ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers

Milena J. Henzlova, MD,[a] W. Lane Duvall, MD,[b] Andrew J. Einstein, MD,[c] Mark I. Travin, MD,[d] and Hein J. Verberne, MD[e]

[a] Mount Sinai Medical Center, New York, NY
[b] Hartford Hospital, Hartford, CT
[c] New York Presbyterian Hospital, Columbia University Medical Center, New York, NY
[d] Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY
[e] Academic Medical Center, Amsterdam, The Netherlands

doi:10.1007/s12350-015-0387-x

Abbreviations

A_{2A}	Adenosine 2a
AHA	American Heart Association
ALARA	As low as reasonably achievable
AV	Atrioventricular
BP	Blood pressure
CBF	Coronary blood flow
CAD	Coronary artery disease
CPET	Cardiopulmonary exercise testing
DSP	Deconvolution of septal penetration
ECG	Electrocardiogram
EF	Ejection fraction
ESRD	End-stage renal disease
HF	Heart failure
HFrEF	Heart failure (with) reduced ejection fraction
HMR	Heart-to-mediastinum ratio
ICD	Implantable cardioversion defibrillator
IV	Intravenous
LBBB	Left bundle branch block
LEHR	Low energy high resolution
LVEF	Left ventricular ejection fraction
MBq	Megabecquerels
mCi	Millicuries
MPI	Myocardial perfusion imaging
MRI	Magnetic resonance imaging
mSv	Millisievert
NE	Norepinephrine
NET1	Norepinephrine transporter-1
NPO	Nil per os (nothing by mouth)
NYHA	New York Heart Association
PET	Positron emission tomography
ROI	Region of interest
SPECT	Single-photon emission computed tomography
TAVR	Transcatheter aortic valve replacement
WR	Washout rate
WPW	Wolff-Parkinson White

EXERCISE STRESS TEST

Exercise testing has been used for more than 60 years for diagnostic purposes in symptomatic patients [including patients with acute chest pain without ischemia by electrocardiogram (ECG) and serum markers] and for prognosis and risk stratification in patients with known coronary artery disease (CAD), such as history of myocardial infarction or documented CAD by coronary angiography or computed tomography angiography and in those with high risk for the presence of CAD, such as patients with diabetes mellitus, peripheral, or cerebral vascular disease.

Reprint requests: Milena J. Henzlova, MD, Mount Sinai Medical Center, New York, NY; Milena.Henzlova@mssm.edu
J Nucl Cardiol
1071-3581/$34.00

Published online: 25 February 2016

Exercise Modalities

(1) Exercise using a treadmill is done according to the standardized protocols (most often the Bruce or modified Bruce protocol) with incremental treadmill speed and incline (Tables 1, 2).
(2) Exercise using an upright or recumbent bicycle uses standard speed with incremental resistance.

Exercise Testing

Detailed recommendations for exercise testing performance including (1) testing environment, (2) equipment [treadmill, bicycle, ECG monitoring, blood pressure (BP) monitoring], (3) emergency preparation and protocols, (4) patient preparation (including informed consent), (5) test performance, and (6) personnel qualifications are described in detail in the 2009 Recommendations for clinical exercise laboratories: a scientific statement from the American Heart Association (AHA).[1]

Performance of exercise testing describing normal and abnormal response to exercise, evaluation of the test results are described in detail in 2013 Exercise Standards for Testing and Training: a scientific statement from the American Heart Association.[2]

Recommendations for performance of exercise testing by nonphysicians (clinical exercise physiologists, registered nurses, nurse practitioners, physician assistants, and physical therapists) as well as the role of supervising physician have been published recently.[3]

Recommendations for testing specific populations [women, older adults, asymptomatic patients, prior to noncardiac surgery and exercise testing combined with cardiopulmonary exercise testing (CPET)] can be found in the following documents:

(1) Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the AHA;[4]
(2) 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines;[5]
(3) Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the AHA.[6]

Table 1. Bruce protocol

Stage	Mins.	Speed, mph	Grade, %
1	3	1.7	10
2	6	2.5	12
3	9	3.4	14
4	12	4.2	16
5	15	5.0	18
6	18	5.5	20
7	21	6.0	22

Absolute Contraindications

Absolute contraindications for exercise stress testing include the following:

(1) High-risk unstable angina. However, patients with chest pain syndromes at presentation who are stable and without ECG evidence of ischemia and without serum biomarker evidence of myocardial injury can undergo exercise stress testing.
(2) Decompensated or inadequately controlled congestive heart failure (HF).
(3) Systolic BP at rest $\geq$200 mmHg or diastolic BP at rest $\geq$110 mmHg.
(4) Uncontrolled cardiac arrhythmias (causing symptoms or hemodynamic compromise).
(5) Severe symptomatic aortic stenosis.[7]
(6) Acute pulmonary embolism.
(7) Acute myocarditis or pericarditis.
(8) Acute aortic dissection.
(9) Severe pulmonary hypertension.
(10) Acute myocardial infarction (less than 2 to 4 days), if clinically stable.
(11) Acute symptomatic medical illness.

Relative Contraindications

Relative contraindications for exercise stress testing include the following:

1. Known significant left main coronary artery stenosis.
2. Asymptomatic severe aortic stenosis.[7]

Table 2. Modified Bruce Protocol

Stage	Mins.	Speed, mph	Grade, %
0	3	1.7	0
1/2	6	1.7	5
1	9	1.7	10
2	12	2.5	12
3	15	3.4	14
4	18	4.2	16
5	21	5.0	18
6	24	5.5	20
7	27	6.0	22

3. Hypertrophic obstructive cardiomyopathy or other forms of severe left ventricular outflow tract obstruction.
4. Significant tachyarrhythmias or bradyarrhythmias.
5. High-degree atrioventricular (AV) block. Electrolyte
6. abnormalities.
7. Mental or physical impairment leading to inability to exercise adequately.
8. If combined with imaging, patients with complete left bundle branch block (LBBB), permanent pacemakers, and ventricular pre-excitation [Wolff-Parkinson-White (WPW) syndrome] should preferentially undergo pharmacologic vasodilator stress test (not a dobutamine stress test).

Limitations

Exercise stress testing has a lower diagnostic value in patients who cannot achieve an adequate heart rate and BP response due to a noncardiac physical limitation, such as pulmonary, peripheral vascular or musculoskeletal abnormalities, or due to lack of motivation. These patients should be considered for pharmacologic stress testing with myocardial perfusion imaging. Also, for a meaningful test evaluation, exercise should last at least 4 to 6 minutes.

Procedure

(1) Patient preparation: nothing should be eaten at least 3 hours before the test. Patients scheduled for later in the morning or afternoon may have a light breakfast (e.g., cereal, fruit). Caffeine should be avoided for at least 12 hours similar to vasodilatory stress testing because exercise stress tests, at times, need to be converted to a pharmacologic stress test. If possible, insulin-dependent diabetics should be scheduled for the morning hours.

(2) BP medication(s) with antianginal properties (β-blocker, calcium channel blocker, and nitrates) will lower a stress test's diagnostic utility.[8] Generally, discontinuation of these medicines is left to the discretion of the referring physician. Regularly taken medication should be recorded prior to testing.

(3) An intravenous (IV) cannula (larger size than 24-gauge is preferred) should be inserted for radiopharmaceutical injection.

(4) The electrocardiogram should be monitored continuously during the exercise test and for at least 4 minutes into the recovery phase. In addition, the resting heart rate should return to close to baseline and exercise-induced ST-segment changes and symptoms should resolve. A 12-lead electrocardiogram should be (automatically) obtained at every stage of exercise, at peak exercise, and at the termination of recovery phase. In addition, in case of abnormalities (e.g., arrhythmias, etc.) a 12-lead electrocardiogram should be obtained.

(5) The heart rate and BP should be recorded at least every 3 minutes during exercise, at peak exercise, and for at least 4 minutes into the recovery phase.

(6) The end point of all exercise tests should be symptoms (moderate to severe chest pain, excessive shortness of breath, fatigue). Achievement of 85% of maximum, age-adjusted, predicted heart rate is not an indication for termination of the test. Note: In patients with known CAD (and particularly if tested taking regular medication), the prognostic value of the test is preserved without reaching 85% of maximum predicted heart rate.

(7) The radiopharmaceutical should be injected as close to peak exercise as possible. Patients should be encouraged to exercise for at least 1 minute after the radiotracer injection. If needed, treadmill speed and/or inclination can be decreased after tracer injection.

(8) Patients referred for a diagnostic stress test may be converted to a pharmacologic stress test or a combination of both if they cannot exercise adequately for a meaningful period of time.

Indications for Early Termination of Exercise

Indications for early termination of exercise include the following:

(1) Moderate to severe angina pectoris.
(2) Marked dyspnea.
(3) Fatigue.
(4) Ataxia, dizziness, or near-syncope.
(5) Signs of poor perfusion (cyanosis and pallor).
(6) Patient's request to terminate the test.
(7) Excessive ST-segment depression (≥2 mm from baseline).
(8) ST elevation (≥1 mm) in leads without diagnostic
(9) Sustained supraventricular or ventricular tachycardia.
(10) Development of LBBB or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia.
(11) Drop in systolic BP of greater than 10 mmHg from baseline, despite an increase in workload, when accompanied by other evidence of ischemia.
(12) Hypertensive response (systolic BP ≥230 mmHg and/or diastolic pressure ≥115 mmHg).

(13) Inability to monitor the electrocardiogram or systolic BP.
(14) In patients with implantable cardioverter defibrillators, when the heart rate attained is within 20 beats per minute of the lowest heart rate at which therapy (antitachycardia pacing or shock) is programmed to be delivered.

Achievement of 85% of maximum, age-adjusted, predicted heart rate is not an indication for early termination of the stress test.

For review of serious complications of myocardial stress testing and their management, refer to the article by Dilsizian and colleagues.[9]

PHARMACOLOGIC VASODILATOR STRESS

There are currently three coronary vasodilator agents available: dipyridamole, adenosine, and regadenoson. Adenosine and its analog regadenoson work by producing stimulation of A_{2A} receptors. Dipyridamole inhibits the phosphodiesterase enzymes that break down cAMP and inhibits the cellular reuptake of endogenous adenosine, thereby indirectly acting as an adenosine agonist. Methylxanthines (e.g., caffeine, theophylline, and theobromine) are competitive inhibitors of adenosine receptors that require withholding methylxanthines prior to testing and permit the reversal of the effect with aminophylline or caffeine when clinically indicated (Figure 1). Aminophylline should be on hand during testing for reversal of serious side effects of vasodilator stressors.

NOTE: Some of the pharmacologic stress protocols described in this section fall outside of manufacturer package insert guidelines but have been documented in the literature and are now commonly used in the clinical practice of nuclear cardiology. The practitioner should be familiar with the package insert

Adenosine

Mechanism of action. Adenosine induces direct coronary arteriolar vasodilation through specific activation of the A_{2A} receptor (Figure 1). This results in a 3.5- to 4-fold increase in myocardial blood flow. Activation of A_1, A_{2B}, and A_3 receptors may cause undesirable side effects of adenosine infusion: AV block (A_1 receptor), peripheral vasodilation (A_{2B} receptor), and bronchospasm (A_{2B} and A_3 receptors). Peak

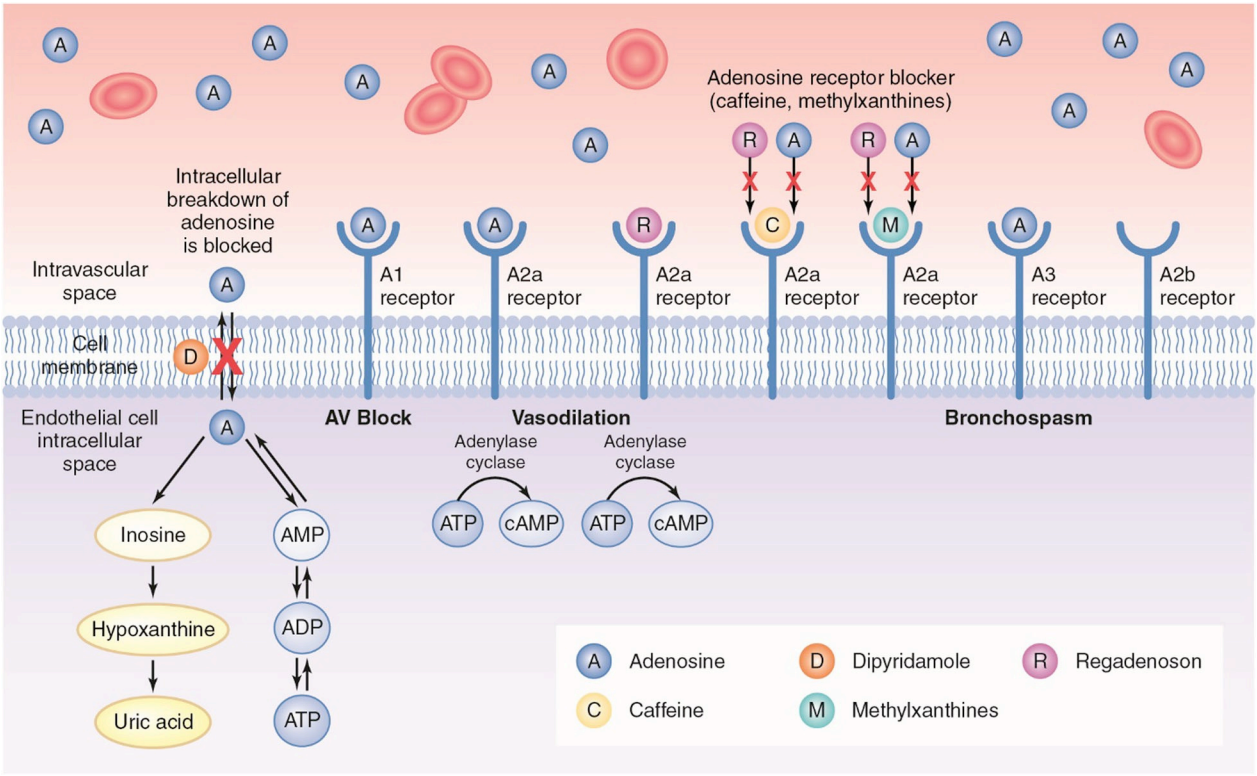

Figure 1. Mechanism of action of coronary vasodilators. *ADP,* Adenosine diphosphate; *AMP,* adenosine monophosphate; *ATP,* adenosine triphosphate; *AV,* atrioventricular; and *cAMP,* cyclic adenosine monophosphate.

vasodilation after adenosine administration occurs within 1 to 2 minutes after the start of the infusion. The half-life of adenosine is approximately 10 seconds. It is either phosphorylated to adenosine monophosphate by adenosine kinase or degraded to inosine by adenosine deaminase.

Adenosine dose. Adenosine is given as a continuous infusion at a rate of 140 mcg/kg/min over a 6-minute period (Figure 2). The correct weight-based dose for the obese and morbidly obese patients is unclear. It is customary to use weight-based doses up to the weight of 250 lbs (or 125 kg) as the upper limit (Table 3). Tracer injection is performed at 3 minutes, and the infusion is continued for another 3 minutes. A shorter duration adenosine infusion, lasting 4 minutes, has been found to be equally effective for the detection of CAD compared to the standard 6-minute infusion. For shorter duration protocols, the minimum time to tracer injection should be 2 minutes, and the infusion should continue for at least 2 minutes after tracer injection.[10]

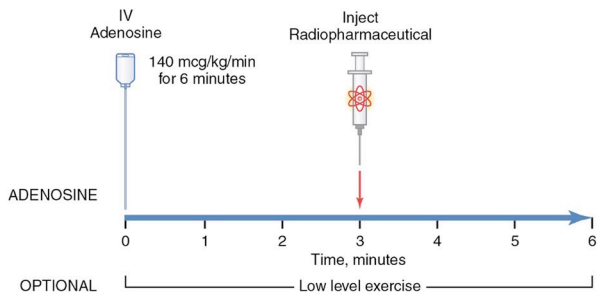

Figure 2. Adenosine protocol. *IV,* Intravenous; *kg,* kilogram; *mcg,* microgram; and *min,* minute.

Side effects of adenosine.

(1) Minor side effects are common and occur in approximately 80% of patients. The common side effects are flushing (35-40%), chest pain (25-30%), dyspnea (20%), dizziness (7%), nausea (5%), and symptomatic hypotension (5%). Chest pain is non-specific and is not necessarily indicative of the presence of CAD.
(2) AV block occurs in approximately 8% of cases. However, the incidence of second-degree AV block is only 4%, and that of complete heart block is less than 1%. Most cases (≥95%) of AV block are self- limiting and do not require termination of the infusion.
(3) ST-segment depression of 1 mm or greater occurs in 5% to 7% of cases. Compared to chest pain, ST changes may be indicative of true ischemia.
(4) Fatal or nonfatal myocardial infarction is extremely rare, but has been reported.[11]
(5) Atrial fibrillation has been reported within several minutes of initiation of adenosine infusion.
(6) New onset or recurrence of convulsive seizures has occurred infrequently following adenosine administration.
(7) Hemorrhagic and ischemic cerebrovascular accidents have occurred.
(8) Due to the exceedingly short half-life of adenosine (≤10 seconds), most side effects resolve in a few seconds after discontinuation of the adenosine infusion, and IV aminophylline administration is only rarely required.

Hemodynamic effects. Adenosine results in a modest increase in heart rate and a modest decrease in both systolic and diastolic BPs. BP systolic decreased by

Table 3. Weight-based dosing of pharmacologic stressors based on metric and standard weights

Weight	Dipyridamole	Adenosine	Regadenoson	Dobutamine
Metric	0.56 mg/kg	140 mcg/kg/min	0.4 mg	5–40 mcg/kg/min
25 kg	14 mg	3.5 mg/min	0.4 mg	0.125–1 mg/min
50 kg	28 mg	7 mg/min	0.4 mg	0.25–2 mg/min
75 kg	42 mg	10.5 mg/min	0.4 mg	0.375–3 mg/min
100 kg	56 mg	14 mg/min	0.4 mg	0.5–4 mg/min
125 kg	70 mg	17.5 mg/min	0.4 mg	0.625–5 mg/min
Standard	0.25 mg/lb	63.5 mcg/lb/min	0.4 mg	2.3–18.1 mcg/kg/min
50 lbs	12.7 mg	3.2 mg/min	0.4 mg	0.11–0.91 mg/min
100 lbs	25.4 mg	6.4 mg/min	0.4 mg	0.23–1.8 mg/min
150 lbs	38.1 mg	9.5 mg/min	0.4 mg	0.34–2.7 mg/min
200 lbs	50.5 mg	12.7 mg/min	0.4 mg	0.45–3.6 mg/min
250 lbs	63.5 mg	15.9 mg/min	0.4 mg	0.57–4.5 mg/min

kg, kilogram; *lbs,* pounds; *mg,* milligram; *mcg,* micrograms; *min,* minute

10 ± 37 mmHg, and BP diastolic decreased 8 ± 19 mmHg, while heart rate increased by 14 ± 30 bpm.[11] Maximum hemodynamic changes after adenosine were as follows: increase in heart rate of more than 40 bpm in 3%, decrease in BP systolic of more than 35 mmHg in 8%, and decrease in BP diastolic of more than 25 mmHg in 5%.

