Value of Stress Myocardial Perfusion Single Photon Emission Computed Tomography in Patients With Normal Resting Electrocardiograms

An Evaluation of Incremental Prognostic Value and Cost-Effectiveness

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***Background*—**The incremental value and cost-effectiveness of stress single photon emission computed tomography (SPECT) is of unclear added value over clinical and exercise treadmill testing data in patients with normal resting ECGs, a patient subset known to be at relatively lower risk.

***Methods and Results*—**We identified 3058 consecutive patients who underwent exercise dual isotope SPECT, who on follow-up (mean, 1.6±0.5 years; 3.6% lost to follow-up) were found to have 70 hard events (2.3% hard-event rate). Survival analysis used a Cox proportional hazards model, and cost-effectiveness was determined by the cost per hard event identified by strategies with versus without the use of SPECT. In this cohort, a normal study was associated with an exceedingly low hard-event rate (0.4% per year) that increased significantly as a function of the SPECT result. After adjusting for pre-SPECT information, exercise stress SPECT yielded incremental value for the prediction of hard events (χ^2 52 to 85, $P<0.001$) and significantly stratified patients. In patients with intermediate to high likelihood of coronary artery disease after exercise treadmill testing, a cost-effectiveness ratio of $25 134 per hard event identified and a cost of $5417 per reclassification of patient risk were found. Subset analyses revealed similar prognostic, and cost results were present in men, women, and patients with and without prior histories of coronary artery disease.

***Conclusions*—**Stress SPECT yields incremental prognostic value and enhanced risk stratification in patients with normal resting ECGs in a cost-effective manner. These findings are opposite those of previous studies examining anatomic end points in this same population and thus, if confirmed, have significant implications for patient management. **(*Circulation*. 2002;105:823-829.)**

Key Words: radioisotopes ■ scintigraphy ■ exercise ■ cost-benefit analysis ■ follow-up studies

Coronary artery disease (CAD) remains the leading cause of death in the United States, and its associated costs are estimated to exceed $300 billion.[1] Attempts to reduce health-care costs by limiting the use of higher cost modalities has significant consequences for noninvasive testing.[2] Presently, the use of a modality in specific patient subsets must be justified by demonstrating that this use yields added value with respect to prognostic, risk stratification, and cost parameters.[2,3]

To date, several well-powered studies have demonstrated that stress myocardial perfusion SPECT yields incremental prognostic value over pre-SPECT data, enhances risk stratification, and, when, applied to appropriate patient populations, reduces costs, in part by decreasing the need for additional invasive evaluation.[4–11] Because the application of a relatively expensive test to a low-risk population results in the identification of relatively few higher risk patients at risk, thus adding little clinical value while resulting in a high cost-effectiveness ratio, the application of stress SPECT to lower risk cohorts has been called into question.[2,3] Hence, it is unclear if nuclear testing adds value over clinical and exercise treadmill testing (ETT) data in patients with normal resting ECG,[8,12–14] a patient subset known to be at relatively lower risk.

Previous studies in patients with normal resting ECG have found that exercise stress redistribution Tl-201 planar imaging fails to add incremental value over historical, clinical, and ETT data for the prediction of adverse events.[8] Exercise radionuclide

Received April 6, 2001; revision received November 29, 2001; accepted December 19, 2001.

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This work was presented in part at the annual scientific session of the Society of Nuclear Medicine, June 3–5, 1996, and published in abstract form (*J Nucl Med*. 1996;27:116P).

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/hc0702.103973**

angiography[13] and stress-redistribution thallium^{201} SPECT[12] have both been shown to add incremental value for the identification of severe anatomic CAD in patients with normal rest ECG, but with sufficiently low yield, so that the cost per reclassification was excessive and the authors questioned the appropriateness of applying testing to this patient group.

To the best of our knowledge, the incremental prognostic value of exercise SPECT in these patients has not been examined. The goals of the present study were to evaluate exercise stress myocardial perfusion SPECT in patients with normal resting ECG to determine its incremental prognostic value over pre-SPECT information, its ability to risk-stratify patients in a clinically relevant fashion, and its cost-effectiveness as part of a testing strategy.

