Effect of caffeine on SPECT myocardial perfusion imaging during regadenoson pharmacologic stress: Rationale and design of a prospective, randomized, multicenter study

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Background. **Caffeine attenuates the coronary hyperemic response to adenosine by competitive A_{2A} receptor blockade. This study aims to determine whether oral caffeine administration compromises diagnostic accuracy in patients undergoing vasodilator stress myocardial perfusion imaging (MPI) with regadenoson, a selective adenosine A_{2A} agonist.**

Methods. **This multicenter, randomized, double-blind, placebo-controlled, parallel-group study includes patients with suspected coronary artery disease who regularly consume caffeine. Each participant undergoes three SPECT MPI studies: a rest study on day 1 (MPI-1); a regadenoson stress study on day 3 (MPI-2), and a regadenoson stress study on day 5 with double-blind administration of oral caffeine 200 or 400 mg or placebo capsules (MPI-3; n = 90 per arm). Only participants with ≥1 reversible defect on the second MPI study undergo the subsequent stress MPI test. The primary endpoint is the difference in the number of reversible defects on the two stress tests using a 17-segment model. Pharmacokinetic/pharmacodynamic analyses will evaluate the effect of caffeine on the regadenoson exposure-response relationship. Safety will also be assessed.**

Conclusion. **The results of this study will show whether the consumption of caffeine equivalent to 2-4 cups of coffee prior to an MPI study with regadenoson affects the diagnostic validity of stress testing (ClinicalTrials.gov number, NCT00826280). (J Nucl Cardiol 2011;18:73–81.)**

Key Words: Regadenoson • pharmacologic stress • caffeine • myocardial perfusion imaging • A_{2A} adenosine receptor agonists

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INTRODUCTION

The role of myocardial perfusion imaging (MPI) in the diagnosis and management of patients with known or suspected coronary artery disease (CAD) is well established.[1] Dynamic exercise is the technique of choice for achieving coronary hyperemia in patients who can achieve adequate exercise endpoints.[2-5] In individuals who have exercise limitations, left bundle branch block on baseline electrocardiogram (ECG), or a ventricular paced rhythm, vasodilator imaging (using dipyridamole, adenosine, or regadenoson in the United States) is an established alternative to dynamic exercise.[4,6-9] Patients who cannot exercise to the target workload due to a lack of motivation or the effects of concomitant medications also add to the numbers undergoing pharmacologic stress studies. A substantial growth has been observed in the use of pharmacologic stress testing over recent

years.[10] This may be partly explained by the aging of the population and increase in prevalence of physical limitations in the population undergoing stress tests.[2,4]

Caffeine, a widely used stimulant, is similar in structure to adenosine and is a nonselective competitive inhibitor of all adenosine receptor subtypes.[11,12] This includes A_{2A} receptors, which mediate coronary vasodilation.[13,14] Prior studies show that caffeine intake blunts the coronary hyperemic effect of dipyridamole and may mask the appearance of perfusion abnormalities during dipyridamole stress MPI.[15-18] This effect of caffeine appears to be dose-related[19] and can be overcome by higher interstitial levels of adenosine than those produced by dipyridamole infusion. The interaction between caffeine and adenosine appears less clear.[20] For example, in a study of patients with CAD, the fractional flow reserve (a measure of the physiologic significance of coronary stenosis obtained with intracoronary injection of adenosine) was similar before and after infusion of 4 mg/kg of intravenous (IV) caffeine.[21] In a subsequent evaluation, ingestion of an 8-ounce cup of coffee 1 hour before adenosine MPI did not affect the imaging results (both total and reversible abnormalities, measured using automated quantitative methods).[22] In contrast, caffeine decreased the ischemic size of the perfusion defect when used with standard dose adenosine (140 mcg/kg/min), but not a 50% higher dose (210 mcg/kg/min, although this dose is not approved in the United States).[23]

