Single-Photon Emission Computed Tomography Myocardial Perfusion Defects Are Associated With an Increased Risk of All-Cause Death, Cardiovascular Death, and Sudden Cardiac Death

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Background—Single-photon emission computed tomography myocardial perfusion imaging defects are associated with increased all-cause mortality and cardiovascular death. However, it is unknown whether single-photon emission computed tomography myocardial perfusion imaging can identify patients at increased risk of sudden cardiac death (SCD).

Methods and Results—We analyzed a cohort of 6383 patients with angiographically documented coronary artery disease who underwent single-photon emission computed tomography imaging. Cox proportional hazards modeling was used to examine the relationship between patient characteristics and SCD. Among patients who died, the median time to SCD was 2.7 years (25th, 75th percentiles 0.9, 4.9, respectively). The incidence of SCD was 3.4% (n=215) over 6.1 years (25th, 75th percentiles 3.7, 9.2, respectively) of follow-up. Patients with SCD had more severe heart failure symptoms, greater comorbidity (Charlson index), and higher summed stress perfusion scores (all \(P<0.001\)). After adjusting for left ventricular ejection fraction and other clinical factors in the multivariable model, the summed stress perfusion score (fixed plus reversible defects) remained significantly associated with the occurrence of SCD: summed stress perfusion score (hazard ratios per 3 U: 1.16 [95% CI, 1.08 to 1.25], \(P<0.001\)), left ventricular ejection fraction (hazard ratios per 5 U: 0.90 [95% CI, 0.85 to 0.95], \(P<0.001\)), and Charlson index (hazard ratios 1.35 [95% CI, 1.23 to 1.49], \(P<0.001\)).

Conclusions—Myocardial perfusion imaging is a significant predictor of SCD and provides information independent of clinical history and left ventricular ejection fraction. Gated single-photon emission computed tomography imaging, which evaluates both myocardial perfusion and function, may represent a more effective means of risk stratification than solitary left ventricular ejection fraction determination and should be evaluated in prospective trials. (Circ Cardiovasc Imaging. 2008;1:180-188.)

Key Words: sudden cardiac death • single-photon emission computed tomography • coronary artery disease • risk stratification

Sudden cardiac death (SCD) claims the lives of more than 400,000 persons each year in the United States.1 The implantable cardioverter defibrillator has been shown in randomized, controlled trials to prevent SCD in patients with prior myocardial infarction (MI) and reduced left ventricular (LV) function.2–5 At the present time, measuring the LV ejection fraction (LVEF) is the primary method for risk stratification for SCD in patients with coronary artery disease (CAD).6 However, ejection factor-based risk stratification for SCD is limited because most SCD events occur in patients with preserved LV function.7 Additional methods of risk stratification, including heart rate variability, microvolt T-wave alternans, and signal-averaged electrocardiography, lack sufficient predictive value in patients at risk for SCD.8–10

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patients with CAD at increased risk of SCD. More specifically, this study will determine whether the pattern of myocardial perfusion provides incremental prognostic information to the LVEF and clinical history.

Methods
To identify clinical and SPECT perfusion variables associated with SCD in patients with CAD, we conducted an observational analysis of patients in the Duke Databank for Cardiovascular Disease. The Duke Databank for Cardiovascular Disease has captured the clinical course of over 57,000 patients who have received cardiovascular care in the Duke University Health System. A longitudinal record is established for each patient with angiographically significant CAD, and an emphasis is placed on yearly follow-up and major clinical events, including SCD.

Study Population
Between January 1993 and December 2006, we identified 6383 patients with CAD who underwent SPECT stress-rest MPI. All study patients had CAD (≥75% stenosis of at least one major epicardial coronary artery) documented by cardiac catheterization within 180 days of their SPECT examination. In the event that a patient underwent serial MPIs, only the most recent examination was included in the analysis. Patients with primary valvular heart disease, congenital heart disease, or an implantable cardioverter defibrillator were excluded. We also excluded patients who underwent revascularization ≤60 days after SPECT MPI and if angiographic data were incomplete.

Follow-Up and Outcomes
The primary outcome was SCD. For the purpose of this analysis, SCD was strictly defined as death within 1 hour of symptom onset, or an unobserved death in which the patient was seen and known to be doing well within 24 hours of death.15 Relatives of patients who died at baseline were used for adjustment in the multivariable analysis.

