Prospective Validation of a Quantitative Method for Differentiating Ischemic versus Nonischemic Cardiomyopathy by Technetium-99m Sestamibi Myocardial Perfusion Single-Photon Emission Computed Tomography

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Summary

Background: Myocardial perfusion single-photon emission computed tomography (SPECT) permits assessment of stress perfusion and resting left ventricular (LV) function. Quantitative analysis of perfusion patterns among patients with LV dysfunction offers an opportunity for developing criteria to differentiate ischemic from nonischemic cardiomyopathy.

Hypothesis: Quantitative assessment of SPECT may allow differentiation between ischemic and nonischemic cardiomyopathy.

Methods: We evaluated 144 patients with LV ejection fraction $\leq 40\%$, divided into 63 patients with nonischemic and 81 with ischemic cardiomyopathy. Mean relative myocardial counts were obtained for regions drawn over defect and normal zones on rest and stress polar perfusion maps.

Results: Multivariate logistic regression analysis of significant univariate SPECT predictors of ischemic cardiomyopathy revealed that the stress defect severity ratio (SDSR) was the best predictor of ischemic cardiomyopathy ($p < 0.0001$). By receiver operator characteristic (ROC) curve analysis, an SDSR of $\leq 45\%$ optimized prediction of ischemic cardiomy-

opathy (sensitivity 81%, specificity 96%). An SDSR of $\leq 45\%$ occurred in 65 of 81 (80%) patients with ischemic cardiomyopathy, but in only 3 of the 63 (4%) patients with nonischemic cardiomyopathy ($p < 0.0001$). Applying the $\leq 45\%$ SDSR threshold to a prospective group of 89 patients yielded a somewhat lower sensitivity (60%), but retained high specificity (91%) for identifying ischemic cardiomyopathy ($p = \text{NS}$ vs. retrospective group).

Conclusions: Presence of a severe and extensive stress perfusion defect is a hallmark of ischemic cardiomyopathy. By contrast, a mild stress perfusion defect (SDSR of $> 45\%$) is commonly present among patients with ischemic and nonischemic cardiomyopathy. An SDSR of $\leq 45\%$ is a reproducible specific marker for identifying the presence of ischemic cardiomyopathy.

Key words: myocardial perfusion single-photon emission computed tomography, cardiomyopathy

Introduction

Patients with ischemic and nonischemic cardiomyopathy present with overlapping signs and symptoms, and clinical differentiation between these two disease entities is often difficult.¹ Treatment of these two entities is different. Treatment of nonischemic cardiomyopathy is confined to optimizing medical therapy, but patients with ischemic cardiomyopathy may additionally benefit from coronary revascularization.^{2–4} The importance of identifying an ischemic etiology for heart failure has not been well appreciated by recent clinical experience. For instance, in the Coronary Artery Surgery Study (CASS) trial, patients with triple-vessel disease and left ventricular (LV) dysfunction fared poorly when treated with medical therapy rather than surgical revascularization.² Similarly, patients with myocardial infarction (MI) in the Studies

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of Left Ventricular Dysfunction (SOLVD) trials had a nearly four-fold increase in cardiac events compared with counterparts without an interceding infarction.⁵⁻⁷ Nevertheless, interpretation of noninvasive imaging studies to assess cardiomyopathy has remained largely a subjective process. Thus, the purpose of this study was to determine whether a simple but robust quantitative method could be developed to aid clinicians in differentiating ischemic from nonischemic cardiomyopathy when using single-photon emission computed tomography (SPECT).

Methods

Study Population

The retrospective group consisted of 144 patients (65 ± 12 years, 66% men). Resting LV ejection fraction was $\leq 40\%$ in all patients as determined by technetium (Tc)-99m sestamibi myocardial perfusion-gated SPECT. Patients were divided into two groups: (1) 63 patients with nonischemic cardiomyopathy based on the presence of normal coronary arteries at cardiac catheterization; these patients had no electrocardiogram (ECG)-Q waves, prior history of myocardial infarction (MI), or coronary revascularization; (2) 81 patients with ischemic cardiomyopathy, based on angiographic evidence of coronary artery disease (CAD) ($\geq 70\%$ luminal diameter stenosis of ≥ 1 coronary artery) and documented segmental wall motion abnormalities on gated SPECT or ventriculography.