Because of concerns that caffeine may interfere with the coronary hyperemia produced by pharmacologic stress agents, the current guidelines of the American Society of Nuclear Cardiology[2] and those of the Society of Nuclear Medicine[3] state that caffeine or other methylxanthine-containing compounds should be withheld for at least 12 hours before vasodilator stress MPI. Caffeine consumption prior to the scheduled imaging test may result in test cancellation or rescheduling, which reduces laboratory efficiency and delays diagnosis. Alternatively, dobutamine may be used as a substitute pharmacologic stress agent.[24] Dobutamine is not, however, an agent of choice for stress MPI. Moreover, if a patient forgets or denies that they have consumed caffeine, a false-negative stress test result may occur[17,18] and a correct diagnosis of cardiac ischemia can be missed. A recent study indicated that approximately 19% of subjects who indicated no caffeine consumption within the previous 24 hours, as recorded on questionnaires administered prior to a dipyridamole MPI, had quantifiable serum caffeine levels.[25]

Regadenoson is a selective, low-affinity human A_{2A} receptor agonist,[26-30] which provides good-quality images yielding accurate diagnostic information.[31,32] It is the first A_{2A} receptor agonist to be approved as a pharmacologic stress agent for use with radionuclide MPI.[33]

Previous preliminary investigations suggest that there is a limited interaction between regadenoson and caffeine, such that prior caffeine intake may not limit the clinical use of regadenoson. Caffeine (1-10 mg/kg, IV) did not significantly alter the regadenoson-induced increase in peak myocardial blood flow in conscious dogs, even at a caffeine plasma concentration of 52 μM.[34] However, caffeine shortened the duration of the pharmacodynamic (PD) effect and blunted the effects on heart rate (HR) and blood pressure (BP). A double-blind, randomized, placebo-controlled, crossover pilot study showed that moderate oral caffeine intake (200-mg capsule) did not significantly affect regadenoson-induced coronary vasodilation in healthy individuals.[35] Moreover, caffeine ingestion alleviated the severity of side-effects (notably headache) and improved tolerability (as assessed by patient questionnaires). The presence or the absence of a caffeine-regadenoson interaction and the potential implications for the efficacy of vasodilator stress testing with regadenoson is now being evaluated in a large multicenter study. This article describes the objectives and design of this study.

STUDY OBJECTIVES

The primary objective of this study is to determine whether oral administration of caffeine 200 or 400 mg will adversely compromise diagnostic accuracy of detecting reversible perfusion defects in patients with suspected or known CAD undergoing single photon emission computed tomography (SPECT) MPI with regadenoson.

The secondary objectives are as follows: (1) to evaluate the exposure-response relationship between regadenoson exposure and the PD effect, including HR, systolic BP, and diastolic BP; (2) to evaluate the effect of caffeine and its metabolites, paraxanthine, and theobromine, on the regadenoson exposure-response relationship; and (3) to assess the safety of concomitant caffeine and regadenoson administration in this population.

METHODS

Participants

Participants in this study are men and women, ≥18 years of age, with a medical history suggesting an intermediate-to-high likelihood of CAD (based on clinical tools including the Diamond and Forrester categorization[36]) and who consume caffeine regularly. Table 1 provides further details of inclusion and exclusion criteria. Of note, smokers are excluded from the

Table 1. Key selection criteria

Inclusion criteria
Men and women with a known likelihood of CAD with any of the following
A previous diagnostic study (e.g., SPECT, echocardiography, magnetic resonance imaging, etc) demonstrating evidence of reversible defects in ≥1 vascular segment (or ≥2 defects if 1 of the defects is in segment 17)
Other stress testing within the past 3 months
A medical history suggesting a ≥50% likelihood of CAD (as determined by the investigator using the Diamond & Forrester categorization[36])*
Age ≥18 years
Stable symptoms and an intermediate/low risk for immediate intervention
Consumes caffeine regularly (≥1 cup of caffeinated coffee per day, or equivalent)
Exclusion criteria
Myocardial infarction ≤30 days prior to enrollment
Percutaneous coronary intervention ≤4 weeks prior to enrollment
Coronary artery bypass graft ≤8 weeks prior to enrollment
Heart transplantation
Unstable angina, known severe left main coronary artery stenosis, severe heart failure, uncontrolled arrhythmias, symptomatic hypotension or severe hypertension (systolic blood pressure <90 or >200 mm Hg, respectively), or >1st degree atrioventricular block in the absence of a functioning pacemaker
Requires emergency cardiac medical intervention or catheterization
Smoking or using any smoking cessation products ≤3 months prior to the first dose of regadenoson
Allergic or intolerant to aminophylline, regadenoson, and/or caffeine
Current participant in another drug/device study, received an investigational drug (or non-active drug) ≤30 days prior to screening, or previous participant in a regadenoson clinical trial
Treatment with theophylline, or theophylline-containing medications, ≤7 days before randomization
History of known or suspected bronchoconstrictive or bronchospastic lung disease
Pregnant or breastfeeding
History of diabetes associated with gastric disorders and/or emptying (which might affect the absorption of caffeine)
End stage renal disease with a glomerular filtration rate <15 mL/min or currently undergoing dialysis