Clinical Information
Demographic and clinical characteristics were recorded prospectively at the time of cardiac catheterization and were entered into the Duke Databank for Cardiovascular Disease.16–17 Clinical variables included age, gender, race, hypertension, diabetes, history of heart failure, New York Heart Association functional classification, CAD severity as reflected by the number of diseased vessels, prior MI, prior revascularization, peripheral vascular disease, renal insufficiency, smoking history, chronic obstructive pulmonary disease, hyperlipidemia, presence of carotid bruits, ventricular S3 gallop, and a modified Charlson comorbidity index.18 A history of heart failure and prior MI were removed from Charlson index and examined independently given their established association with SCD. Quantitative assessment of LV function was also prospectively recorded in 5423 patients (85%). When multiple imaging modalities were used to assess LV function, the following hierarchy of LVEF assessment was used: SPECT was given priority over ventriculography at cardiac catheterization, which was given priority over echocardiography. Results that used LVEF were based on this subset whereas all other results not requiring LVEF were generated for the total population and this subgroup for comparison. Use of β-blockers and antiarrhythmic medications at baseline were used for adjustment in the multivariable analysis.

Stress Testing and SPECT Imaging
Patients capable of exercising underwent treadmill stress testing according to the Bruce protocol, unless another protocol was specifically requested by the referring physician. Patients unable to exercise underwent pharmacological stress testing. SPECT MPI was performed according to the Duke University nuclear laboratory protocol, as previously described.9–20 In brief, SPECT images were obtained with multihed detectors with 30 seconds per projection at rest and 20 seconds per projection during stress. Most patients (6351 of 6383, 99.5%) underwent imaging with a single isotope (99mTc). Stress-rest SPECT studies were independently evaluated and relative perfusion was recorded in each segment using 4 gradations (0 = no defect, 1 = mild defect, 2 = moderate defect, and 3 = severe defect). A cumulative perfusion score, summed stress score (SSS), was calculated by adding the perfusion scores in all myocardial segments. Accordingly, the SSS incorporates both fixed and reversible defects and would equal zero in a normal study. The SSS is an independent predictor of cardiovascular outcomes, including MI, cardiovascular death, and all-cause mortality.11,21–24 The summed rest score (SRS), which is the sum of the perfusion scores in all segments at rest (fixed defects), and the summed difference score (SDS), which is the sum of the differences between the stress and rest perfusion scores (reversible defects), were also determined for each patient using the same scoring system.

Statistical Analysis
Clinical characteristics were examined among patients according to the primary outcome (SCD, nonsudden death, and alive at last contact) using percentages for categorical variables and medians (25th and 75th percentiles) for continuous variables. The occurrence of SCD as a function of time after SPECT imaging was examined using the Kaplan–Meier method. Patients who died from causes other than SCD were censored at the time of death. The Cox proportional hazards regression model was used to examine individual and joint relations between baseline clinical characteristics and the occurrence of SCD over time and to identify factors which were independently associated with SCD. The candidate variables considered in these analyses included baseline demographics, history and physical examination results, number of diseased vessels, SSS, SRS, and SDS, and LVEF. For continuous clinical variables, we examined the shape and strength of the relation between individual variables and SCD by use of a flexible model-fitting approach involving cubic spline functions (cubic polynomials).25 These functions were graphically and statistically examined to assess the assumption of this regression model that patient characteristics are linearly related to the logarithm of the hazard function. Where relations were nonlinear variable transformations or spline functions were used to satisfy this model assumption. Unadjusted models were also examined to explore the relationship between baseline use of β-blockers and SCD, and baseline use of antiarrhythmic drugs and SCD. In addition, the Cox model assumption of proportional hazards was examined for selected variables (LVEF and the SPECT perfusion scores) by introducing a time-dependency variable in the model. Risk relationships were characterized using hazard ratios (HR) and 95% CIs generated using the Cox model.

