Stress only myocardial perfusion imaging: Is it time for a change?

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Stress single photon emission computed tomographic (SPECT) myocardial perfusion imaging has enjoyed great success over the past several decades as the modality of choice for accurately diagnosing and risk stratifying patients with suspected or known coronary artery disease. Same-day low-dose rest/high-dose stress imaging protocols have generally been widely adopted for this purpose. However, recent studies indicate that rest imaging may be unnecessary in patients with a normal initial stress SPECT. Elimination of the additional imaging would decrease costs, streamline patient evaluations, and reduce radiation exposure. SPECT imaging guidelines should be revised to reflect this new information.

Key Words: Stress-only imaging • radiation • myocardial perfusion imaging • SPECT • diagnostic and prognostic application

INTRODUCTION

At various stages during the development of a technique, it becomes necessary to reassess what we do and how best to do it. This is particularly true as the clinical landscape changes and external forces reshape what has been traditionally referred to as ''the norm''. Stress single photon emission computed tomographic myocardial perfusion imaging (SPECT) is no exception. Stress SPECT has enjoyed great success over the past several decades as a technique for accurately diagnosing[1] and risk stratifying[2] patients with suspected or known coronary artery disease (CAD). However, it is currently being challenged by other imaging modalities particularly in light of national emphasis on cost containment, streamlining patient evaluations, and reducing radiation exposure from medical imaging.

There are several SPECT imaging protocols recommended by the American Society of Nuclear Cardiology (ASNC) in their guidelines which incorporate the separate or combined use (i.e., dual isotope approach) of thallium (Tl)-201 and technetium (Tc)-99m radiopharmaceuticals.[3,4] The high energy Tc-99m based radiopharmaceuticals have gained considerable popularity over the years because they afford improved image quality and thereby increased diagnostic accuracy as compared to that obtained with Tl-201.[1,5] Protocols exclusively using Tc-99m sestamibi or tetrofosmin can be performed all in one day as an initial rest followed by stress (or stress followed by rest) acquisition or as a two-day protocol in patients with a high body mass index. The same day low-dose rest/high-dose stress protocol has been widely adopted since it allows acquisition of both image sets over a relatively short-time period and requires little physician involvement until the end of the day when the study is reviewed and an interpretation rendered. Since there is a requirement for two separate radiotracer injections, the radiation exposure from this protocol is relatively high at ~11–18 mSv (for Tc-99m tracers) and ~27–30 mSv (for dual isotope rest Tl-201/stress Tc-99m procedures).[6,7]

An alternative approach is a same day stress/rest imaging protocol where a relatively low dose of radiotracer is injected at peak stress (i.e., 8–15 mCi) with avoidance of the higher 25–35 mCi rest dose if the stress acquisition is normal. This affords a significant reduction in radiation exposure to patients who have a normal stress study and conserves Tc-99m which has become increasingly more difficult to obtain due to ongoing worldwide shortages. Conservation of Tc-99m translates into less reliance on Tl-201 with its associated higher radiation exposure (22 mSv for a 3.5 mCi dose).[6,7] Furthermore, a stress-only imaging protocol should

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improve laboratory efficiency by eliminating rest imaging in a sizeable percentage of patients, increase patient satisfaction and convenience by markedly decreasing their time spent at the laboratory and reduce cost by eliminating the higher second dose of radiotracer and the second imaging procedure.

We have been strong advocates of stress-only imaging and have effectively implemented this routinely in both our hospital and clinic-based laboratories for over a decade. Reluctance to more uniformly adopt stress-only imaging as the preferred protocol is primarily based on four fundamental issues: (1) the requirement to assess each patient at the time of their arrival to the laboratory so as to chose the most appropriate imaging protocol rather than a ''one test fits all'' approach; (2) the need for staff flexibility so as to manage daily patient flow; (3) the added demand on physicians to interpret, and with confidence, that a stress image is normal and prior to the administration of a rest dose; and (4) the lack of sufficient clinical data to demonstrate the safety of stress-only imaging over the integrated interpretation of two sets of images (stress and rest). A fifth reason for the success of a standard rest/stress protocol may be the additional reimbursement offered by insurance companies (including CMS) as compared to a single-stress SPECT acquisition alone. Thus, there is implicit disincentive for stress-only procedures where a physician must be readily available to interpret a study, ensure that the study is interpreted correctly as normal based on less image information and yet receive less remuneration for the added inconvenience.