CAD, Coronary artery disease; *SPECT*, single-photon emission computed tomography.
* Diamond and Forrester provide estimates for the pretest likelihood of CAD according to the following age groups: 30-39, 40-49, 50-59, and 60-69 years. For the current study, subjects under 30 years of age were assessed according to probabilities for the 30-39-year age group, and subjects over 69 years were assessed according to probabilities for the 60-69-year age group.

study. Smoking induces cytochrome P450 1A2 (CYP1A2), the main enzyme involved in caffeine metabolism.[37,38] As a result, caffeine is metabolized more rapidly in smokers, with an increase in clearance of 56%.[39] Thus, a smoking caffeine drinker might be less likely to display any caffeine-regadenoson interaction, if one is present, due to faster caffeine clearance.

Participants are discontinued from the study if they experience a serious or intolerable adverse event; if, in the investigator's opinion, they are noncompliant with the protocol requirements (i.e., there is a protocol violation); if their health would be jeopardized by continuation; or if they withdraw consent.

Study Design

This is a Phase 3b, multicenter (24 centers in the United States), randomized, double-blind, placebo-controlled, parallel-group study (ClinicalTrials.gov number, NCT00826280). The first participant was enrolled in March 2009, and the study was completed in July 2010.

The study is conducted in compliance with the principles of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice. The Institutional Review Board/Independent Ethics Committee of each study center approved the protocol, and written informed consent is obtained from each participant prior to any study-related procedures.

Study Protocol

A flow chart of the study protocol is shown in Figure 1 and the schedule of assessments in Table 2. Each participant is scheduled to have three serial sets of images using gated SPECT, as follows:

(1) MPI-1 is a rest study conducted on day 1.
(2) MPI-2 is an open-label regadenoson stress SPECT MPI conducted on day 3. Participants with ≥1 reversible defect

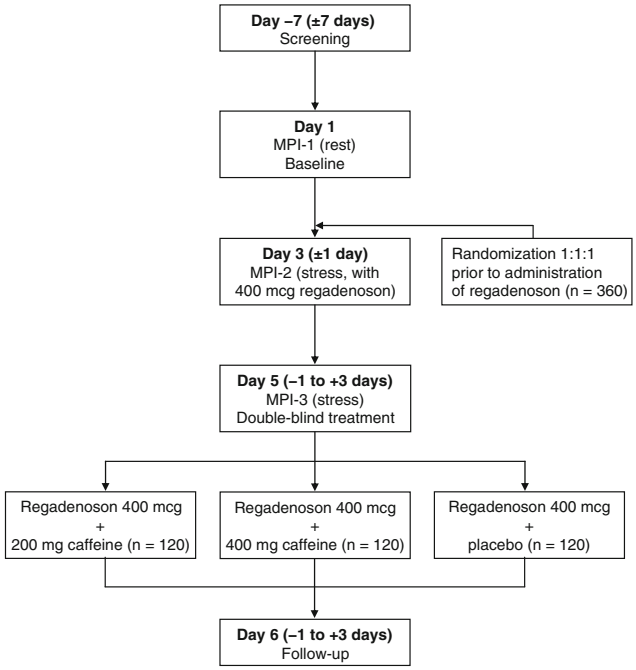

Figure 1. Flow chart of study procedures.