A second prospective group, defined according to the same criteria, consisted of 89 patients with cardiomyopathy (67 ± 11 years, 66% men), 31 of whom had nonischemic and 58 had ischemic cardiomyopathy. This group was used to validate the predictive algorithm derived from analysis of the retrospective patient group.

Stress Testing

Stress myocardial perfusion SPECT was performed with exercise (67%) and dipyridamole (33%) stress. For pharmacologic SPECT imaging, intravenous dipyridamole was injected at 0.14 mg/kg/min for 4 min. Technetium-99m sestamibi was injected 3 to 5 min after the end of dipyridamole infusion. Intravenous aminophylline (100 mg) was routinely administered to all patients at test conclusion.

Rest/Stress Technetium-99m Sestamibi Myocardial Perfusion-Gated SPECT

A 1-day protocol was performed. Patients were injected with 8–10 mCi of Tc-99m sestamibi at rest and tomographic images were obtained 60 min later. These patients were then injected with 25–30 mCi of Tc-99m sestamibi at peak exercise or dipyridamole infusion and then imaged approximately 30 min after exercise or 90 min after dipyridamole stress. Left ventricular volumes and ejection fraction from gated SPECT

images were obtained from the stress study and analyzed separately by two independent blinded observers.

Analysis of Rest/Stress Technetium-99m Sestamibi SPECT Polar Perfusion Maps

Severity and extent of perfusion defects were quantified by computer analysis of polar perfusion maps at rest and stress. An experienced physician manually drew regions-of-interest separately over boundaries of the most severe and largest perfusion defect, and the most normal (maximum counts) region of the myocardium on the polar perfusion map (Fig. 1). The ratio of the average defect count density, when compared with a defined normal region, was computed in order to obtain a rest or a stress defect severity ratio (SDSR). The lower this ratio, the more severe was the underlying perfusion defect. In addition, the absolute number of pixels in the defined defect zone reflected a rest or stress defect extent ratio. These measurements were obtained for each patient on both the rest and stress polar perfusion maps. Intra- and interobserver variation of this quantitative approach of polar perfusion maps analysis was $<5\%$.

FIG. 1 Pictorial diagram showing calculation of stress defect severity and extent ratios (SDSR and SDER) for stress polar perfusion maps over normal and defect zones. (A) Patient with ischemic cardiomyopathy without prior myocardial infarction (SDSR = 42 and SDER = 535); (B) patient with nonischemic cardiomyopathy and normal coronary arteries (SDSR = 52 and SDER = 235).

TABLE I Baseline clinical characteristics among patients with cardiomyopathy

	Nonischemic (n = 63)	Ischemic (n = 81)	p Value
Age (years)	62 ± 13	67 ± 11	0.01
Male sex	39 (62)	55 (69)	0.83
Prior myocardial infarction	0 (0)	47 (58)	0.0001
Prior PCI	0 (0)	13 (16)	0.005
Prior bypass surgery	0 (0)	28 (35)	0.0001
Congestive heart failure	27 (43)	18 (23)	0.08
Hypertension	51 (82)	51 (64)	0.42
Diabetes mellitus	18 (29)	34 (43)	0.33
Hyperlipidemia	27 (43)	32 (40)	0.92
Smoking	20 (33)	13 (16)	0.12
Family history CAD	13 (21)	19 (24)	0.90
Electrocardiogram			
Q waves	0 (0)	47 (58)	0.0001
Left ventricular hypertrophy	34 (54)	24 (30)	0.08

Parenthetical numbers are percents.

Abbreviations: CAD = coronary artery disease, PCI = percutaneous coronary intervention.