Although all of these arguments have validity, the safety of a stress-only protocol and its questioned applicability to the heterogeneous group of patients referred each year for SPECT imaging are of paramount importance. A recent statement from ASNC in 2009 highlights these concerns indicating that ''the limited data available seem to support the physician-guided highly selective use of this logical [Imaging] approach'' but that it requires ''the interpreting physicians [to] be highly experienced [where] the interpreting physicians make the decisions about who will benefit from resting images.'' In conclusion, ''additional studies in this area are needed, particularly studies addressing clinical outcomes of patients who have decisions made on the basis of stress-only imaging. This strategy does not yet have sufficient data to support a widespread utilization''.[8]

PREVIOUS STUDIES USING STRESS-ONLY IMAGING

There are several published studies addressing the feasibility of stress-only imaging and subsequent patient outcome. Gibson et al. evaluated 652 patients with a low to intermediate probability of CAD who underwent stress-only imaging (with the aid of attenuation correction techniques) and were then followed for a mean of 22.3 months.[9] Most of the patients (93%) were stressed using treadmill exercise, with the remaining receiving pharmacologic stress with dipyridamole. Thirty-seven percent would have required rest imaging but were interpreted as normal on the basis of attenuation-corrected images. The overall cardiac event rate was low a 0.6% with no cardiac deaths and only 1 nonfatal myocardial infarction. Similarly, Gal et al. followed 116 patients after a normal stress-only SPECT with a subsequent annual 0.9% mortality rate.[10] In a more recent study by Bateman et al., half-time stress-only images acquired with attenuation correction were compared to standard rest-stress images in the same 110 patients.[11] Interpretation of the images was performed by consensus of two readers blinded to the study acquisition. Image interpretation as definitely normal or definitely abnormal was similar with a stress-only (95%) vs a rest-stress (88%) approach. Among the 92 patients (84%) who had coronary angiography, the diagnostic accuracy was similar for half-time stress-only images with attenuation correction as compared to rest/stress imaging (Figure 1).

All of these studies suggest that stress-only imaging may be an attractive alternative to conventional rest/stress procedures but are limited by their relatively small sample sizes and short patient follow-up.

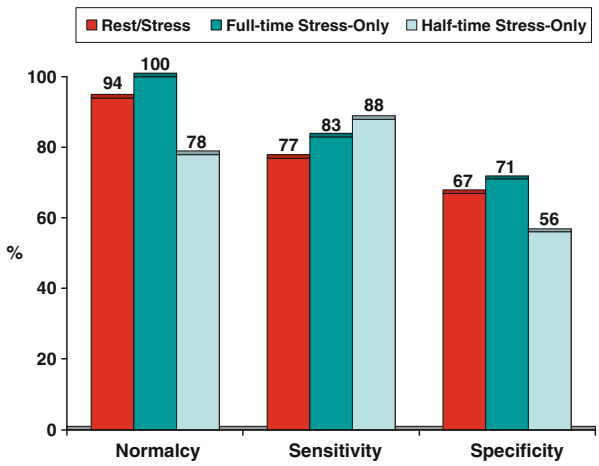

Figure 1. Diagnostic accuracy of rest/stress (*red bars*) as compared to full-time stress-only images (*dark aqua bars*) and half-time stress-only images (*light aqua bars*) with attenuation correction. There were no statistical differences between half-time stress-only vs rest/stress or half-time stress-only vs full-time stress-only results. From Bateman et al.[11]

RECENT PUBLICATION

In an attempt to clarify the safety and generalizability of stress-only imaging in a heterogeneous patient population referred for SPECT, we recently compared standard stress/rest (or rest/stress) imaging to stress-only imaging in 16,854 consecutive patients who had a normal gated stress SPECT study and were followed for a median of 4.5 years (25th and 75th percentiles: 2.7 and 6.6 years, respectively).[12] The primary endpoint was overall mortality which was determined from the Social Security Death Index. Consistent with other studies,[13-15] our cohort with normal SPECT studies represented ~60% of the 27,540 total patients imaged over an 8-year-time period, with 29% (8,034) undergoing a stress-only procedure.

