Use of Regadenoson for a Stress Echocardiogram Protocol Using Speckle Tracking Imaging.

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1.0 Background

Current protocols used in clinical practice for stress echocardiography evaluation include exercise efforts (bicycle and treadmill) and pharmacologic stimulation. The pharmacologic stress echocardiography in the US is almost exclusively performed with Dobutamine.

In clinical practice vasodilator agents for stress testing have been limited for the use of perfusion imaging with nuclear isotopes. Nuclear stress testing is more expensive, equipment heavy, less available and much less portable than echocardiography imaging systems. It also exposes patients to a significant radiation dose (1).

Stress echocardiography is known for its comparable accuracy in detection of obstructive coronary artery disease when compared with nuclear methods. In a highly quoted pooled analysis of 18 studies in 1304 patients who underwent exercise or pharmacologic stress echocardiography in conjunction with thallium or technetium- labeled radioisotope imaging, sensitivity and specificity were 80% and 86% for echocardiography. Corresponding values were 84% and 77% for myocardial perfusion imaging, respectively (2).

The main limitation of stress echocardiography has been imaging quality and the fact that segmental dysfunction recognition depends on the human eye assessment of wall thickening (3). New, validated, ultrasound imaging technology now exists to aid in the recognition of segmental systolic dysfunction in more objective ways, namely the use of speckle tracking imaging(4). This technology uses the systolic tracking of speckles to define tissue deformation of the different cardiac segments in all the dimensions of cardiac, systolic, mechanical motion. The quality of this technology for precise segmental function analysis relies on the use of higher frame rates (5); which can be defeated in the case of tachycardia. Since a certain level of tachycardia is needed for accuracy in Dobutamine stress echocardiography testing (DSE), therefore combining DSE with speckle tracking imaging would be sub optimal. Speckle tracking imaging values in its longitudinal dimension has also proven more reliable for all-cause mortality prediction than more traditionally accepted measures such as Left Ventricular ejection fraction (LVEF) and wall motion score index (WMSI) (6).

The use of vasodilatation for stress echocardiography examination has been performed successfully in the past, also with the use of regadenoson, but for the

main purpose of perfusion imaging with echocardiography, using ultrasound contrast agents.
Regadenoson is a pharmacologic stress agent indicated for radionuclide myocardial perfusion imaging in patients unable to undergo adequate exercise stress. It is a low affinity agonist for the A_1 adenosine receptor with weak to no affinity for the A_{2B} and A_3 adenosine receptors. Activation of the A_{2A} adenosine receptor by regadenoson produces coronary vasodilation and increases coronary blood flow.

We propose a study in our cancer patients already scheduled for regadenoson nuclear stress testing obtaining rest and peak hyperemia longitudinal strain images to compare accuracy in detection of coronary artery disease between modalities as well as obtaining possible additional prognostic information in this population.
If the regadenoson-strain data accuracy is comparable to perfusion imaging this would constitute a new stress modality that is free of radiation exposure to our cancer patients. The main comparison group will be those cases interpreted as abnormal with nuclear imaging that proceed to coronary angiography (Grp 1). Patients undergoing stress testing in anticipation of a cancer related surgery of intermediate to significant risk (Grp 2) will provide 30d post-operative major cardiac event (MACE) rates for comparision. MACE is defined as:

1. Acute coronary syndrome (ACS):
   - unstable angina
   - abnormal troponin consistent with current guidelines for the diagnosis of acute myocardial infarction (AMI)
   - AMI
   - revascularization
2. LV dysfunction defined as either a drop in LVEF to $\leq$50% or $\geq$10% decrease from baseline.
3. Ventricular arrhythmias:
   - ventricular tachycardia (VT)
   - ventricular fibrillation (VF)
4. Stroke
5. Sudden cardiac death

2.0 Objectives

Primary objective: We aim at demonstrating that the angiogram (by either coronary angiography or coronary CT angiogram) and the regadenoson stress

echocardiography (ReSTE) are equivalent in classifying ischemia among SPECT positive patients; this corresponds to test if ReSTE is as accurate as SPECT in the diagnosis of ischemia at least among SPECT positive patients (Grp 1).
Secondary aims: assess whether or not ReSTE adds predictive information above and beyond SPECT in predicting 30d post-operative cardiac events (Grp 2).

