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Relationship of Tc-99m Tetrofosmin Gated Rest SPECT Myocardial Perfusion Imaging to Death and Hospitalization in Heart Failure Patients: Results from the Nuclear Ancillary Study of the HF-ACTION Trial

Allen E. Atchley, MD^a, Ami E. Iskandrian, MD^b, Dan Bensimhon, MD^a, Stephen J. Ellis, PhD^a, Dalane W. Kitzman, MD^c, Linda K. Shaw, MS^a, Robert A. Pagnanelli, NCT^a, David J. Whellan, MD^d, Julius M. Gardin, MD^e, Andrew Kao, MD^f, Khaled Abdul-Nour, MD^g, Greg Ewald, MD^h, Mary Norine Walsh, MDⁱ, William E. Kraus, MD^a, Christopher M. O'Connor, MD^a, and Salvador Borges-Neto, MD^a on behalf of the HF-ACTION Trial Nuclear Ancillary Study Investigators

^aDuke University Medical Center, Durham, NC

^bUniversity of Alabama at Birmingham, Birmingham, AL

^cWake Forest University School of Medicine, Winston-Salem, NC

^dJefferson Medical College, Philadelphia, PA

^eHackensack University Medical Center, Hackensack, NJ

^fMid-America Heart Institute, Kansas City, MO

^gHenry Ford Hospital, Detroit, MI

^hWashington University, St. Louis, MO

ⁱSaint Vincent Hospital, Indianapolis, IN

Abstract

Background—We hypothesized that the severity of resting perfusion abnormalities assessed by the summed rest score (SRS) would be associated with a higher rate of adverse outcomes in patients with heart failure (HF) and reduced left ventricular (LV) ejection fraction (EF).

Methods—A subset of 240 subjects from HF-ACTION underwent resting Tc99m tetrofosmin gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). Images were evaluated using a 17-segment model to derive the SRS and additional nuclear variables.

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Corresponding author: Salvador Borges-Neto, MD, Department of Medicine and Radiology, Duke University Medical Center, Durham, NC 27710. Phone: (919) 684-7857; Fax: (919) 684-7167. borge001@mc.duke.edu.

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Disclosure information

Drs. Kraus, Iskandrian, Whellan, O'Connor, Ewald, Gardin, Kao, Bensimhon, Walsh, Abdul-Nour, and Kitzman have no conflicts of interest to disclose.

Results—After adjusting for pre-specified covariates, SRS was significantly associated with the primary endpoint (hazard ratio [HR] 0.98; 95% confidence interval [CI] 0.97–1.00, $P=0.04$), with a higher SRS corresponding to lower risk of an event. This association was not present in the unadjusted analysis. The relationship between SRS and the primary outcome was likely due to a higher event rate in patients with ischemic HF and a low SRS. The LV phase standard deviation (SD) was not predictive of the primary outcome (HR 1.00; 95% CI 0.99–1.01, $P=0.49$). In a post hoc analysis, nuclear variables provided incremental prognostic information when added to clinical information ($P=0.006$).

Conclusions—Gated SPECT MPI provides important information in patients with HF and reduced LVEF. In the adjusted analysis, SRS has an unexpected relationship with the primary endpoint. Phase SD was not associated with the primary endpoint. Rest gated SPECT MPI provides incrementally greater prognostic information than clinical information alone.

Keywords

heart failure; SPECT; outcomes; coronary artery disease; cardiomyopathy

Despite significant advances in medical and device therapy, the morbidity, mortality, and economic burden of heart failure (HF) remain high.^{1–8} Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION) is the largest randomized study of exercise therapy in HF patients to date. The overall HF-ACTION study design and primary results have been published.^{9,10} The HF-ACTION nuclear substudy was designed to test the hypotheses that the extent and severity of resting perfusion abnormalities will predict outcomes.

The prognostic significance of perfusion defects as assessed by single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has been well established.^{11–13} Recent developments in gated SPECT imaging have led to a method for objectively quantifying dyssynchrony.^{14–21}

The primary hypothesis of the study was that the severity of resting perfusion abnormalities assessed by the summed rest score (SRS) would be associated with a higher endpoint rate for the substudy. A secondary hypothesis was that SPECT dyssynchrony analysis would correlate with adverse events.²²

Methods

The primary endpoint was combined all-cause mortality and cardiovascular hospitalization. Ischemic etiology was defined in HF-ACTION as 1 of the following: 75% lesion in at least 1 major epicardial vessel, history of myocardial infarction (MI), history of revascularization, or perfusion defects in the setting of ischemic symptoms.