Baseline Patient Characteristics

The study population was diverse in that 56% were women, 27% had diabetes and 31% had a history of CAD or myocardial infarction. In the 69% of patients without known CAD, most (6,764 or 58%) had at least an intermediate pretest likelihood for CAD. The major indications for performing SPECT were evaluation of chest pain (12,281 or 73%) or exertional dyspnea (994 or 5.9%); and preoperative clearance (2,010 or 11.9%). Treadmill exercise was used as the stressor in 5,487 patients (32.6%) whereas most (11,367 or 67.4%) received pharmacologic stress with either adenosine (62.9%) or dobutamine (4.5%).

Protocol Decisions

The imaging protocol chosen was individualized for a given patient based on consideration of body weight and habitus. The routine protocol in our laboratory is to perform stress imaging first as either a same day low dose stress (8–15 mCi)/high-dose rest (25–40 mCi) procedure or as a 2-day high-dose stress/high-dose rest procedure in patients weighing >200 lb or in women with $a > C$ breast cup size. Rest imaging is performed as the initial test only in those who present to the laboratory late in the afternoon or report caffeine intake within 12 h of a scheduled pharmacologic vasodilator stress test. In this regard, most patients (77%) had stress imaging as their initial procedure. Another important issue is that stress-only studies were not restricted to thin patients. Rather, weight was used only to determine the initial isotope dose and not the imaging protocol. Thirty-eight percent of all stress-only patients weighed > 200 lb and 53% of all patients weighing > 200 lb had stress-only imaging. In this regard, our study results were applicable to patients of all body weights.

Criteria for a Normal Stress-Only Study

Although this was a retrospective study, the criteria for interpreting a study as normal were rigorous and routinely applied to all patients throughout the 8-year period. There was also consistency in interpretation with only two cardiologists reading all of the studies and only one after year 2001. Initial stress images were interpreted based on integration of the rotating raw projection data, the reoriented tomographic perfusion images, the gated SPECT information, and the quantified polar plot SPECT perfusion results. A study was interpreted as normal only if perfusion was assessed to be homogeneous throughout the myocardium, left ventricular (LV) cavity size was normal, the LV ejection fraction was ≥50% with normal regional wall motion, and the quantified perfusion defect size was 0% at 2.5 standard deviations. Subsequent rest imaging was performed if the stress images did not fulfill these criteria and were therefore deemed to be either abnormal or equivocal. Unlike other studies, attenuation-corrected images were reviewed only to confirm that a study was normal but were not otherwise used in the decision process. We did not perform rest imaging based on other findings such as increased lung uptake, right ventricular uptake, evidence of coronary artery calcification on a CT attenuation image, or an abnormal stress test result. Although these findings are considered clinically important and may indicate the presence of significant CAD in a patient with an otherwise normal set of stress-gated SPECT images, a normal set of rest images will not add any additional diagnostic or prognostic information if the stress images are already normal. Rather than performing rest imaging we generally recommend CT coronary angiography in our patients who have disparate perfusion and stress test results or in those whose symptoms are still highly suggestive of angina despite a normal gated SPECT study.

