Etiology and pathophysiology of new-onset heart failure: Evaluation by myocardial perfusion imaging

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Objective. **The IMAGING in Heart Failure study was a prospective, multi-national trial designed to explore the role of single-photon emission computed tomographic (SPECT) myocardial perfusion imaging (MPI) as an initial investigative strategy in patients hospitalized with new-onset heart failure.**

Methods. **We recruited 201 patients (age 65.3 ± 14.5 years, 43% women) hospitalized with their first episode of heart failure. Rest/stress gated SPECT Tc-99m sestamibi MPI was performed during or within 2 weeks of the index hospitalization, in addition to standard care.**

Results. **SPECT MPI revealed a broad range of ejection fractions with preserved systolic function in 36% of patients. Forty-one percent of patients had normal perfusion. In the remaining patients, perfusion abnormalities were predominantly due to prior myocardial infarction, with extensive ischemia seen only in 6%. Among patients who underwent coronary angiography, SPECT performance characteristics revealed excellent negative predictive value (96%) for extensive coronary artery disease (CAD). In multivariable analyses, the extent of perfusion abnormality and advancing age predicted the presence of extensive CAD.**

Conclusions. **These preliminary data derived from a non-randomized observational cohort suggest potential diagnostic utility of MPI for ischemic LV dysfunction in new-onset HF, and**

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sets the stage for a prospective randomized study to confirm these findings. (J Nucl Cardiol 2009;16:82–91)

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Data from observational studies suggest that up to 70% of patients with heart failure (HF) have coronary artery disease (CAD) as the underlying etiology.[1] However, these data have generally accrued from clinical trials that enrolled patients with *chronic* HF, and the prevalence of CAD in patients with *new-onset* HF is less well studied. Determining HF etiology is further confounded by the lack of a uniform definition of CAD in clinical trials of HF.[2] The standard angiographic definition of CAD (≥50% diameter stenosis in any coronary artery) may be inadequate for the characterization of HF etiology and risk stratification because it does not enable a distinction between extensive CAD that is likely to be the etiology of HF, and limited extent CAD coexisting with HF of other etiologies. Given this uncertainty, the optimal initial evaluation strategy of patients presenting with new-onset HF remains unclear. While coronary angiography is frequently used to exclude CAD in such patients, several earlier clinical studies have demonstrated a very high negative predictive value (NPV) of radionuclide myocardial perfusion imaging (MPI) in patients with HF.[3-7] However, these studies predated contemporary imaging methodology (many were performed with planar imaging), and mostly included patients with chronic HF. A prospective assessment of the performance characteristics of contemporary radionuclide MPI for the diagnosis of CAD in patients presenting with *new-onset* HF has not been performed.

In this article, we report results of The Investigation of Myocardial Gated SPECT Imaging (IMAGING) in HF trial that was designed to determine the prevalence of CAD, reversible ischemia, prior myocardial infarction (MI), and preserved left ventricular (LV) systolic function using MPI in patients hospitalized with their *first* episode of HF, and to assess the performance characteristics of MPI for the diagnosis of extensive CAD, which is potentially etiologically relevant to HF in these patients.

METHODS

Patient Inclusion Criteria

Consenting patients 18 years and older, hospitalized with their first presentation of HF at participating sites in this multicenter trial were included in this study. The clinical diagnosis of HF was established by the simultaneous presence of two major or one major and two minor Framingham criteria.[8] Patients were excluded if the acute HF was the result of an acute myocardial infarction, or if HF was previously documented.

Study Protocol

The study was approved by the Institutional Review Boards of all participating sites. Informed consent was obtained from all patients, followed by a detailed demographic and medical history and physical examination. Stress/rest gated SPECT imaging was performed during or within 2 weeks of the index hospitalization. Coronary angiography was performed based on available clinical information which may have included the results of MPI.

Imaging Procedures and Analysis

Stress and rest SPECT imaging with Tc-99m sestamibi was performed using either a one-day rest-stress or two-day protocol according to the standard practice at the participating laboratory. Exercise or pharmacological stress testing was used based on standard clinical indications at the discretion of the treating physician. Gating was always performed on the high dose, post-stress acquisition. The results of MPI were made available to the attending physicians.