Table 2. Schedule of dosing, pharmacokinetic/pharmacodynamic sampling, and myocardial perfusion imaging

Sample timing (minutes) Window (minutes)	−90 ±5	−60 ±5	−3 ±2	0	3 +2	15 ±5	30 ±5	60 +30	120 ±10	180 ±10
MPI-1 (day 1)										
Radiotracer administration				X						
Heart rate and blood pressure			X		X	X	X	X		
Resting scan								X		
MPI-2 (day 3)										
Radiotracer administration				X						
Heart rate and blood pressure			X		X	X	X	X		
Caffeine/paraxanthine/theobromine PK blood collection			X							
Regadenoson administration				X						
Stress scan								X		
MPI-3 (day 5)										
Radiotracer administration				X						
Heart rate and blood pressure	X	X	X		X	X	X	X	X	X
Caffeine/paraxanthine/theobromine PK blood collection	X*	X	X		X		X	X	X	X
Caffeine/placebo oral administration	X									
Regadenoson administration				X						
Regadenoson PK blood collection					X		X	X	X	
Stress scan								X		

* Blood sample obtained prior to caffeine or placebo administration.
PK, Pharmacokinetic.

continue into the double-blind period; however, if only 1 reversible defect exists and the defect is in the apex (segment 17), then another reversible defect (including a mild defect) must be present for the participant to continue to MPI-3.

(3) MPI-3 is a regadenoson stress SPECT MPI conducted on day 5. It is carried out after a 4-hour fast with blinded administration of oral caffeine 200 or 400 mg or placebo capsules with water. MPI-3 is conducted with open-label regadenoson 90 minutes after caffeine or placebo intake.

Double-blind randomization is conducted on day 3, prior to the administration of regadenoson in MPI-2. Participants are randomized (1:1:1) according to an online computer-generated randomization schedule into low-dose caffeine (200 mg), high-dose caffeine (400 mg), or placebo arms (~ 90 participants per arm). Consumption of caffeinated products is prohibited within 24 hours of each clinic visit. Safety data are collected on days 3 and 5, and over the follow-up period on day 6 (i.e., at least 24 hours after the last SPECT MPI procedure).

Caffeine Dosing

The amount of caffeine in a regular cup of coffee varies considerably.[40-42] Therefore, oral caffeine capsules were used in this study to standardize the doses among centers, and because some individuals may not tolerate multiple cups of coffee on an empty stomach. The effects of two doses of caffeine were evaluated, 200 and 400 mg, to assess whether there is a dose-response effect of caffeine on the number of reversible defects detected using pharmacologic stress with regadenoson. These doses were selected based on the following findings. A 200-mg caffeine dose did not significantly increase the incidence of adverse events compared with regadenoson alone in the study by Gaemperli et al[35] and additional risks were not anticipated with a 2-fold higher dose of 400 mg. In addition, IV administration of caffeine at 5 mg/kg[43] or 4 mg/kg[21] (levels similar to those expected in this study) to healthy volunteers and individuals with CAD were not associated with an increase in side-effects or any clinically relevant differences in hemodynamic parameters. A 200-mg dose of caffeine is deemed equivalent to two cups of coffee.[44] The 400-mg caffeine dose results can be used to describe a ''worst case scenario.''

Gated SPECT Imaging Procedures

All SPECT MPI procedures are performed according to American Society of Nuclear Cardiology guidelines.[2] Rest SPECT MPI (MPI-1) is performed 60-90 minutes after the administration of technetium-99m sestamibi or tetrofosmin. Regadenoson stress SPECT MPI (MPI-2 and MPI-3) is performed with 400-mcg regadenoson, given as an IV bolus dose into a peripheral vein over approximately 10 seconds, followed by a saline flush. Technetium-99m sestamibi or tetrofosmin is administered 10-20 seconds after the saline flush. Gated SPECT MPI is conducted 60-90 minutes after radiotracer administration. The same radiotracer is used in all three MPI studies for each participant.

SPECT Image Analysis

A 17-segment model is used to count the number of segments with reversible defects.[45] Segments are considered to have a reversible defect if the stress perfusion score is greater than the rest score and the stress score is $\geq$2. Scores are based on tracer activity in each segment on a 5-point scale for radiotracer uptake: 0 = normal uptake, 1 = slightly reduced uptake, 2 = moderately reduced uptake, 3 = severely reduced uptake, and 4 = absent uptake. The following variables are calculated: the summed stress score (SSS; the sum of the stress scores across the 17 segments), the summed rest score (SRS; the sum of the rest scores across the 17 segments), and the summed difference score (SDS; the difference between the SSS and SRS).

MPI-1 and MPI-2 images are read locally at each site to determine eligibility to continue to MPI-3. The final reading of all MPI images for those subjects completing MPI-3 is conducted separately by three independent blinded readers at the central core imaging laboratory. The core laboratory interpretation has no bearing on whether the subject continues to MPI-3 or not. However, for final data analysis purposes, the core laboratory overreads the initial rest/stress study (MPI-2). If there is discordance between the local and the core laboratory interpretations, deference will be to the core laboratory interpretation.