Indications. The indications for adenosine stress perfusion imaging are the same for exercise myocardial perfusion imaging (MPI) and in the presence of the following conditions:

(1) Inability to perform adequate exercise due to noncardiac physical limitations (pulmonary, peripheral vascular, musculoskeletal, or mental conditions) or due to lack of motivation. Of note, as with exercise testing, anti-ischemic cardiac medications (including b-blockers, nitrates, and calcium antagonists) have been reported to decrease the diagnostic accuracy of vasodilator stress testing.
(2) Baseline electrocardiographic abnormalities: LBBB, ventricular pre-excitation (WPW syndrome), and permanent ventricular pacing.
(3) Risk stratification of clinically stable patients into low- and high-risk groups after acute myocardial infarction.
(4) Diagnosis or risk stratification following presentation to the emergency department with a presumptive acute coronary syndrome that has been excluded by serial clinical evaluation, ECGs, and serum markers.

Contraindications. Contraindications for adenosine stress testing include the following:

(1) Patients with bronchospastic lung disease with ongoing wheezing or a history of significant reactive airway disease should not undergo adenosine stress testing.
(2) Second- or third-degree AV block without a functioning pacemaker.
(3) Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia, without a functioning pacemaker.
(4) Systolic BP less than 90 mmHg. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency.
(5) Uncontrolled hypertension (systolic BP $\geq$200 mmHg or diastolic BP $\geq$110 mmHg).
(6) Recent (<48 hours) use of dipyridamole or dipyridamole-containing medications (e.g., Aggrenox).
(7) Known hypersensitivity to adenosine.
(8) Unstable angina, acute coronary syndromes, or less than 2 to 4 days after an acute myocardial infarction.

Relative contraindications. Relative contraindications for adenosine stress testing include the following:

(1) Profound sinus bradycardia (heart rates <40/min).
(2) Mobitz Type 1 second-degree AV block (Wenckebach).
(3) Ingestion of caffeinated foods or beverages (e.g., coffee, tea, sodas) within the last 12 hours should be avoided (Appendix 1).
(4) Severe aortic stenosis (see Special Populations section).
(5) Seizure disorder. New onset or recurrence of convulsive seizures has been reported following adenosine administration. Methylxanthine (aminophylline) use is not recommended in patients who experience seizures in association with adenosine administration.

Procedure.

(1) Patient preparation: nothing should be eaten for at least 3 hours prior to testing. Avoid consumption of any products containing methylxanthines, including caffeinated coffee, tea, or other caffeinated beverages, caffeine-containing drug products (Appendix 1) and theophylline for at least 12 hours prior to the testing. Dipyridamole should be withheld for at least 48 hours (2 days) prior to adenosine administration.
(2) An infusion pump is required for adenosine to be administered at a constant infusion rate.
(3) An IV line with a dual-port Y-connector is required for the injection of the radiotracer during adenosine infusion.
(4) ECG monitoring should be carried out as with exercise stress testing. A 12-lead electrocardiogram will be recorded every minute during the adenosine infusion (4 to 6 minutes).
(5) BP should be monitored every minute during infusion and 3 to 5 minutes into recovery or until stable.
(6) Adenosine infusion should be given at a rate of 140 mcg/kg/min for 3 minutes followed by the injection of the radiotracer. The infusion should be continued for another 3 minutes. For patients deemed to be at a higher risk for complications (e.g., borderline hypotension, controlled asthma), adenosine infusion may be started at a lower dose (70 to 110 mcg/kg/min). If this dose is tolerated well for 1 minute, the infusion rate should be increased to 140 mcg/kg/min and should be

continued for 4 minutes. The radiotracer should be injected 1 minute after starting the 140-mcg/kg/min dose. If the shortened protocol is used (4-minute adenosine infusion), tracer is injected after 2 minutes and is continued for 2 minutes after tracer injection. Adenosine infusion has to continue during tracer injection. Thus, if two IVs are not employed, tracer injection needs to be slow using the dual-port Y-connector. If the adenosine infusion is interrupted, it needs to be restarted immediately.

Combination of low-level exercise with adenosine infusion. Patients who are ambulatory may undergo low-level exercise (e.g., treadmill 1.7 mph, 0% grade) during the adenosine infusion. This results in a significant reduction in the side effects of adenosine (e.g., flushing, dizziness, nausea, and headache) and attenuates the adenosine-induced drop in BP.[12] Image quality is improved by decreasing high hepatic and gut radiotracer uptake, which is common with pharmacologic stress perfusion imaging. Low-level exercise is not recommended in patients with LBBB, WPW, and ventricular pacing due to heart rate-related imaging artifacts.

Indications for early termination of adenosine infusion. The adenosine infusion should be stopped early under any of the following circumstances:

(1) Severe hypotension (systolic BP <80 mmHg).
(2) Development of symptomatic, persistent second-degree or complete AV block.
(3) Other significant cardiac arrhythmia. Wheezing.
(4) Severe chest pain associated with ST depression of
(5) 2 mm or greater.
Signs of poor perfusion (pallor, cyanosis, cold skin).
(6) Technical problems with the monitoring equipment.
(7) Patient's request to stop.
(8)
(9) Note: For signs or symptoms not significant enough to terminate the test, one can consider shortening the time of infusion from 6 to 4 minutes. The adenosine infusion should be terminated early if there are pronounced hemodynamic changes or wheezing or other symptoms, which are not enough to stop the test.

Reversal of complications and side effects of Adenosine. Most side effects are self-limiting due to the short half-life of adenosine (<10 seconds). Indications for reversal of adenosine using IV aminophylline (50 to 250 mg intravenously at least 1 minute after the tracer injection) include the following:

1. Severe hypotension (systolic BP <80 mmHg).
2. Development of symptomatic, persistent second-degree or complete heart block.
3. Other significant cardiac arrhythmia.
4. Wheezing.
5. Severe chest pain associated with ST depression of 2 mm or greater.
6. Signs of poor perfusion (pallor, cyanosis, cold skin).

Cost/time/pharmacy. Medicare Part B drug average sales price is calculated by the manufacturer every calendar quarter and submitted to CMS (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html). The average price for a single study at 140-mcg/kg/min adenosine over a 6-minute period during the 7 quarters since 2013 was $65 for a 75-kg patient (Table 4).

Regadenoson

Mechanism of action. Regadenoson is an A_{2A} adenosine receptor agonist (Figure 1). Regadenoson is a

Table 4. Medicare Part B drug average sales price during the 7 quarters since 1/2013 (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html)

HCPCS code	Medication	Dosage	Average cost
J1245	Dipyridamole	0.56 mg/kg[t]	$6.30
	Adenosine	140 mcg/kg/min*	$64.55
J0150	Regadenoson	0.4 mg	$213.26
J2785			
J1250	Dobutamine	250 mg IV bag	$6.59

IV, Intravenous; *kg,* kilogram; *mcg,* microgram; *mg,* milligram; *min,* minute
[t] 75-kg patient
*6-minute infusion for 75-kg patient

high-affinity agonist for the A_{2A} adenosine receptor, with at least 10-fold lower affinity for the A_1 adenosine receptor, and weak, if any, 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 (CBF) by the same mechanism by which adenosine and dipyridamole produce coronary vasodilation. The maximal plasma concentration of regadenoson is achieved within 1 to 4 minutes after injection and parallels the onset of the pharmacodynamic response. The half-life of this initial phase is approximately 2 to 4 minutes. An intermediate phase follows, with a half-life on average of 30 minutes coinciding with loss of the pharmacodynamic effect. The last phase consists of a decline in plasma concentration with a half-life of approximately 2 hours.

Regadenoson dose. The recommended intra- venous dose of regadenoson is 0.4 mg (5-mL solution) and should be given as an approximately injection into a peripheral vein using a 22-gauge or larger catheter or needle. A 5-mL saline flush is administered immediately after the injection of regadenoson. The radionuclide tracer is injected 10 to 20 seconds after the saline flush using the same IV line used for regadenoson (Figure 3).

Side effects of regadenoson.

(1) The most common reactions to administration of regadenoson are shortness of breath, headache, and flushing. The minor adverse events were headache (29%), dyspnea (25%), flushing (17%), chest discomfort (11%), chest pain (8%), angina (8%), dizziness (7%), nausea (6%), and abdominal discomfort (6%).
(2) Rhythm or conduction abnormalities were seen in 26%. First-degree AV block was detected in 3% and second-degree AV block in 0.1%. Asystole and QT interval prolongation have been reported.
(3) Most adverse reactions begin soon after dosing and generally resolve within approximately 15 minutes, except for headache, which resolves in most patients within 30 minutes.

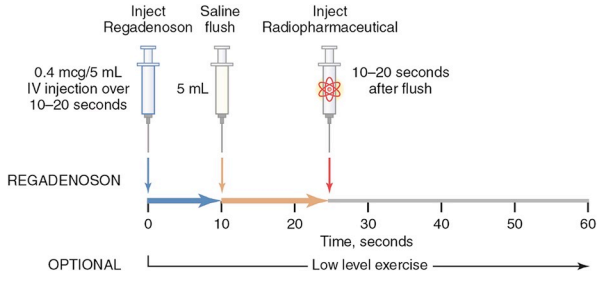

Figure 3. Regadenoson protocol. *IV*, Intravenous; *mcg,* microgram; and *mL,* milliliter.

(4) Aminophylline may be administered in doses ranging from 50 to 250 mg by slow intravenous injection (50 mg to 100 mg over 30 to 60 seconds) to attenuate severe and/or persistent adverse reactions at least 1 minute after tracer injection.
(5) New-onset or recurrent atrial fibrillation and atrial flutter have been reported following regadenoson administration.
(6) New onset or recurrence of convulsive seizures has occurred following regadenoson administration.
(7) Refractory ischemia/myocardial infarction, hemorrhagic, and ischemic cerebrovascular accidents have been reported.
(8) Refractory ischemia and myocardial infarction have occurred.

Hemodynamic effects. In clinical studies, the majority of patients had an increase in heart rate and a decrease in BP within 15 minutes after administration of regadenoson. Systolic BP decreased by 13 ± 14 mmHg and diastolic BP decreased 10 ± 8 mmHg, rate increased by 25 ± 11 bpm.[13] Maximum hemodynamic changes after regadenoson were as follows: increase in heart rate of more than 40 bpm in 5%, decrease in systolic BP of more than 35 mmHg in 7%, and decrease in diastolic BP of more than 25 mmHg in 4%.

Indications. The indications for regadenoson stress perfusion imaging are the same for exercise myocardial perfusion imaging, and in the presence of the following conditions:

(1) Inability to perform adequate exercise due to noncardiac physical limitations (pulmonary, peripheral vascular, musculoskeletal, or mental conditions) or due to lack of motivation. Of note, as with exercise testing, anti-ischemic cardiac medications (including b-blockers, nitrates, and calcium antagonists) have been reported to decrease the diagnostic accuracy of vasodilator stress testing.
(2) Baseline electrocardiographic (ECG) abnormalities: LBBB, ventricular pre-excitation (WPW syndrome), and permanent ventricular pacing.
(3) Risk stratification of clinically stable patients into low- and high-risk groups after acute myocardial infarction.
(4) Diagnosis or risk stratification following presentation to the emergency department with a presumptive acute coronary syndrome that has been excluded by serial clinical evaluation, ECGs, and serum markers.

Contraindications. Contraindications for rega- denoson stress testing include the following:

(1) Patients with bronchospastic lung disease with ongoing wheezing or a history of significant reactive airway disease should not undergo regadenoson stress testing.
(2) Second- or third-degree AV block or sinus node dysfunction without a functioning pacemaker.
(3) Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia, without a functioning pacemaker.
(4) Systolic BP less than 90 mmHg. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency.
(5) Uncontrolled hypertension (systolic BP ≥200 mmHg or diastolic BP ≥110 mmHg).
(6) Recent (≤48 hours) use of dipyridamole or dipyridamole-containing medications (e.g., Aggrenox).
(7) Known hypersensitivity to adenosine or regadenoson.
(8) Unstable angina, acute coronary syndrome, or less than 2 to 4 days after an acute myocardial infarction.

Relative contraindications. Relative contraindications for regadenoson stress testing include the following:

(1) Profound sinus bradycardia (heart rate <40/min).
(2) Mobitz Type 1 second-degree AV block (Wenckebach).
(3) Severe Aortic Stenosis (see ''Special Populations'' section).
(4) Ingestion of caffeinated foods or beverages (e.g., coffee, tea, sodas) within the last 12 hours should be avoided (Appendix 1).
(5) Seizure disorder. Regadenoson may lower seizure threshold, and aminophylline should not be used in cases of seizures associated with regadenoson. These seizures may be of new onset, or may be recurrences. In addition, some seizures are prolonged and may require urgent anticonvulsive management.[14,15]

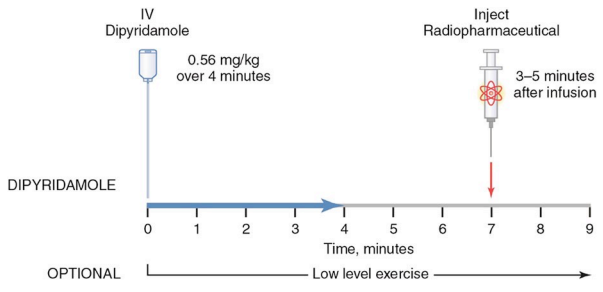

Figure 4. Dipyridamole protocol. *IV,* Intravenous; *kg,* kilogram; and *mg,* milligram.

Procedure.
(1) Patient preparation: nothing should be eaten for at least 3 hours prior to testing. Avoid consumption of any products containing methylxanthines, including caffeinated coffee, tea, or other caffeinated beverages, caffeine-containing drug products (Appendix A), and theophylline for at least 12 hours prior to the testing. Dipyridamole should be withheld for at least 2 days prior to regadenoson administration.
(2) ECG monitoring should be carried out as with exercise stress testing. A 12-lead electrocardiogram will be recorded every minute during the infusion.
(3) BP should be monitored every minute during infusion and 3 to 5 minutes into recovery or until stable.
(4) 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. Administer the radionuclide MPI agent 10 to 20 seconds after the saline flush. The radionuclide may be injected directly into the same catheter as regadenoson.

Combination of exercise with regadenoson administration. Patients who are ambulatory may undergo low-level exercise (e.g., treadmill 1.7 mph, 0% grade) for 1.5 minutes followed by regadenoson administration, tracer injection, and an additional 2 minutes of exercise.[16,17] Combining low-level exercise with regadenoson resulted in improved image quality, and was well tolerated without an increase in adverse events. Low-level exercise supplementation is not recommended in patients with LBBB, WPW, and ventricular pacing due to heart rate-related imaging artifacts.

Ambulatory patients with uncertain functional capacity who do not reach their target heart rate may receive regadenoson to supplement submaximal exercise stress with preserved image quality.[18-21] Regadenoson administration has been studied at peak exercise holding the maximally attained stage, at reduced exercise, during walk recovery, and at rest. While two of the studies found no differences in the safety and side-effect profile based on the time of regadenoson administration, one study suggested more exaggerated BP responses when administered at peak exercise.

Reversal of complications and side effects of regadenoson. Indications for reversal of regade- noson (50- to 250-mg aminophylline intravenously at least 1 minute after the tracer injection) include the following:

(1) Severe hypotension (systolic BP <80 mmHg).
(2) Development of symptomatic, persistent second-degree or complete heart block.
(3) Other significant cardiac arrhythmia.
(4) Wheezing.
(5) Severe chest pain associated with ST depression of 2 mm or greater.
(6) Signs of poor perfusion (pallor, cyanosis, cold skin).

Cost/time/pharmacy. Medicare Part B average sales price is calculated by the manufacturer every calendar quarter and submitted to CMS (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html). The average price for 0.4 mg of regadenoson during the 7 quarters since 2013 was $213.26 (Table 4).

Dipyridamole

Mechanism of action. Dipyridamole is an indirect coronary artery vasodilator that increases the tissue levels of adenosine by preventing the intracellular reuptake and deamination of adenosine (Figure 1). This results in a 3.8- to 7-fold increase in CBF velocity. Dipyridamole-induced hyperemia lasts for more than 50 minutes. Peak vasodilation after dipyridamole administration occurs on average 6.5 minutes after the start of the infusion. The half-life of dipyridamole is approximately 30 to 45 minutes. It is metabolized in the liver to the glucuronic acid conjugate and excreted in the bile.

Dipyridamole dose. Dipyridamole is administered at 0.56 mg/kg intravenously over a 4-minute period (Figure 4). The correct weight-based dose for the obese and morbidly obese patients is unclear. It is customary to use weight-based doses up to the weight of 250 lbs or 125 kg as the upper limit (Table 3).

Side effects of dipyridamole.

(1) Minor side effects are common and occur in approximately 50% of patients. These adverse events include the following: chest pain (20%), headache (12%), dizziness (12%), ventricular extrasystoles (5%), nausea (5%), hypotension (5%), and flushing (3%). Chest pain is nonspecific and is not necessarily indicative of the presence of CAD.
(2) The incidence of AV block with dipyridamole is less than that observed with adenosine (2%).
(3) ST-segment and T-wave changes occurred (8%); however, unlike chest pain, ST changes may be indicative of true ischemia.
(4) Fatal or nonfatal myocardial infarction is extremely rare, but has been reported.[22]
(5) Symptoms may last for a longer period of time than other vasodilators (15 to 25 minutes) and may vary significantly in individual patients. Aminophylline (50 to 250 mg intravenously) is often required to reverse these side effects.

Hemodynamic effects. Dipyridamole adminis- tration results in a modest increase in heart rate and a modest decrease in both systolic and diastolic BPs. Systolic BP decreased by 14 ± 15 mmHg, while heart rate increased by 17 ± 11 bpm.[22] Systolic BP fell to <90 mmHg in 2% of patients.

Indications. The indications for dipyridamole stress perfusion imaging are the same as for exercise MPI and in the presence of the following conditions:

(1) Inability to perform adequate exercise due to noncardiac physical limitations (pulmonary, peripheral vascular, musculoskeletal, or mental conditions) or due to lack of motivation. Of note, as with exercise testing, anti-ischemic cardiac medications (including b-blockers, nitrates, and calcium antagonists) have been reported to decrease the diagnostic accuracy of vasodilator stress testing.
(2) Baseline electrocardiographic abnormalities: LBBB, ventricular pre-excitation (WPW syndrome), and permanent ventricular pacing.
(3) Risk stratification of clinically stable patients into low- and high-risk groups after acute myocardial infarction.
(4) Diagnosis or risk stratification following presentation to the emergency department with a presumptive acute coronary syndrome that has been excluded by serial clinical evaluation, ECGs, and serum markers.