Significant variables were determined using stepwise selection (and backwards elimination) at the 0.05 level of significance from the candidate variables that included demographics, clinical characteristics, nuclear perfusion scores, LVEF, use of β-blockers, and antiarrhythmic pharmacotherapy. The interaction between the perfusion scores (SSS, SRS, SDS) and radionuclides, and the interaction between SSS and LVEF were also assessed in the adjusted model to determine whether relationships differed across levels of SSS and LVEF. CAD severity (as reflected by the number of diseased vessels) was excluded from the primary multivariable model to assess the prognostic use of the perfusion scores in the setting where the angiographic anatomic data may not be known. The C-statistic based on survival methods was calculated for each final model to evaluate the predictive (discriminatory) accuracy of the model for the occurrence of SCD.26
All tests were 2-tailed, and statistical significance was declared at $\alpha=0.05$. All analyses were performed using SAS software version 8.2 (SAS Institute).

The study was approved by the Duke University Institutional Review Board. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Outcomes**

Among the 6383 patients with CAD in this cohort, 215 (3.4%) patients died suddenly (109 [51%] witnessed, 76 [35.3%] unobserved, and 30 [14%] postresuscitation). Among the patients who died, the median time to SCD was 2.7 years (25th, 75th percentiles 0.9, 4.9, respectively). The incidence of nonsudden death was 31.2% (n=1992), over a median follow-up of 6.1 years (25th, 75th percentiles 3.7, 9.2, respectively).

**Patient Characteristics**

Shown in Table 1 are the clinical characteristics of the patients according to outcomes, including SCD. The median age of those with SCD was 62 years. The median LVEF in those with SCD was 47% (25th, 75th percentiles 35, 58, respectively), and most (65%) patients with SCD had an LVEF $\leq$40%. As expected, the incidence of SCD was increased in patients with advanced heart failure, as reflected...
by New York Heart Association classification. Similarly, the incidence of SCD increased with CAD severity (defined by the number of diseased vessels), although it paralleled the incidence of nonudden death in patients with multivessel disease.

Unadjusted Time-to-Event Analyses

After examining patient characteristics and the results of MPI, we identified several factors associated with SCD in unadjusted Cox models (Table 2). Notably, age was not associated with an increased incidence of SCD in this CAD population. Black race, increasing New York Heart Association classification, cerebrovascular disease, peripheral vascular disease, and carotid bruits were all significantly associated with increased risk of SCD. The extent of medical comorbidities, as reflected by the Charlson index, was also associated with an increased risk of SCD. The extent of coronary disease has been associated with an increased risk of SCD (as reflected by the number of diseased vessels on angiography), LVEF, and other clinical characteristics, the SSS remained significantly associated with the occurrence of SCD as evidenced by the similar Wald $\chi^2$ in the multivariable model. Figure 2 provides survival free from SCD stratified by LVEF < or $\geq$35% and SSS < or $\geq$6. Using these same subgroups, SCD event rates at 3, 5, and 10 years of follow-up are shown in Table 4. The incidence of SCD was greatest in those patients with an LVEF <35% and SSS $\geq$6, with a SCD event rate of 13% at 10 years.

The extent of coronary disease has been associated with an increased risk of SCD. After adjusting for the severity of CAD (as reflected by the number of diseased vessels on angiography), LVEF, and other clinical characteristics, the SSS remained significantly associated with the occurrence of SCD (HR per 3-U change in SSS 1.11 [95% CI, 1.03 to 1.19], $P=0.0064$).

We tested the time dependency of SSS and ejection factor in the adjusted Cox model to determine whether proportional hazards was violated; both time interactions (with SSS and LVEF) were significant ($P<0.001$). This indicated that nonproportional hazard was present, and therefore, reduced power to detect statistical significance. Despite this reduction in power, significance was observed (linear terms for SSS and LVEF retained their significance).

LV Function and Interaction With SCD

Because quantification of LV function is the current accepted standard for risk stratification in SCD, we sought to determine whether the relationship between SSS and SCD was different across LVEF levels. An interaction term for LVEF and SSS was examined in the Cox multivariable regression model and was determined to be nonsignificant ($P=0.72$), suggesting that the risk of SCD associated with the SSS is constant across all LVEF values.