The primary variable of interest is the change in the number of reversible defects using regadenoson with caffeine or placebo (MPI-3) minus the number of reversible defects using regadenoson alone (MPI-2). The secondary variables are the change in SDS (SDS using regadenoson with caffeine or placebo [MPI-3] minus SDS using regadenoson alone [MPI-2]) and the change in perfusion abnormality assessed using a quantitative program incorporated within the Corridor4DM (INVIA, Ann Arbor, Michigan) software platform[46] for total and reversible abnormality.

Pharmacokinetic/Pharmacodynamic Assessments

Serial blood samples are collected to determine plasma levels of caffeine, its two major metabolites (paraxanthine and theobromine), and regadenoson using validated bioanalytical methods for noncompartmental pharmacokinetic (PK) analysis, as appropriate, and subsequent population-based PK/PD modeling (Table 2). The primary non-compartmental PK parameters for regadenoson and caffeine include maximum plasma concentration (C_{max}) and area under the concentration-time curve from time 0 (for caffeine and regadenoson administration, respectively) as well as clearance, volume of distribution, elimination half-life, and paraxanthine/theobromine-caffeine ratio, as appropriate. The primary assessment is the maximal caffeine concentration obtained within 3 minutes of regadenoson administration and the impact it has on the

diagnostic accuracy in patients undergoing vasodilator stress MPI with regadenoson.

Supine HR, systolic BP, and diastolic BP are obtained according to the schedule in Table 2. These data will be used in a population PK/PD analysis to explore the regadenoson exposure-response relationship. The effect of caffeine, paraxanthine, and theobromine, on the regadenoson exposure-response relationship will also be explored.

Safety Assessments

Safety assessments include vital signs, adverse events (nature, severity, causal relationship to study drug, outcome, and serious adverse events), standard laboratory assessments, blood cardiac markers (creatinine phosphokinase-MB fraction and troponin T), and 12-lead ECGs.

Statistical Analyses

The target is to randomize approximately 360 individuals. A 40% attrition rate is expected such that approximately 200 participants are anticipated to complete the study. The sample size is based on previous Phase 3 trials with regadenoson in which a standard deviation of 1.59 for the change in number of reversible defects from repeated scans was observed. An analysis of variance (ANCOVA) and Fisher's least significant difference with a type 1 error rate of 5% will be used to test for at least one significantly different mean change in the number of reversible defects among the arms. If 200 subjects are randomized 1:1:1 and have a similar standard deviation to that observed in the Phase 3 trials, and placebo has a mean effect of 0 on the change in number of reversible defects, this test will be able to detect a change of ±1 reversible defects relative to placebo with 95% power.

The data sets will include all randomized participants with interpretable MPI-1, MPI-2, and MPI-3 scans (full analysis set) and a subset of the full analysis set with no major protocol deviations (per protocol set). All randomized participants who receive at least one dose of regadenoson will be included in the safety analysis, and all participants who provide adequate PK samples will be included in the PK analysis.

Demographic and other baseline characteristics will be analyzed using a one-way analysis of variance to compare the means of continuous variables among treatment groups and a chi-square test will be used to compare discrete variables.

For the primary endpoint (the change in number of reversible defects, as assessed by the central imaging laboratory, between MPI-2 and MPI-3), an ANCOVA with treatment arm as a factor and the number of reversible defects at the initial stress scan (MPI-2) as a covariate will be used (full analysis set). The Fisher's least square difference will be applied to test for an overall treatment arm effect with a type 1 error rate of 5%. Pairwise comparisons will be used to assess which treatment arm(s) is/are statistically different if the overall test for treatment arm effect is significant.

For a secondary analysis, the primary analysis will be repeated using only subjects having $\geq$1 reversible defect(s), except if the only defect present is in segment 17 (apex), at MPI-2. If the reversible defect is located in segment 17, at least one other reversible defect must be evident. The primary analysis will also be repeated using the per protocol and safety analysis sets.