Statistical Analysis

A probability (p) value of <0.05 was used to define statistical significance. Continuous variables were compared using the Student's *t*-test. Frequencies of categorical variables were compared using chi-square analysis. Univariate and multiple logistic regression analyses were used to determine significant independent predictors of ischemic cardiomyopathy. Receiver operator characteristic (ROC) curve analysis was used to determine the SDSR with the maximal informational content

(area under ROC curve), which optimized both sensitivity and specificity. All analyses were performed using commercially available statistical software (GB-STAT V6.0, Dynamic Microsystems, Inc., Silver Spring, Md., USA).

Results

Retrospective Group

Baseline clinical characteristics of patients with ischemic versus nonischemic cardiomyopathy are summarized in Table I. Patients with ischemic cardiomyopathy were older than those with nonischemic cardiomyopathy, and by definition included a large proportion of patients with prior MI, percutaneous coronary intervention, bypass surgery, and ECG Q waves.

Perfusion (rest and stress) defect severity and extent ratios in patients with nonischemic and ischemic cardiomyopathy are shown in Table II. The mean value for the SDSR was significantly lower, and the stress defect extent ratio (SDER) was significantly higher in patients with ischemic cardiomyopathy. A low SDSR was uncommon among patients with nonischemic cardiomyopathy. An SDSR of ≤45% occurred in 65 of 81 (80%) patients with ischemic cardiomyopathy, but in only 3 of the 63 (4%) patients with nonischemic cardiomyopathy ($p < 0.0001$). A plot of the quantitatively determined values for the SDSR, plotted on the y axis for the retrospective cardiomyopathy group and divided by patients with nonischemic and ischemic cardiomyopathy, is shown in Figure 2. Furthermore, whereas normal stress perfusion studies were uncommon in this patient population with cardiomyopathy, they were performed in 6 (10%) patients with nonischemic cardiomyopathy compared with only 1 (1%) patient with ischemic cardiomyopathy ($p < 0.05$). Defect reversibility was not found to be a discriminator of ischemic from nonischemic cardiomyopathy.

TABLE II Left ventricular function and perfusion defect ratios

	Retrospective group		Prospective group	
	Nonischemic (n = 63)	Ischemic (n = 81)	Nonischemic (n = 31)	Ischemic (n = 58)
LV function parameters				
Ejection fraction (%)	25 ± 9	26 ± 8	31 ± 8	29 ± 7
End-systolic volume (ml)	143 ± 62	135 ± 57	113 ± 53	124 ± 99
End-diastolic volume (ml)	188 ± 74	182 ± 66	166 ± 70	169 ± 116
Resting study				
Defect severity ratio	51 ± 5	42 ± 7 ^b	50 ± 5	46 ± 7 ^a
Defect extent ratio	222 ± 160	529 ± 346 ^b	246 ± 161	462 ± 306 ^b
Stress study				
Defect severity ratio	51 ± 4	40 ± 7 ^b	51 ± 6	42 ± 7 ^b
Defect extent ratio	219 ± 190	603 ± 339 ^b	244 ± 167	535 ± 366 ^b

^a $p < 0.05$ or ^b $p < 0.0001$ vs. corresponding nonischemic subgroup.

Abbreviation: LV = left ventricular.

FIG. 2 Quantitatively determined values for stress defect severity ratio in the retrospective patient group divided into patients with nonischemic (median = 53) and ischemic (median = 41) cardiomyopathy.

Univariate and Multivariate Regression Analyses of SPECT Parameters

Clinical and perfusion (rest and stress) defect severity and extent ratios were compared by univariate regression analysis (Table III). Significant univariate variables ($p < 0.05$) were then entered into a multivariate stepwise logistic regression model in order to determine independent predictors of ischemic cardiomyopathy (Table III). By univariate analysis, all SPECT perfusion parameters were significant predictors of ischemic cardiomyopathy, including, both rest and stress defect severity and extent ratios. By multivariate logistic regression analysis, the SDSR was the best predictor of ischemic cardiomyopathy, with the other SPECT perfusion parameters no longer significant. The presence of typical angina or tran-

sient ischemic cavity dilatation were not significant predictors of ischemic cardiomyopathy.