Finally, after adjusting for clinical characteristics, we explored the incremental predictive power of LVEF and SSS for the occurrence of SCD. Using Cox proportional hazards modeling, the addition of LVEF to baseline characteristics led to a significant improvement in the predictive power of the model as reflected by the global $\chi^2$ increment ($P<0.001$). As shown in Figure 3, addition of SSS resulted in further significant improvement in the model for predicting SCD, even after adjustment for clinical characteristics and LVEF ($P=0.002$). We also examined the C-statistics for these same

Table 2. Univariate Associations With Sudden Cardiac Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>Wald $\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (HR per 10 yrs)</td>
<td>1.00</td>
<td>0.89–1.12</td>
<td>&lt;0.01</td>
<td>0.989</td>
</tr>
<tr>
<td>Black</td>
<td>1.38</td>
<td>0.97–1.98</td>
<td>2.89</td>
<td>0.089</td>
</tr>
<tr>
<td>Male</td>
<td>1.15</td>
<td>0.85–1.54</td>
<td>0.85</td>
<td>0.338</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.43</td>
<td>1.06–1.94</td>
<td>5.62</td>
<td>0.018</td>
</tr>
<tr>
<td>NYHA classification</td>
<td>1.29</td>
<td>1.16–1.42</td>
<td>19.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. diseased vessels</td>
<td>1.44</td>
<td>1.23–1.69</td>
<td>20.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1.14</td>
<td>0.87–1.50</td>
<td>0.94</td>
<td>0.333</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.54</td>
<td>1.09–2.17</td>
<td>5.53</td>
<td>0.019</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.67</td>
<td>1.21–2.31</td>
<td>8.79</td>
<td>0.003</td>
</tr>
<tr>
<td>Smoking history</td>
<td>1.21</td>
<td>0.91–1.62</td>
<td>1.69</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.58</td>
<td>1.20–2.09</td>
<td>10.24</td>
<td>0.001</td>
</tr>
<tr>
<td>Charlson comorbidity ($\geq$2)</td>
<td>1.39</td>
<td>1.27–1.52</td>
<td>43.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Carotid bruits</td>
<td>1.29</td>
<td>1.14–1.45</td>
<td>13.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S3 gallop</td>
<td>1.59</td>
<td>0.78–3.22</td>
<td>1.44</td>
<td>0.230</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.10</td>
<td>0.83–1.47</td>
<td>0.45</td>
<td>0.503</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>0.79</td>
<td>0.60–1.05</td>
<td>2.73</td>
<td>0.098</td>
</tr>
<tr>
<td>Antiarrhythmic drug use</td>
<td>1.58</td>
<td>0.81–3.07</td>
<td>1.55</td>
<td>0.213</td>
</tr>
<tr>
<td>Summed stress score (HR per 3 U)</td>
<td>1.24</td>
<td>1.17–1.32</td>
<td>48.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Summed rest score (HR per 3 U)</td>
<td>1.23</td>
<td>1.15–1.31</td>
<td>33.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Summed difference score (HR per 3 U)</td>
<td>1.12</td>
<td>1.02–1.24</td>
<td>4.74</td>
<td>0.029</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>0.771</td>
<td>0.59–1.01</td>
<td>3.58</td>
<td>0.059</td>
</tr>
</tbody>
</table>

HR indicates hazards ratios; NYHA, New York Heart Association; MI, myocardial infarction.

Adjusted Analyses of Survival Free From SCD

The results of the final multivariable model for SCD are shown in Table 3. When considering the perfusion indices, both the SDS and SSS were candidate variables in the multivariable stepwise regression analysis. The SDS was dropped in the step-wise process (and in the backwards elimination process) and was not associated with SCD. An additional analysis was done in which the SSS and SRS (more significant than SDS in the univariate model) were included, but not the SDS. SSS was again selected and the SRS was not.

Black race, comorbidity as reflected by the Charlson index, carotid bruits, prior revascularization status, LVEF, and the SSS were all significant predictors of SCD. Increasing SSS was associated with a HR 1.16 per 3-U increase (95% CI, 1.08 to 1.25). The strength of the association of SSS with SCD was similar to that of LVEF with SCD as evidenced by the similar Wald $\chi^2$ in the multivariable model. Figure 2 provides survival free from SCD stratified by LVEF < or $\geq$35% and SSS < or $\geq$6. Using these same subgroups, SCD event rates at 3, 5, and 10 years of follow-up are shown in Table 4. The incidence of SCD was greatest in those patients with an LVEF <35% and SSS $\geq$6, with a SCD event rate of 13% at 10 years.

