motion assessment was only 60, 72 and 76 % using a ≥50 % angiographic diameter stenosis as Ref. [33]. This improved only when a perfusion component was added. Our REGAT protocol carried a higher sensitivity and specificity for detection of ≥70 % angiographic stenosis (no difference when examined with ≥50 % angiographic stenosis) compared to prior REGECHO studies looking at wall motion as end point. Furthermore, when ischemia is detected with a positive REGAT scan, there is high likelihood of significant CAD. Fifty-nine percent of positive scans (10/17) had either significant proximal LAD or a severe two/three-vessel CAD (Table 7). Of the positive scans, 23.5 % (4/17) had either mid LAD lesions or significant LCX with branch vessel disease. The majority of the false-negative scans were patients with either small vessel or distal branch vessel disease (Table 7).

Limitations

The major limitation of our study was slow patient recruitment leading to premature termination of the study. Recruitment was very slow mainly due to the substantial number of patients refusing to participate in a study prior to CA due to having already had a stress test in most instances and not wanting to undergo additional testing with a combination of agents (REG + AT) that had not been previously studied. A substantial number of patients were ineligible for enrollment secondary to primary providers declining additional testing on their patient prior to CA. This, plus the exclusion criteria, served as the major source of lack of adequate recruitment. Based on our observations of enrolled patients in the REGAT study, we do not believe that additional recruitment would have changed the results of our conclusions. Only 30 % of our patients achieved target heart rate, which could have significantly affected the sensitivity for detection of ischemia. The addition of REG, which is known to cause some degree of reflex tachycardia, was insufficient to augment the heart rate beyond 85 % PMHR in most patients. We did not have a control group of REGECHO alone compared to REGAT but based on our results; it is obvious that the REGECHO group would have even more unacceptable sensitivities and NPV than REGAT. There was no comparison of the REGAT protocol to other stress modalities within the cohort. Although such a comparison to prior stress tests was desirable, due to a small sample size with a mixture of different stress modalities, from a statistical analysis standpoint, would have been of uncertain clinical value. And finally, the assessment of angiographic stenosis was done qualitatively, not with formal QCA. We certainly acknowledge the limitation in our study that lack of quantitative angiographic estimation of the stenosis severity using FFR precluded the comparison of the stress data to angiographic data with regards to physiologic significance. However, we wanted to simulate real world practice where usually stress testing serves as the noninvasive FFR for patients going to the cath lab although limited by false positives.

Conclusions

The REGAT protocol is fast, safe, and well-tolerated with good specificity for CAD detection on a patient level, but it has a relatively poor sensitivity and NPV for diagnosis of CAD. This is likely due to its inability to precipitate ischemic wall motion abnormalities despite maximal hyperemia when compared to other vasodilator agents, such as dipyridamole or adenosine. Thus, although REG is of comparable efficacy for nuclear myocardial perfusion imaging, due to fundamental differences in mechanism of detection for CAD (heterogeneity of flow), it is not appropriate to be utilized for vasodilator SE, even in conjunction with AT.

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Conflict of interest Dr Ananthasubramaniam receives research grants from Astellas Pharma US Inc.

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