Prospective versus Retrospective Cardiomyopathy Group

Perfusion defect severity and extent ratios (rest and stress) in patients with nonischemic and ischemic cardiomyopathy are shown in Table II. Compared with the retrospective group, the mean value for the SDSR in the prospective patients with nonischemic cardiomyopathy did not change significantly (51 ± 4 vs. 51 ± 6 , $p = \text{NS}$); however, the mean SDSR was slightly higher in the prospective patients with ischemic cardiomyopathy (40 ± 7 vs. 42 ± 7 , $p = \text{NS}$). As with retrospective patients with nonischemic cardiomyopathy, the frequency of an SDSR of $\leq 45\%$ remained uncommon in prospective patients with nonischemic cardiomyopathy (4 vs. 9%, $p = \text{NS}$). The frequency of an SDSR of $\leq 45\%$ in the prospective ischemic cardiomyopathy group fell from 81 to 60%; however, this difference was not statistically significant.

Quantitatively determined values are shown in Figure 3 for the SDSR plotted on the y axis for the prospective group of patients with cardiomyopathy, grouped as patients with nonischemic and ischemic cardiomyopathy. An ROC curve analysis was performed to compare the areas under the curve for the SDSR in retrospective versus prospective cardiomyopathy groups (Fig. 4). The ROC curve areas for retrospective and prospective groups were similar (94 ± 6 and $81 \pm 8\%$; $p = \text{NS}$).

Discussion

There has been a long-standing interest in using noninvasive imaging techniques for differentiating patients with ischemic from those with nonischemic cardiomyopathy. Prior scintigraphic studies, all based on visual analysis, have observed that patients with ischemic cardiomyopathy tend to have myocardial perfusion defects of more substantial mag-

Table III Univariate and multivariate predictors of ischemic cardiomyopathy

Variable	Risk ratio	95% CI	p Value
Univariate regression analysis			
Age	1.25	1.36–1.58	0.47
Gender	1.38	1.38–1.57	0.21
Hypertension	1.22	1.27–1.51	0.34
Smoking	1.11	0.80–1.36	0.11
Diabetes	1.34	1.27–1.53	0.72
Chest pain	1.52	1.37–1.64	0.40
Rest study			
Defect severity ratio	2.30	1.10–4.90	0.03
Defect extent ratio	1.01	0.05–1.97	0.04
Stress study			
Defect severity ratio	2.60	1.60–4.10	0.0001
Defect extent ratio	3.00	1.60–5.30	0.0003
Multivariate regression analysis			
Stress defect severity ratio	1.69	1.41–2.01	0.001

Abbreviation: CI = confidence interval.

FIG. 3 Quantitatively determined values for stress defect severity ratio in the prospective cardiomyopathy group, divided into patients with nonischemic (median = 53) and ischemic (median = 42) cardiomyopathy.

FIG. 4 Receiver operator characteristic (ROC) curves for ischemic and nonischemic cardiomyopathy by stress defect severity ratio in the retrospective (top curve) and prospective patients (bottom curve); ROC areas were 94 ± 6 and $81 \pm 8\%$.

nitude than do patients with nonischemic cardiomyopathy.^{8–17} Because of the subjective nature of visual analysis, such studies do not provide objective guidelines for interpreting the results in any given patient. Hence, a quantitative approach to measuring perfusion defects was developed in this study. Two quantitative parameters—the severity and the extent of myocardial perfusion defects—were significant univariate predictors of ischemic cardiomyopathy. Of these, the severity of stress myocardial perfusion defects was the most potent predictor by multivariate logistic regression analysis. The lower the SDSR, the greater the likelihood of ischemic cardiomyopathy. In particular, an SDSR of $\leq 45\%$ was a specific indicator of ischemic cardiomyopathy in our retrospective population, with only 4% of patients with nonischemic cardiomyopathy manifesting ratios that fell below this value.