Contraindications. The contraindications for dipyridamole stress testing include the following:

(1) Patients with bronchospastic lung disease with ongoing wheezing or a history of significant reactive airway disease should not undergo dipyridamole stress testing.
(2) Systolic BP less than 90 mmHg. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency.
(3) Uncontrolled hypertension (systolic BP ≥200 mmHg or diastolic BP ≥110 mmHg).
(4) Ingestion of caffeinated foods or beverages (e.g., coffee, tea, sodas) within the last 12 hours should be avoided (Appendix 1).
(5) Known hypersensitivity to dipyridamole.

(6) Unstable angina, acute coronary syndrome, or less than 2 to 4 days after an acute myocardial infarction.

Note: In patients taking oral dipyridamole, IV dipyridamole may be administered safely and efficaciously.

Relative contraindications. Relative contraindications for dipyridamole stress testing include the following:

(1) Profound sinus bradycardia (heart rates <40/min).
(2) Second- or third-degree AV block without a functioning pacemaker.
(3) Severe aortic stenosis (see Special Populations section).
(4) Seizure disorder. Methylxanthine (aminophylline) use is not recommended in patients who experience seizures in association with dipyridamole stress testing.

Procedure.
(1) Patient preparation: nothing should be eaten for at least 3 hours prior to testing. Avoid consumption of any products containing methylxanthines, including caffeinated coffee, tea, or other caffeinated beverages, caffeine-containing drug products (Appendix 1), and theophylline for at least 12 hours prior to the testing.
(2) ECG monitoring should be carried out as with exercise stress testing. A 12-lead electrocardiogram will be recorded every minute during the infusion.
(3) BP and ECG should be monitored every minute during infusion and 3 to 5 minutes into recovery or until stable.
(4) The drug is infused intravenously over 4 minutes. Although an infusion pump is preferable, dipyridamole can also be administered by hand injection or drip. The radiotracer is injected 3 to 5 minutes after the completion of dipyridamole infusion.

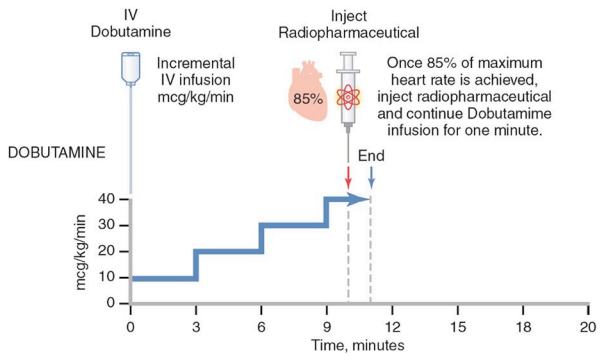

Figure 5. Dobutamine protocol. *IV,* intravenous; *kg,* kilogram; *mcg,* microgram; and *min,* minute.

Combination of low-level exercise with dipyridamole infusion. Patients who are ambulatory may undergo low-level exercise (e.g., treadmill 1.7 mph, 0% grade) for 4 to 6 minutes soon after the completion of dipyridamole infusion. Radiotracer is injected during this low-level exercise, and the exercise continues for an additional 2 minutes to allow for tracer uptake in the myocardium. This significantly reduces the side effects and improves image quality.[23-26] Low-level exercise supplementation is not recommended for patients with LBBB, WPW, and ventricular pacing due to heart rate-related imaging artifacts.

Indications for early termination of dipyridamole infusion. The dipyridamole infusion should be stopped early under any of the following circumstances:

(1) Severe hypotension (systolic BP ↘80 mmHg).
(2) Development of symptomatic, persistent second-degree or complete heart block.
(3) Other significant cardiac arrhythmia. (4) Wheezing.
(5) Severe chest pain associated with ST depression of 2 mm or greater.
(6) Signs of poor perfusion (pallor, cyanosis, cold skin).
(7) Technical problems with the monitoring equipment.
(8) Patient's request to stop.

Reversal of complications and side effects of dipyridamole. Indications for reversal of dipyri- damole (50- to 250-mg aminophylline intravenously at least 1 minute after the tracer injection) include the following:

(1) Severe hypotension (systolic BP <80 mmHg).
(2) Development of symptomatic, persistent second-degree or complete heart block.
(3) Other significant cardiac arrhythmia.
(4) Wheezing.
(5) Severe chest pain associated with ST depression of 2 mm or greater.
(6) Signs of poor perfusion (pallor, cyanosis, cold skin).
(7) Can be considered in the presence of less-severe side effects or ischemic ECG changes if at least 1 minute has elapsed since radiotracer injection.

Cost/time/pharmacy. The average price based on Medicare Part B drug average sales price is calculated by the manufacturer every calendar quarter and submitted to CMS (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAv gSalesPrice/index.html) for a

dipyridamole for a 75-kg patient during the 7 quarters since 2013 was $6.30 (Table 4).

PHARMACOLOGIC SYNTHETIC CATECHOLAMINE STRESS

There is one synthetic catecholamine stress agent available: dobutamine. This agent works by stimulating the b receptor, resulting in an increase in heart rate, BP, and myocardial contractility similar to exercise.

Dobutamine

Mechanism of action. Dobutamine infusion results in direct b_1 and b_2 stimulation with a dose-related increase in heart rate, BP, and myocardial contractility. Dobutamine increases regional myocardial blood flow based on physiologic principles of coronary flow reserve. A similar dose-related increase in subepicardial and subendocardial blood flow occurs within vascular beds supplied by normal coronary arteries. However, blood flow increases minimally within vascular beds supplied by significantly stenosed arteries, with most of the increase occurring within the subepicardium rather than the subendocardium. At a dose of 20 mcg/kg/min, however, dobutamine-induced coronary flow heterogeneity is similar to exercise but less than that induced by adenosine or dipyridamole. The plasma half-life of dobutamine is 2 minutes with the onset of action within 1 to 2 minutes; however, up to 10 minutes may be required to obtain the peak effect (Figure 5).

Dobutamine dose. Dobutamine is infused incrementally starting at a dose of 5 or 10 mcg/kg/min, which is increased at 3-minute intervals to 20, 30, and 40 mcg/kg/min. Radiotracer is injected at peak heart rate with dobutamine infusion continuing for 1 minute following tracer injection. As with exercise stress, achieving greater than 85% of the predicted heart rate is desirable.

Side effects of dobutamine.

1. The common side effects are palpitation (29%), chest pain (31%), headache (14%), flushing (14%), dyspnea (14%), and significant supraventricular or ventricular arrhythmias (8% to 10%).
2. Ischemic ST-segment depression occurs in approximately one-third of patients undergoing dobutamine infusion.
3. Severe side effects may require IV administration of a short-acting b-blocker (esmolol, 0.5 mg/kg over 1 minute). IV metoprolol (5 mg) can also be used.

Hemodynamic effects. The hemodynamic response to dobutamine infusion is dose dependent and varies based on the maximal infusion rate obtained. In studies titrating to a maximal dose of 40 mcg/kg/min, heart rate increased 45 ± 18 bpm, while systolic BP increased 30 ± 21 mmHg in one study, and 12 ± 29 mmHg in another.[27,28]

Indications. Indications for dobutamine stress testing include the following:

(1) Dobutamine is a secondary pharmacologic stressor that is recommended only in patients who cannot undergo exercise stress and who also have contraindications to pharmacologic vasodilator stressors (mainly bronchospastic airway disease).
(2) Dobutamine perfusion imaging has not been studied as extensively as vasodilator stress perfusion imaging in the evaluation and prognostication of patients with CAD.

Contraindications. Contraindications for dobu- tamine stress testing include the following:

(1) Unstable angina, acute coronary syndrome, or less than 2 to 4 days after an acute myocardial infarction.
(2) Hemodynamically significant left ventricular outflow tract obstruction.
(3) Atrial tachyarrhythmias with uncontrolled ventricular response.
(4) Prior history of ventricular tachycardia.
(5) Uncontrolled hypertension (systolic BP ≥200 mmHg or diastolic BP ≥110 mmHg).
(6) Patients with aortic dissection.
(7) Known hypersensitivity to dobutamine.

Relative contraindications.

(1) Patients who are on b-blockers where the heart rate and inotropic responses to dobutamine will be attenuated.
(2) Severe aortic stenosis (see ‘‘Special Populations’’ section).
(3) Patients with with symptomatic or large aortic aneurysm.
(4) Left bundle branch block. (5) Paced ventricular rhythm.

Procedure.

(1) Patient preparation: nothing should be eaten for at least 3 hours.
(2) An infusion pump is necessary for dobutamine administration.
(3) An IV line with a dual-port Y-connector is required for injecting radioisotope during dobutamine infusion.
(4) ECG monitoring and BP monitoring should be performed as with other pharmacologic stressors.
(5) Dobutamine infusion should start at a dose of 5 to 10 mcg/kg/min. The dobutamine dose should then

be increased at 3-minute intervals up to a maximum of 40 mcg/kg/min. The radiotracer should be injected at 1 minute into the highest dobutamine dose (achieving at least 85% of maximal predicted heart disease is desirable), and dobutamine infusion should be continued for 1 minute after the radiotracer injection.

(6) Some investigators recommend the addition of atropine (divided doses of 0.25 to 0.5 mg up to 1 to 2 mg) in patients who do not achieve target heart rate with dobutamine alone.

Indications for early termination of dobutamine infusion. The dobutamine infusion should be stopped early under any of the following circumstances:

(1) Achieving ≥85% of the age-predicted peak heart rate (after maintaining for 1 minute following radiotracer injection).
(2) Severe hypotension (systolic BP<80 mmHg).
(3) Severe hypertension (systolic BP≥230 mmHg or diastolic pressure ≥115 mmHg)
(4) Significant cardiac arrhythmia. Termination for ventricular tachycardia or atrial tachyarrhythmia is more likely with dobutamine than with other stressors.
(5) Severe chest pain associated with ST depression of 2 mm or greater. Termination for ST-segment depression is more likely with dobutamine than with other stressors.
(6) Signs of poor perfusion (pallor, cyanosis, cold skin).
(7) Technical problems with the monitoring equipment.
(8) Patient's request to stop.

Reversal of complications and side effects of dobutamine. Severe side effects, arrhythmia, or ST changes may require IV administration of a short-acting b-blocker (esmolol, 0.5 mg/kg over 1 minute). IV metoprolol (5 mg) can also be used.

(1) Severe hypertension (systolic BP ≥220/110 mmHg).
(2) Significant cardiac arrhythmia.
(3) Severe chest pain associated with ST depression of 2 mm or greater.

Cost/time/pharmacy. The average price based on Medicare Part B drug average sales price is calculated by the manufacturer every calendar quarter and submitted to CMS (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvg SalesPrice/index.html) for a 250-mg IV bag of dobu- tamine during the 7 quarters since 2013 was $6.59 (Table 4).

For review of serious complications of myocardial stress testing and their management, refer to the article by Dilsizian and colleagues.[9]

SPECIAL POPULATIONS FOR PHARMACOLOGIC STRESS

Obesity

The correct dose for the obese and morbidly obese patient is unclear. It is customary to use a weight-based dose of IV dipyridamole, IV adenosine, and IV dobutamine up to the weight of 250 lbs as the upper limit.

Left Bundle Branch Block, Ventricular Pacing, Ventricular Pre-excitation (WPW Syndrome)

Pharmacologic stress with coronary vasodilators (not IV dobutamine) is the preferred stress modality with above rest ECG patterns, both for safety (inability to monitor for ischemia) and diagnostic reasons (e.g., the presence of septal perfusion defects, not always related to obstructive CAD). If rate-dependent LBBB is diagnosed during exercise, the test should be converted to a pharmacologic stress test.

Reactive Airway Disease

Adenosine, regadenoson, and dipyridamole should be administered with caution in patients with a history of reactive airway disease or severe obstructive pulmonary disease. Aminophylline should be available for the treatment of vasodilator-induced bronchospasm. Dobutamine is the preferred agent for pharmacologic stress in patients with a history of significant reactive airway disease or severe obstructive pulmonary disease.

Several studies have shown that a titrated dose adenosine infusion preceded by an inhaled bronchodilator was well tolerated in patients with mild reactive airway disease from COPD or asthma.[29-31] Because of its selectivity for the A_{2A} receptor and not the A_{2B} receptor, regadenoson shows promise to avoid bronchoreactivity seen in adenosine and dipyridamole. Two small pilot studies of moderate to severe COPD and moderate asthma showed no statistically significant difference between regadenoson and placebo in bronchoconstrictive reactions as measured by spirometry.[32,33] While several other studies have examined the issue,[34] the only randomized study enrolled 999 patients with spirometry defined COPD or asthma and found no difference in the rate of bronchoconstriction

between regadenoson and placebo, but did find more dyspnea.[35]

Renal Disease

Dipyridamole, adenosine, and dobutamine have no contraindications to renal dysfunction. The package label of regadenoson states that no serious events were reported through 24 hours of follow-up in stage III or IV renal impairment. In an initial pharmacologic model, regadenoson elimination half-life appeared to be prolonged with decreasing renal function.[36] Subsequent published literature, including 423 patients with end-stage renal disease (ESRD) and 745 patients with impaired renal function but not ESRD, has found that the drug was safe, with minimal side effects, and hemodynamic responses similar to patients with normal renal function.[37-41]

Aortic Stenosis

The use of vasodilator stress for MPI in patients with significant aortic stenosis is limited as surgical valve replacement is recommended for symptomatic patients necessitating an invasive angiogram as opposed to noninvasive testing. Occasionally, MPI was preferred to angiography due to specific clinical considerations, which has become a more frequent occurrence with the advent of transcatheter aortic valve replacement (TAVR). A number of small studies have evaluated the diagnostic accuracy and to varying degrees the safety and tolerability of dipyridamole (141 patients),[42-44] adenosine (180 patients),[45-48] and regadenoson (50 patients).[49] When assessed, there were no significant differences in the hemodynamic responses between patients with severe aortic stenosis and controls.[43,48] In a group of 50 pre-TAVR patients with a mean EF of 39%, transient hypotension occurred in 16% of subjects receiving regadenoson.[49]

There is insufficient safety data on SPECT dobutamine stress in patients with severe aortic stenosis.

Pre Solid-Organ Transplantation

The role of cardiac disease evaluation prior to solid-organ transplantation (e.g., kidney and liver) candidates was discussed recently in an expert consensus document by the AHA.[50]

The safety of regadenoson has been studied in patients with renal impairment (see Renal Disease section) and also in end-stage liver disease. In a study of 168 patients, regadenoson was found to be safe in end-stage liver disease patients with no significant adverse events, and a lower heart-rate response but similar BP response was seen.[37] There is a case report of three cases of sinus arrest with adenosine in liver transplant patients with graft failure, so caution should be taken in this particular patient population.[51]

Women

The role of noninvasive testing in the evaluation of women with suspected ischemic heart disease was recently covered in an AHA consensus statement.[4]

Caffeine and Coronary Vasodilators

Caffeine, a methylxanthine alkaloid derivative, is a competitive inhibitor of the adenosine receptor due to its similar molecular structure to adenosine. Caffeine binds to the adenosine receptor without activating it, thereby requires withholding methylxanthines prior to testing with adenosine, dipyridamole, or regadenoson. The half-life of caffeine varies widely among individuals based on factors such as age, liver function, medication, smoking use, and pregnancy, and is approximately 5 hours in a healthy adult.[52] Caffeine is most commonly found in coffee, tea, soda, energy drinks, and chocolate (Appendix 1). While the caffeine content depends on the particular product and method of preparation, the caffeine contents of some common products are shown in the table in Appendix 1. Decaffeinated coffee still contains up to 13.9 mg of caffeine. A number of studies have shown that even when patients report abstinence from caffeine for 12 to 24 hours, a substantial portion of patients have detectable serum caffeine levels.

The effect of caffeine on the coronary hyperemia induced by adenosine, dipyridamole, and regadenoson may be explained by the difference in their mechanism of action. While dipyridamole is an indirect agonist on the A_{2A} receptor by increasing the concentration of endogenous adenosine, adenosine is a direct stimulator, and regadenoson has a higher A_{2A} receptor affinity. A number of studies have shown limited increase in myocardial blood induced by dipyridamole after caffeine use as well as attenuated myocardial perfusion defects.[53-58] Two studies assessing the coronary hyperemia induced by adenosine found no significant attenuation of the effect by caffeine.[56,59] It is unclear whether the degree of attenuation of the magnitude of coronary hyperemia caused by caffeine would result in a clinically significant change to myocardial perfusion results.[60] A number of studies have investigated the effects of caffeine consumption on the MPI results using adenosine stress finding some effect on imaging,[61] but often no significant effect.[62,63] The data on regadenoson are somewhat mixed with an animal study reporting that caffeine did not affect the maximum increase in

Table 5. Current SPECT myocardial perfusion imaging protocols: recommended radiopharmaceutical activities and their corresponding radiation effective doses

	First injection				Second injection				Total Dose (mSv)	Total dose if Stress only (mSv)
	Given at	Activity (mCi)	Activity (MBq)	Dose (mSv)	Given at	Activity (mCi)	Activity (MBq)	Dose (mSv)		
Tc-99m protocols										
Tc-99m one-day stress-first/ stress-only	Stress	8–12	296–444	2.0–3.0	(Rest)	24–36	888–1332	7.0–10.5	9.0–13.5	2.0–3.0
Tc-99m one-day rest/stress	Rest	8–12	296–444	2.3–3.5	Stress	24–36	888–1332	6.1–9.1	8.4–12.6	n/a
Tc-99m two-day stress/rest	Stress	8–12	296–444	2.0–3.0	(Rest)	8–12	296–444	2.3–3.5	4.3–6.5	2.0–3.0
Tc-99m two-day stress/rest—large patient	Stress	18–30	666–1110	4.5–7.6	(Rest)	18–30	666–1110	5.2–8.7	9.8–16.3	4.5–7.6
Tc-99m two-day rest/stress	Rest	8–12	296–444	2.3–3.5	Stress	8–12	296–444	2.0–3.0	4.3–6.5	n/a
Tc-99m two-day rest/stress large patient	Rest	18–30	666–1110	5.2–8.7	Stress	18–30	666–1110	4.5–7.6	9.8–16.3	n/a
Tl-201 protocols										
Tl-201 stress/redistribution rest	Stress	2.5–3.5	92.5–129.5	10.9–15.3	n/a	n/a	n/a	n/a	10.9–15.3	10.9–15.3
Tl-201 stress/redistribution rest/ reinjection	Stress	2.5–3.5	92.5–129.5	10.9–15.3	Rest	1–2	37–74	4.4–8.8	15.3–24.1	n/a
Tl-201 rest/redistribution	Rest	2.5–3.5	92.5–129.5	10.9–15.3	n/a	n/a	n/a	n/a	10.9–15.3	n/a
Dual-isotope Tl-201 rest/Tc-99m stress	Rest	2.5–3.5	92.5–129.5	10.9–15.3	Stress	8–12	296–444	2.0–3.0	13.0–18.3	n/a
Dual-isotope Tl-201 rest/Tc-99m stress—large patient	Rest	3.0–3.5	111–129.5	13.1–15.3	Stress	18–30	666–1110	4.5–7.6	17.7–22.9	n/a
I-123 protocol										
*m*IBG	Rest	10	370	4.6	n/a	n/a	n/a	n/a	4.6	n/a
Newer technology reduced-dose protocols										
Tc-99m one-day stress-first/ stress-only	Stress	4–6	148–222	1.0–1.5	(Rest)	12–18	444–666	3.5–5.2	4.5–6.7	1.0–1.5
Tc-99m one-day rest/stress	Rest	4–6	148–222	1.2–1.7	Stress	12–18	444–666	3.0–4.5	4.2–6.3	n/a
Tc-99m two-day stress/rest	Stress	4–6	148–222	1.0–1.5	(Rest)	4–6	148–222	1.2–1.7	2.2–3.3	1.0–1.5
Tc-99m two-day stress/rest—large patient	Stress	9–15	333–555	2.3–3.8	(Rest)	9–15	333–555	2.6–4.4	4.9–8.1	2.3–3.8
Tc-99m two-day rest/stress	Rest	4–6	148–222	1.2–1.7	Stress	4–6	148–222	1.0–1.5	2.2–3.3	n/a
Tc-99m two-day rest/stress—large patient	Rest	9–15	333–555	2.6–4.4	Stress	9–15	333–555	2.3–3.8	4.9–8.1	n/a