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LV Function and Interaction With SCD

Because quantification of LV function is the current accepted standard for risk stratification in SCD, we sought to determine whether the relationship between SSS and SCD was different across LVEF levels. An interaction term for LVEF and SSS was examined in the Cox multivariable regression model and was determined to be nonsignificant ($P=0.72$), suggesting that the risk of SCD associated with the SSS is constant across all LVEF values.

Finally, after adjusting for clinical characteristics, we explored the incremental predictive power of LVEF and SSS for the occurrence of SCD. Using Cox proportional hazards modeling, the addition of LVEF to baseline characteristics led to a significant improvement in the predictive power of the model as reflected by the global $\chi^2$ increment ($P<0.001$). As shown in Figure 3, addition of SSS resulted in further significant improvement in the model for predicting SCD, even after adjustment for clinical characteristics and LVEF ($P=0.002$). We also examined the C-statistics for these same
models, which revealed improved SCD end point discrimination after inclusion of the SSS: clinical history alone (C-statistic = 0.58 [95% CI, 0.54 to 0.62]), clinical history and LVEF (C-statistic = 0.70 [95% CI, 0.66 to 0.74]), clinical history and SSS (C-statistic = 0.69 [95% CI, 0.65 to 0.72]), and clinical history with LVEF and the SSS (C-statistic = 0.72 [95% CI, 0.68 to 0.75]).

Sensitivity Analysis
To address possible heterogeneity in our SCD end point, we conducted a sensitivity analysis in which we included only those SCDs which occurred within 1 hour of symptom onset (n=139). When restricting our definition to death within 1 hour of the onset of symptoms, the SSS remained a predictor of SCD after adjustment (HR per 3-U change in SSS 1.20 [95% CI, 1.10 to 1.32], \( P<0.0001 \)) for LVEF and other clinical factors.

Relationship Between SPECT MPI Results and Other Causes of Death
We also examined Cox proportional hazards models to address the relationship between SPECT MPI results and other causes of death. Both the SRS and SSS were associated with cardiovascular death, death other than SCD, and all-cause mortality in univariate analyses (Table 5). However, in multivariable analyses the SSS was a strong predictor of cardiovascular death (HR per 3 U, SSS 1.13 [95% CI, 1.10 to 1.16], \( P<0.0001 \)) whereas the SRS was a stronger predictor of death other than SCD (HR per 3 U 1.09 [95%CI, 1.06 to 1.13], \( P<0.0001 \)) and all-cause mortality (HR per 3 U 1.09 [95% CI, 1.06 to 1.12], \( P<0.0001 \)). The SSS was not retained in the step-wise selection process for the final multivariable model for death other than SCD and all-cause mortality.

Discussion
SPECT myocardial perfusion defects are associated with increased all-cause mortality and cardiovascular death. In this observational analysis of 6383 patients with CAD, we have shown that impaired myocardial perfusion, as reflected by the SSS, is also associated with an increased risk of SCD. Our findings suggest that SCD events are driven by both myocardial scar and ischemia. More importantly, we demonstrate that the SSS provides incremental prognostic power to clinical history and the LVEF, the current gold-standard for the risk stratification of SCD.
The SSS is a well-validated index of myocardial scintigraphy which quantifies the degree and extent of perfusion abnormalities. Hachamovitch et al. investigated the predictive value of the SSS in a study of 2200 consecutive patients referred for MPI for suspected CAD. After a mean follow-up of 1.6 years, patients with a normal SSS score (0 to 4) had a cardiovascular event rate of 0.3% (MI, death), compared with 12% in those with an SSS score >13. In another large study of patients with CAD, after adjusting for the results of coronary angiography, a 1-U change in SSS was associated with a 4% increase in all-cause death and 7% increase in cardiovascular death. However, the SSS did not provide any additional prognostic information regarding cardiovascular death or mortality after adjustment for LVEF. In this report, for the first time, we show that the SSS provides incremental predictive value for the occurrence of SCD relative to the ejection fraction.