3.0 Patient Eligibility

Inclusion Criteria:

1. Cancer patients who are scheduled for (perfusion) nuclear stress testing using regadenoson as stress agent.
2. Indications for stress testing is either:
   as part of a pre-operative evaluation prior to a planned cancer related surgery that is considered to be at least of intermediate risk (Intra-peritoneal, intra-thoracic, head and neck surgery, orthopedic or prostate surgery) **OR**
   as part a cardiology evaluation for symptoms described in a cardiology consult as typical angina, or of significant suspicion for coronary disease or symptoms described as likely of a cardiac/coronary etiology.
3. Patients with a history of LV dysfunction will be still candidates for enrollment in the study if they have documented LVEF recovery (most recent documented LVEF of 50% or higher) for at least 6 months prior to SPECT regardless of current cardiac medication regimen.
4. Age 18 - 80 years.

Exclusion Criteria:

1. Patients consented for the trial that on the baseline 2D study have poor acoustic echo windows (i.e. a reader is unable to see in definition 2 or more segments from the apical views) will not be eligible to continue in the trial and peak hyperemia images will not be obtained.
2. Any patient with tachycardia defined as HR of 100 or higher at the day of SPECT will not be eligible for this study.
3. Second or third degree AV block.
4. Sinus node dysfunction.
5. Patients with allergy to regadenoson.
6. Patients with left bundle branch block (LBBB) and/or artificial pacemaker.

4.0 Research Plan and Methods

Study Outline:
Upon signed informed consent and enrollment, patients will be imaged during regadenoson infusion using the stated imaging protocol. If two contiguous segments in any of the apical views are not visible patients will not be registered in the study and will be entered in CoRE as screen failures due to eligibility criteria.
For ECHO, images will be stored for strain analysis in the ECHO PAC system and will be analyzed by a single blinded investigator (Jose Banchs). All strain will be obtained using the 2D strain analysis pathway. Global longitudinal strain (GLS), 2D LVEF with bi-plane Simpsons method of calculation, end diastolic volume (EDV bi-plane), end systolic volume (ESV bi-plane) and stroke volume (SV) values will be obtained and saved.
SPECT images will be interpreted by a blinded pool of faculty that includes radiologists and cardiologists from the institution. On those patients (Grp 2) who are studied pre-operatively the proposed surgery description and total surgical time will be recorded. Immediate post-op cardiac events (MACE) and 30 day post-operative cardiac events (MACE) will be recorded from inpatient records by chart review or if needed by telephone contact to patients. The post-operative events will be used to report prognostic accuracy of both testing methods and for comparison.
Patients who have coronary angiography or coronary CT angiograms will have the imaging data and test report data saved and stored for the final analysis (Grp 1).
The accuracy of both tests will be compared in those patients with angiogram data (Grp 1).
Study Design: Prospective comparison for demonstration of equivalence. Will attempt to show same specificity and sensitivity with ReSTE compared to SPECT at detecting (segmental/coronary) distribution defects.
Study "treatment":
The only agent will be standard dose regadenoson for nuclear stress test; unchanged from our current protocol: "Regadenoson (5 mL, containing 0.4 mg of regadenoson) should be given as a rapid (approximately 10 seconds) injection into a peripheral vein using a 22 gauge or larger catheter or needle. Administer a 5 mL saline flush immediately after the injection of regadenoson."
Study Population: The study population consists of cancer patients being evaluated with regadenoson nuclear stress tests for evaluation of chest pain or pre-operatively (cancer related surgery). We will concentrate on recruiting patients who are being evaluated pre-operatively for surgery that is considered to be at least of intermediate risk based on the American College of Cardiology Guidelines on Perioperative Cardiovascular Evaluation and Care for Non-

cardiac Surgery (7); since a large number of patients that come for the test in our center are ordered to have perfusion stress test directly from the surgical or the pre-operative assessment clinics.

Planned Study Duration: Approximately 48 months. Given that approximately 900 patients come thru our department per year to get evaluation with SPECT but only approximately 300 will undergo catheterization, final timing depends on recruitment rate and volumes given our inclusion criteria items 2-3.