Methods

Study Population

We identified 4572 consecutive patients who underwent exercise dual-isotope SPECT between January 15, 1991 and December 30, 1993. Patients with any abnormality on their resting ECG other than sinus bradycardia were excluded (N=1168), and 166 patients (3.6%) were lost to follow-up. The remaining 3238 patients were included in this study. Revascularization performed within 60 days after their index SPECT study is predominantly in response to SPECT results[15]; hence, the 180 patients undergoing early revascularization were also excluded from the prognostic analyses. Thus, the primary population of this study consisted of 3058 patients.

Exercise Myocardial Perfusion SPECT Protocol

Whenever possible, β-blockers and calcium channel antagonists were discontinued 48 hours before testing. Patients were initially injected intravenously at rest with thallium^{201} (2.5 to 3.5 mCi with dose variation based on patient weight). Rest thallium imaging was initiated 10 minutes after injection of the isotope.[16] Subsequently, patients underwent a symptom-limited treadmill exercise test using standard protocols with twelve-lead electrocardiographic recording of each minute of exercise and continuous monitoring of leads AVF, V1, and V5. At near-maximal exercise, a 25- to 35-mCi dose of technetium-99 m sestamibi was injected (actual patient dose varied with patient weight), and exercise was continued for 1 additional minute after injection.

Sestamibi SPECT acquisition was initiated 30 minutes after isotope injection.[16] SPECT studies were performed as previously described using a circular 180-degree acquisition for 64 projections at 20 seconds per projection.[16] During imaging, 2 energy windows were used for thallium^{201} (a 30% window centered on the 68- to 80-keV peak and a 10% window centered on the 167-keV peak), and a 15% window centered on the 140-keV peak was used for technetium-99 m sestamibi. No attenuation or scatter correction was used.

Image Interpretation

A semiquantitative visual interpretation was performed using 6 evenly spaced regions in the apical, midventricular, and basal slices of the short-axis views and 2 apical segments on the midventricular long-axis slice[4] (20 segments total). Each segment was scored by the consensus of 2 experienced observers using a 5-point scoring system (0 indicated normal; 1, equivocal; 2, moderate; 3, severe reduction of radioisotope uptake; and 4, absence of detectable tracer uptake in a segment) as previously described.[4]

The summed stress score and summed rest score were obtained by adding the scores of the 20 segments of the stress sestamibi and rest thallium images, respectively.[4] Summed stress scores <4 were considered normal, 4 to 8 were considered mildly abnormal, and >8 were considered moderately to severely abnormal. The sum of the differences between each of the 20 segments on the stress and rest images was defined as the summed difference score. Each of these variables incorporate both the extent and severity of perfusion defects, both of which independently add prognostic information.[17]

Patient Follow-Up

Patient follow-up was performed by scripted telephone interview by individuals blinded to the patients' test results. The mean follow-up interval was 1.6±0.5 years. Events were defined as either cardiac death or nonfatal myocardial infarction (MI). MI was said to have occurred if a patient presented with signs and symptoms suggestive of MI in addition to elevations of CK-MB or abnormal LDH profile, use of emergent percutaneous intervention or thrombolysis, new Q waves on ECG, or new Q waves or enzymatic increases sufficient to diagnose perioperative MI were noted. Cardiac death was defined as death attributable to any cardiovascular cause, as noted and confirmed by review of death certificate and hospital chart or physician's records. Patients included in this study were not contacted until at least 1 year after their index SPECT study.

Likelihood of Coronary Artery Disease

We used analysis of the pre- and post-ETT likelihood of CAD as a composite variable of proven prognostic importance, based on Bayesian analysis of patient data and calculated using CADENZA.[18] The pre-ETT likelihood of CAD included the patient's age, sex, presenting symptoms, resting blood pressure, smoking history, cholesterol, presence of glucose intolerance, and resting ECG (the latter normal in all patients). The post-ETT likelihood of CAD included the variables listed above as well as the exercise protocol used, exercise duration, maximum heart rate and blood pressure achieved, exertional hypotension, exercise induced symptoms, ST segment change, and slope.

Statistical Analysis

Comparisons between patient groups were performed using a one-way ANOVA for continuous variables and a χ^2 test for categorical variables. All continuous variables are described as mean±SD. $P<0.05$ was considered statistically significant.