Table 5 continued

	First injection				Second injection				Total	Total dose if Stress only (mSv)
	Given at	Activity (mCi)	Activity (MBq)	Dose (mSv)	Given at	Activity (mCi)	Activity (MBq)	Dose (mSv)	Dose (mSv)	
Tl-201 stress/redistribution rest	Stress	1.3–1.8	48.1–66.6	5.7–7.9	n/a	n/a	n/a	n/a	5.7–7.9	5.7–7.9
Dual-isotope Tl-201 rest/Tc-99m stress	Rest	1.3–1.8	48.1–66.6	5.7–7.9	Stress	4–6	148–222	1.0–1.5	6.7–9.4	n/a
Dual-isotope Tl-201 stress/Tc-99m rest	Stress	1.3–1.8	48.1–66.6	5.7–7.9	(Rest)	4–6	148–222	1.2–1.7	6.9–9.6	5.7–7.9

Note that 1 mCi = 37 MBq, e.g., activity of 8 to 12 mCi = 8 9 37 to 12 9 37 MBq = 296 to 444 MBq. Note 3:1 ratio of activity of the second injection to that of the first injection. For example, the range for dose #1 is 8–12 mCi, and the range for dose #2 is 24–36 mCi. (Rest) denotes optional rest injection; it is recommended that stress images be reviewed by a nuclear cardiology physician prior to rest injection, and the rest injection only performed where clinically warranted.* Newer technology reduced-dose protocols have been studied for high-efficiency cameras,** and for image reconstruction with iterative reconstruction, depth-dependent resolution recovery, and noise modeling. Radiation effective dose values listed here are dose to a reference individual. Doses were determined using the most recent published International Commission on Radiological Protection (ICRP) organ dose coefficients, and ICRP Publication 103 tissue weighing factors. Tc-99m doses represent an average for sestamibi and tetrofosmin

* Gibson, Chang, Duvall[77-79]
** Einstein, Duvall[73,74]
*** DePuey[72]

coronary blood flow, but that the duration of hyperemia was shorter.[64] Regadenoson-induced hyperemic myocardial blood flow measured by PET was not affected by caffeine ingestion,[65] but reversible defects on SPECT myocardial perfusion imaging were smaller with caffeine consumption.[66]

Patients should abstain from caffeinated products for at least 12 hours, which allows for selection of any of the three vasodilator stressors.

RADIOTRACERS AND PROTOCOLS

There are a variety of different protocols currently used for SPECT myocardial perfusion imaging. Table 5 contains information about these protocols: the radiopharmaceuticals used, their activities [millicuries, (mCi) or megabecquerels (MBq)], and their radiation effective doses. Figures 6 to 10 provide additional information regarding the timing of stress, injections, and imaging for each protocol. Gated imaging is recommended where feasible, at least during post-stress imaging.

The protocol selected for a particular study should be tailored to the patient and to the clinical scenario. No single protocol is optimal for every patient, and nuclear cardiology laboratories should strive to implement patient-centered imaging rather than performing the same protocol for each patient. This includes selecting an appropriate protocol and choosing administered activities that are appropriate for the patient's habitus, i.e., weight-based dosing. The American Society of Nuclear Cardiology (ASNC) has provided detailed guidance regarding protocol selection for different patient populations in the Preferred Practice Statement on Patient-Centered Imaging,[67] and recommends use of that document in tandem with these guidelines. As per the ASNC Information Statement on Recommendations for Reducing Radiation Exposure in Myocardial Perfusion Imaging, using a protocol and administered activities that will result in radiation exposure as low as reasonably achievable (ALARA) for each patient, with radiation effective dose of $\leq$9 mSv in at least 50% of studies, is an extremely important goal for each laboratory to attain.[9] Several techniques can be used to keep radiation ALARA.[68] Their under utilization in contemporary practice provides nuclear cardiology laboratories with multiple opportunities to improve patient care.[69,70] Where feasible, and particularly for procedures with higher radiation exposure, e.g., effective dose $\geq$20 mSv, shared decision-making principles should be employed,[71] including discussion of options with the patient.

Selection for a particular patient of the administered activity, within the range of activities for a given radiopharmaceutical, is not an exact science; the same administered activity can result in dramatically different

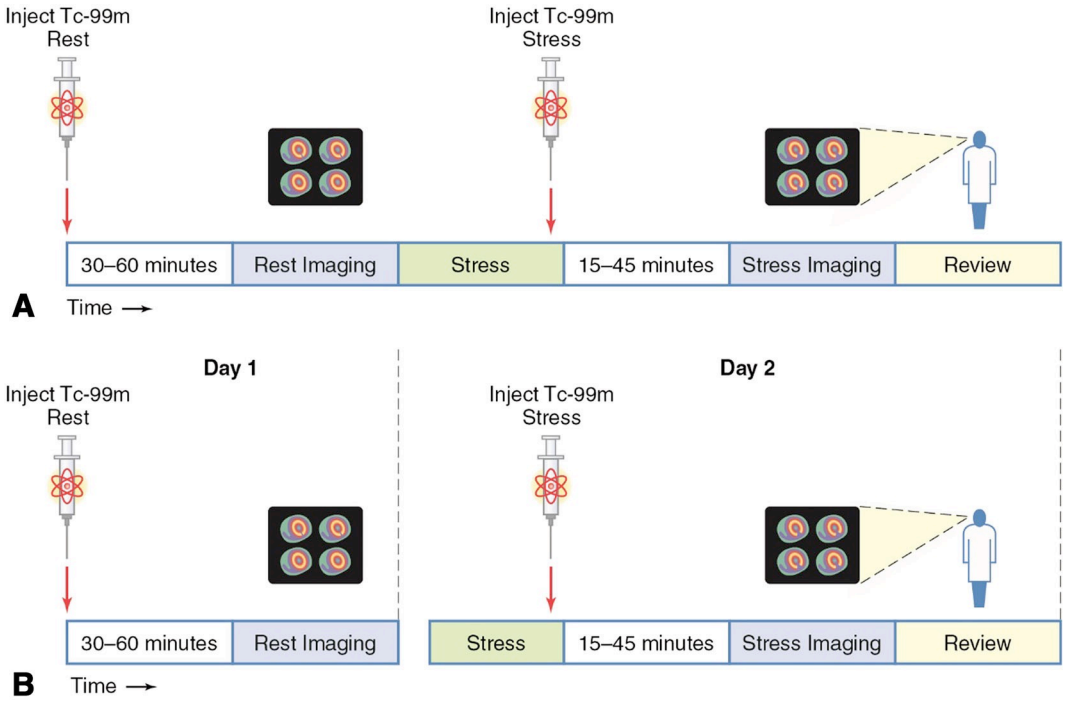

Figure 6. One (A) and two (B) day rest-stress Tc99m imaging protocols.

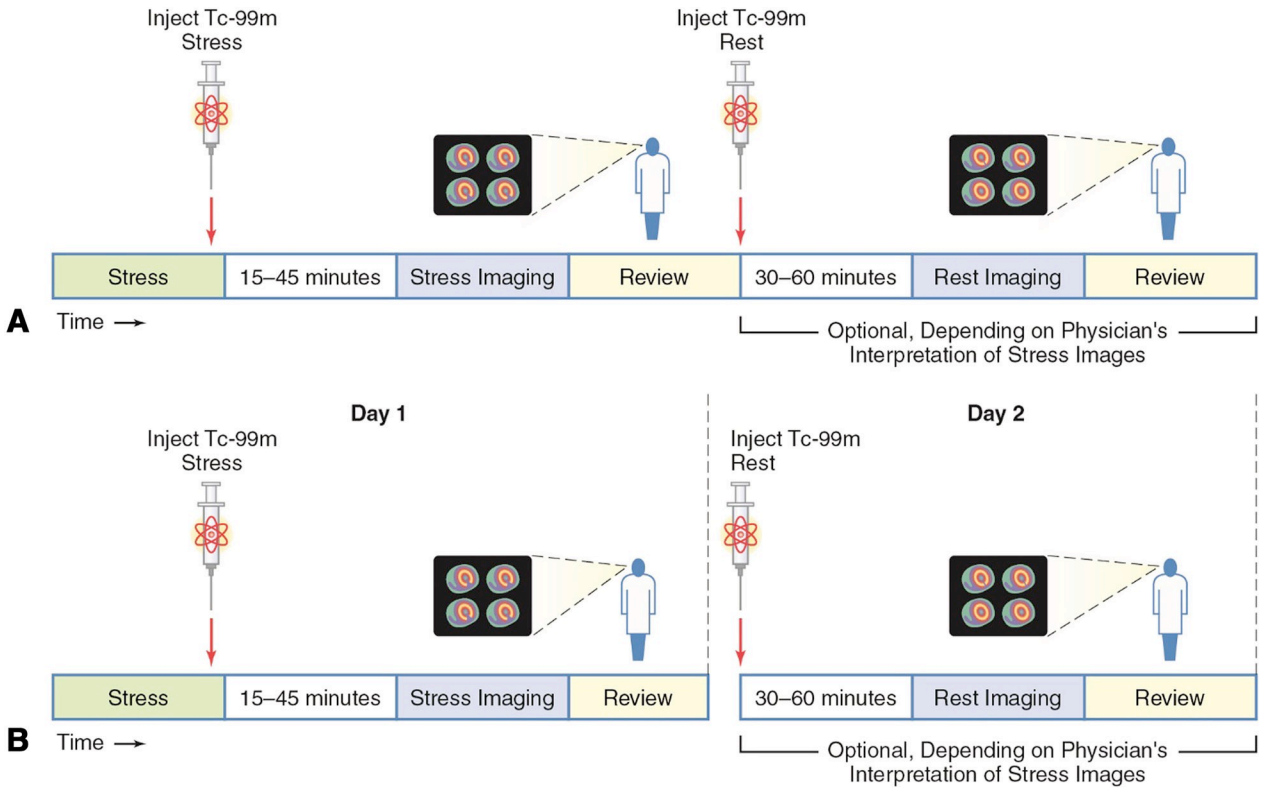

Figure 7. One (A) and two (B) day stress-rest Tc99m imaging protocols.

count statistics and image quality in different patients due to differences in pharmacokinetics. Nevertheless, an effort to tailor the administered activity to the patient's habitus and imaging equipment should be made. For example, thin patients without excessive breast tissue should receive activities at the low end of the recommended range, while many patients weighing more than 250 pounds benefit from the increased count statistics of a 2-day protocol with 18 to 30 mCi administered each day. A variety of weight-based strategies can be used, in that strong evidence supporting one particular weight-based dosing scheme does not exist. As one strategy to consider, many laboratories may find it suitable in 1-day studies to perform the first injection with 8 mCi of Tc-99m for patients with BMI $\leq$25 kg/m^2, 9 mCi of Tc-99m for patients with BMI $>$25-30 kg/m^2, 10 mCi of Tc-99m for patients with BMI $>$30-35 kg/m^2, and 12 mCi of Tc-99m for patients with BMI $>$35 kg/m^2 or a large chest, with three times this activity used for the second dose of the day. In obese patients undergoing 2-day protocols, radiation dose can be optimized by performing stress imaging on the first day, and only performing rest imaging if these images are abnormal. For laboratories with advanced software (e.g., incorporating noise reduction and resolution recovery) and/or hardware (e.g., cameras with multiple cadmium-zinc-telluride detectors) enabling more efficient count detection,[72-74] reduced-dose protocols should be considered, a set of which are included in Table 5.

SPECT myocardial perfusion imaging protocols utilize three radiopharmaceuticals: thallium 201 and two technetium 99m agents (Tc-99m sestamibi and Tc-99m tetrofosmin). Details regarding these radiopharmaceuticals and the protocols using them follow. Information related to PET protocols and radiopharmaceuticals are described in the PET Imaging Guidelines.[75]

NOTE: The suggested radiopharmaceutical activities in this section are for current camera and processing protocols as defined in the SPECT Imaging Guidelines.[76] Some of the radiopharmaceutical activities described in this section fall outside of the manufacturer package insert guidelines but are now commonly used in the clinical practice of nuclear cardiology.

The radiation dosimetry values provided in Table 5 are point estimates of doses to a typical patient. Doses were determined using average administered activities, most recently published International Commission on Radiological Protection (ICRP) dose coefficients, and ICRP Publication 103 tissue weighing factors. Tc-99m doses represent an average for sestamibi and tetrofosmin.

Gated imaging is recommended where feasible. Results of gating are most reliable with higher doses of technetium-based perfusion tracers but satisfactory results have been reported with lower dose technetium as well as thallium-201.

Radiation effective dose values listed here are dose to a reference individual. Doses were determined using the most recent published International Commission on Radiological Protection (ICRP) organ dose coefficients, and ICRP Publication 103 tissue weighing factors. Tc-99m doses represent an average for sestamibi and tetrofosmin.

Tc-99m-Labeled Tracers

Mechanism of action. Tc-99m sestamibi and Tc-99m tetrofosmin have very similar characteristics: lipid-soluble, cationic, physical half-life of 6 hours, produces 140-keV photons, first-pass extraction less than Tl-201, uptake and mitochondrial retention dependent on blood flow, and transmembrane energy potentials. Their myocardial washout (redistribution) is clinically negligible. These agents are excreted via the hepatobiliary system and excreted into the gastrointestinal tract. Lacking significant redistribution, Tc-99m-labeled tracers require two separate injections at stress and rest. The two agents have sufficiently similar characteristics, in that recommended protocols use similar camera setup and acquisition times and vary only in the optimal time for image acquisition following rest, exercise, and pharmacologic stress. Optimal validation of imaging times has not been extensively studied, and factors such as camera availability and the presence of liver and gastrointestinal activity influence the optimal imaging times. In the figures, a range of imaging times is suggested. The whole-body effective dose for Tc-99m-based perfusion agents varies between sestamibi and tetrofosmin, and between administration at rest and stress, and between data sources and methods of calculation, but as a very rough figure is approximately 0.3 mSv per mCi of Tc-99m injected.

Imaging Protocols (Figures 6, 7).

(1) *Tracer-specific imaging times*

(a) For Tc-99m sestamibi, minimum delays of 15 to 20 minutes for exercise, 45 to 60 minutes for rest, and 60 minutes for pharmacologic stress are recommended.

(b) For Tc-99m tetrofosmin, minimum delays of 10 to 15 minutes for exercise, 30 to 45 minutes for rest, and 45 minutes for pharmacologic stress are optimal. Because there is minimal redistribution with these agents, longer delays—up to 2 hours—between the radiotracer injection and imaging can be used when needed.

(2) *Two-day protocol.* Ideally, stress and rest imaging with Tc-99m agents should be performed on two separate days, as shown in Figure 7B, to avoid having residual activity (''shine-through'' or ''crosstalk'') from the first injection interfere with

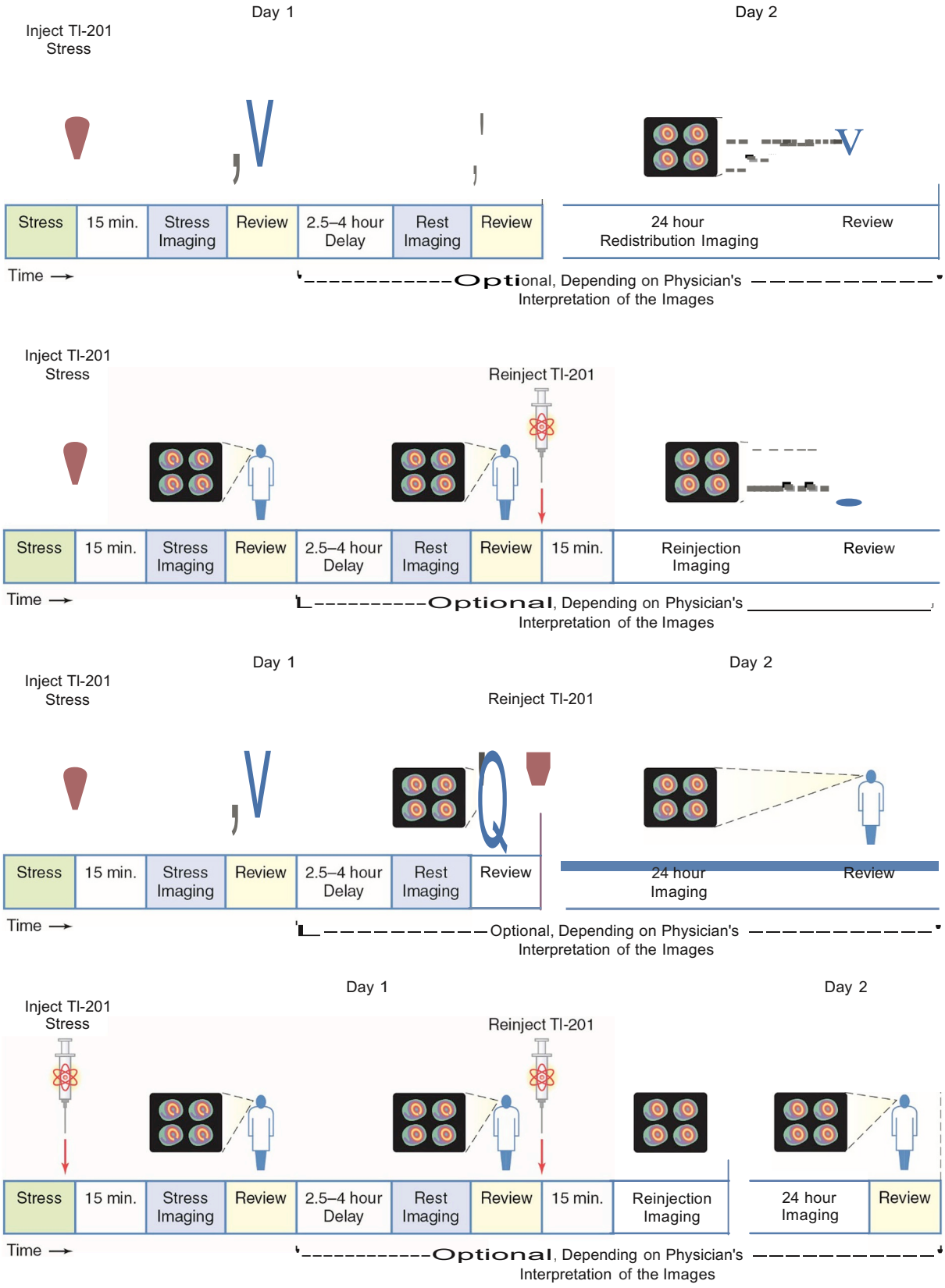

Figure 8. TL-201 stress-rest imaging protocols.

interpretation of images reflecting the second injection. In larger patients (e.g., ≥250 lbs or BMI ≥35) or in female patients where significant breast attenuation is anticipated, a low dose of Tc-99m radiotracer may result in suboptimal images and a 2-day imaging protocol with higher activities (18 to 30 mCi) for each injection may be preferable.