Imaging Protocol:

All ReSTE studies will be performed on GE systems (VIVID E9). Special attention will be given to avoid foreshortening.

The patients will be positioned on standard L recumbent position.

Transthoracic echocardiography will be performed using the Vivid E9 (GE Healthcare, Milwaukee, Wisconsin).

The same system will be used to acquire all echocardiograms. All echocardiograms will be analyzed in our laboratory. LVEF will be calculated from the apical 4- and 2-chamber views using a modified Simpson's biplane method by single investigator.

To measure myocardial strain, 2-dimensional grayscale images will be obtained in the parasternal short-axis view at the mid-papillary and apical levels; as well as the 3 standard apical views (apical 4-, 3- and 2-chamber views).

The timing of aortic valve closure will be obtained using pulsed-wave Doppler traces in the apical 3 or 5 views (using the more direct angle). Peak systolic radial and circumferential strain will be measured by averaging the peak systolic strain values in all 6 segments of the parasternal short-axis view (EchoPAC; GE Healthcare).

Summary of views: All ReSTE images will be obtained at rest and at peak hyperemia (between 2-4 min period post regadenoson injection).

1. Apical 4 view, at highest possible frame rate (>40fps)
2. Apical 3, at highest possible frame rate (>40fps)
3. Apical 2, at highest possible frame rate (>40fps)
4. Base SAX view, for torsion analysis
5. Apex SAX view (pass the insertion of the papillary muscles), for torsion analysis
6. One full 3D loop, at least 2 beats.
7. All images must be sent to ECHO-PAC system (internal disk).

In light of several publications (8,9) supporting the state of peak hyperemia with regadenoson at the 2-4 min after injection interval, including a study used

for perfusion echocardiography (10), we will obtain these images after the 2nd minute and expect to complete by the 4th minute.
SPECT protocol will be performed as the current MDACC standard.
ReSTE will be performed concomitantly with SPECT as planned by ordering clinician. Therefore the same dose of regadenoson will be in effect used for both tests. We anticipate the potential need for ReSTE re-imaging of approximately 10% of participants to ensure that images are adequate for research quality measurements. In this event, an additional dose of regadenoson will be given after nuclear imaging is complete so that ReSTE peak hypermia images can be redone.

Data management and consent

Consent will be obtained by designated personnel who will be well informed about the purpose of the study and potential risks prior to patient enrollment. Detailed information regarding the purpose of the study and potential risks will be discussed with the patient. An opportunity will be provided to patients to address any questions or concerns related to participation. Patients will be informed that participation is voluntary and consent and participation may be withdrawn at any time. Patients will also be informed that there is no compensation for participation.
Provisions taken to maintain confidentiality of specimens/data:
Unique study numbers will be assigned and all identifiers will be removed. Data will be stored in PDMS to ensure CFR Title 21 Part 11 compliance. Paper records will be kept locked in file cabinet and secured in locked office. Only study collaborators and Cardiology department personnel will have access to the data. Study records and data files will be disposed of in accordance to institutional policies after study is completed.

Security plan for data:

Collection of Identifiers:
Identifiers (name, medical record number) will be collected but will be replaced by study numbers. The key linking these numbers will be retained in a locked file by the investigator designated personnel.

Breaking of Blind:

The PI will remain blinded to the nuclear results obtained during the ReSTE until strain interpretation is completed to prevent bias. Breaking of the blind will not be necessary for safety as no clinical decision making will be based upon the strain results.

Training of personnel: Only MDACC personnel designated by the Principal investigator will have access to study records. These personnel will be fully trained to maintain the patient health information confidentiality.

Data Storage: Patient information and relevant data will be stored on password-protected institution computers behind the institution firewall. Data will not be transferred to laptop computers that are removed from the institution.
Data Sharing: Study data will not be shared with any individuals or entities that are not involved in the study.
Final disposition of study records: These data will be used only for this research study. Study data will be retained by the PI and will be disposed of in accordance to institutional policies after study is completed. No more than 5 years after manuscript publication.
Sample Size: 300 patients.
Criteria for Removal (If indicated): Any time, at patient request.