Impact of SPECT Protocol on Radiopharmaceutical Dosage and Radiation Exposure

The radiopharmaceutical dosage was 61% lower in the stress-only group (21.3 ± 10.7 mCi) vs those who had both stress and rest imaging (55.1 ± 11.9 mCi, $P < .001$) (Table 1). This was particularly true in the 29.4% of patients who received only a low stress-only dose (mean 13.5 ± 2 mCi, $P < .001$). An effective total body radiation exposure of <10 mSv is considered desirable with a reported <1 in 1,000 risk for developing cancer and $a < 1$ in 2000 risk of a fatal malignancy.[16,17] This level of exposure can be achieved with $a < 33$ mCi dose of Tc-99m sestamibi and $a < 38$ mCi dose of Tc-99m tetrofosmin.[6,7]

Table 1. SPECT protocol and Tc-99m radiopharmaceutical doses

	Total (N = 16,854)	Stress-only (N = 8034)	Stress and rest (N = 8820)	*P* value
Tc-99m dose (mCi)	39 ± 20	21.3 ± 10.7	55.1 ± 11.9	<.001
SPECT protocol				
Stress-only				
1. Low dose stress-only	4948 (29.4%)	4948 (61.6%)		
Tc-99m dose (mCi)	13.5 ± 2	13.5 ± 2	55.1 ± 11.9	<.001
2. High dose stress-only	3086 (18.3%)	3086 (38.4%)		
Tc-99m dose (mCi)	33.8 ± 6.2	33.8 ± 6.2	55.1 ± 11.9	<.001
Stress and rest				
1. Same day low dose/high dose stress with rest	5869 (34.8%)		5869 (66.5%)	
Tc-99m dose (mCi)	49.6 ± 4.9		49.6 ± 4.9	
2. Two-day low dose stress with low dose rest	217 (1.3%)		217 (2.5%)	
Tc-99 m dose (mCi)	28.3 ± 3.6		28.3 ± 3.6	
3. Two-day high dose stress with high dose rest	2734 (16.2%)		2734 (31.0%)	
Tc-99m dose (mCi)	68.9 ± 9.4		68.9 ± 9.4	

mCi, Millicuries; SPECT, single photon myocardial perfusion tomography; Tc-99m, technetium-99m.
From Chang et al.[12]

Based on these assumptions, and if administered Tc-99m sestamibi, 76% (or 6,125) of our 8,034 stress-only patients would have received $a < 10$ mSv exposure as compared to only 2.6% (or 231) of those undergoing stress/rest imaging ($P < .001$). If administered tetrofosmin, the percentages increase to 87% ($n = 7{,}009$) of stress-only patients vs 3.0% ($n = 266$) of stress/rest patients ($P < .001$). A <5 mSv exposure (comparable to prospective gating with CT coronary angiography) would have been possible in approximately 60% of all patients undergoing a stress-only procedure with either radiotracer. Overall, 6,356 (37.7%) and 7,275 (43.2%) of our entire cohort of patients with normal studies would have received a low (<10 mSv) radiation exposure with sestamibi and tetrofosmin using a stress-only protocol, respectively. This translates into approximately 25% of all 27,540 consecutive patients imaged in our laboratory over the same time period.

Mortality Rates Based on SPECT Protocol and in Specific Patient Subsets

The annual mortality rate for the entire cohort of 16,854 patients with a normal SPECT study was 2.74%. This translates into an estimated annual cardiac mortality of 0.8% assuming that 30% of all deaths are due to cardiac causes.[18,19] Patients undergoing pharmacologic stress are reported to have an annual cardiac mortality of 0.8% as compared to 0.15% among those undergoing exercise stress.[16] In the 5,487 patients (32.5%) who performed treadmill exercise, the annual all-cause mortality was 0.6% which translates into a comparable cardiac mortality of 0.18% using the aforementioned assumptions. Mortality rates were also significantly higher in the following patient subsets: older vs younger; diabetic vs nondiabetic; nonobese vs obese; inpatients vs outpatients; patients with vs those without CAD; patients undergoing pharmacologic vs treadmill exercise stress testing; and those with an intermediate vs a low Duke treadmill score. All of these observations are consistent with what is currently reported for such patient subgroups undergoing SPECT imaging and indicate that our cohort was representative of patients currently referred for SPECT.