(3) *One-day protocols.* For many patients, 2-day imaging is impractical, and thus stress and rest studies are usually performed using a 1-day protocol as shown in Figures 6A and 7A for exercise and pharmacologic stress. This requires administration of a lower dose (approximately one-fourth of the total dose) for the first injection and a higher dose (approximately three-fourths of the total dose) for the second injection. One-day stress/rest and rest/stress Tc-99m protocols are now typically performed with no significant delay between obtaining the first set of images and injection of the second dose of Tc-99m at stress or rest, as appropriate. The initially proposed 1990 protocol specified a 2-hour delay between injections to allow the first dose to decay in order to maximize the count density ratio and minimize shine-through. However, simply increasing the activity of the second injection provides the same count density ratio achieved by letting the first dose decay (20% in 2 hours). Thus, a 3:1 ratio of activities with a 2-hour delay and a 3.5 to 4:1 ratio with no delay provide similar results.

In patients without a high pre-test probability of a stress perfusion defect or left ventricular dysfunction or dilatation, a low-dose stress/high-dose rest Tc-99m protocol is advantageous because a significant percentage of these patients will have normal stress imaging, thereby enabling obviating the need for the rest imaging with its additional radiation exposure, and permitting performance of stress-only imaging.

Tl-201

Mechanism of action. Tl-201 is an analog of potassium (monovalent cation), with a physical half-life of 73.1 hours, decay by electron capture to Hg-201 with

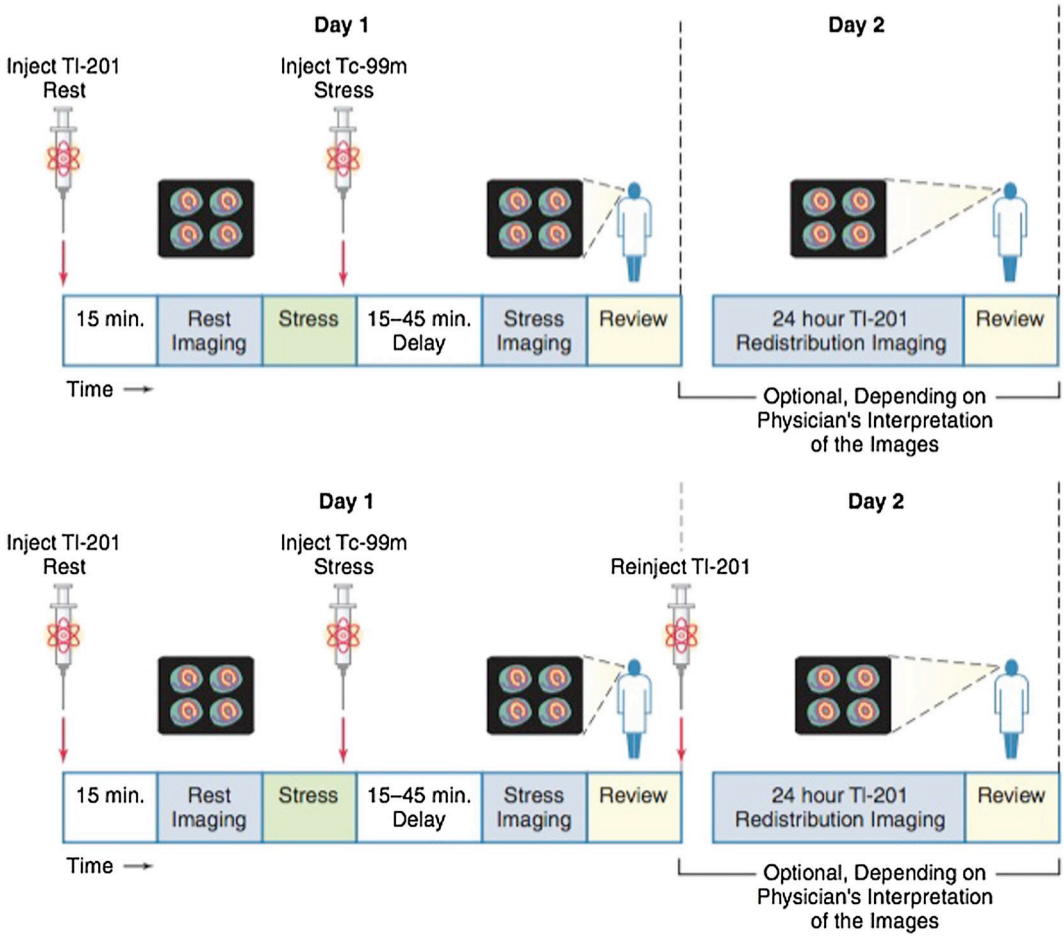

Figure 9. Dual-isotope (Tl-201-Tc99m) imaging protocols (discouraged).

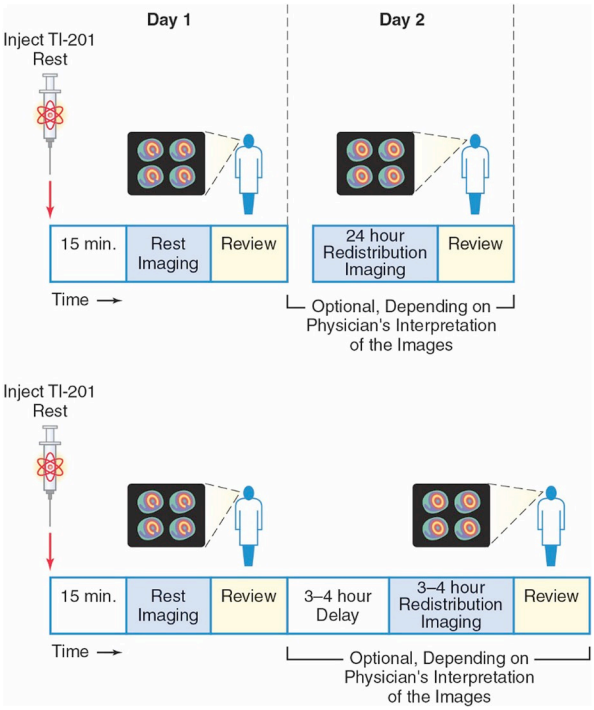

Figure 10. Rest thallium.

principal emission of 68- to 80-keV X-rays, high first-pass myocardial extraction (85%), active membrane transport into the myocyte, rapid clearance from the intravascular space, and monoexponential washout (redistribution), which starts 10 to 15 minutes after injection. Washout depends on initial tracer concentration in the myocyte and on myocardial blood flow. Clearance occurs via the kidneys. The effective radiation dose for Tl-201 is approximately 4.4 mSv per mCi of Tl-201 injected.

Imaging protocols (Figures 8, 9, and 10). A single dose of 2.5 to 3.5 mCi of Tl-201 is injected prior to peak exercise stress or at peak pharmacologic vasodilatation, and SPECT imaging starts 10 to 15 minutes later. Redistribution (rest) imaging is done 2.5 to 4.0 hours later. In cases where standard stress-redistribution imaging shows a fixed or minimally reversible perfusion abnormality, myocardial viability can be assessed with a rest image at 18 to 24 hours or following reinjection of an additional 1- to 2-mCi dose of Tl-201. An alternative method for viability assessment is injection of 2.5 to 3.5 mCi of Tl-201 at rest followed by 3- to 4-hour or 18- to 24-hour redistribution imaging. Protocol options and timing for assessment of perfusion and viability are shown in Figures 8 and 10.

Use of dual-isotope imaging, with Tl-201 for initial rest imaging and a Tc-99 labeled tracer for stress perfusion imaging, as shown in Figure 9, allows a shorter duration of the entire imaging protocol. However, there is a significantly higher radiation dose to the patient, and rest and stress images are obtained with different tracers that may increase the false positive rate for ischemia. Except in those elderly patients who require a shorter protocol, or for patients in whom there is a clear indication for both perfusion imaging and viability assessment, and PET or MRI viability assessment is not possible, ASNC recommends against performing dual-isotope MPI.

Cardiac Iodine-123 meta-iodobenzylguanidine (^{123}I-*m*IBG) Imaging

Mechanism of action. Cardiac iodine-123 *meta*-iodobenzylguanidine (^{123}I-*m*IBG) imaging assesses sympathetic innervation of the myocardium. *MIBG* is an analog of the sympathetic mediator norepinephrine (NE), although it is designed to more closely

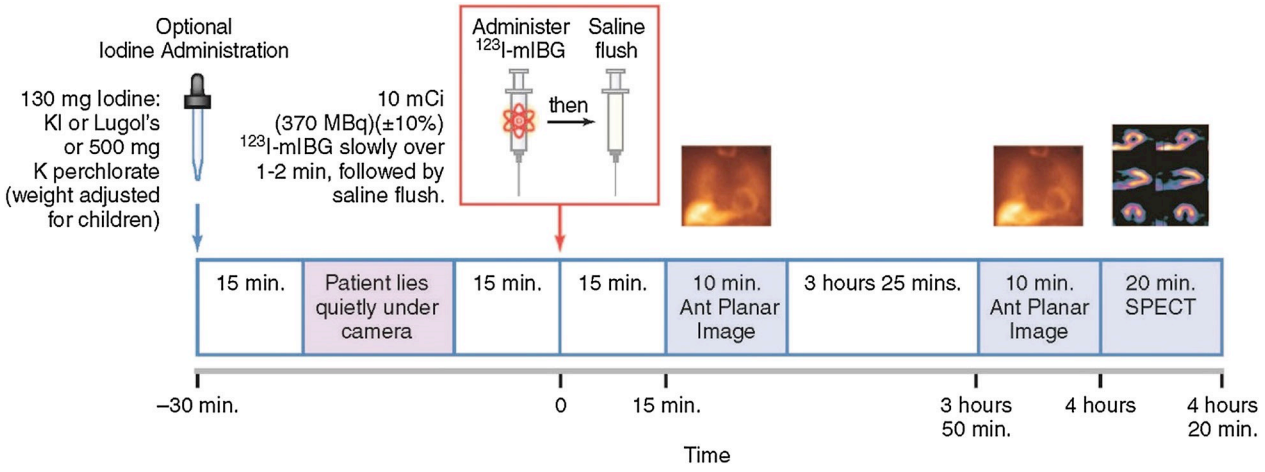

Figure 11. ^{123}I-*m*IBG imaging protocols.

Table 6. Acquisition setup for ^{123}I-mIBG

Parameter	Planar	SPECT
Subject position	Supine	Supine
Energy window	159 keV, 20%	159 keV, 20%
Collimator	Low energy, high resolution	Low energy, high resolution
Camera orientation for planar Orbit	Anterior	NA
type and angular rotation Number	NA	Circular: 180° (45° RAO–45°LPO)
of projections (dual head) Matrix	NA	20 per head
Time/projection	128 9 128	64 9 64 (6.4 mm pixel size)
Acquisition duration	NA	30 s
ECG gated	10 mins	Approximately 20 mins
	No	No

ECG, Electrocardiogram; *mins,* minutes; *NA,* not applicable; *secs,* seconds

mimic the false neurotransmitter guanethidine. When injected intravenously, *m*IBG diffuses into the synaptic cleft and is taken up into pre-synaptic sympathetic terminals via the NE transporter-1 (NET1) energy-dependent ''uptake-1'' process.[80-82] Physiologically the uptake-1 process is designed to terminate local sympathetic stimulation by storage and catabolic disposal of NE, but as *m*IBG behaves as a false neurotransmitter, it is not metabolized and instead accumulates in the pre-synaptic terminal. So, when labeled with a radioisotope, such as iodine-123 (^{123}I), ^{123}I-*m*IBG imaging depicts function of the uptake-1 process, and thus the integrity and health of cardiac sympathetic innervation.[83]

Human cardiac imaging of ^{123}I-*m*IBG was first reported by Kline et al in 1981,[84] described at the time as providing ''clinicians with insights into 'wiring of the heart'.''[85] Cardiac disease, such as HF and myocardial ischemia, lead to low ^{123}I-*m*IBG concentration in cardiac innervating sympathetic neurons and is customarily quantified as a heart-to-mediastinum ratio (HMR), as well as an accelerated tracer washout rate (WR) between early and delayed anterior planar images. Much literature demonstrates that an abnormally low HMR and an abnormally high WR are associated with a poorer patient prognosis in patients with HF and reduced ejection fraction (HFrEF).[86-90]

Indications. Cardiac ^{123}I-*m*IBG imaging is currently indicated for ''scintigraphic assessment of sympathetic innervation of the myocardium in patients with New York Heart Association [NYHA] class II or class III HF and left ventricular ejection fraction [LVEF] $\leq$35% … and to help identify patients with lower one- and two-year mortality risks, as indicated by an [HMR] ratio $\geq$1.6.''

Nevertheless, much literature suggests a potential broader use,[91] including identification of patients at increased risk of lethal cardiac arrhythmias in the setting of HF,[92-95] evaluating primary arrhythmic conditions,[96-100] assessing the presence and risk of ischemic heart disease,[101,102] including in situations of hibernating myocardium[103,104] and post-infarction,[105-107] evaluating pre- and post-cardiac transplant patients,[108-110] identifying diabetic patients at increased risk from cardiac autonomic dysfunction,[111,112] and monitoring toxicity from chemotherapy.[113] However, based on currently available literature, published guidelines, and the FDA package insert, the following indications can be recommended:[114]

- For patients with NYHA class II or III heart failure with LVEF $\leq$35% to help stratify risk and to promote more informed clinical decision-making when the result of ^{123}I-*m*IBG study is likely to influence the decision regarding ICD implant.

The following can be considered a potential emerging indication:

- For patients who received an ICD for primary and or secondary prevention of SCD who subsequently underwent complete device and lead removal due to definite infection and there is uncertainty on the part of treating physician to proceed with ICD replacement, when the result of ^{123}I-*m*IBG study is likely to influence the decision regarding device replacement.

Procedure: performing cardiac ^{123}I-*m*IBG imaging. A schematic of the ^{123}I-*m*IBG administration and imaging procedure is shown in Figure 11, with details below. Imaging parameters are as shown in Table 6.

Tracer Administration

^{123}I-*m*IBG is performed at rest and requires only minimal preparation. The standard procedure used in a

recent multicenter study was to keep the patient NPO (except for water) after midnight on the day of imaging.[115] It is accepted that standard HF medications such as ß-blockers, angiotensin-converting enzyme inhibitors (ACE-I), and/or angiotensin receptor blockers (ARBs) need not be held.[116-119] However, it is recommended to temporarily discontinue medications and substances known to interfere directly with the mechanisms of NE uptake and granule storage, such as opioids, cocaine, tramadol, tricyclic antidepressants sypathomimetrics, some antihypertensive and cardiovascular agents, and antipsychotics (see detail in Table 7).[118] In addition, foods containing vanillin and catecholamine-like compounds (e.g., chocolate and blue cheese) should be stopped.[120,121] A subanalysis of data from the ADMIRE-HF study showed that neuropsychiatric medications with high potency can result in a falsely low HMR and thus an overestimation of cardiac risk.[122]

There are differing views regarding the need for pre-test administration of iodine to prevent thyroid uptake of I-123. Historically, such blockade had been undertaken to shield the thyroid from exposure to unbound radionuclide iodine impurities, but with modern production methods the amount of these is minimal, and many feel that pre-treatment is unnecessary. Nevertheless, a recent study showed that even with an ^{123}I-*m*IBG preparation of 98% radiochemical purity, unblocked patients have a 50% higher 4-hour thyroid accumulation of unbound ^{123}I compared with pre-treated patients, with an estimated 70-mGy exposure from a 10-mCi administered dose.[123] Thus, it is recommended that pre-treatment should be individually determined, to be considered in perhaps younger patients, but less worthwhile in elderly patients with multiple comorbidities and potential risk of iodine allergy. If desired, thyroid blockade can be achieved with oral administration of solutions of potassium iodide or Lugol's (130-mg iodide for adults, body weight adjusted for children), or for patients allergic to iodine, potassium perchlorate (500 mg for adults, weight adjusted for children), orally administered at least 30 minutes prior to *m*IBG injection.[118]

Older studies used a dose of 3 to 5 mCi [111 to 185 megabecquerels (MBq)] administered over 1 minute. However, as it is often difficult to obtain satisfactory SPECT images using these doses, especially in patients with severe cardiac dysfunction, investigators have recently been using up to 10 mCi (370 MBq).[80,115] A 10-mCi dose results in radiation exposure of approximately 5 mSv, with highest exposure to the bladder, liver, spleen, gall bladder, heart, and adrenals; the absorbed dose may be higher in patients with severe renal impairment.[118]

It has been recommended that patients lie quietly in a supine position for about 5 to 15 minutes before administration. As initial images are acquired a few minutes later, the patient should be lying under the camera or in close proximity. The tracer is then administered slowly over 1 to 2 minutes, followed by a saline flush.