5.0 Reporting Requirements

Adverse Events
All serious adverse events related to regadenoson will be documented and reported to Astellas Pharm Inc. The use of aminophylline as an antidote will be reserved for severe adverse events experienced due to regadenoson per MDACC protocol.

6.0 Statistical Considerations

Statistical analysis:
Design and sample size/power
This is a 1-arm trial in cancer patients who are considered in the Department of Cardiology for stress testing. The primary objective of the study is to evaluate the ability of ReSTE (novel screening method) to identify patients with ischemia with as much accuracy as the conventional method, SPECT. Due to budgetary and other constraints (see below), the evaluation will be conducted among SPECT positive patients (Grp 1).
A total of 300 eligible patients will be enrolled into this trial. Each patient will undergo both SPECT and ReSTE stress testing for the diagnosis of ischemia. The gold standard test for the diagnosis of ischemia is angiography. However not all of the 300 patients will receive an angiogram due to patient's availability (many patients' primary concerns will be cancer related), current practice

guidelines as well as financial limitations. Currently, only those who are SPECT positive may potentially receive an angiogram. We expect 210 (70%) of the 300 patients will be SPECT positive. Out of those 210 patients, 178 (85%) will actually undergo an angiography (Grp 1).

Since not all of the 300 patients will receive an angiogram, we will not be able to demonstrate directly the non-inferiority of ReSTE with regard to its accuracy of identifying ischemia when compared to SPECT imaging. However if ReSTE is truly as accurate as SPECT in its ability of identifying ischemia, then among those who are SPECT positive and also undergo an angiogram test, we expect minimum discordance between the angiogram and the ReSTE. Therefore, we aim at demonstrating that the angiogram and the ReSTE are equivalent in classifying ischemia among the SPECT positive patients; this corresponds to test if ReSTE is as accurate as SPECT in the diagnosis of ischemia at least among SPECT positive patients. Assuming that the true respective ischemia rates diagnosed by angiogram and ReSTE are P0 and P1, we will perform equivalence test to test the following hypotheses:

$$H0: |P1-P0|>0.05;$$
$$H1: |P1-P0|\leq 0.05;$$

If we observe a 7% discordance rate (equivalent to 12 of the 178 patients) between the angiogram and ReSTE results, and we were to allow a +/-5% tolerance limit, we would have 80% power to declare equivalence using a one-sided paired test of equivalence in proportion (alpha of 0.05), i.e. we will reject the null hypothesis that $|P1-P0| >0.05$ and accept the alternative hypothesis that $|P1-P0| \leq 0.05$. Lower discordance rates would yield higher power, so this estimate of power is rather conservative. The sample size calculation was performed using nQuery Advisor 7.0.

Analysis Plans

Patients' demographic and clinical characteristics will be summarized using descriptive statistics such as mean, standard deviation, median, interquartile range (IQR), frequency where appropriate. We will apply Student t-test/Wilcoxon test and Kruskal-Wallis test/ANOVA to compare continuous variables, and the chi-square test or the Fisher's exact test (14) to compare categorical variables in different patient groups (Grp 1).

As the primary analysis, we will use a paired test of equivalence for proportions proposed by Tango (11) to test the equivalence of the two ischemia tests among the SPECT positive patients.

Among the SPECT positive patients, Standard measures of clinical performance of ReSTE including sensitivity, specificity and positive and negative predictive values (12) will be estimated first. Additionally, the corresponding 2-sided 95% CI of binomial proportion will be calculated. We will use Receiver operating