Although mortality rates differed based on the above considerations, there were no significant differences in overall mortality rates (Figure 2) or in mortality rates among the important patient subgroups mentioned above based on stress-only vs stress + rest imaging (Figures 3, 4, and 5). In this regard, elimination of rest imaging in patients with normally appearing stress images was safe and did not result in a worse outcome due to misdiagnosis.

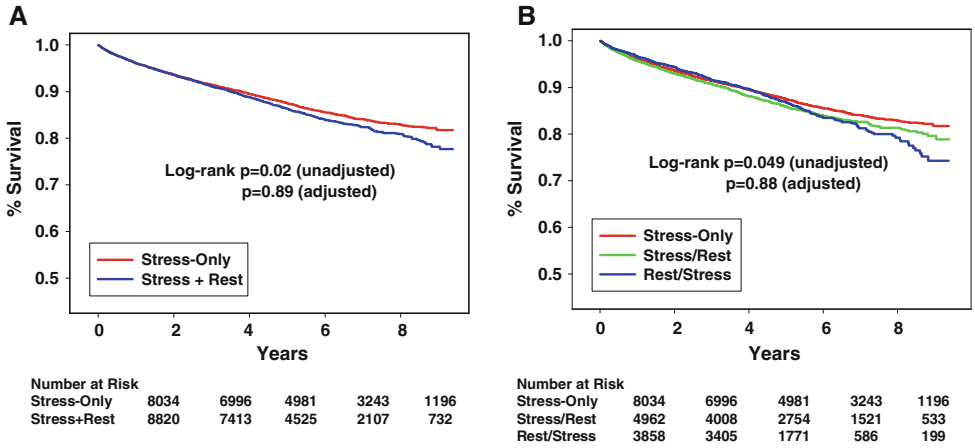

Figure 2. Survival curves for the entire cohort according to SPECT protocol based on whether patients with a normal single-photon emission computed tomographic myocardial perfusion imaging (SPECT) had stress-only vs additional rest imaging (**A**) or stress-only vs stress-rest or rest-stress imaging (**B**). From Chang et al.[12]

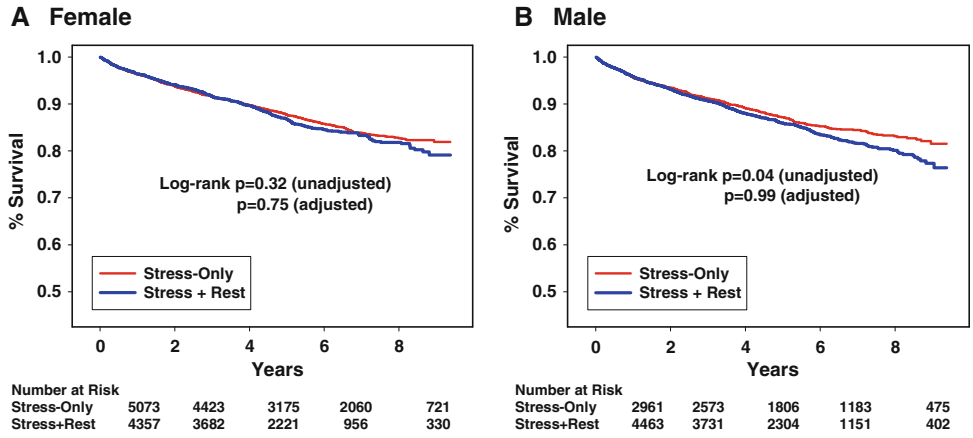

Figure 3. Survival curves based on female (**A**) or male (**B**) gender for each SPECT protocol. From Chang et al.[12]