Survival Analysis

Risk-adjusted, multivariable survival modeling was performed using a Cox proportional hazards model[19] in a stepwise fashion. Three distinct models were defined: (1) a pre-ETT model representing clinical and historical information; (2) a post-ETT model adjusted for (1); and (3) a final model adjusting for (2) and with the most predictive SPECT variables added. The end point for all models was the occurrence of hard events. The threshold for entry of variables into all models was $P<0.05$. A statistically significant increase in the global χ^2 of the model after the addition of the nuclear variables defined incremental prognostic value. Assumptions of proportional hazards, linearity, and additivity were examined.

Cost-Effectiveness

The incremental cost of stress SPECT in patients with low pre-ETT likelihood of CAD, low post-ETT likelihood of CAD, and intermediate to high post-ETT likelihood of CAD was examined as previously described.[4] Thus the cost of SPECT used for all cost analyses was $840, as in previous studies, to permit more direct comparisons to be made.

Reclassification

To replicate the analysis used in previous studies, we determined the number of patients who were reclassified with respect to their risk of adverse outcomes by the addition of SPECT data to pre-SPECT information. Multiple logistic regression modeling of the variables from the final survival analysis was used to calculate predicted likelihood of adverse outcomes on the basis of the post-ETT and SPECT models. After classification of patients by the post-ETT model as low ($\leq$1%) versus intermediate to high predicted risk ($>$1%), the number of reclassifications (change of risk category) by the results of the SPECT model was determined. The difference between correct reclassification (change in predicted risk from $>$1% to $\leq$1% in patients without events or from $\leq$1% to $>$1% in patients

TABLE 1. Patient Characteristics in Patients With Normal Resting Electrocardiogram

	No Hard Event	Hard Event
n	2988	70
Male sex	65% (1956)	74% (52)
Age	61±12	64±13*
Prior myocardial infarction	17% (520)	47% (33)†
Prior angiography	28% (837)	56% (39)†
Prior percutaneous intervention	12% (347)	26% (18)†
Prior coronary bypass surgery	10% (299)	16% (11)
Anginal symptoms	35% (1042)	51% (36)‡
Cardiac risk factors	1.3±1.0	1.7±1.1†
Pre-ETT Lk CAD	0.35±0.25	0.49±0.19†
Post-ETT Lk CAD	0.31±0.33	0.53±0.36†
% Maximum predicted heart rate	93±9.2	89±10†
Ischemic clinical response to exercise	9% (267)	29% (20)†
Ischemic ECG response to exercise	32% (936)	43% (30)§
Summed stress score	4.5±7.4	12.7±10.7†
Summed difference score	3.0±5.0	7.4±7.4†
Summed rest score	1.3±4.3	5.0±7.6†

Values are given as percent (n) or mean±SD. Lk indicates likelihood.

*$P<0.05$, †$P<0.001$, ‡$P<0.01$, §$0.05<P<0.10$ vs patients with no hard events.

with events) and incorrect reclassification (change in a patient's predicted risk from >1% to ≤1% in patients with events or from ≤1% to >1% in patients without events) was defined as the net change in reclassifications. Costs per reclassification of risk were calculated as above.

Results

Patient Characteristics

The 3058 patients included in the primary population are characterized in Table 1. Compared with the patients without hard events, patients with events were significantly older, more commonly had previous catheterization, MI, or percutaneous intervention, more frequently had anginal symptoms, had more cardiac risk factors, and had a greater pre-ETT likelihood of CAD. With respect to ETT, patients who had hard events achieved a lower percent of predicted maximal heart rate, had higher post-ETT likelihood of CAD, and more

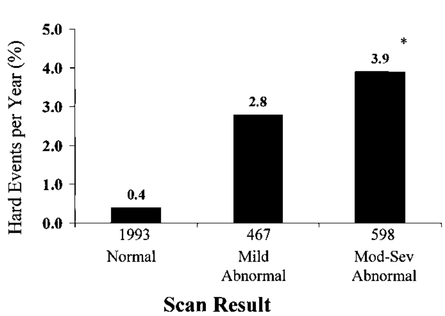

Figure 1. Annualized rates of hard events in patients with normal, mildly abnormal, and moderately to severely abnormal SPECT. Statistically significant increase in hard events occurred as a function of the SPECT result. Mod-Sev indicates moderately to severely abnormal. *$P<0.05$ across SPECT categories.