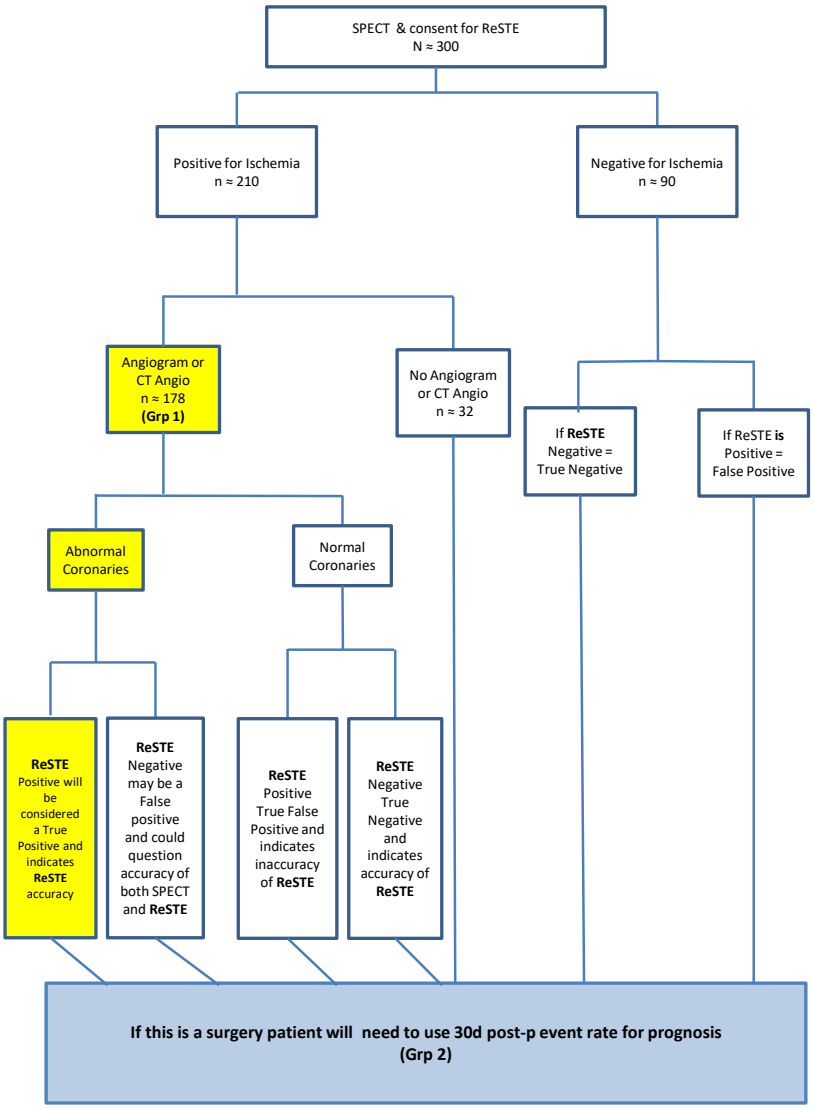
characteristic (ROC) curve analysis (13) to assess the best cut-off for the ReSTE test, and calculate the area under the ROC curve to assess the performance of different cut-offs of ReSTE for the group.
For the secondary endpoints including cardiac event rates at Day 30 post-operation, we will provide estimates along with 95% confidence intervals (Grp 2). Univariate and multivariate logistic regression models will be fit to identify risk factors associated with the Day 30 events. Specifically, we will assess whether or not ReSTE adds predictive information above and beyond SPECT in predicting the Day 30 events. We hypothesize that patients who are positive on both SPECT and ReSTE have the highest Day 30 cardiac complication rates while those who are negative on both tests have the lowest cardiac complication rates. We will test whether the difference in statistical predictive accuracy between different logistic regression models (with or without ReSTE in the models) is significant (14). The predictive accuracy of the various logistic regression models will be quantified by C statistic, which provides the area under the receiver operating characteristics curve (13,14). To protect against over-fitting in the stepwise regression, we will use a bootstrap procedure to obtain an unbiased estimate of the C-index. These analyses will be performed using all patients for whom we have available data.

7.0 Study Timeline

Our numbers are estimated based on the actual cardiac catheterizations performed in our lab. The cardiac catheterization lab opened in November 2009. It is the only full service cath lab in any cancer center. There were 250 angiograms performed in the first 12 months and the annual number has continued to increase annually. The percentage of angiograms performed in our cancer population is different than the population in any general cardiac center since our patients often find themselves in the position of needing a complete cardiac evaluation in order to proceed with anti-cancer therapies.
Final disposition of the data: in accordance to MD Anderson institutional policies after the study is completed.

8.0 Figures

Figure 1. ReSTE = Regadenoson Speckle tracking Echocardiogram. Yellow fill is Group 1, Blue is 2



9.0 References

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