Proposed algorithms often do not travel well geographically after their development. Applying criteria to a training set often only makes a particular proposed test criterion look effective incorrectly. Hence, we tested the potential utility of the defined SDSR by applying it to a prospective population. Within this group, a defect severity ratio of $\leq 45\%$ occurred less often in patients with ischemic cardiomyopathy (frequency 60 vs. 81% in the retrospective group of ischemic patients, although this difference was not statistically significant). This defect severity ratio did, however, remain a specific predictor, with only 9% of patients with nonischemic cardiomyopathy manifesting an SDSR of $\leq 45\%$. For the retrospective patients group, the ROC curve area for differentiating between patients with ischemic and nonischemic cardiomyopathy by the stress defect ratio was $94 \pm 6\%$. This represents an extremely high ROC curve area, generally well above that seen in clinical practice. While the ROC curve area for the SDSR was lower in our prospective population, the observed value in this group ($81 \pm 8\%$) constitutes an excellent value for a noninvasive imaging test. For instance, ROC areas for tests employing exercise ECG for diagnosis of a CAD range between 60 and 70%, and those for myocardial perfusion SPECT to diagnose a CAD range between 70 and 80%.^{18, 19} Hence, results within the prospective group confirm the utility of the SDSR as an accurate quantitative method with reproducibly high specificity for detecting ischemic cardiomyopathy.

Study Significance and Clinical Implications

Since cardiomyopathy represents an important source of morbidity and mortality among patients with CAD, there is a strong emphasis on identifying its treatable components. An ischemic etiology may be suspected if there are pathologic Q waves on the resting ECG or prior documented MI. These criteria and/or clinical demographics, however, are often inadequate to differentiate ischemic from nonischemic cardiomyopathy in individual patients, resulting in significant differences in management strategy. Patients with ischemic cardiomyopathy are candidates for diagnostic catheterization and coronary revascularization, if suitable; patients with nonischemic cardiomyopathy are generally treated medically.

It could be argued that results from a noninvasive SPECT study, regardless of accuracy, could never be strong enough to obviate coronary angiography in patients with suspected ischemic cardiomyopathy. This is well accepted in many clinical situations. However, definitive diagnosis can also be elusive despite catheterization in some instances, whereby the presence of CAD may be an incidental finding superimposed on a suspected myopathic process. In addition, in individual clinical situations such as that of a young patient with no coronary risk factors or that of an older patient with many comorbidities (e.g., diabetes and renal insufficiency), the low yield and/or higher risks of catheterization may strongly favor an initial (or only) noninvasive SPECT study to exclude the presence of CAD. In such clinical cases, a simple, robust, and objective quantitative measurement of an SDSR is a specific, validated marker that may be useful in distinguishing the etiology of cardiomyopathy. This may potentially obviate the need for cardiac catheterization in some clinical situations.

Study Limitations

A potential limitation of this study is the relative subjectivity in manually tracing regions of interest over defect zones. However, regardless of a given tendency of a particular technologist or physician to trace “tighter” or “looser” borders around defects, the absolute stress defect ratio should be very similar. Indeed, the intra- and interobserver correlations in our study were excellent. In addition, to assure a simple methodology, the calculation of quantitative summed scores or utilization of vendor specific software was not used. An additional limitation may be the particular focus of this study on perfusion parameters alone. Since gated SPECT wall motion analysis is subjective,²⁰ we did not include this parameter in our multivariate analysis. Ischemic cardiomyopathy is often characterized by more focal regional abnormalities,^{8, 14} but significant group overlap (with nonischemic cardiomyopathy) has been reported.¹³ However, it is possible that a multivariate model incorporating the stress defect severity and extent ratios with a parameter of regional LV function could further improve upon the differentiation between ischemic and nonischemic cardiomyopathy. In this current and in prior studies, the presence of defect reversibility was not found to be a reliable discriminator of ischemic from nonischemic cardiomyopathy.^{9, 10, 16}

Conclusions

Presence of a severe and extensive stress perfusion defect is a hallmark of ischemic cardiomyopathy. In particular, an SDRS of $\leq 45\%$ is a reproducible specific marker for identifying the presence of ischemic cardiomyopathy.

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