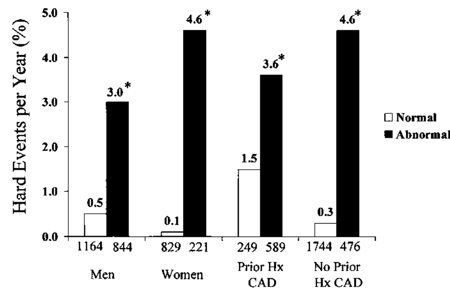

Figure 2. Annualized rates of hard events in patients with normal and abnormal SPECT in men, women, and patients with and without prior history of CAD. A statistically significant difference in hard events occurred as a function of the SPECT results. Hx indicates history. *$P<0.05$.

frequently had ischemic clinical responses to exercise. With respect to SPECT results, patients with hard events on follow-up had more severe and extensive defects on both the rest and stress images as well as more severe and extensive inducible ischemia.

Outcome Events

Among the 3508 patients, 16 cardiac deaths and 58 MIs occurred (frequency, 0.5% cardiac death, 1.6% MI, 2.0% hard event). Four patients experienced both events, but only cardiac death was considered for purposes of analysis.

Perfusion Abnormalities and Outcomes

A normal study was associated with an exceedingly low hard-event rate (0.4% per year), with risk increasing significantly as a function of the SPECT result ($P<0.01$; Figure 1). Similarly, the results of stress SPECT significantly stratified patients subgrouped by sex and history if they had prior CAD (Figure 2). The risk associated with a normal stress SPECT tended to be lower in women and patients without prior CAD than in men and patients with prior CAD. The results of the SPECT study additionally risked stratified patients, even after initial stratification by the results of the Duke treadmill score (Figure 3). In patients with low, intermediate, and high Duke treadmill score subgroups, the results of a normal study were low, and event rates increased significantly as a function of the SPECT result. Of note, in patients with an intermediate

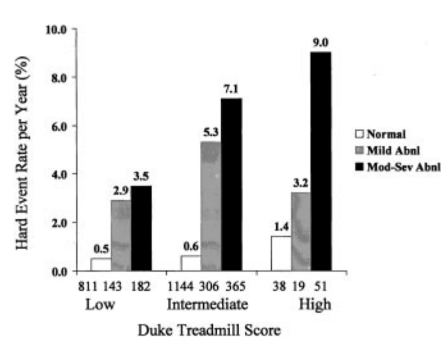

Figure 3. Rates of hard events per year as a function of the result of stress SPECT in patients with low, intermediate, and high Duke treadmill scores groups. Abnl indicates abnormal; and Mod-Sev, moderately to severely. *$P<0.05$ across SPECT categories in all Duke treadmill score subgroups.

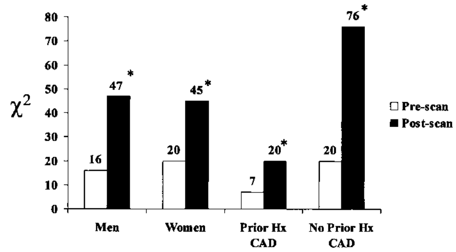

Figure 4. Results of the Cox proportional hazards model in selected subgroups. Values shown are for global χ^2 from the models using pre-SPECT data (white column) and addition of SPECT data (black column). The increase in χ^2 is statistically significant (*$P<0.001$) in all groups.

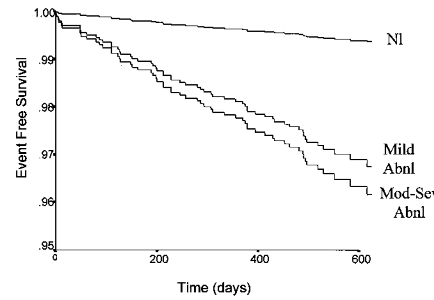

Figure 5. Risk-adjusted event-free survival curves based on Cox proportional hazards model in the cohort of all patients. The difference between curves are statistically significant ($P<0.001$). Nl indicates normal SPECT; Abnl, abnormal; and Mod-Sev, moderately to severely.

treadmill score, a normal SPECT identified 63% of patients (1144 of 1815) as being at low risk.