Adverse Reactions

Adverse reactions to ^{123}I-*m*IBG are uncommon. Among the side effects reported when ^{123}I-*m*IBG is administered too quickly are palpitations, shortness of breath, heat sensations, transient hypertension, and abdominal cramps. A rare anaphylactic reaction is also possible.[118]

Imaging Techniques

While acquisition and processing of planar and SPECT ^{123}I-*m*IBG images are most often performed with techniques typical for perfusion imaging, there are special issues that need to be considered that will likely result in changes in methodology over time. The current key parameters for ^{123}I-*m*IBG image interpretation—HMR and washout—require accurate and robust quantitative analysis of counts in the heart and adjacent background regions, and thus could vary in relation to issues, such as the acquisition field of view, the type of collimator used, and how the multiple energy emissions of ^{123}I are taken into account during acquisition and processing. In addition, data in the literature are based on images obtained without using correction for attenuation, Compton scatter or depth-dependent loss of spatial resolution, with use of such techniques likely to produce different values. Finally, increased use of solid-state cameras will likely produce different quantitative ^{123}I-*m*IBG results from what has been reported for standard Anger cameras.

Anterior planar ^{123}I-*m*IBG images are acquired for 10 minutes with the patient supine approximately 15 minutes (early) and beginning approximately 3 hours, 50 minutes (late) after tracer administration, and stored in a 128 x 128 or 256 x 256 matrix.[115,118] The imaging field of view should include as much of the heart and upper chest as possible, with avoidance of positioning the heart too close to the edge of the field or too close to the center. Positioning should be consistent for the early and late planar images.

With a large field of view, anterior planar image is important for obtaining the desired HMR. The technique for obtaining suitably equivalent images from small-field-of-view SPECT cameras is unclear. In a report from a pilot group of 67 subjects, HMRs calculated from

SPECT images using mean counts between heart and mediastinum volumes of interest drawn on transaxial images were equivalent to those obtained by planar techniques for differentiating subjects with normal versus abnormal *m*IBG uptake.[124] More investigations are required to validate this further, including for images obtained with solid-state cameras.

Although the utility of SPECT imaging assessment of regional defects is currently uncertain, based on theoretic consideration[106,125,126] and some literature data particularly for primary arrhythmias,[96-100] tomographic acquisitions are commonly performed immediately following both the early and late planar images. They are obtained with a minimum of 60 projections at 30 seconds/stop over a 180° arc (45° right anterior oblique to 45°left posterior oblique) and stored in a 64 9 64 matrix.

Much literature is based on ^{123}I-*m*IBG image acquisition using low-energy high-resolution (LEHR) collimators, with a symmetrically centered energy window of 20% around the main 159-keV isotope photopeak. However, HMR values vary depending on the collimator used, different for low-energy versus medium-energy collimators, but also varying among different low-energy collimator brands.[127-129] In part these differences relate to ^{123}I also emitting multiple low-abundance high-energy (≥400 keV) photons, especially a 529-keV emission. While on an intrinsic ^{123}I spectrum, the higher energy emissions are small in relation to the principle 159-keV peak, a low-energy collimator blocks many of the 159-keV emissions while allowing septal penetration of the higher energy photons that degrade image quality and affect accuracy of quantitative values, such as HMR.[130,131] Although most clinical literature is based on use of a LEHR, in fact the reported HMRs are severely underestimated in relation to the true value.[132] Several methods have been explored attempting to overcome this problem when an LEHR is used, including mathematical deconvolution of septal penetration (DSP),[130] image acquisition using ^{123}I-dual window acquisition (IDW),[133] decreasing the 159-kEV energy window to 15%.[132] Although it has been suggested that a medium-energy collimator may be preferred,[129] use of a calibration phantom to derive a conversion coefficient for each camera-collimation system may be a better approach.[134,135]

There have been recent reports on the ^{123}I-*m*IBG imaging with solid-state cameras. While data from these are encouraging, given the aforementioned discussion, one must consider the image that derived quantitative parameters from these camera(s) may differ from those reported in the literature upon which clinical use is recommended.[136-138] Solid-state cameras may provide the image resolution and detail necessary for higher quality SPECT images that can allow assessment of regional sympathetic activity that might be superior to HMR in predicting adverse cardiac events, particularly arrhythmias.[139]

Derivation of the HMR and Washout (Figures 12, 13)

As the HMR is currently the key result of a ^{123}I-*m*IBG study, it is important it be derived in a standard way. While there have been attempts to automate the process,[140] at present the standard is to manually draw the cardiac and mediastinal regions of interest (ROI).

While various techniques have been reported for deriving heart counts,[141-143] the currently accepted method[118] is an irregular ROI defining the epicardial border of the heart, as this technique permits the most consistency and results in the best estimate of cardiac uptake in counts per pixel. If the myocardium is not visualized well, the ROI should be based on the presumed location of the heart. One should try to avoid adjacent lung and liver, but counts from these organs sometimes need to be included if that is the only way to get sufficient myocardial counts. Mediastinal counts are derived from a square ROI (7 x 7 pixels) in the upper mediastinum below the lung apices and midway between the lungs, and within these constraints positioning the ROI in the area of lowest counts. Mediastinal counts per pixel are determined. The HMR is then calculated by dividing the mean counts/pixel in the total myocardium ROI by the mean counts/pixel in the mediastinal ROI. The technique appears to be fairly robust with a recent study showing only minimal, inconsequential changes in HMR when there are changes in the visually defined heart ROI.[144]

Although there are various methods of washout rate determination reported, recent European guidelines indicate the following.[118]

$$WR_{BKGcorrected} = \frac{(H_e - M_e) - (H_l - M_l) \times 1.21}{(H_e - M_e)} \times 100:$$

*^{123}I decay corrected for 3 hour and 45 minutes, e is the early images, l the late images, BKG the background, H the heart counts per pixel, M the mediastinal counts per pixel, and WR is the washout rate.

There is some controversy regarding whether background subtraction should be performed. Obtaining the WR without background subtraction has been shown to result in lower variability, but also lower value.[145]

Table 7. Important medications that may affect organ uptake of *m*IBG

Drug		Mechanism of interference (known or expected)	Discontinuation prior to *m*IBG scan (days)
Opioids		Uptake inhibition	7–14
Cocaine		Uptake inhibition	7–14
Tramadol		Uptake inhibition	7–14
Tricyclic antidepressants		Uptake inhibition	7–21
	Amitriptyline and derivatives, imipramine and derivatives, amoxapine, doxepine, others		
Sympathicomimetics[a]		Depletion of granules	7–14
	Phenylpropanolamine, ephedrine, pseudoephedrine, phenylephrine, amphetamine, dopamine, isoproterenol, salbutamol, terbutaline, phenoterol, xylometazoline		
Antihypertensive/cardiovascular agents		Inhibition uptake and depletion	21
	Labetalol		
	Reserpine	Depletion and transport inhibition	14
	Bretylium, guanethidine	Depletion and transport inhibition	14
	Calcium channel blockers (nifepidine, nicardipine, amlodipine)	Increased uptake and retention	14
Antipsychotics		Uptake inhibition	21–28
	Phenothiazines[b] (chloropromazine, promethazine, fluphenazine, others)		
	Thioxanthenes (maprotiline, trazolone)	Uptake inhibition	21–28
	Butyrophenones (droperidol, haloperidol)	Uptake inhibition	21–28
	Loxapine	Uptake inhibition	7–21

Modified from Bombardieri et al[146]
[a]Components of bronchodilators, decongestants, and diet aids
[b]Frequent components of antiemetic and antiallergic agents

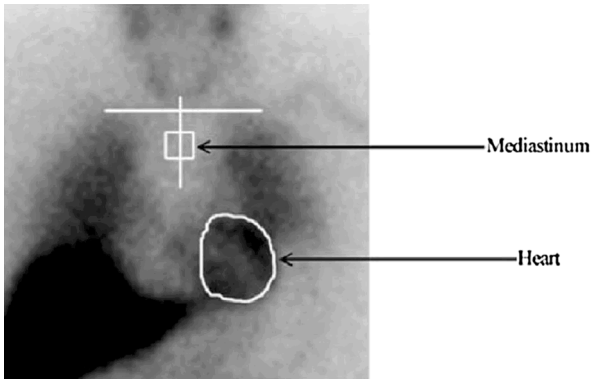

Figure 12. Heart-to-mediastinal ratio (HMR) determination. Illustration of creation of ROI for determination of the heart-to-mediastinal ratio (HMR or H/M): The following steps are recommended: (1) **Heart counts:** Draw an irregular ROI defining the epicardial border of the heart, with visual determination of the valve plane. If the myocardium is not visualized well, draw the ROI based on the presumed location of the heart. Try to avoid adjacent lung and liver, but counts from these organs sometimes need to be included if that is the only way to get sufficient myocardial counts. (2) **Mediastinal counts:** (a) Draw a horizontal line to mark the estimated location of the lung apices. If the superior aspect of the image does not include the lung apices because of a limited field of view camera, draw this line at the top of the image display. (b) Draw a vertical line approximately equidistant from the medial aspects of the right and left lungs. (c) Examine the counts for the 12 pixels along the vertical line starting 4 pixels at the horizontal/vertical line intersection point. Identify the pixel with the lowest number of counts; if more than one, choose the most superior. Draw a 7 x 7 square ROI around the pixel. (d) Calculate HMR by dividing the counts/pixel in the total myocardium ROI by the counts/pixel in the 7 x 7 mediastinal ROI.

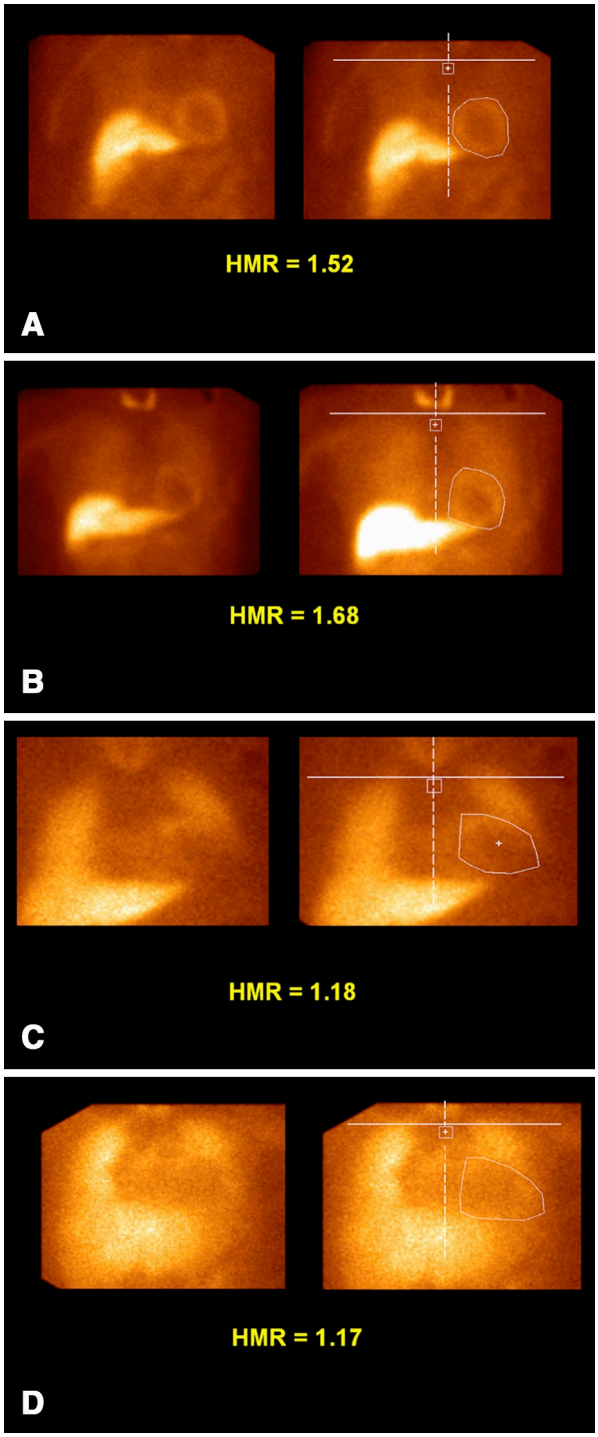

Figure 13. Examples of HMR. Case Examples: (A) Easily seen myocardial border well separated from liver and without signif- icant lung activity. HMR = 1.52; (B) Easily seen myocardial border but with contiguous liver. Myocardial ROI drawn as close to epicardial border as possible with avoidance of liver.
HMR = 1.68; (C) Low cardiac counts with adjacent lung activity. Myocardial ROI drawn as close to epicardial border as possible with avoidance of lung. HMR = 1.18; and (D) Barely seen cardiac counts with adjacent lung activity. Myocardial ROI drawn estimating epicardial border with minimization of lung inclusion.

APPENDIX 1

Serving sizes are based on commonly eaten portions, pharmaceutical instructions, or the amount of the leading-selling container size. For example, beverages sold in 16-ounce or 20-ounce bottles were counted as one serving.

(Data from the Center for Science in the Public Interest: http://www.cspinet.org/new/cafchart.htm).[147] Right for republication requested through the Copyright Clearing House.

Caffeine found in common foods and beverages

	Serving size	Caffeine (mg)
Coffees		
Dunkin' Donuts Coffee with Turbo Shot	Large, 20 fl. oz.	436
Starbucks Coffee	Venti, 20 fl. oz.	415
Starbucks Coffee	Grande, 16 fl. oz.	330
Panera Frozen Mocha	16.5 fl. oz. Tall, 12	267
Starbucks Coffee	fl. oz. Grande, 16 fl.	260
Starbucks Caffè Americano	oz. Regular, 16.8 fl.	225
Panera Coffee	oz. Venti, 24 fl. oz.	189
Starbucks Espresso Frappuccino	Medium, 14 fl. oz.	185
Dunkin' Donuts Coffee	Grande, 16 fl. oz.	178
Starbucks Caffè Mocha	Grande, 16 fl. oz.	175
Starbucks Iced Coffee	2 Tbs., makes 12 fl. oz.	165
Maxwell House Ground Coffee—100% Colombian, Dark Roast, Master Blend, or Original Roast		100–160
Dunkin' Donuts Cappuccino	Large, 20 fl. oz.	151
Starbucks—Caffè Latte, Cappuccino, or Caramel Macchiato	Grande, 16 fl. oz.	150
Starbucks Espresso	Doppio, 2 fl. oz.	150
Keurig Coffee K-Cup, all varieties Folgers	1 cup, makes 8 fl. oz.	75–150
Classic Roast Instant Coffee Starbucks	2 tsp., makes 12 fl. oz.	148
Doubleshot Energy Coffee, can Starbucks	15 fl. oz.	146
Mocha Frappuccino	Venti, 24 fl. oz.	140
Starbucks VIA House Blend Instant Coffee	1 packet, makes 8 fl. oz.	135
McDonald's Coffee	Large, 16 fl. oz.	133
Maxwell House International Café, all flavors	2 Tbs., makes 12-16 fl. oz.	40–130
Seattle's Best Coffee—Iced Latte or Iced Mocha, can	9.5 fl. oz.	90
Starbucks Frappuccino Coffee, bottle	9.5 fl. oz.	90
International Delight Iced Coffee	8 fl. oz.	76
Maxwell House Lite Ground Coffee	2 Tbs., makes 12 fl. oz.	50–70
Dunkin' Donuts, Panera, or Starbucks Decaf Coffee	16 fl. oz.	15–25
Maxwell House Decaf Ground Coffee	2 Tbs., makes 12 fl. oz.	2–10
Teas		
Starbucks Tazo Awake—Brewed Tea or Tea Latte	Grande, 16 fl. oz.	135
Starbucks Tazo Earl Grey—Brewed Tea or Tea Latte	Grande, 16 fl. oz.	115
Starbucks Tazo Chai Tea Latte	Grande, 16 fl. oz.	95
Starbucks Tazo Green Tea Latte—Iced or regular	Grande, 16 fl. oz.	80
Black tea, brewed for 3 minutes	8 fl. oz.	30–80
Snapple Lemon Tea	16 fl. oz.	62
Lipton Pure Leaf Iced Tea	18.5 fl. Oz.	60
Green tea, brewed for 3 minutes	8 fl. oz.	35–60
Lipton 100% Natural Lemon Iced Tea, bottle	20 fl. oz.	35

	Serving size	Caffeine (mg)
Arizona Iced Tea, black, all varieties	16 fl. oz.	30
Nestea Unsweetened Iced Tea Mix	2 tsp., makes 8 fl. oz.	20–30
Arizona Iced Tea, green, all varieties	16 fl. oz.	15
Lipton Decaffeinated Tea—black or green, brewed	8 fl. oz.	5
Herbal Tea, brewed	8 fl. oz.	0
Soft drinks		
FDA official limit for cola and pepper soft drinks	12 oz.	71 (200 parts per million)
Pepsi MAX	12 oz.	69
Mountain Zevia (Zevia)	12 oz.	55
Mountain Dew, regular or diet	12 oz.	54 (20 oz. = 90)
Diet Coke	12 oz.	47 (20 oz. = 78)
Dr Pepper or Sunkist, regular or diet	12 oz.	41 (20 oz. = 68)
Pepsi	12 oz.	38 (20 oz. = 63)
Coca-Cola, Coke Zero, or Diet Pepsi	12 oz.	35 (20 oz. = 58)
Barq's Root Beer, regular	12 oz.	23 (20 oz. = 38)
7-Up, Fanta, Fresca, ginger ale, or Sprite	12 oz.	0
Root beer, most brands, or Barq's Diet Root Beer	12 oz.	0
Energy drinks		
Bang Energy Drink	16 fl. oz.	357
Redline Energy Drink	8 fl. oz.	316
Jolt Energy Drink	23.5 fl. oz.	280
Rockstar Citrus Punched	16 fl. oz.	240
NOS Active Sports Drink (Coca-Cola)	22 fl. oz.	221
5-hour Energy	1.9 fl. oz.	208
Full Throttle	16 fl. oz.	200
Monster Energy	16 fl. oz.	160
Rockstar	16 fl. oz.	160
Venom Energy Drink (Dr Pepper/Seven Up Inc.)	16 fl. oz.	160
NOS Energy Drink (Coca-Cola)	16 fl. oz.	160
AMP Energy Boost Original (PepsiCo)	16 fl. oz.	142
NoDoz Energy Shots	1.89 fl. oz.	115
Mountain Dew Kick Start	16 fl. oz.	92
Red Bull	8.4 fl. oz.	80
V8 V-Fusion?Energy	8 fl. oz.	80
Playboy Energy Drink	8.4 fl. oz.	70
Ocean Spray Cran-Energy	20 fl. oz.	55
Glacéau Vitaminwater Energy	20 fl. oz.	50
Starbucks Refreshers	12 fl. oz.	50
Caffeinated snack foods		
Crackheads[2]	1 box, 40g	600
Crackheads Espresso Bean Candies, regular	1 package, 28 pieces	200
Wired Waffles	1 waffle	200
Perky Jerky	1 package, 1 oz.	150
Arma Potato Chips	1 package, 2 oz.	70
Cracker Jack'D	1 package, 2 oz.	70
MiO Energy, all flavors	1 squirt, 1/2 tsp.	60
Crystal Light Energy	1/2 packet	60
Jelly Belly Extreme Sport Beans	1 package, 1 oz.	50
Jolt Gum	1 piece	45
Alert Gum	1 piece	40
Blue Diamond Almonds, Roasted Coffee Flavored	1 oz.	25