The MPI data were analyzed in a core laboratory (Tufts Medical Center, Boston, MA) by two experienced readers blinded to all of the clinical data. A 17-segment LV model[9] was used for interpretation, and segments were graded for myocardial perfusion using a visual, semi-quantitative scale (0 = normal, 1 = mildly abnormal, 2 = moderately abnormal, 3 = severely abnormal, 4 = absent perfusion). The summed stress score (SSS) was obtained by adding the individual segment scores on the stress study and was indicative of the combined extent of myocardial ischemia and infarction. The summed rest score (SRS), which was the sum of individual segment scores at rest, reflected the total extent of previous MI while the summed difference score (SDS), obtained by subtracting SRS from the SSS, was indicative of the extent of ischemia. A value of zero was assigned when the SDS was negative (i.e., when the SRS was greater than the SSS). LV volumes and ejection fractions were analyzed using standard automated software (Cedars-Sinai QGS). Based on previously validated criteria relating summed scores to prognosis, a SSS > 3 and SDS ≥ 2 were considered indicative of the presence of CAD and the presence of ischemia, respectively.[10] Based on the SSS, the extent and severity of stress perfusion abnormality was stratified into mild (SSS = 4-8), moderate (SSS = 9-12), and severe (SSS > 12) categories. This stratification of perfusion defect extent and severity has

been shown to correlate linearly with the risk of cardiac death and non-fatal MI.[10]

Coronary Arteriography

Coronary arteriography was performed when clinically indicated, with timing in relation to MPI left to the discretion of the physician. Therefore, catheterization in some patients was performed after, and driven by the results of the MPI study. CAD was defined as ≥70% stenosis in any epicardial coronary artery. *Extensive CAD* was defined as ≥70% in the left main or proximal (LAD) coronary artery, ≥70% in the two or more epicardial vessels, or any stenosis ≥70% with a prior history of myocardial infarction or coronary revascularization. These two separate definitions were used to differentiate HF patients with extensive, etiologically relevant CAD from those with more limited, co-existing CAD.[2]

Statistical Analysis

Analyses were performed with SPSS (version 14.0) and MedCalc (Version 9.2.0.0) software. Continuous data are presented as mean ± standard deviation, and were compared using *t*-tests. Categorical data are presented as proportions, and were compared using the chi-square test. Separate multivariable analyses were preformed to determine variables predictive of any angiographic CAD and extensive CAD by using models that included relevant clinical variables that were significant on univariable analysis. Body surface area (BSA) was calculated using the Mosteller formula.[11]

Role of the Funding Source

The study was sponsored by an unrestricted grant from Bristol Myers-Squibb Medical Imaging (Billerica, MA). The sponsor did not play any role in developing the study design, collection, analysis and interpretation of data, manuscript writing, or in the decision to publish the results.

RESULTS

Patient Demographics

Two hundred and one patients were recruited from 14 centers in the United States and United Kingdom, with a mean age (min-max) of 65.3 ± 14.5 (21-92) years. Eighty-six (43%) were women, 65 (32%) had known CAD (24% prior MI, 11% percutaneous revascularization, and 12% coronary artery bypass grafting), and 70(35%) had diabetes mellitus (Table 1). Only 24 (12%) patients reported active anginal symptoms. The average (±SD) patient weight was 81 ± 23 kg.

Stress Testing

One hundred and seventy-six (88%) and 25 (12%) patients underwent pharmacological and exercise stress testing, respectively. Of the former group, 93 (53%), 68 (37%), and 12 (7%) had dipyridamole, adenosine, and dobutamine stress, respectively.

Among the patients who underwent exercise testing, the Bruce protocol was used in the majority (23 of 25). The mean exercise duration was 6 ± 2 minutes, and the peak heart rate was 132 ± 27 beats per minute (equivalent to 86 ± 13% of maximum predicted heart rate).

Table 1. Patient characteristics

Patient characteristics	n (%)
Demographics	
Female gender	86 (43)
Age	65.3 ± 14.5 years
Weight	81 ± 23 kg
History	
Known CAD	65 (32)
Prior MI	49 (24)
Coronary revascularization	47 (23)
Hypertension	119 (59)
Diabetes mellitus	70 (35)
Lipid abnormalities	54 (27)
Current smoking	42 (21)
Clinical features	
Active angina	24 (12)
Paroxysmal nocturnal dyspnea	74 (37)
Heart rate ≥120 bpm	27 (13)
Elevated jugular venous pressure	73 (36)
Third heart sound	39 (19)
Pulmonary rales	137 (68)
Ankle edema	120 (60)
Radiographic cardiomegaly	78 (39)

Left Ventricular Function and Prevalence of Perfusion Abnormalities by Gated SPECT Imaging

One hundred and ninety-eight patients had interpretable stress and rest perfusion images. In addition, two patients had interpretable stress but not rest images. LV function data was available in 180 patients who had gated MPI. Therefore, 177 patients had complete data on both perfusion and LV function.