Incremental Prognostic Value

Multivariable survival analysis revealed that after adjusting for clinical and historical information (post-ETT likelihood of CAD, history of prior MI; global χ^2 of 52; $P<0.001$), the addition of the most predictive nuclear variable, summed stress score, additionally increased the global χ^2 to 85 ($P<0.001$). Even after adjusting for pre-SPECT data, summed stress score was a significant predictor of adverse events in men, women, and patients with and without history of prior CAD (Figure 4). Risk-adjusted survival curves generated from the initial model (Figure 5) demonstrate that even after adjusting for pre-SPECT data, a striking gap was present with respect to event-free survival between the normal SPECT patients and the patients with mildly and moderately to severely abnormal nuclear studies.

Cost-Effectiveness of SPECT

The cost-effectiveness of stress perfusion studies when applied in a clinically relevant manner are demonstrated in Figure 6. Clinical information in the form of the pre-ETT likelihood of CAD stratified patients into low-risk (low pre-ETT likelihood of CAD, event rate 0.4%) versus intermediate-risk (intermediate to high pre-ETT likelihood of CAD, event rate 3.2%; $P<0.05$ versus low risk) subgroups. Patients at intermediate pre-ETT risk were additionally stratified by the results of ETT into low (low post-ETT likelihood of CAD, event rate 1.3%) and intermediate post-ETT risk (intermediate to high post-ETT likelihood of CAD, 3.9% event rate; $P<0.05$ versus low risk) subgroups. The results of stress SPECT in low-risk (low pre-ETT and post-ETT likelihood of CAD groups, respectively) and intermediate-risk (intermediate to high post-ETT likelihood of CAD) subgroups is shown. The results of stress SPECT risk-stratified patients in all 3 subgroups, but this stratification reached statistical significance ($P<0.01$) only in the low pre-ETT and intermediate-to-high post-ETT likelihood groups (normal SPECT, 0%, 1%, and 1.1% event rates, respectively; abnormal SPECT, 2.7%, 2.5%, and 6.4%, respectively). Importantly, the cost-effectiveness ratio (cost per hard event detected by abnormal SPECT) of applying stress SPECT in each of these 3 subgroups (Figure 6) was \$211 470 and \$147 000, respectively, in the low pre-ETT and low post-ETT risk groups. On the other hand, the use of stress SPECT in patients with intermediate post-ETT

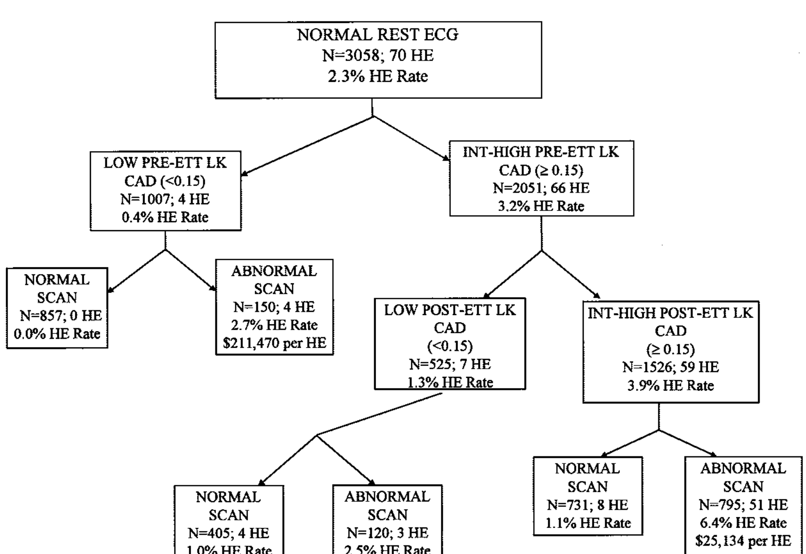

Figure 6. Outcomes and cost-effectiveness ratios. Shown within each box are the number of patients (N), number of hard events (HE), and hard-event rates (HE Rate). In the boxes reporting the results of abnormal SPECT, the dollar amount shown is the cost-effectiveness ratio. Numbers in parenthesis in the boxes reporting likelihood of CAD represent the threshold of low (≤0.15) versus intermediate to high (>0.15). LK indicates likelihood; and INT, intermediate.