	Serving size	Caffeine (mg)
Ice cream & yogurt		
Bang!! Caffeinated Ice Cream	4 fl. oz.	125
Cold Stone Creamery Mocha Ice Cream	Gotta Have It, 12 fl. oz.	52
Starbucks Coffee Ice Cream	4 fl. oz.	45
TCBY Coffee Frozen Yogurt	Large, 13.4 fl. oz.	42
Dannon All Natural Coffee Lowfat Yogurt	6 oz.	30
Häagen-Dazs Coffee Ice Cream	4 fl. oz.	29
Stonyfield Gotta Have Java Nonfat Frozen Yogurt	4 fl. oz.	28
Starbucks Mocha Frappuccino Ice Cream	4 fl. oz.	25
Baskin Robbins Jamoca Ice Cream	4 fl. oz.	20
Dreyer's or Edy's Grand Ice Cream—Coffee or Espresso Chip	4 fl. oz.	17
Breyers Coffee Ice Cream	4 fl. oz.	1
Häagen-Dazs Coffee Almond Crunch Snack Size Bar	1.8 oz.	10
Dreyer's, Edy's, or Häagen-Dazs Chocolate Ice Cream	4 fl. oz.	Less than 1
Chocolate Candy & Chocolate Drinks		
Starbucks Hot Chocolate	Grande, 16 fl. oz.	25
Hershey's Special Dark Chocolate Bar	1.5 oz.	20
Hershey's—Milk Chocolate Bar	1.6 oz.	9
Hershey's Kisses	9 pieces, 1.4 oz.	9
Hershey's Cocoa	1 Tbs.	8
Dove Dark Chocolate Silky Smooth Promises	5 pieces, 1.4 oz.	4
Silk Chocolate Soymilk	8 fl. oz.	4
Hershey's Chocolate Lowfat Milk, bottle	12 fl. oz.	2
Over-The-Counter Pills		
Zantrex-3 weight-loss supplement	2 capsules	300
NoDoz, Vivarin, or over the counter caffeine tablets	1 caplet	200
Excedrin Migraine	2 tablets	130
Midol Complete	2 caplets	120
Bayer Back & Body	2 caplets	65
Anacin	2 tablets	64

References

1. Myers J, Arena R, Franklin B, Pina I, Kraus WE, McInnis K, et al. Recommendations for clinical exercise laboratories: A scientific statement from the American Heart Association. Circulation 2009;119:3144-61.
2. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: A scientific statement from the American Heart Association. Circulation 2013;128:873-934.
3. Myers J, Forman DE, Balady GJ, Franklin BA, Nelson-Worel J, Martin BJ, et al. Supervision of exercise testing by nonphysicians: A scientific statement from the American Heart Association. Circulation 2014;130:1014-27.
4. Mieres JH, Gulati M, Bairey Merz N, Berman DS, Gerber TC, Hayes SN, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: A consensus statement from the American Heart Association. Circulation 2014;130:350-79.
5. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: Executive summary: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Nucl Cardiol 2015;22:162-215.
6. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's guide to cardiopulmonary exercise testing in adults: A scientific statement from the American Heart Association. Circulation 2010;122:191-225.
7. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1-23.
8. Zoghbi GJ, Dorfman TA, Iskandrian AE. The effects of medications on myocardial perfusion. J Am Coll Cardiol 2008;52:401-16.
9. Dilsizian VGH, Gewirtz H, Paivanas N, Kitsiou AN, Hage FG, Crone NE, et al. Serious and potentially life 1735 threatening complications of cardiac stress testing: Physiological 1736 mechanisms and management strategies. J Nucl Cardiol 2015;1737(22):1198-213.

10. Bokhari S, Ficaro EP, McCallister BD Jr. Adenosine stress protocols for myocardial perfusion imaging. J Nucl Cardiol 2007;14:415-6.
11. Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imaging: Results from the adenoscan multicenter trial registry. J Am Coll Cardiol 1994;23:384-9.
12. Thomas GS, Miyamoto MI. Should simultaneous exercise become the standard for adenosine myocardial perfusion imaging? Am J Cardiol 2004;94:3D-10D.
13. Iskandrian AE, Bateman TM, Belardinelli L, Blackburn B, Cerqueira MD, Hendel RC, et al. Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: Results of the ADVANCE phase 3 multicenter international trial. J Nucl Cardiol 2007;14:645-58.
14. Agarwal V, DePuey EG. Regadenoson and seizures: A real clinical concern. J Nucl Cardiol 2014;21:869-70.
15. Page RL 2nd, Spurck P, Bainbridge JL, Michalek J, Quaife RA. Seizures associated with regadenoson: A case series. J Nucl Cardiol 2012;19:389-91.
16. Cabrera R, Husain Z, Palani G, Karthikeyan AS, Choudhry Z, Dhanalakota S, et al. Comparison of hemodynamic and stress testing variables in patients undergoing regadenoson stress myocardial perfusion imaging to regadenoson with adjunctive low-level exercise myocardial perfusion imaging. J Nucl Cardiol 2013;20:336-43.
17. Thomas GS, Thompson RC, Miyamoto MI, Ip TK, Rice DL, Milikien D, et al. The RegEx trial: A randomized, double-blind, placebo- and active-controlled pilot study combining regadenoson, a selective a(2a) adenosine agonist, with low-level exercise, in patients undergoing myocardial perfusion imaging. J Nucl Cardiol 2009;16:63-72.
18. AlJaroudi WA, Alraies MC, Cerquiera MD, Jaber WA. Safety and tolerability of regadenoson in 514 SPECT mpi patients with and without coronary artery disease and submaximal exercise heart rate response. Eur J Nucl Med Mol Imaging 2013;40:341-8.
19. Parker MW, Morales DC, Slim HB, Karthikeyan AS, Choudhry Z, Dhanalakota S, et al. A strategy of symptom-limited exercise with regadenoson-as-needed for stress myocardial perfusion imaging: A randomized controlled trial. J Nucl Cardiol 2013;20:185-96.
20. Ross MI, Wu E, Wilkins JT, Gupta D, Shen S, Aulwes D, et al. Safety and feasibility of adjunctive regadenoson injection at peak exercise during exercise myocardial perfusion imaging: The Both Exercise and Regadenoson Stress Test (BERST) trial. J Nucl Cardiol 2013;20:197-204.
21. Thompson RC, Patil H, Thompson EC, Thomas GS, Al-Amoodi M, Kennedy KF, et al. Regadenoson pharmacologic stress for myocardial perfusion imaging: A three-way comparison between regadenoson administered at peak exercise, during walk recovery, or no-exercise. J Nucl Cardiol 2013;20:214-21.
22. Lette J, Tatum JL, Fraser S, Miller DD, Waters DD, Heller G, et al. Safety of dipyridamole testing in 73,806 patients: The multicenter dipyridamole safety study. J Nucl Cardiol 1995;2:3-17.
23. Candell-Riera J, Santana-Boado C, Castell-Conesa J, Aguadé-Bruix S, Olona M, Palet J, et al. Simultaneous dipyridamole/maximal subjective exercise with 99mtc-mibi SPECT: Improved diagnostic yield in coronary artery disease. J Am Coll Cardiol 1997;29:531-6.
24. Casale PN, Guiney TE, Strauss HW, Boucher CA. Simultaneous low level treadmill exercise and intravenous dipyridamole stress thallium imaging. Am J Cardiol 1988;62:799-802.
25. Stern S, Greenberg ID, Corne RA. Quantification of walking exercise required for improvement of dipyridamole thallium-201 image quality. J Nucl Med 1992;33:2061-6.
26. Vitola JV, Brambatti JC, Caligaris F, Lesse CR, Nogueira PR, Joaquim AI, et al. Exercise supplementation to dipyridamole prevents hypotension, improves electrocardiogram sensitivity, and increases heart-to-liver activity ratio on tc-99m sestamibi imaging. J Nucl Cardiol 2001;8:652-9.
27. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium-201 tomography for evaluating patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. J Am Coll Cardiol 1993;21:1583-90.
28. Marwick T, Willemart B, D'Hondt AM, Baudhuin T, Wijns W, Detry JM, et al. Selection of the optimal nonexercise stress for the evaluation of ischemic regional myocardial dysfunction and malperfusion. Comparison of dobutamine and adenosine using echocardiography and 99mtc-mibi single photon emission computed tomography. Circulation 1993;87:345-54.
29. Johnston DL, Scanlon PD, Hodge DO, Glynn RB, Hung JC, Gibbons RJ. Pulmonary function monitoring during adenosine myocardial perfusion scintigraphy in patients with chronic obstructive pulmonary disease. Mayo Clin Proc 1999;74:339-46.
30. Reyes E, Loong CY, Wechalekar K, Latus K, Anagnostopoulos C, Underwood SR. Side effect profile and tolerability of adenosine myocardial perfusion scintigraphy in patients with mild asthma or chronic obstructive pulmonary disease. J Nucl Cardiol 2007;14:827-34.
31. Sundram F, Notghi A, Smith NB. Pharmacological stress myocardial perfusion scintigraphy: Use of a modified adenosine protocol in patients with asthma. Nucl Med Commun 2009;30:217-25.
32. Leaker BR, O'Connor B, Hansel TT, Barnes PJ, Meng L, Mathur VS, et al. Safety of regadenoson, an adenosine A2A receptor agonist for myocardial perfusion imaging, in mild asthma and moderate asthma patients: A randomized, double-blind, placebo-controlled trial. J Nucl Cardiol 2008;15:329-36.
33. Thomas GS, Tammelin BR, Schiffman GL, Marquez R, Rice DL, Milikien D, et al. Safety of regadenoson, a selective adenosine A2A agonist, in patients with chronic obstructive pulmonary disease: A randomized, double-blind, placebo-controlled trial (RegCOPD trial). J Nucl Cardiol 2008;15:319-28.
34. Golzar Y, Doukky R. Regadenoson use in patients with chronic obstructive pulmonary disease: The state of current knowledge. Int J Chron Obstruct Pulmon Dis 2014;9:129-37.
35. Prenner BM, Bukofzer S, Behm S, Feaheny K, McNutt BE. A randomized, double-blind, placebo-controlled study assessing the safety and tolerability of regadenoson in subjects with asthma or chronic obstructive pulmonary disease. J Nucl Cardiol 2012;19:681-92.
36. Gordi T, Blackburn B, Lieu H. Regadenoson pharmacokinetics and tolerability in subjects with impaired renal function. J Clin Pharmacol 2007;47:825-33.
37. Aljaroudi W, Iqbal F, Koneru J, Bhambhvani P, Heo J, Iskandrian AE. Safety of regadenoson in patients with end-stage liver disease. J Nucl Cardiol 2011;18:90-5.
38. Ananthasubramaniam K, Weiss R, McNutt B, Klauke B, Feaheny K, Bukofzer S. A randomized, double-blind, placebo-controlled study of the safety and tolerance of regadenoson in subjects with stage 3 or 4 chronic kidney disease. J Nucl Cardiol 2012;19:319-29.
39. Doukky R, Rangel MO, Wassouf M, Dick R, Alqaid A. Morales Demori R. The safety and tolerability of regadenoson in patients with end-stage renal disease: The first prospective evaluation. J Nucl Cardiol 2013;20:205-13.
40. Laighold S, Druz R. Initial clinical experience with a selective A2A receptor agonist, regadenoson, in a patient with end-stage renal disease on hemodialysis. J Nucl Cardiol 2009;16:478-80.

41. Palani G, Husain Z, Salinas RC, Karthikeyan V, Karthikeyan AS, Ananthasubramaniam K. Safety of regadenoson as a pharmacologic stress agent for myocardial perfusion imaging in chronic kidney disease patients not on hemodialysis. J Nucl Cardiol 2011;18:605-11.
42. Avakian SD, Grinberg M, Meneguetti JC, Ramires JA, Mansur AP. SPECT dipyridamole scintigraphy for detecting coronary artery disease in patients with isolated severe aortic stenosis. Int J Cardiol 2001;81:21-7.
43. Demirkol MO, Yaymaci B, Debes H, Basaran Y, Turan F. Dipyridamole myocardial perfusion tomography in patients with severe aortic stenosis. Cardiology 2002;97:37-42.
44. Kupari M, Virtanen KS, Turto H, Viitasalo M, Mänttäri M, Lindroos M, et al. Exclusion of coronary artery disease by exercise thallium-201 tomography in patients with aortic valve stenosis. Am J Cardiol 1992;70:635-40.
45. Burgstahler C, Kunze M, Gawaz MP, Rasche V, Wöhrle J, Hombach V, et al. Adenosine stress first pass perfusion for the detection of coronary artery disease in patients with aortic stenosis: A feasibility study. Int J Cardiovasc Imaging 2008;24:195-200.
46. Patsilinakos SP, Kranidis AI, Antonelis IP, Filippatos G, Houssianakou IK, Zamanis NI, et al. Detection of coronary artery disease in patients with severe aortic stenosis with noninvasive methods. Angiology 1999;50:309-17.
47. Patsilinakos SP, Spanodimos S, Rontoyanni F, Kranidis A, Antonelis IP, Sotirellos K, et al. Adenosine stress myocardial perfusion tomographic imaging in patients with significant aortic stenosis. J Nucl Cardiol 2004;11:20-5.
48. Samuels B, Kiat H, Friedman JD, Berman DS. Adenosine pharmacologic stress myocardial perfusion tomographic imaging in patients with significant aortic stenosis. Diagnostic efficacy and comparison of clinical, hemodynamic and electrocardiographic variables with 100 age-matched control subjects. J Am Coll Cardiol 1995;25:99-106.
49. Cremer PC, Khalaf S, Lou J, Rodriguez L, Cerqueira MD, Jaber WA. Stress positron emission tomography is safe and can guide coronary revascularization in high-risk patients being considered for transcatheter aortic valve replacement. J Nucl Cardiol 2014;21:1001-10.
50. Lentine KL, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: A scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2012;60:434-80.
51. Giedd KN, Bokhari S, Daniele TP, Johnson LL. Sinus arrest during adenosine stress testing in liver transplant recipients with graft failure: Three case reports and a review of the literature. J Nucl Cardiol 2005;12:696-702.
52. Kovacs D, Pivonka R, Khosla PG, Khosla S. Effect of caffeine on myocardial perfusion imaging using single photon emission computed tomography during adenosine pharmacologic stress. Am J Ther 2008;15:431-4.
53. Bottcher M, Czernin J, Sun KT, Phelps ME, Schelbert HR. Effect of caffeine on myocardial blood flow at rest and during pharmacological vasodilation. J Nucl Med 1995;36:2016-21.
54. Kubo S, Tadamura E, Toyoda H, Mamede M, Yamamuro M, Magata Y, et al. Effect of caffeine intake on myocardial hyperemic flow induced by adenosine triphosphate and dipyridamole. J Nucl Med 2004;45:730-8.
55. Lapeyre AC 3rd, Goraya TY, Johnston DL, Gibbons RJ. The impact of caffeine on vasodilator stress perfusion studies. J Nucl Cardiol 2004;11:506-11.
56. Salcedo J, Kern MJ. Effects of caffeine and theophylline on coronary hyperemia induced by adenosine or dipyridamole. Catheter Cardiovasc Interv 2009;74:598-605.
57. Smits P, Aengevaeren WR, Corstens FH, Thien T. Caffeine reduces dipyridamole-induced myocardial ischemia. J Nucl Med 1989;30:1723-6.
58. Smits P, Corstens FH, Aengevaeren WR, Wackers FJ, Thien T. False-negative dipyridamole-thallium-201 myocardial imaging after caffeine infusion. J Nucl Med 1991;32:1538-41.
59. Aqel RA, Zoghbi GJ, Trimm JR, Baldwin SA, Iskandrian AE. Effect of caffeine administered intravenously on intracoronary-administered adenosine-induced coronary hemodynamics in patients with coronary artery disease. Am J Cardiol 2004;93:343-6.
60. Hage FG, Iskandrian AE. The effect of caffeine on adenosine myocardial perfusion imaging: Time to reassess? J Nucl Cardiol 2012;19:415-9.
61. Reyes E, Loong CY, Harbinson M, Donovan J, Anagnostopoulos C, Underwood SR. High-dose adenosine overcomes the attenuation of myocardial perfusion reserve caused by caffeine. J Am Coll Cardiol 2008;52:2008-16.
62. Lee JC, Fraser JF, Barnett AG, Johnson LP, Wilson MG, McHenry CM, et al. Effect of caffeine on adenosine-induced reversible perfusion defects assessed by automated analysis. J Nucl Cardiol 2012;19:474-81.
63. Zoghbi GJ, Htay T, Aqel R, Blackmon L, Heo J, Iskandrian AE. Effect of caffeine on ischemia detection by adenosine single-photon emission computed tomography perfusion imaging. J Am Coll Cardiol 2006;47:2296-302.
64. Zhao G, Messina E, Xu X, Ochoa M, Sun HL, Leung K, et al. Caffeine attenuates the duration of coronary vasodilation and changes in hemodynamics induced by regadenoson (cvt-3146), a novel adenosine A2A receptor agonist. J Cardiovasc Pharmacol 2007;49:369-75.
65. Gaemperli O, Schepis T, Koepfli P, Siegrist PT, Fleischman S, Nguyen P, et al. Interaction of caffeine with regadenoson-induced hyperemic myocardial blood flow as measured by positron emission tomography: A randomized, double-blind, placebo-controlled crossover trial. J Am Coll Cardiol 2008;51:328-9.
66. Tejani FH, Thompson RC, Kristy R, Bukofzer S. Effect of caffeine on SPECT myocardial perfusion imaging during regadenoson pharmacologic stress: A prospective, randomized, multicenter study. Int J Cardiovasc Imaging 2014;30:979-89.
67. Depuey EG, Mahmarian JJ, Miller TD, Einstein AJ, Hansen CL, Holly TA, et al. Patient-centered imaging. J Nucl Cardiol 2012;19:185-215.
68. Fazel R, Gerber TC, Balter S, Brenner DJ, Carr JJ, Cerqueira MD, et al. Approaches to enhancing radiation safety in cardiovascular imaging: A scientific statement from the American Heart Association. Circulation 2014;130:1730-48.
69. Einstein AJ, Pascual TN, Mercuri M, Karthikeyan G, Vitola JV, Mahmarian JJ, et al. Current worldwide nuclear cardiology practices and radiation exposure: Results from the 65 country IAEA nuclear cardiology protocols cross-sectional study (INCAPS). Eur Heart J 2015;36:1689-96.
70. Einstein AJ, Tilkemeier P, Fazel R, Rakotoarivelo H, Shaw LJ, American Society of Nuclear Cardiology. Radiation safety in nuclear cardiology-current knowledge and practice: Results from the 2011 American Society of Nuclear Cardiology Member Survey. JAMA Intern Med 2013;173:1021-3.
71. Einstein AJ, Berman DS, Min JK, Hendel RC, Gerber TC, Carr JJ, et al. Patient-centered imaging: Shared decision making for cardiac imaging procedures with exposure to ionizing radiation. J Am Coll Cardiol 2014;63:1480-9.