The mean ejection fraction (EF) was 36% ± 17%. Sixty-five (36%) patients had preserved LV systolic function (LVEF ≥ 40%). The distribution of EF is shown in Figure 1.

The distribution of perfusion abnormalities is shown in Figure 2: 41 (20.5%) patients had normal stress perfusion (SSS = 0); in addition, 42 (21%) patients had a

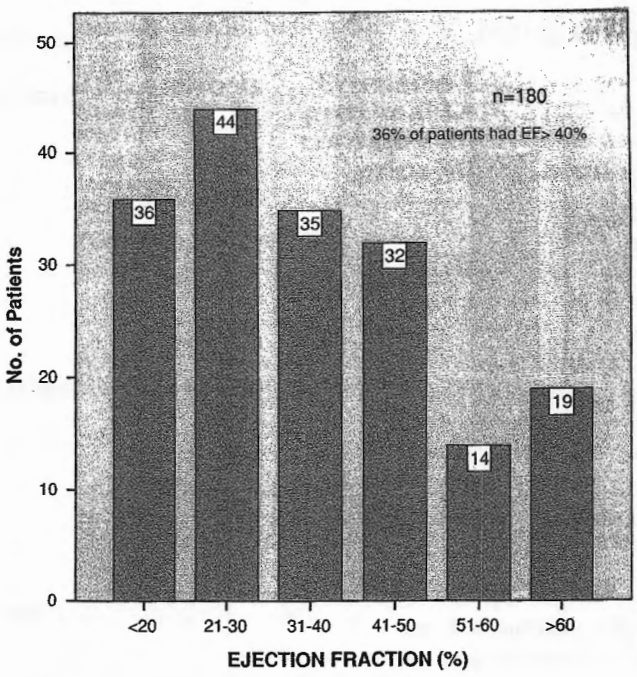

Figure 1. Distribution of EF among the 180 patients who had gated MPI: 36% had preserved LV systolic function (LVEF ≥ 40%). Data labels represent number of patients.

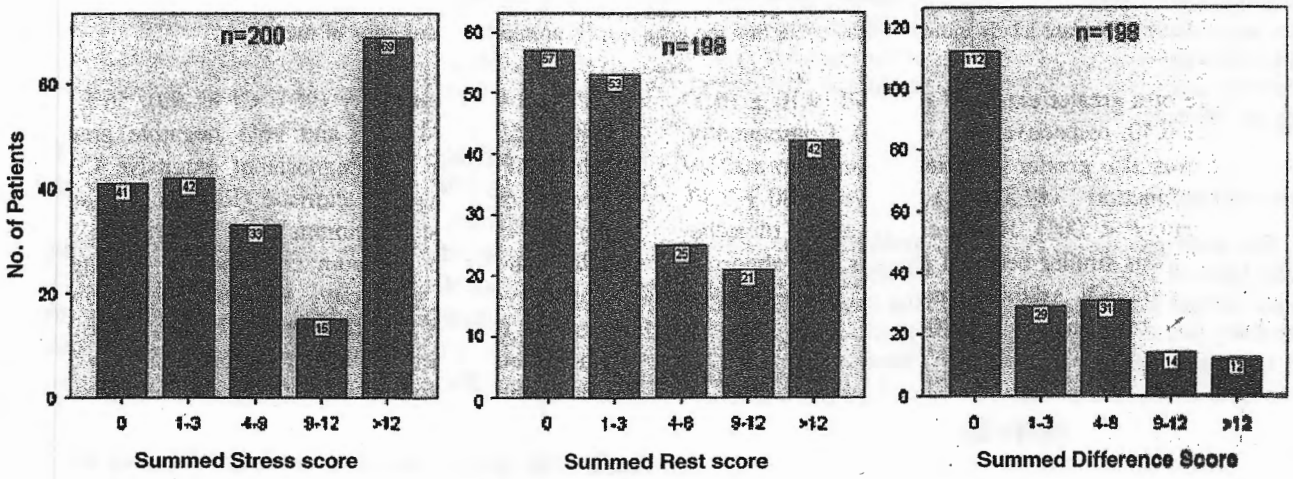

Figure 2. Distribution of Summed Stress, Summed Rest, and Summed Difference Scores. The data labels represent number of patients.