Participants with missing data for the number of reversible defects at MPI-3 will have the score imputed as 0 (i.e., complete blunting of the double-blind MPI). Those missing data for the number of reversible defects at MPI-2 will have the score imputed to the number of reversible defects at MPI-3 (i.e., no change in number of reversible defects). Participants with missing data for the number of reversible defects at MPI-2 and MPI-3 will have both scores imputed to 0. The change in SDS and perfusion abnormality assessed by automated quantitation will be analyzed using the same methods as the primary analysis with the corresponding variable at the initial stress scan used as a covariate.

The PK analysis set will include all subjects who provide adequate PK samples to calculate the primary PK parameters. The preliminary PK analyses will be performed by model-independent, non-compartmental methods using WinNonlin® version 5.3 (Pharsight, Mountain View, CA). Descriptive statistics including the number of subjects, mean, standard deviation, minimum, median, and maximum caffeine concentration values obtained immediately before regadenoson dosing will be presented.

DISCUSSION

This is the largest and only multicenter study examining the interaction between caffeine and a pharmacologic cardiac stress agent. Specifically, it will evaluate whether caffeine interferes with regadenoson-induced coronary hyperemia and the ability of MPI to detect ischemia. The participants selected for the study are those who are likely to demonstrate myocardial ischemia, but are not sick enough to warrant coronary interventions before the completion of all three imaging studies. The primary objective was prespecified as the change in the number of reversible defects and not just any defect.

Inter-individual differences in caffeine metabolism[47,48] may lead to variations in plasma caffeine concentrations, which may, in turn, produce variations in its physiologic effects. Thus, plasma levels of caffeine and its metabolites are being measured in this study and a population PK/PD approach is being employed to assess the effect of caffeine and its metabolites on the regadenoson exposure-response relationship.

This study uses serial SPECT imaging to assess whether the ingestion of caffeine prior to a regadenoson stress MPI study affects the diagnostic accuracy of the test. Although the reproducibility of serial regadenoson SPECT studies has not been specifically evaluated, a quantitative analysis of sequential adenosine and regadenoson SPECT studies showed excellent agreement between the two image sets.[49] Furthermore, several

elements of the study design aim to limit variability associated with serial imaging. Inherent patient variability is minimized by enrolling only patients with stable symptoms who are at intermediate/low risk of requiring immediate intervention. In addition, the two regadenoson stress tests are conducted within a short time frame (MPI-2 on day 3; MPI-3 on day 5), during which no changes in concomitant medications are allowed and changes in clinical status are unlikely. Variability in study acquisition variables is minimized using the same radiopharmaceutical for all three MPI studies and by standardizing the timings of regadenoson and radiotracer administration and image acquisition. Finally, interpreter variability in visual assessment of serial perfusion scans is limited by using three independent expert readers at a central core imaging laboratory, and quantitation of MPI scans using a computerized software package will provide an objective analysis of the serial images.

Several potential methodological limitations need to be kept in mind when evaluating the general applicability of the results of this study. First, this study is not powered to detect an average difference of <1 reversible defect and, therefore, a smaller effect might be undetected. Second, since measurements of caffeine plasma concentrations are not available to the investigator immediately, a greater number of the study participants than anticipated might have consumed caffeinated beverages during the preceding 12 hours, thereby limiting the statistical power of the study. Third, since the study is being performed in regular caffeine consumers, it is possible that caffeine may have different effects on the vasodilatory action of regadenoson in patients who consume caffeine less frequently. Fourth, the study is being performed in a North American population, which may limit the applicability of the results to other populations. Finally, although the administration of placebo/caffeine is blinded, the side effects of caffeine could potentially be apparent to site personnel. They are, however, blinded to the dose of caffeine (200 or 400 mg), and the readers at the central core imaging laboratory will be unaware of side-effects witnessed at the local site.

Inadvertent caffeine consumption, leading to cancellation, or rescheduling of a pharmacologic stress MPI study or use of dobutamine, is a very common problem in nuclear cardiology laboratories today. If the results of this well-controlled study show that the consumption of caffeine equivalent to 2-4 cups of coffee prior to an MPI study with regadenoson does not affect SPECT image quality or the diagnostic validity of stress testing, utilization of regadenoson as the pharmacologic stress agent may lead to fewer rescheduled or cancelled MPI studies. In turn, this may reduce overall costs, decrease throughput time, and potentially reduce false-negative SPECT MPI scans. It may also decrease the time to diagnosis of the subject's underlying disease at a time when critical decisions need to be made with regard to appropriate treatment and intervention.

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