A total of 240 patients were enrolled in the substudy (Figure 1). All subjects underwent resting gated SPECT MPI with Tc-99m tetrofosmin. Image acquisition and processing has been previously described.^{11,14} No stress imaging was obtained to prevent interference with the main trial. Studies were independently interpreted by 2 blinded nuclear cardiologists using a 17-segment model and a 5-grade severity score. Differences between the 2 interpreters were resolved by consensus. To evaluate left ventricle (LV) mechanical dyssynchrony, a phase standard deviation (SD) $>40^\circ$ was used as the cutoff point.¹⁸

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Statistical analyses

Statistical analyses were performed using SAS software version 8.2 (SAS Institute Inc., Cary, NC). Baseline characteristics were summarized using medians and interquartile ranges for continuous variables and frequencies and percentages for categorical variables. All statistical tests were 2-tailed with a significance level $\alpha=0.05$.

The principal analysis of the pre-specified primary endpoint was performed using Cox proportional hazards regression with baseline SRS as the independent variable of interest, with the covariates age, sex, New York Heart Association class, baseline LV ejection fraction, HF etiology, and body mass index. An additional pre-specified analysis investigated the univariate relationship between baseline SRS and the primary endpoint (no covariates).

The secondary hypothesis involving dyssynchrony was assessed with a Cox proportional hazards regression model including phase SD as the independent variable of interest, with the same covariates as above. Subjects with a biventricular pacemaker at baseline were excluded from dyssynchrony analyses. A Kaplan-Meier curve of the primary endpoint by high versus low phase SD (based on a cut point of 40°) was examined as well.

The primary endpoint results were further assessed with additional post hoc analyses. Kaplan-Meier curves of the primary endpoint by HF etiology were examined, as well as curves of the primary endpoint by etiology and high/low SRS, with an SRS cut-point of 15, suggested by a spline fit of the log hazard ratio versus SRS. All *P* values for Kaplan-Meier curves were generated using the log-rank test, except for the plot by etiology and SRS, for which the interaction *P* value was also examined, keeping SRS as a dichotomous variable. Also, the main analysis of baseline SRS was repeated with the composite endpoint of cardiovascular mortality and HF hospitalization, with and without covariates. Another post hoc analysis involved examining the incremental prognostic value of 3 gated SPECT variables (SRS, LV ejection fraction, and end systolic volume) beyond baseline clinical variables (age, sex, New York Heart Association class, etiology of HF, and body mass index) in predicting the primary endpoint. Finally, the incremental prognostic value of phase SD beyond the combined set of clinical variables and the 3 gated SPECT variables was investigated. These 2 analyses were performed by assessing Cox proportional hazards models of the primary endpoint, ensuring the same sample size in each model, and comparing the likelihood ratio chi-square statistics.

Results

Patient demographics can be found in Table I. Most patients were optimally treated with standard medical therapy (Table II). Table III highlights baseline clinical and gated SPECT information.

Baseline SRS had a statistically significant association with the primary endpoint with a higher SRS corresponding to a lower risk of event (Table IV). This relationship was not observed in the unadjusted analysis (hazard ratio [HR] 1.00; 95% confidence interval [CI] 0.99–1.01, *P*=0.94). In a post hoc analysis of the primary endpoint, differences were identified within the cohort based on the etiology of HF (ischemic versus nonischemic) and SRS (high versus low) (Figure 2). Patients with an ischemic etiology of HF and a low SRS had the highest event rate, primarily driven by cardiovascular hospitalization. Patients with a high SRS had a similar event rate regardless of the HF etiology, and patients with a nonischemic etiology and a low SRS had the lowest event rate.

Overall, 115 (48%) of the 240 patients enrolled experienced the primary endpoint of all-cause mortality or cardiovascular hospitalization. All-cause mortality occurred in 14% (n=33) of the entire cohort whereas 45% (n=107) were hospitalized for cardiovascular causes. The primary endpoint occurred in 68 (53%) of those with an ischemic etiology (n=129). Among those with an ischemic etiology, all-cause mortality occurred in 18% (n=23) and hospitalization for cardiovascular causes occurred in 49% (n=63). For those with a nonischemic etiology (n=111), the primary endpoint occurred in 47 (42%) patients. Among those with a nonischemic etiology, all-cause mortality occurred in 9% (n=10) and hospitalization for cardiovascular causes occurred in 40% (n=44).