72. DePuey EG, Bommireddipalli S, Clark J, Leykekhman A, Thompson LB, Friedman M. A comparison of the image quality of full-time myocardial perfusion SPECT vs wide beam reconstruction half-time and half-dose SPECT. J Nucl Cardiol 2011;18:273-80.
73. Duvall WL, Croft LB, Ginsberg ES, Einstein AJ, Guma KA, George T, et al. Reduced isotope dose and imaging time with a high-efficiency CZT SPECT camera. J Nucl Cardiol 2011;18:847-57.
74. Einstein AJ, Blankstein R, Andrews H, Fish M, Padgett R, Hayes SW, et al. Comparison of image quality, myocardial perfusion, and left ventricular function between standard imaging and single-injection ultra-low-dose imaging using a high-efficiency SPECT camera: The millisievert study. J Nucl Med 2014;55:1430-7.
75. Machac J, Bacharach SL, Bateman TM, Bax JJ, Beanlands R, Bengel F, et al. Positron emission tomography myocardial perfusion and glucose metabolism imaging. J Nucl Cardiol 2006;13:e121-51.
76. Hansen CL, Goldstein RA, Akinboboye OO, Berman DS, Botvinick EH, Churchwell KB, et al. Myocardial perfusion and function: Single photon emission computed tomography. J Nucl Cardiol 2007;14:e39-60.
77. Chang SM, Nabi F, Xu J, Raza U, Mahmarian JJ. Normal stress-only versus standard stress/rest myocardial perfusion imaging: Similar patient mortality with reduced radiation exposure. J Am Coll Cardiol 2010;55:221-30.
78. Duvall WL, Wijetunga MN, Klein TM, Razzouk L, Godbold J, Croft LB, et al. The prognosis of a normal stress-only tc-99m myocardial perfusion imaging study. J Nucl Cardiol 2010;17:370-7.
79. Gibson PB, Demus D, Noto R, Hudson W, Johnson LL. Low event rate for stress-only perfusion imaging in patients evaluated for chest pain. J Am Coll Cardiol 2002;39:999-1004.
80. Flotats A, Carrio I. Cardiac neurotransmission SPECT imaging. J Nucl Cardiol 2004;11:587-602.
81. Haider N, Baliga RR, Chandrashekhar Y, Narula J. Adrenergic excess, hNET1 down-regulation, and compromised mIBG uptake in heart failure poverty in the presence of plenty. JACC Cardiovasc Imaging 2010;3:71-5.
82. Hattori N, Schwaiger M. Metaiodobenzylguanidine scintigraphy of the heart: What have we learnt clinically? Eur J Nucl Med 2000;27:1-6.
83. Sisson JC, Wieland DM. Radiolabeled meta-iodobenzylguanidine: Pharmacology and clinical studies. Am J Physiol Imaging 1986;1:96-103.
84. Kline RC, Swanson DP, Wieland DM, Thrall JH, Gross MD, Pitt B, et al. Myocardial imaging in man with I-123 meta-iodobenzylguanidine. J Nucl Med 1981;22:129-32.
85. Raffel DM, Wieland DM. Development of mibg as a cardiac innervation imaging agent. JACC Cardiovasc Imaging 2010;3:111-6.
86. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective admire-hf (adreview myocardial imaging for risk evaluation in heart failure) study. J Am Coll Cardiol 2010;55:2212-21.
87. Merlet P, Valette H, Dubois-Rande JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. J Nucl Med 1992;33:471-7.
88. Nakata T, Nakajima K, Yamashina S, Yamada T, Momose M, Kasama S, et al. A pooled analysis of multicenter cohort studies of (123)I-mIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. JACC Cardiovasc Imaging 2013;6:772-84.
89. Ogita H, Shimonagata T, Fukunami M, Kumagai K, Yamada T, Asano Y, et al. Prognostic significance of cardiac (123)I metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: A prospective study. Heart 2001;86:656-60.
90. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial ^{123}I-metaiodobenzylguanidine (mIBG) parameters in patients with heart failure: A systematic review. Eur Heart J 2008;29:1147-59.
91. Travin MI. Cardiac autonomic imaging with SPECT tracers. J Nucl Cardiol 2013;20:128-43.
92. Al Badarin FJ, Wimmer AP, Kennedy KF, Jacobson AF, Bateman TM. The utility of admire-hf risk score in predicting serious arrhythmic events in heart failure patients: Incremental prog- nostic benefit of cardiac ^{123}I-mIBG scintigraphy. J Nucl Cardiol 2014;21:756-62.
93. Arora R, Ferrick KJ, Nakata T, Kaplan RC, Rozengarten M, Latif F, et al. I-123 mIBG imaging and heart rate variability analysis to predict the need for an implantable cardioverter defibrillator. J Nucl Cardiol 2003;10:121-31.
94. Klein T, Dilsizian V, Cao Q, Chen W, Dickfeld TM. The potential role of iodine-123 metaiodobenzylguanidine imaging for identifying sustained ventricular tachycardia in patients with cardiomyopathy. Curr Cardiol Rep 2013;15:359.
95. Nagahara D, Nakata T, Hashimoto A, Wakabayashi T, Kyuma M, Noda R, et al. Predicting the need for an implantable cardioverter defibrillator using cardiac metaiodobenzylguanidine activity together with plasma natriuretic peptide concentration or left ventricular function. J Nucl Med 2008;49:225-33.
96. Miranda CH, Figueiredo AB, Maciel BC, Marin-Neto JA, Simoes MV. Sustained ventricular tachycardia is associated with regional myocardial sympathetic denervation assessed with ^{123}i-metaiodobenzylguanidine in chronic chagas cardiomyopathy. J Nucl Med 2011;52:504-10.
97. Mitrani RD, Klein LS, Miles WM, Hackett FK, Burt RW, Wellman HN, et al. Regional cardiac sympathetic denervation in patients with ventricular tachycardia in the absence of coronary artery disease. J Am Coll Cardiol 1993;22:1344-53.
98. Paul M, Schafers M, Kies P, Acil T, Schäfers K, Breithardt G, et al. Impact of sympathetic innervation on recurrent life- threatening arrhythmias in the follow-up of patients with idio- pathic ventricular fibrillation. Eur J Nucl Med Mol Imaging 2006;33:866-70.
99. Paul M, Wichter T, Kies P, Gerss J, Wollmann C, Rahbar K, et al. Cardiac sympathetic dysfunction in genotyped patients with arrhythmogenic right ventricular cardiomyopathy and risk of recurrent ventricular tachyarrhythmias. J Nucl Med 2011;52:1559-65.
100. Wichter T, Matheja P, Eckardt L, Kies P, Schäfers K, Schulze-Bahr E, et al. Cardiac autonomic dysfunction in brugada syndrome. Circulation 2002;105:702-6.
101. Tomoda H, Yoshioka K, Shiina Y, Tagawa R, Ide M, Suzuki Y. Regional sympathetic denervation detected by iodine 123 metaiodobenzylguanidine in non-q-wave myocardial infarction and unstable angina. Am Heart J 1994;128:452-8.
102. Watanabe K, Takahashi T, Miyajima S, Hirokawa Y, Tanabe N, Kato K, et al. Myocardial sympathetic denervation, fatty acid metabolism, and left ventricular wall motion in vasospastic angina. J Nucl Med 2002;43:1476-81.
103. Fallavollita JA, Canty JM Jr. Dysinnervated but viable myocardium in ischemic heart disease. J Nucl Cardiol 2010;17:1107-15.
104. Fallavollita JA, Heavey BM, Luisi AJ Jr, Michalek SM, Baldwa S, Mashtare TL Jr, et al. Regional myocardial sympathetic

denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. J Am Coll Cardiol 2014;63:141-9.
105. McGhie AI, Corbett JR, Akers MS, Kulkarni P, Sills MN, Kremers M, et al. Regional cardiac adrenergic function using I-123 meta-iodobenzylguanidine tomographic imaging after acute myocardial infarction. Am J Cardiol 1991;67:236-42.
106. Simoes MV, Barthel P, Matsunari I, Nekolla SG, Schömig A, Schwaiger M, et al. Presence of sympathetically denervated but viable myocardium and its electrophysiologic correlates after early revascularised, acute myocardial infarction. Eur Heart J 2004;25:551-7.
107. Stanton MS, Tuli MM, Radtke NL, Heger JJ, Miles WM, Mock BH, et al. Regional sympathetic denervation after myocardial infarction in humans detected noninvasively using I-123-metaiodobenzylguanidine. J Am Coll Cardiol 1989;14:1519-26.
108. Bengel FM, Ueberfuhr P, Schiepel N, Nekolla SG, Reichart B, Schwaiger M. Effect of sympathetic reinnervation on cardiac performance after heart transplantation. N Engl J Med 2001;345:731-8.
109. Flotats A, Carrio I. Value of radionuclide studies in cardiac transplantation. Ann Nucl Med 2006;20:13-21.
110. Gerson MC, McGuire N, Wagoner LE. Sympathetic nervous system function as measured by I-123 metaiodobenzylguanidine predicts transplant-free survival in heart failure patients with idiopathic dilated cardiomyopathy. J Card Fail 2003;9:384-91.
111. Hattori N, Tamaki N, Hayashi T, Masuda I, Kudoh T, Tateno M, et al. Regional abnormality of iodine-123-mIBG in diabetic hearts. J Nucl Med 1996;37:1985-90.
112. Nagamachi S, Fujita S, Nishii R, Futami S, Tamura S, Mizuta M, et al. Prognostic value of cardiac i-123 metaiodobenzylguanidine imaging in patients with non-insulin-dependent diabetes mellitus. J Nucl Cardiol 2006;13:34-42.
113. Carrio I, Estorch M, Berna L, Lopez-Pousa J, Tabernero J, Torres G. Indium-111-antimyosin and iodine-123-mIBG studies in early assessment of doxorubicin cardiotoxicity. J Nucl Med 1995;36:2044-9.
114. Sciammarella M, Gerson M, Buxton AE, Bartley SC, Doukky R, Merlino DA, et al. Model coverage policy: Myocardial sympathetic innervation imaging: Iodine-123 meta-iodobenzylguanidine (^{123}I-mIBG). J Nucl Cardiol 2015;22:804-11.
115. Jacobson AF, Lombard J, Banerjee G, Camici PG. ^{123}I-mIBG scintigraphy to predict risk for adverse cardiac outcomes in heart failure patients: Design of two prospective multicenter international trials. J Nucl Cardiol 2009;16:113-21.
116. Agostini D, Carrio I, Verberne HJ. How to use myocardial ^{123}I-mIBG scintigraphy in chronic heart failure. Eur J Nucl Med Mol Imaging 2009;36:555-9.
117. Carrio I, Cowie MR, Yamazaki J, Udelson J, Camici PG. Cardiac sympathetic imaging with mIBG in heart failure. JACC Cardiovasc Imaging 2010;3:92-100.
118. Flotats A, Carrio I, Agostini D, Le Guludec D, Marcassa C, Schäfers M, et al. Proposal for standardization of ^{123}i-metaiodobenzylguanidine (mIBG) cardiac sympathetic imaging by the eanm cardiovascular committee and the european council of nuclear Cardiology Eur J Nucl Med Mol Imaging 2010;37:1802-12.
119. Yamashina S, Yamazaki J. Neuronal imaging using SPECT. Eur J Nucl Med Mol Imaging 2007;34(Suppl 1):S62-73.
120. Solanki KK, Bomanji J, Moyes J, Mather SJ, Trainer PJ, Britton KE. A pharmacological guide to medicines which interfere with the biodistribution of radiolabelled meta-iodobenzylguanidine (mibg). Nucl Med Commun 1992;13:513-21.
121. Wafelman AR, Hoefnagel CA, Maes RA, Beijnen JH. Radioiodinated metaiodobenzylguanidine: A review of its biodistribution and pharmacokinetics, drug interactions, cytotoxicity and dosimetry. Eur J Nucl Med 1994;21:545-59.
122. Jacobson A, Travin M. Impact of neuropsychiatric medications on cardiac uptake of ^{123}I- mIBG in heart failure subjects. J Nucl Med 2013;54:1708.
123. Friedman NC, Hassan A, Grady E, Matsuoka DT, Jacobson AF. Efficacy of thyroid blockade on thyroid radioiodine uptake in ^{123}I-mIBG imaging. J Nucl Med 2014;55:211-5.
124. Chen J, Folks RD, Verdes L, Manatunga DN, Jacobson AF, Garcia EV. Quantitative i-123 mIBG SPECT in differentiating abnormal and normal mibg myocardial uptake. J Nucl Cardiol 2012;19:92-9.
125. Inoue H, Zipes DP. Results of sympathetic denervation in the canine heart: Supersensitivity that may be arrhythmogenic. Circulation 1987;75:877-87.
126. Minardo JD, Tuli MM, Mock BH, Weiner RE, Pride HP, Wellman HN, et al. Scintigraphic and electrophysiological evidence of canine myocardial sympathetic denervation and reinnervation produced by myocardial infarction or phenol application. Circulation 1988;78:1008-19.
127. Dobbeleir AA, Hambye AS, Franken PR. Influence of high-energy photons on the spectrum of iodine-123 with low- and medium-energy collimators: Consequences for imaging with 123i-labelled compounds in clinical practice. Eur J Nucl Med 1999;26:655-8.
128. Inoue Y, Suzuki A, Shirouzu I, Machida T, Yoshizawa Y, Akita F, et al. Effect of collimator choice on quantitative assessment of cardiac iodine 123 mIBG uptake. J Nucl Cardiol 2003;10:623-32.
129. Verberne HJ, Feenstra C, de Jong WM, Somsen GA, van Eck-Smit BL, Busemann Sokole E. Influence of collimator choice and simulated clinical conditions on ^{123}I-mIBG heart/mediastinum ratios: A phantom study. Eur J Nucl Med 2005;32:1100-7.
130. Chen J, Garcia EV, Galt JR, Folks RD, Carrio I. Optimized acquisition and processing protocols for i-123 cardiac SPECT imaging. J Nucl Cardiol 2006;13:251-60.
131. Chen J, Garcia EV, Galt JR, Folks RD, Carrio I. Improved quantification in 123i cardiac SPECT imaging with deconvolution of septal penetration. Nucl Med Commun 2006;27:551-8.
132. Inoue Y, Abe Y, Itoh Y, Asano Y, Kikuchi K, Sakamoto Y, et al. Acquisition protocols and correction methods for estimation of the heart-to-mediastinum ratio in ^{123}I-metaiodobenzylguanidine cardiac sympathetic imaging. J Nucl Med 2013;54:707-713.
133. Matsuo S, Nakajima K, Okuda K, Kawano M, Ishikawa T, Hosoya T, et al. Standardization of the heart-to-mediastinum ratio of ^{123}i-labelled-metaiodobenzylguanidine uptake using the dual energy window method: Feasibility of correction with different camera-collimator combinations. Eur J Nucl Med 2009;36:560-6.
134. Nakajima K, Okuda K, Matsuo S, Yoshita M, Taki J, Yamada M, et al. Standardization of metaiodobenzylguanidine heart to mediastinum ratio using a calibration phantom: Effects of correction on normal databases and a multicentre study. Eur J Nucl Med 2012;39:113-9.
135. Nakajima K, Okuda K, Yoshimura M, Matsuo S, Wakabayashi H, Imanishi Y, et al. Multicenter cross-calibration of i-123 metaiodobenzylguanidine heart-to-mediastinum ratios to overcome camera-collimator variations. J Nucl Cardiol 2014;21:970-8.
136. Bellevre D, Manrique A, Legallois D, Bross S, Baavour R, Roth N, et al. First determination of the heart-to-mediastinum ratio in i-123-mIBG cardiac adrenergic CZT imaging in patients with heart failure. A d-SPECT versus a-SPECT prospective study. Eur J Nucl Med Mol Imaging 2015;42:1912-9.
137. Rouzet F, De Paola Chequer R, Milliner M, BenAzzouna R, Mikail N, Askienazy S, et al. Comparison of mIBG heart-to-

mediastinum ratio determined on conventional and cardiac CZT camera. J Nucl Med 2014;55(supplement 1):133.
138. Strydhorst J, Wells RG, Ruddy T. Phantom validation of ^{123}I-mIBG imaging with a dedicated solid state SPECT camera. J Nucl Med 2014;55(supplement 1):1689.
139. Gimelli A, Liga R, Giorgetti A, Genovesi D, Marzullo P. Assessment of myocardial adrenergic innervation with a solid-state dedicated cardiac cadmium-zinc-telluride camera: First clinical experience. Eur Heart J Cardiovasc Imaging 2014;15: 575-85.
140. Okuda K, Nakajima K, Hosoya T, Ishikawa T, Konishi T, Matsubara K, et al. Semi-automated algorithm for calculating heart-to-mediastinum ratio in cardiac iodine-123 mIBG imaging. J Nucl Cardiol 2011;18:82-9.
141. Agostini D, Belin A, Amar MH, Darlas Y, Hamon M, Grollier G, et al. Improvement of cardiac neuronal function after carvedilol treatment in dilated cardiomyopathy: A ^{123}I-mIBG scintigraphic study. J Nucl Med 2000;41:845-51.
142. Gerson MC, Craft LL, McGuire N, Suresh DP, Abraham WT, Wagoner LE. Carvedilol improves left ventricular function in heart failure patients with idiopathic dilated cardiomyopathy and a wide range of sympathetic nervous system function as measured by iodine 123 metaiodobenzylguanidine. J Nucl Cardiol 2002;9:608-15.
143. Yamada T, Shimonagata T, Fukunami M, Kumagai K, Ogita H, Hirata A, et al. Comparison of the prognostic value of cardiac iodine-123 metaiodobenzylguanidine imaging and heart rate variability in patients with chronic heart failure: A prospective study. J Am Coll Cardiol 2003;41:231-8.
144. Jacobson AF, Matsuoka DT. Influence of myocardial region of interest definition on quantitative analysis of planar ^{123}I-mIBG images. Eur J Nucl Med Mol Imaging 2013;40:558-64.
145. Veltman CE, Boogers MJ, Meinardi JE, Al Younis I, Dibbets-Schneider P, Van der Wall EE, et al. Reproducibility of planar (123)i-meta-iodobenzylguanidine (mIBG) myocardial scintigraphy in patients with heart failure. Eur J Nucl Med Mol Imaging 2012;39:1599-608.
146. Bombardieri E, Giammarile F, Aktolun C, Baum RP, Bischof Delaloye A, Maffioli L, et al. 131i/^{123}I-metaiodobenzylguanidine (mIBG) scintigraphy: Procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging 2003;30:132-9.
147. Center for Science in the Public Interest. Caffeine content of food & drugs. 2014.Table containing the caffeine content of food and drugs. http://www.cspinet.org/new/cafchart.htm.