CONCLUSION

Our results reinforce that additional rest imaging is unnecessary in patients with a normally appearing initial stress SPECT when the images are of good quality and can be interpreted confidently by an experienced reader. Stress-only imaging is applicable to the large majority of patients referred for SPECT imaging and only excludes those with clear evidence of previous myocardial infarction and/or known congestive heart failure. A strategy of initial stress imaging with selective rest imaging only among those with equivocal or clearly abnormal stress results should lower cost by eliminating unnecessary imaging time and radiopharmaceutical doses, improve laboratory throughput and significantly lower radiation exposure in a substantial percentage of patients. Since the publication of our results, another large study has reported similar findings with no difference in total or cardiac mortality among 4,910 patients undergoing stress-only vs conventional imaging who had normal test results.[20] There comes a time when change is necessary—our time is now. A stress/rest protocol should be embraced as the preferred imaging strategy for most patients and endorsed as such by ASNC in their imaging guidelines.

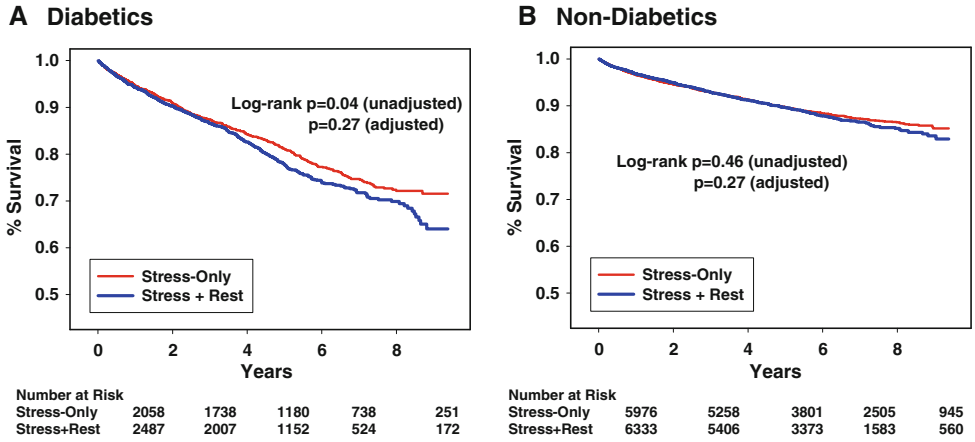

Figure 4. Survival curves based on the presence (**A**) or absence (**B**) of diabetes mellitus for each SPECT protocol. Diabetics had a significantly higher mortality rate than nondiabetics but death rates were similar in the 2 imaging protocols. From Chang et al.[12]

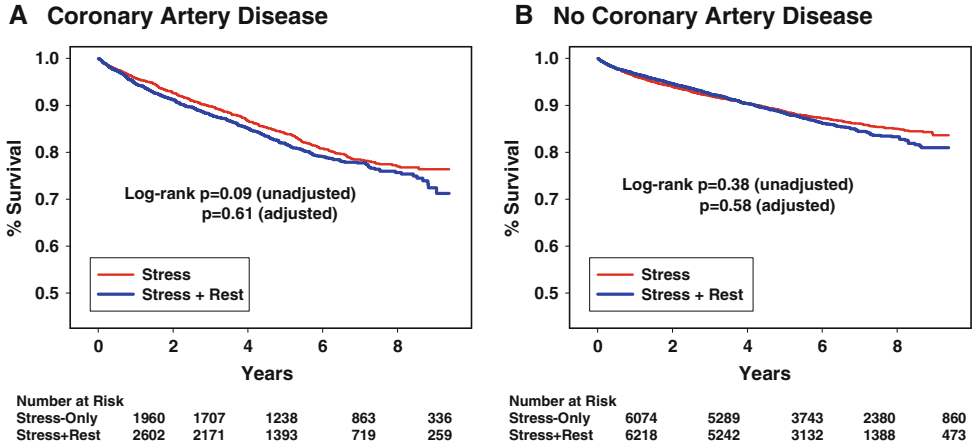

Figure 5. Survival curves based on the presence (**A**) or absence (**B**) of coronary artery disease (CAD) for each SPECT protocol. Patients with CAD had a higher mortality rate than non-CAD patients but irrespective of the imaging protocol used to evaluate them. From Chang et al.[12]

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