SSS of 1-3. Therefore, 41% of patients had no significant stress perfusion abnormality. Of the remaining patients, the distribution of severity of stress perfusion abnormality was mild in 33 (16.5%), moderate in 15 (7.5%), and severe in 69 (34.5%) patients.

The stress perfusion abnormalities were largely driven by resting perfusion abnormalities, and the prevalence of reversible perfusion defects was relatively low in this group of patients with new-onset heart failure; 112 (56%) patients had a SDS of zero, indicative of the absence of any ischemia. Only 26 patients (13.2%) had a SDS > 9, and 12 patients (6.1%) a SDS > 12. The distribution of resting perfusion abnormalities was as follows: SRS = 0 in 57 patients (28.8%), SRS = 1-3 in 53 patients (26.8%), SRS = 4-8 in 25 patients (12.6%), SRS = 9-12 in 21 patients (10.6%), and SRS > 12 in 42 patients (21.2%).

Relationship Between Perfusion Abnormalities and LV Function

As shown in Figure 3, patients with abnormal LV systolic function had a greater SRS (mean ± SD) compared with patients with preserved LV systolic function,

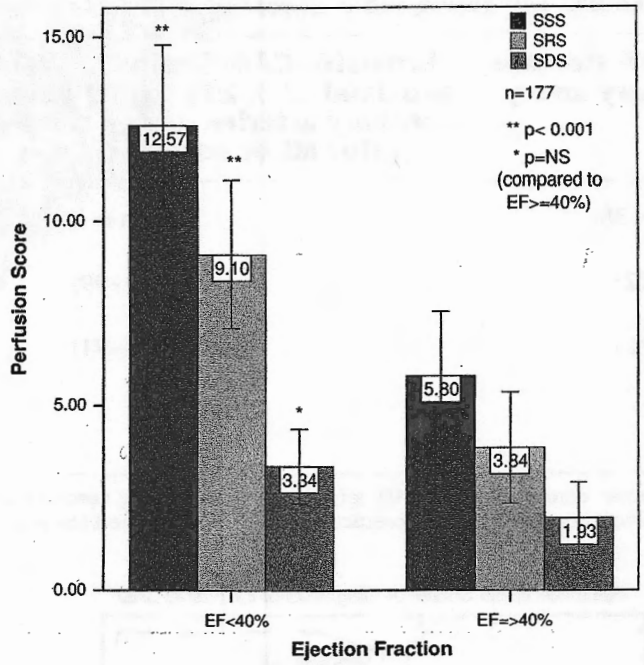

Figure 3. Comparison of the Summed Stress (SSS), Summed Rest (SRS), and Summed Difference (SDS) scores between patients with abnormal LV systolic function (LVEF < 40%) and preserved LV systolic function. The mean Summed Stress and Summed Rest scores were significantly different, while the Summed Difference Score was not, indicating LV dysfunction due to prior MI. The data labels indicate mean score and the error bars represent standard error of mean.

indicative of a greater extent of prior MI (9.10 ± 10.37 vs 3.84 ± 6.30, respectively, $P < .001$). Consequently, the SSS was also greater in patients with abnormal LV systolic function (12.57 ± 11.66 vs 5.80 ± 7.37, respectively, $P < .001$). However, the extent of ischemia (SDS) was similar between patients with abnormal and preserved LV systolic function (3.34 ± 5.30 vs 1.93 ± 4.09, respectively, $P = .06$).

Performance Characteristics of Gated SPECT Imaging for the Diagnosis of CAD

Based on clinical indications, 75 (37%) patients underwent coronary arteriography [25 of 65 patients (38%) with known CAD and 50 of 136 patients (36%) without known CAD].

Patients who underwent coronary arteriography were younger (61.9 years ± 41.4 vs 67.3 years ± 14.2, respectively, $P = .01$) and had lower EFs (32% ± 15% vs 37% ± 17%, respectively, $P = .03$). Gender, prior history of CAD, presence of angina and hypertension were similar between patients who did and did not undergo coronary arteriography.