Other outcome measures pertinent to this study included the composite endpoint of cardiovascular mortality and HF hospitalization (n=67 [28%]). Baseline SRS was not predictive of this post hoc endpoint (unadjusted HR 1.01; 95% CI 0.99–1.02, $P=0.25$). This relationship persisted when adjusted for age, sex, New York Heart Association class, HF etiology, and body mass index (adjusted HR 0.99; 95% CI 0.97–1.01, $P=0.27$). There were 56 subjects with at least 1 HF hospitalization (23%), which included 13 subjects with a subsequent cardiovascular death. Cardiovascular mortality occurred in 22 subjects (9%), and there were 3 deaths of unknown cause classified as cardiovascular death for purposes of this analysis.

In the analysis of dyssynchrony, phase SD was not significantly associated with the primary endpoint (Table V). When examined as a dichotomous variable split at 40° in a post hoc analysis, there was a nonsignificant trend toward increased adverse events in those with a higher phase SD (Figure 3).

In other post hoc analyses, key variables obtained from gated SPECT imaging (SRS, LV ejection fraction (EF), and end systolic volume (ESV) added prognostic value to clinical information ($P=0.006$) (Figure 4). Phase SD did not contribute significantly to the incremental information obtained from gated SPECT imaging ($P=0.72$). Figure 5 presents a Kaplan-Meier curve for the primary endpoint by HF etiology where patients with an ischemic etiology had a higher event rate than those with a nonischemic etiology ($P=0.049$).

Discussion

The main conclusions of this study are as follows. First, in the adjusted analysis, SRS was predictive of the primary outcome, but the point estimate was contrary to our original hypothesis. Second, post hoc analysis of the unexpected results between SRS and the primary outcome showed that this relationship was driven primarily by cardiovascular hospitalization in patients with an ischemic etiology and low SRS. Third, mechanical dyssynchrony was not significantly associated with death and cardiovascular hospitalization. Fourth, key variables (SRS, EF, and end systolic volume) derived from gated SPECT MPI added prognostic information to baseline clinical characteristics.

Ischemic etiology

SPECT MPI provides independent prognostic information in patients with cardiovascular disease.^{12,13,23–25} Furthermore, the ability to use gated SPECT MPI as a noninvasive method to distinguish ischemic from nonischemic etiologies of HF has also been described.^{26–33} Soman et al. demonstrated an excellent negative predictive value (96%) for the presence of significant coronary artery disease (CAD) in patients with newly diagnosed HF.³⁴ Additionally, both the summed stress score (SSS) and summed difference score (SDS) have been shown to be independent predictive variables of adverse outcomes.^{35–37}

This study demonstrated an inverse association between SRS and the primary endpoint, a relationship that appears to have been driven by cardiovascular hospitalizations in patients with known CAD and a low SRS. This likely represents patients with a higher degree of underlying ischemia where the SRS alone was not sufficient to fully ascertain the risk of adverse events. This hypothesis is supported by Bouzas-Mosquera et al., which demonstrated an increased risk of death or hospitalization in patients with resting wall motion abnormality and evidence of ischemia by new stress-induced wall motion abnormality versus the ones with no further evidence of ischemia.³⁸

Nonischemic etiology

The prognostic significance of scar and/or fibrosis in HF patients with a nonischemic etiology is under investigation. In a study by Wu et al., patients with nonischemic cardiomyopathy with a high degree of myocardial scar (>10% of LV) had an 8-fold increased risk of HF hospitalization, appropriate implantable cardioverter defibrillator therapy, or death compared with those with lower scar burdens.³⁹ There are currently limited data with respect to scar assessment and outcomes in nonischemic cardiomyopathy by nuclear imaging. To our knowledge, this is the first study to correlate outcomes in nonischemic cardiomyopathy with resting perfusion defects by gated SPECT imaging. Patients with a nonischemic etiology of HF and a high SRS had a trend toward increased mortality and cardiovascular hospitalization compared with those who had a low SRS (Figure 2).

Dyssynchrony

Dyssynchrony has been shown to be a predictor of adverse outcomes in HF patients.⁴⁰ However, the measurement of dyssynchrony by echocardiography has suffered from a lack of standardization and high variability. There is a growing body of literature with respect to the clinical applicability of phase analysis of gated SPECT MPI to assess LV dyssynchrony.^{14,18,20,21,41} One early study, demonstrated that a phase SD 43° (normal $9^\circ \pm 3^\circ$) had a sensitivity and specificity of 74% for predicting response to cardiac resynchronization therapy.^{18,42} Previous analysis from HF-ACTION have also shown an association between the severity of dyssynchrony and worsening New York Heart Association class.^{43,44}

This study demonstrated a nonsignificant relationship between mortality and cardiovascular hospitalization in those with more severe dyssynchrony despite a trend over the 2-year follow-up period.