TABLE 2. Reclassification of Patient Risk Category by the Addition of SPECT Data: Cost Implications

	n	Reclassifications			Cost per Reclassification
		Correct	Incorrect	Net	
All patients					
Overall	3058	300	138	162	$18 190
Male	2008	162	109	53	$31 825
Female	1050	138	29	109	$ 8092
No history CAD	2220	259	89	170	$10 871
Prior history CAD	838	121	49	72	$12 341
Only intermediate-to-high post-ETT risk					
Overall	1909	298	2	296	$ 5417
Male	1282	160	2	158	$ 6816
Female	627	138	0	138	$ 3816
No history CAD	732	254	0	254	$ 2421
Prior history CAD	557	121	5	116	$ 8481

risk resulted in a cost-effectiveness ratio of only $25 134, an amount considered in the acceptable range of cost-effectiveness.

Reclassification of Risk

In the overall cohort, 300 patients were correctly reclassified and 138 incorrectly reclassified by SPECT, for a net of 162 correct reclassifications (Table 2). This resulted in a cost of $18 190 per reclassification given 3508 patients tested. However, eliminating patients at low risk after ETT, thus limiting the analysis to patients who are appropriate for SPECT, results in the same number of correct reclassifications (298) and decreased number of incorrect reclassifications, thus yielding a net of 296 correct reclassifications and a lowered cost ($5417 per reclassification).

Similar analyses in subgroups of men, women, and patients with and without prior CAD revealed a lowering of cost per reclassification by excluding low-risk patients from additional testing. The impact of this is attenuated in women and in patients with prior CAD. On the other hand, this approach has a dramatic effect in men because of the frequent incorrect reclassifications by SPECT in male patients with low pre-SPECT risk (eg, abnormal SPECTS without events on follow-up).

Discussion

The present study found that in patients with normal resting ECG, exercise stress myocardial perfusion SPECT yields incremental prognostic value over clinical, historical, and ETT data for the prediction of hard events. Unadjusted analysis showed that a normal SPECT was associated with a very low risk of cardiac death or MI ($\leq$0.4% per year); with worsening SPECT results, a statistically significant increase in the rate of these events was found. Risk-adjusted survival analyses demonstrated that even after adjusting for pre-SPECT information, SPECT results yielded incremental information and significant risk stratification. When applied to appropriate patient subgroups, stress SPECT was cost-effective for identifying patients at risk for adverse outcomes. However, when applied to low-risk patients, cost-effectiveness ratios were markedly greater and the cost per reclassification of patient risk associated with SPECT was within an acceptable range when patients with low pre-SPECT risk were excluded.

Comparison to Previous Studies

The results of the present study differ significantly from those of previous investigations. Ladenheim et al,[8] in first describing incremental value in a cohort of 1659 patients without prior CAD and no previous revascularization or MI, found that the results of the stress study did not add additional information over pre-SPECT data in a subgroup of 1451 patients with normal resting ECG. A subsequent study from the Mayo Clinic in 265 patients with normal resting ECG undergoing exercise radionuclide angiography and prognostic follow-up demonstrated that after adjusting for prenuclear information, nuclear results yielded no additional information.[14]

The Mayo Clinic[20] group, examining the added value of exercise radionuclide angiography for identifying left main or 3-vessel CAD in 391 patients with normal resting ECG, found that although the nuclear results added incremental value over prenuclear data, the test correctly reclassified the risk of severe CAD in few additional patients compared with the prenuclear information. Thus, although statistical incremental value was present, minimal clinical value was added. These investigators extended these findings in a similarly defined cohort of 411 patients who underwent exercise stress-redistribution thallium SPECT and catheterization.[12] Although SPECT added incremental value for identification of left main or 3-vessel CAD, very few patients (3%) were reclassified with respect to predicted risk of severe CAD, and the cost per additional reclassification with SPECT was found to be high ($20 550).

Several important differences exist between these previous studies and the present study, including the type of testing performed (perfusion imaging versus radionuclide angiography), the imaging technique (SPECT versus planar), the isotope used for the stress images (thallium[201] versus Tc-99 m sestamibi), and the statistical analysis (logistic regression versus Cox proportional hazards model). All 4 of these differences may explain, in part, the disparity in results between the present and previous studies.