The performance characteristics of MPI for the diagnosis CAD are shown in Table 2. Thirty-eight patients had CAD (prevalence 51%), while 27 (36%) had extensive CAD. Using a threshold of SSS > 3, MPI had 96% sensitivity (95% CI 81-99), 56% specificity (95% CI 41-70), and 96% negative predictive value (NPV) for the diagnosis of extensive CAD. A receiver operating characteristic (ROC) curve analysis showed that the maximum area under the curve, indicative of the optimum combination of diagnostic sensitivity and specificity, was achieved using the criterion of SSS > 8 (Figure 4). However, using an established and well-validated cut off of SSS > 3, provided better sensitivity and NPV for excluding extensive CAD.[10] As shown in Figure 5, the mean SSS clearly differentiated between patients with and without extensive CAD (17.07 ± 8.24 and 7.38 ± 9.42, respectively, $P < .001$). The diagnostic values of MPI for more limited CAD (any stenosis ≥70%) were lower (sensitivity 82%, specificity 57%, NPV 75%). Among the 50 patients who underwent coronary angiography and did not have known CAD, prior MI, or coronary revascularization, the prevalence of any CAD and extensive CAD was 36% and 18%, respectively. The sensitivity, specificity, and NPV of MPI (using the criterion of SSS > 3) for the diagnosis of extensive CAD in this group was 89% (CI 52-98), 54% (37-69), and 95%, respectively. The results of the multivariable logistic regression analysis for prediction of angiographic CAD are shown in Table 3. The SSS was predictive of CAD and extensive CAD. Diabetes

Table 2. Performance characteristics of MPI (using SSS > 3) for angiographic CAD diagnosis (n = 75)

CAD definition	Any CAD: ≥70% stenosis in any coronary artery	Extensive CAD: Stenosis ≥ 70% in the LM or proximal LAD, ≥70% in ≥two major epicardial coronary arteries or any stenosis ≥70% with a prior MI or coronary revascularization
Patients fulfilling CAD criterion	51% (n = 38)	36% (n = 27)
Sensitivity % (95% CI)	82 (66-92)	96 (81-99)
Specificity % (95% CI)	57 (40-72)	56 (41-71)
PPV %	67	55
NPV %	75	96

CAD, Coronary artery disease; *LM*, Left main coronary artery; *LAD*, left anterior descending coronary artery; *MPI*, myocardial perfusion imaging; *NPV*, negative predictive value; *PPV*, positive predictive value; *SSS*, summed stress score.

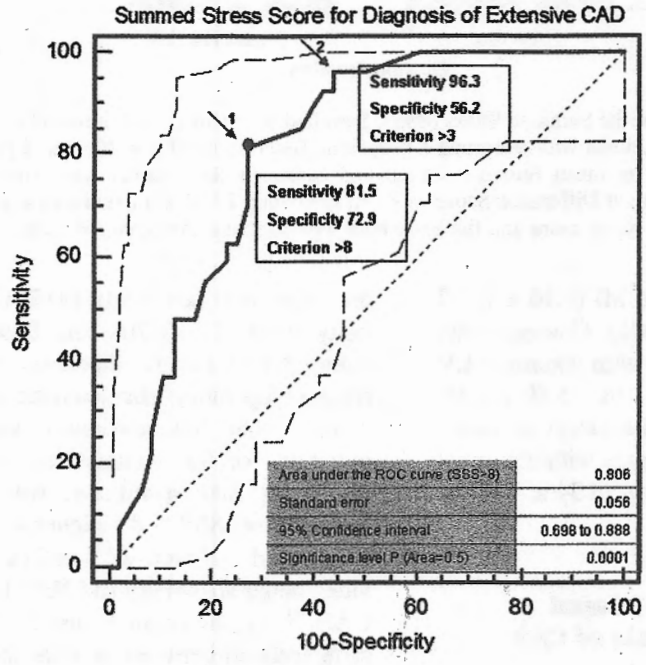

Figure 4. Receiver Operating Characteristic (ROC) curve analysis of the summed stress score (SSS) for diagnosis of extensive CAD. The optimal combination of sensitivity and specificity was obtained using the criteria of SSS > 8 (AUC = 0.806, SE = 0.05, $P < .001$ compared to AUC of 0.5, coordinates indicated by *arrowhead* 1). The coordinates of sensitivity and specificity obtained using the standard criterion of SSS > 3 are indicated by *arrowhead* 2. The interrupted curves represent the 95% confidence bounds for the ROC curve.

Mellitus was predictive of CAD, but not extensive CAD, and advancing age was associated with extensive CAD. NYHA class, SDS, and EF < 40% were included in the model, but were not predictive of CAD or extensive CAD. Figure 6 shows typical MPI examples from patients with HF due to ischemic LV dysfunction, idiopathic dilated cardiomyopathy, and HF with preserved LV systolic function.