Incremental prognostic value

The ability of gated SPECT imaging to provide prognostic information above and beyond clinical information has been well established.^{11,37,45–49} In this study, gated SPECT variables more than doubled the prognostic power of baseline clinical information. These findings are worth noting when considering that the clinical information used in this analysis was robust and included both New York Heart Association functional class and HF etiology, both of which are independent predictors of adverse outcomes in HF patients with reduced LV EF.

Clinical implications

Results from this study suggest the following clinical implications. In patients with heart failure, a resting gated SPECT MPI Tc-99m Myo view study has the ability to identify the ischemic versus non-ischemic etiology of cardiomyopathy. However, to detect any obstructive CAD in HF patients, a stress gated SPECT MPI study would be recommended.

The ability to simultaneously evaluate perfusion, function, volumes, and dyssynchrony makes SPECT MPI a potential gatekeeper in the evaluation of HF patients.

Limitations

Although relatively large for an HF nuclear imaging study, the sample size is approximately 10% of the overall study population. There may also have been selection bias as only patients willing to provide informed consent were enrolled in the nuclear substudy. The limited sample size obtained for the substudy means that the subgroups were small and potentially subject to variability. Another limitation is that only resting images were obtained and there was no imaging performed for assessment of stress-induced ischemia. This was mandated by the overall HF-ACTION trial design as it was felt that it could lead to alterations in medical care, particularly revascularization, which could introduce bias in endpoints related to the overall study intervention. There may be unmeasured variables that are related to both the nuclear variables and the primary endpoint that affected the results. Finally, dyssynchrony as assessed by SPECT MPI has not yet been integrated into routine clinical care. This is primarily due to a relative lack of data regarding the prognostic significance of this modality and its ability to predict other clinically relevant outcomes such as response to cardiac resynchronization therapy or appropriate defibrillator therapy.

Conclusion

Rest Tc-99m tetrofosmin gated SPECT MPI provides important information in patients with HF and reduced LV ejection fraction. The degree of resting perfusion defects demonstrated an unexpected relationship with the primary endpoint—a higher SRS corresponding to a lower risk of event, although this relationship was not observed in the unadjusted analysis. This relationship appears to have been driven by an underlying ischemic burden not assessed in this study. No significant relationship was documented between dyssynchrony and the primary endpoint, although an apparent trend toward worsened outcomes with more severe dyssynchrony was noted. Finally, gated SPECT MPI provides prognostic information in HF patients with reduced LV function beyond that provided by clinical variables.

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Figure 1.

Patient enrollment: 240 patients from the HF-ACTION trial were enrolled in the nuclear substudy; 2 studies were not interpretable and were not included in the SRS analysis; LV ejection fraction and volumes were not available in 6 studies; 29 studies were not gated and an additional 37 patients with biventricular pacemakers were excluded from the dyssynchrony analysis.

Figure 2.

Primary endpoint by etiology and SRS Kaplan-Meier curves for the primary endpoint stratified by HF etiology and SRS. Patients with a nonischemic etiology and a low SRS had the lowest event rate. Those with a high SRS, regardless of etiology, had similar event rates, with the subjects with nonischemic HF having slightly higher rates. Patients with an ischemic etiology and a low SRS had the highest event rate, likely from a high underlying ischemic burden.

Figure 3.

Primary endpoint by phase SD Kaplan-Meier curve for the primary endpoint in those with significant dyssynchrony (phase SD $>40^\circ$) and those without significant dyssynchrony (phase SD $\leq 40^\circ$). In this post hoc analysis, there was no significant difference in the primary endpoint of death and cardiovascular hospitalization between these groups (log-rank $P=0.232$). The P value was computed treating dyssynchrony as a dichotomous variable with a phase SD cutoff of 40° . Subjects with a biventricular pacemaker at baseline were excluded ($n=174$).

Figure 4.

Incremental value of nuclear variables gated SPECT variables (SRS, LV ejection fraction, and end systolic volume) provides significant prognostic value beyond baseline clinical information for the prediction of the primary endpoint (death and cardiovascular hospitalization). In both models, the sample size was limited to subjects with non-missing values of SRS, ejection fraction, and end systolic volume (n=234). Clinical variables used were age, sex, New York Heart Association class, body mass index, and etiology of HF. Phase SD did not contribute significantly to the incremental information obtained from gated SPECT imaging ($P=0.72$), analysis not shown.