Despite abundant evidence demonstrating that the SSS is a well-validated independent predictor of MI, cardiovascular death, and all-cause mortality, few studies have addressed the relationship between impaired myocardial perfusion, as determined by SPECT imaging, and ventricular arrhythmias. In a study of 153 survivors of resuscitated sudden death who subsequently underwent stress-rest perfusion imaging, LVEF and the extent of myocardial scar were shown to be significant predictors of recurrent ventricular arrhythmias and/or all-cause death. Paganelli et al. investigated the effect of residual myocardial ischemia on inducible ventricular arrhythmias during programmed stimulation. In 90 survivors of MI, they found that residual myocardial ischemia on SPECT201TI imaging was associated with a 1.6-fold increase in the risk of inducible ventricular arrhythmias during electrophysiology testing. Despite these and other reports, which addressed recurrent arrhythmic death and inducible ventricular tachycardia, to our knowledge, there are no data regarding the predictive power of SPECT for future SCD in patients with CAD (ie, primary prevention).

Both myocardial scar and ischemia promote ventricular arrhythmias. Revascularization has been shown to decrease the risk of SCD. Consistent with this observation, trials of implantable cardioverter defibrillator implantation in patients with CAD and recent revascularization have failed to demonstrate a mortality benefit. Taken together, the results of these and other trials argue that ischemia is an important risk factor for SCD after MI. In this study, we found that the SSS and SRS were associated with an increased risk of SCD in unadjusted analysis. The SDS, which reflects the portion of impaired perfusion evident only during stress, but not at rest (ie, “pattern of ischemia”) trended toward an association with SCD, but did not meet statistical significance. In the adjusted analyses, among the perfusion indices, only the SSS remained predictive, which suggests that the combination of scar and ischemia together, has greater predictive power than either scar or ischemia alone. The SSS may represent an ideal

<table>
<thead>
<tr>
<th>Table 4. Sudden Cardiac Death Event Rates at 3, 5, and 10 Years According to Left Ventricular Ejection Fraction and Summed Stress Scores</th>
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<td></td>
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<tr>
<td>SSS</td>
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<tr>
<td>SSS &lt; 6</td>
</tr>
<tr>
<td>SRS</td>
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<tr>
<td>SSS</td>
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<tr>
<td>SDS</td>
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<tr>
<td>3-yr SCD rate</td>
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<tr>
<td>5-yr SCD rate</td>
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<tr>
<td>10-yr SCD rate</td>
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<tr>
<td>SSS ≥ 6</td>
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<tr>
<td>SRS</td>
</tr>
<tr>
<td>SSS</td>
</tr>
<tr>
<td>SDS</td>
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<tr>
<td>3-yr SCD rate</td>
</tr>
<tr>
<td>5-Yr SCD rate</td>
</tr>
<tr>
<td>10-yr SCD rate</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score.

*Nuclear perfusion indices are shown as medians with interquartile ranges.

The survival data is shown as 3-, 5-, and 10-year sudden cardiac death rates.

Figure 2. Survival free from sudden cardiac death according to summed stress scores and LVEF (log-rank probability value <0.001).
risk stratification index for SCD in ischemic heart disease, because it reflects scarred, hibernating, and ischemic myocardium.

The LVEF is an important risk factor for SCD; however, it has limited sensitivity and specificity, failing to distinguish between patients at risk for arrhythmic death and those at risk of death from pump failure.34 In the Multicenter Unsustained Tachycardia Trial, the percentage of arrhythmic death was similar in patients with LVEF <30% compared with patients with LVEF ≥30.35 In addition, as we and others have shown, most SCD occurs in patients with relatively preserved LV function.7,36 Other factors have been shown to convey similar risk prediction to the LVEF.37,38 In our model, MPI provided incremental prognostic information when compared with the LVEF and the clinical history. Impaired myocardial perfusion identified those at increased risk of SCD across all values of LVEF. This finding suggests that nuclear perfusion imaging may have a role in risk stratification in patients with CAD without severe LV dysfunction.

It is important to emphasize that the SSS suffers from the same lack of specificity that limits the LVEF. Although the hazard associated with the SSS was greater for SCD relative to all-cause mortality and the SRS was a better discriminator for all-cause mortality compared with the SSS, the SSS is not specific for SCD. The intent of this analysis, however, was to show that SPECT MPI can add incremental prognostic information to established methods of risk stratification, including the LVEF (as demonstrated by the improved global \( \chi^2 \) and increased C-statistic). SPECT MPI can delineate both myocardial function and perfusion in a single test. Given the incremental association and improved discrimination for SCD, future studies should examine the SSS score, in combination with other clinical data (including the ejection factor) for the risk stratification of SCD.