Gender Differences in LV Function and Perfusion

Women comprised 43% of the patients in this cohort, and were older compared with men (68 ± 15 years vs 63 ± 14 years, respectively, $P = .04$). A significantly larger proportion of women had preserved LV systolic function (LVEF ≥ 40%) compared with men (52% vs

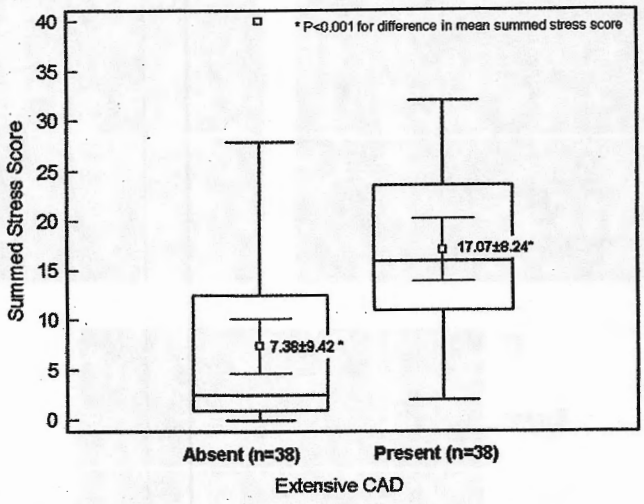

Figure 5. Comparison of the SSS in patients with and without extensive CAD. The central box represents the values from the lower to upper quartile (from 25 to 75 percentile), with the outside line extending from the minimum to the maximum (excluding one outlier) value. The solid horizontal line within the boxes represents the median value; the marker with error bars represents the mean ± SD. The single data point outside the two boxes is an outlier.

Table 3. Multivariable regression analysis for prediction of coronary artery disease (CAD)

Covariate	Wald chi-square (WSC)	WSC *P* value	Odds ratio	Odds ratio 95% CI
Prediction of *any* CAD: Overall model chi-square 23.7120 ($P < .0001$)				
Diabetes (yes vs no)	9.03	0.00	12.31	2.39-63.30
Summed stress score	6.87	0.01	1.08	1.03-1.21
Prediction of *extensive* CAD: Overall model chi-square 41.2215 ($P < .0001$)				
Age group	13.19	0.01		
50-59 yrs vs <50 yrs	0.05	0.83	0.70	0.03-15.83
60-69 yrs vs <50 yrs	1.37	0.24	5.63	0.31-101.84
70-79 yrs vs <50 yrs	5.57	0.02	32.52	1.80-586.49
≥80 yrs vs <50 yrs	8.23	0.00	203.13	5.39-7659.2
Summed stress score	12.5201	0.00	1.20	1.08-1.33

NYHA class, summed difference score, and impaired left ventricular systolic function were included in the model, but not predictive.

30%, respectively, $P < .007$). The mean LVEFs of women and men were 40 ± 16% and 32 ± 15%, respectively ($P = .003$), with end-diastolic volumes indexed to BSAs of 124.1 ± 63.7 mL/m^2 and 198.9 ± 85 mL/m^2 ($P < .001$) and end-systolic volume indexes of 45.74 ± 37.92 mL/m^2 and 72.54 ± 40.05 mL/m^2 ($P < .001$), for women and men, respectively. The prevalence of hypertension was similar in women and men (56% and 54%, respectively). There were also significant differences in perfusion scores between genders. Women had a lower SSS (7.3 ± 9.1 vs 11.5 ± 11 for women and men, respectively, $P < .01$) and SRS (4.1 ± 6.5 vs 9.3 ± 10.2 for women and men, respectively, $P < .001$), while the SDS was similar (3.2 ± 5.2 vs 2.5 ± 4.7 for women and men, respectively, $P =$ NS.