Use of Anatomic Versus Outcomes End Points

The present study suggests that the clinical effectiveness and cost-effectiveness of SPECT varies dramatically with the end point used (anatomic versus outcomes). Although angiographic and stress perfusion measure different characteristics of the same disease, the latter is a physiological measure that, unlike angiographic data, closely agrees with flow reserve and thus also reflects the vasomotor component medicated by endothelial function[21] (eg, abnormalities in the setting of hemodynamically significant stenoses that seem anatomically quiescent). Hence, a normal stress perfusion study is associated with a low risk even in the setting of multivessel CAD,[22,23] and SPECT is predictive of both cardiac death and MI.[6] Thus, the differences between the present and previous studies may be attributable to stress SPECT being better suited as a prognostic than anatomic measure, thus having measurably superior performance characteristics and cost-effectiveness for predicting outcomes than anatomic end points.

Potential Implications for Clinical Management

The present study has significant implications with respect to the evaluation and management of CAD in patients with normal resting ECG. The sequential use of clinical information and, in appropriate patients, ETT aids in the identification of low-risk patients unlikely to benefit from additional testing (Figure 6). It is important to emphasize that these patients are not appropriate for stress imaging procedures, and applying advanced, expensive technology in these patients results in an unacceptably low yield and extra cost. Conversely, patients who have undergone clinical and ETT evaluation and remain at intermediate to high risk are ideal candidates for stress imaging and are very likely to benefit from testing.

In the present American College of Cardiology and American Heart Association guidelines for the management of stable CAD,[24] ETT is a class I recommendation for diagnosis of obstructive CAD in patients with an intermediate pretest probability of CAD. Patients with chest pain and an intermediate probability of CAD are considered candidates for catheterization if high-risk ETT results are found, but no additional testing is indicated in patients not at high risk in whom adequate information on diagnosis and prognosis is available at this decision node. In the case of the latter, the present study suggests that ETT can identify a low-risk group of patients in whom additional, expensive testing is not cost-effective and thus is consistent with these recommendations. However, with respect to the former, although the guidelines make no recommendation regarding a second tier of evaluation after ETT, and exercise imaging studies are a class IIb recommendation, the present study suggests that the use of stress myocardial perfusion imaging as the second test after an exercise treadmill test may result in significant cost savings and reduction in the number of catheterizations performed. Previous studies have also shown that SPECT lowers both short- and long-term costs of care and reduces the rate of normal coronary arteries at the time of catheterization.[25] Thus, it may be advantageous to apply SPECT as the second tier of testing in patients with normal resting ECGs and intermediate to high post-ETT likelihood of CAD.

Importance of Patient Selection in Achieving Cost-Effective Use of SPECT

In the present study, although the results of stress SPECT risk-stratified all patient subsets, cost-effectiveness was only achieved in patients who were not identified as low risk by either clinical or ETT criteria. Testing-associated costs were reduced in all patient subsets by limiting testing to patients at significant risk of adverse events on the basis of less-expensive noninvasive tests. These results are identical to previous reports[4,5,25,26] in patients with and without normal resting ECG and suggest that patients with a low pre-SPECT likelihood of CAD should probably not be referred to stress imaging, except under unusual circumstances, because of their low risk and the excess cost of identifying the few events that occur. Interestingly, the cost savings associated with limiting SPECT to patients at intermediate to high post-ETT risk was far lower in women than in other subgroups, possibly suggesting the inability of pre-SPECT data, particularly ETT, to identify risk in women.

Limitations

The patients in this study were typical of those referred to a university-affiliated community hospital in a major urban area, and the results of this study should be applicable to this setting. At the time of the testing, quantitative software was not available on all of our camera and computer systems. The standardized, validated semiquantitative method in the present study was the basis for the quantitative software developed in our center[27]; the present results should be similar to those of quantitation.

Conclusion

Exercise stress myocardial perfusion SPECT adds incremental prognostic value to clinical and ETT data for the prediction of adverse events in patients with normal resting ECGs. Clinically relevant risk stratification is achieved by stress SPECT in all clinical risk subgroups. When applied to an appropriate patient population—those with intermediate to high post-ETT risk—SPECT was cost-effective.

Acknowledgment

This work was supported in part by a grant from DuPont-Pharma.

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