Table 5. Unadjusted Hazards Ratios per 3-U Change in the Summed Stress Score for Different Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR per 3 U</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden cardiac death</td>
<td>1.24</td>
<td>1.17–1.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.21</td>
<td>1.19–1.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death other than SCD</td>
<td>1.13</td>
<td>1.11–1.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.14</td>
<td>1.12–1.16</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HR indicates hazards ratios.

Recently there has been increased interest in the development of imaging techniques for improved risk stratification in SCD. MRI has been shown to reliably detect myocardial scar which may also predict inducibility of ventricular tachycardia during electrophysiology testing.39,40 Whether MRI can predict spontaneous ventricular arrhythmias or cardiac arrest is unknown. Application of cardiac MRI for risk stratification of SCD is restricted by its limited availability. In contrast to cardiac MRI, perfusion SPECT imaging is widely available, uses current technology, and as we have shown for the first time, has incremental value in predicting those at risk for SCD. Recent work with \(^{123}\)I-labeled metaiodobenzylguanidine in patients with cardiomyopathy suggests that SPECT imaging with this tracer may identify patients with autonomic dysfunction who are at risk for SCD.41 Although promising, these studies have been small, with limited outcome data, and without knowledge of the predictive value of conventional SPECT perfusion imaging for SCD.42,43

Study Limitations

The main limitations of this study are the observational nature of the analysis and the possibility of selection bias. However, the association between the SSS and SCD remained significant after extensive adjustment for clinical covariates, severity of CAD, and LV function. Although we adjusted for pharmacotherapy, including \( \beta \)-blockade and antiarrhythmic drugs at baseline, we could not account for changes in pharmacotherapy over time. In addition, clinical characteristics and SPECT perfusion data were collected prospectively, in consecutive patients, as part of routine clinical care, thus limiting sampling and diagnostic bias. Another limitation is that despite quantification of LV function for most subjects, LVEF determination was not uniform and represented several imaging modalities, including angiography, SPECT, and echocardiography. Nonetheless, there was no association between the source of LVEF determination and SCD in adjusted analysis (\( P=0.27 \)). Despite these limitations, given the large number of patients included, the wide range of CAD and heart failure severity in this cohort, the prospective data collection, and the strict definition and adjudication of SCD, the results are not likely to be spurious.

Conclusions

In this study, we show an association between impaired myocardial perfusion on SPECT imaging and the incidence
of SCD. In addition, we have shown that impaired myocardial perfusion, via the SSS, provides incremental prognostic information, beyond clinical characteristics and the LVEF among patients with ischemic heart disease. SPECT imaging may provide a more effective method of risk stratification for SCD than isolated ejection factor determination. However, independent validation and prospective trials are required to establish the predictive power of SPECT.

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Disclosures
Dr Piccini is listed as an inventor on a US provisional patent application (0211,150,004) covering methods for preventing sudden cardiac death. Dr Al-Khatib reports receiving research support from Medtronic and honoraria for presentations from Medtronic. Dr Borges-Neto is a consultant for General Electric Health. Dr Iskandrian, Dr Lee, John Horton, and Linda Shaw report that they have no conflicts of interest relevant to the subject matter discussed in the article.

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Sudden cardiac death: epidemic, transient risk, and intervention assessment.


CLINICAL PERSPECTIVE

Single-photon emission computed tomography (SPECT) myocardial perfusion imaging defects are associated with increased all-cause mortality and cardiovascular death. To determine whether SPECT myocardial perfusion imaging can identify patients at increased risk of sudden cardiac death, we analyzed a cohort of 6383 patients with coronary artery disease undergoing SPECT imaging on clinical grounds. Our results show an association between impaired myocardial perfusion on SPECT imaging and the incidence of sudden cardiac death. In addition, we found that impaired myocardial perfusion provides incremental prognostic information, beyond clinical characteristics and the left ventricular ejection fraction among patients with ischemic heart disease. Gated SPECT imaging, which evaluates both myocardial perfusion and function, may represent a more effective means of risk stratification for implantable cardioverter defibrillator implantation than solitary left ventricular ejection fraction determination and should be evaluated in prospective trials.
Single-Photon Emission Computed Tomography Myocardial Perfusion Defects Are Associated With an Increased Risk of All-Cause Death, Cardiovascular Death, and Sudden Cardiac Death


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