DISCUSSION

This pilot study is the first, prospective, multi-center study to explore the role of MPI in new-onset HF. To optimize the specificity of the clinical diagnosis of HF, patients were required to have symptoms severe enough to warrant hospitalization, and the Framingham criteria were used to support the diagnosis.[12,13] These preliminary data derived from a subset of the study population that underwent clinically indicated coronary

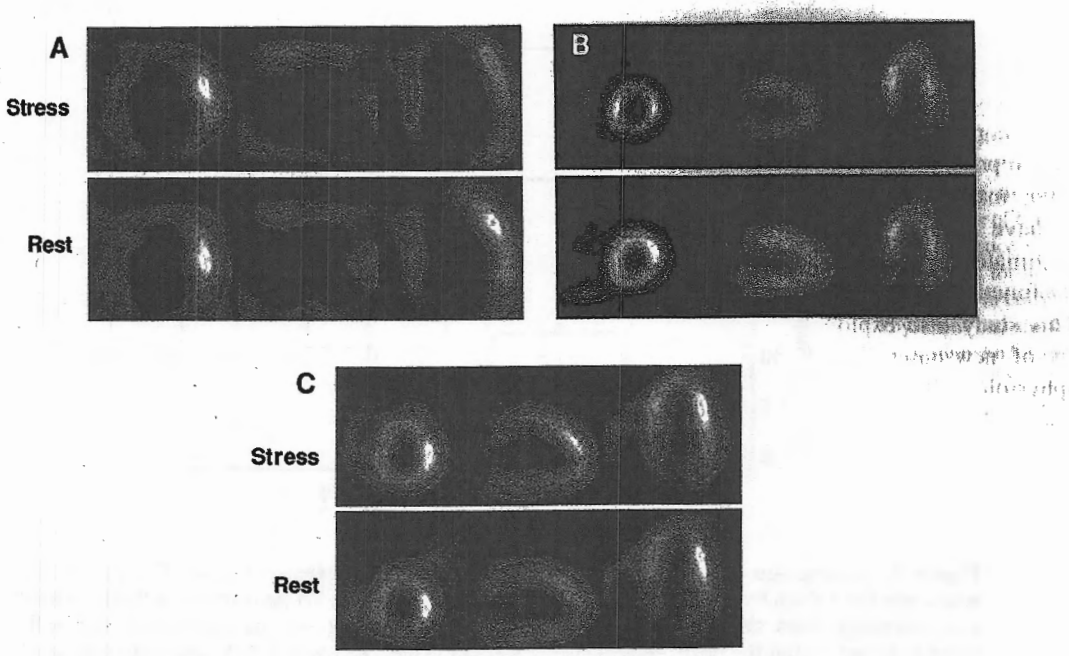

Figure 6. Categorization of HF etiology using Tc-99m sestamibi MPI. **A**, Left ventricular (LV) dilation (abnormal LV systolic function by gated SPECT not shown) with large, fixed perfusion defects in the septum, anterior wall, apex, and inferior wall suggestive of CAD-related (''ischemic'') cardiomyopathy. **B**, Normal stress-rest perfusion and LV size (normal LVEF on gated SPECT not shown) indicative of HF likely related to diastolic mechanisms. **C**, LV dilation (with abnormal LV systolic function on gated SPECT, not shown) and normal perfusion suggestive of non-CAD related (''nonischemic'') cardiomyopathy. The normal perfusion in the latter two categories has a high NPV for extensive CAD.

angiography suggest that Tc-99m sestamibi MPI has high diagnostic sensitivity and NPV for extensive, potentially etiologically related CAD in patients hospitalized for new-onset HF. Whereas the diagnostic values for more limited CAD were lower, prior studies have established that the prognosis of patients with HF and single-vessel CAD is similar to those with non-ischemic LV dysfunction.[2] Hence, these patients are unlikely to derive prognostic benefit from coronary revascularization. On the other hand, patients with HF and extensive CAD may derive a mortality benefit from coronary revascularization[14] and, therefore, identifying etiologically relevant CAD in HF patient is a critical step in their initial evaluation. To this end, current guidelines mandate coronary angiography in HF patients who have angina.[15] However, up to 60% of patients with ischemic LV dysfunction have no angina,[16] and the optimal evaluation strategy for these patients continues to be debated. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of HF ascribe class IIA and IIB indications to coronary angiography and noninvasive imaging, respectively, in HF patients without angina,[15] while the ACC/AHA/American Society of Nuclear Cardiology radionuclide imaging guidelines ascribe level IIA to radionuclide MPI for the same indication.[17] While prior studies have reported a high sensitivity ($\sim$100%) and NPV of MPI for the diagnosis of CAD in HF patients, these studies generally pre-dated current imaging techniques, using planar thallium-201 rather than Tc-99m SPECT.[3-7] A more contemporary study using ECG-gated Tc-99m sestamibi SPECT imaging demonstrated 94% sensitivity for the diagnosis of CAD in patients with EF $<$ 40%.[18] All of these studies were performed in patients with chronic LV dysfunction. The results of the current study in patients with new-onset HF were concordant in demonstrating a high sensitivity and NPV for detecting extensive CAD that is likely to be etiologically relevant, and indicate that MPI should be investigated in a randomized trial as an initial diagnostic strategy to identify patients with new-onset HF who may not require coronary angiography. This high sensitivity of MPI for CAD detection is commensurate with the pathophysiological basis of CAD-related LV dysfunction. Persistent LV dysfunction in CAD is the result of one of three pathophysiological states—previous MI with subsequent remodeling, extensive and severe CAD leading to hibernation or repetitive stunning, or a combination of these pathophysiologies—all of which should be readily detected by MPI. While the specificity