Figure 5. Primary endpoint by ischemic and nonischemic etiology Kaplan-Meier curve for the primary endpoint in patients with an ischemic etiology of HF compared with those with a nonischemic etiology. Patients with ischemic etiology had a significantly higher rate of the primary endpoint ($P=0.049$).

Table I**Demographics**

	HF-ACTION Nuclear Substudy (n=240)
Age, median (25th, 75th), yrs	59 (51, 68)
Female	74 (31)
Race	
Black	78 (33)
White	150 (63)
Body mass index, median (25th, 75th), kg/m ²	30 (26, 35)
Ischemic etiology	129 (54)
Atrial fibrillation/flutter	38 (16)
Hypertension	154 (65)
Hyperlipidemia	160 (67)
Stroke	27 (11)
Diabetes	78 (33)
Chronic obstructive pulmonary disease	39 (17)
Peripheral vascular disease	15 (6)
Coronary artery bypass grafting	61 (25)
Percutaneous coronary intervention	63 (26)
Pacemaker	41 (17)
Automated internal cardioverter defibrillator	128 (53)
Biventricular pacemaker	44 (18)
Automated internal cardioverter defibrillator or biventricular pacemaker	136 (57)

All data presented as n (%), unless otherwise noted.

Table II**Medications**

HF-ACTION Nuclear Substudy	
(n=240)	
Angiotensin-converting enzyme inhibitor	168 (70)
Angiotensin receptor blocker	63 (26)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	225 (94)
Beta-blocker	230 (96)
Digoxin	96 (40)
Spironolactone	108 (45)
Aspirin	175 (73)
Loop diuretic	172 (72)
Non-loop diuretic	17 (7)
Lipid-lowering agent	157 (65)
Statin	125 (52)
Nitrate	53 (22)
Calcium channel blocker	7 (3)
Glitazone	7 (3)
Selective serotonin reuptake inhibitor	40 (17)

All data presented as n (%).

Table III**Baseline variables**

HF-ACTION Nuclear Substudy (n=240)	
Clinical and exercise	
New York Heart Association class, n (%)	
II	154 (64)
III	86 (36)
Resting heart rate, beats/min	69 (64, 76)
Resting systolic blood pressure, mm Hg	112 (102, 126)
Resting diastolic blood pressure, mm Hg	70 (64, 80)
Peak VO ₂ , mL/kg/min	15.3 (12.3, 18.5)
Exercise duration, min	10.0 (7.4, 12.5)
6-minute walk distance, meters	381 (305, 454)
Gated SPECT	
SRS	20 (5, 31)
LV ejection fraction, %	26 (21, 34)
End systolic volume, mL	165 (117, 238)
End diastolic volume, mL	226 (168, 297)
Phase SD, °	41 (23, 63)
Bandwidth, °	111 (71, 207)

Data presented as median (25th, 75th), unless otherwise noted. LV, left ventricular; SD, standard deviation; SPECT, single photon emission computed tomography; SRS, summed rest score.

Table IV

Multivariable analysis of SRS and the primary endpoint

Parameter	Chi-square	P Value	HR	(95% CI)
SRS	4.24	0.040	0.98	(0.97, 1.00)
Age	3.66	0.056	1.02	(1.00, 1.04)
Body mass index	0.75	0.385	1.01	(0.98, 1.04)
Sex	0.94	0.333	1.24	(0.80, 1.90)
New York Heart Association class	2.63	0.105	1.38	(0.94, 2.03)
HF etiology	5.23	0.022	0.56	(0.35, 0.92)
LV ejection fraction	8.32	0.004	0.97	(0.95, 0.99)

CI, confidence interval; HF, heart failure; HR, hazard ratio; LV, left ventricular; SRS, summed rest score.

Table V

Multivariable analysis of phase SD and the primary endpoint

Parameter	Chi-square	P Value	HR	(95% CI)
Dyssynchrony phase SD	0.48	0.49	1.00	(0.99, 1.01)
Age	0.45	0.50	1.01	(0.99, 1.03)
Body mass index	0.72	0.39	1.01	(0.98, 1.05)
Sex	1.17	0.28	1.34	(0.79, 2.26)
New York Heart Association class	4.06	0.044	1.60	(1.01, 2.51)
HF etiology	5.69	0.017	0.50	(0.28, 0.88)
LV ejection fraction	2.15	0.14	0.98	(0.95, 1.01)

CI, confidence interval; HF, heart failure; HR, hazard ratio; LV, left ventricular; SD, standard deviation.