of MPI for the detection of angiographic CAD is only modest, some of these "false-positive" results reflect the presence of myocardial fibrosis or true coronary flow reserve abnormalities in non-ischemic LV dysfunction, and thus represent true physiologic phenomenon. Studies using magnetic resonance imaging[19] and autopsy data[20] have shown that coronary angiography may underestimate the true prevalence of ischemic myocardial dysfunction in HF patients.

This study also explored other pathophysiological aspects of new-onset HF. Current knowledge of HF pathophysiology has been mostly derived from clinical trials or observational datasets of patients with *chronic* heart failure.[1] Patients with new-onset HF differ in important ways from those with chronic disease because the latter may have had pharmacological or mechanical interventions that alter LV structure, function, and ischemic burden. To our knowledge, a prospective assessment of ischemic burden in unselected patients with new-onset HF has not been previously reported. In this study, despite a prevalence of CAD that was comparable to that reported in the chronic HF population, significant reversible ischemia was infrequent, and perfusion abnormalities were predominantly due to prior MI. Fifty-six percent of patients had no ischemia, and only 13% had extensive ischemia (SDS > 9). While prior studies[16] have reported a higher prevalence of reversible ischemia in chronic HF patients, this is probably a reflection of selection bias in viability studies that enrolled patients with chronic HF and known CAD. In keeping with prior reports, 37% of patients had preserved LV systolic function, and this was more common in women compared to men.

Study Limitations

This was an observational cohort of non-consecutive patients. Thus the applicability of these results to all patients with new-onset HF needs further confirmation. Since coronary angiography was performed in only 37% of the patients, and was driven by clinical indications including the MPI results, there was verification bias which is known to falsely lower specificity and overestimate sensitivity. Selection bias may also have been operative in patients with new-onset HF and known CAD, who are sometimes referred directly for coronary angiography. Hence these results require confirmation in a prospective, randomized study. Because MPI operates on the basis of relative myocardial perfusion, a balanced reduction in perfusion involving all the three coronary vascular territories as a result of severe triple-vessel disease will be missed. Although this may be a relatively infrequent occurrence in clinical practice, the true prevalence in HF patients is not known. Furthermore, this phenomenon would be of particular relevance in patients with severe LV dysfunction, who may derive functional and prognostic benefit from coronary revascularization. The prevalence of this phenomenon would be better estimated if a larger proportion of patients were to prospectively undergo both MPI and coronary angiography. Finally, some patients may have had myocardial ischemia masked by anti-ischemic medication, which was held for testing only at the discretion of the treating physician.

Thus, while this pilot study provides encouraging preliminary data regarding the utility of MPI for the diagnosis of ischemic LV dysfunction in patients with new-onset HF, further confirmation of these results is required before clinical implementation can be recommended.

CONCLUSION

In patients hospitalized with new onset HF, MPI with Tc-99m sestamibi SPECT imaging reveals a broad range of LV function with proportions of patients with preserved and abnormal LV systolic function similar to that reported in the chronic HF setting. Extensive reversible perfusion abnormalities consistent with extensive ischemia are present in only a minority of patients. Patients with "nonischemic" HF (that is, no significant epicardial coronary stenosis) have a significantly smaller extent of perfusion abnormality compared with those with epicardial CAD, but minor abnormalities are common. In a subset of patients who underwent clinically indicated coronary angiography, MPI had a high NPV for ischemic LV dysfunction.

These preliminary data set the stage for a randomized study of MPI vs coronary angiography as the initial diagnostic modality for CAD detection in HF patients. The relative value of MPI and other imaging modalities such as computed tomography, magnetic resonance imaging, and positron emission tomography in the initial assessment of HF patients also need to be established in clinical trials.

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