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Myocardial Perfusion Imaging Is a Strong Predictor of Death in Women

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OBJECTIVES We sought to assess the prognostic value and risk classification improvement using contemporary single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) to predict all-cause mortality.

BACKGROUND Myocardial perfusion is a strong estimator of prognosis. Evidence published to date has not established the added prognostic value of SPECT-MPI nor defined an approach to detect improve classification of risk in women from a developing nation.

METHODS A total of 2,225 women referred for SPECT-MPI were followed by a mean period of 3.7 ± 1.4 years. SPECT-MPI results were classified as abnormal on the presence of any perfusion defect. Abnormal scans were further classified as with mild/moderate reversible, severe reversible, partial reversible, or fixed perfusion defects. Risk estimates for incident mortality were categorized as <1%/year, 1% to 2%/year, and >2%/year using Cox proportional hazard models. Risk-adjusted models incorporated clinical risk factors, left ventricular ejection fraction (LVEF), and perfusion variables.

RESULTS All-cause death occurred in 139 patients. SPECT-MPI significantly risk stratified the population; patients with abnormal scans had significantly higher death rates compared with patients with normal scans, 13.1% versus 4.0%, respectively ($p < 0.001$). Cox analysis demonstrated that after adjusting for clinical risk factors and LVEF, SPECT-MPI improved the model discrimination (integrated discrimination index = 0.009; $p = 0.02$), added significant incremental prognostic information (global chi-square increased from 87.7 to 127.1; $p < 0.0001$), and improved risk prediction (net reclassification improvement = 0.12; $p = 0.005$).

CONCLUSIONS SPECT-MPI added significant incremental prognostic information to clinical and left ventricular functional variables while enhancing the ability to classify this Brazilian female population into low- and high-risk categories of all-cause mortality. (J Am Coll Cardiol Img 2011;4:880–8) © 2011 by the American College of Cardiology Foundation

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Interest and emphasis on research concerning women and heart disease has grown substantially with increasing recognition of the importance of heart disease related to the female sex (1). However, a concerning gap in the knowledge, understanding, and general awareness of ischemic heart disease (IHD) in women still remains. Evidence-based guidelines for the prevention and treatment of IHD rely largely on the results of randomized clinical trials where women are usually underrepresented (2–4).

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The ability of single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) to evaluate myocardial perfusion and left ventricular ejection fraction (LVEF) is well documented (5,6). Previous studies have determined the incremental prognostic value of myocardial perfusion and LVEF data to predict adverse outcomes in several subgroups, using different stress methods and radionuclide tracers (7–11). Most studies that evaluated the prognostic value of SPECT-MPI in women collected data before the year 2000 (12–14). In the following years, important changes in IHD treatment were introduced in clinical practice (15,16).

The spectrum of IHD varies across different ethnic populations and environments. Statistics from the World Health Organization reveal that IHD is the leading cause of death worldwide for adult women. Brazil, like other developing countries, has a highly variable racial, variable ethnical, and socioeconomically diverse population with a projected 40% increase in IHD mortality in young-to-middle-aged individuals (17). This study assessed the contemporary prognostic value of SPECT-MPI in women of a developing nation, with all-cause mortality as the main adverse outcome. We also evaluated the extent to which adding myocardial perfusion to a model based on traditional risk factors and LVEF correctly reclassified subjects in terms of risk of future all-cause mortality events.

METHODS

Study population. The study cohort comprised 2,427 consecutive female patients between 55 and 75 years of age who underwent SPECT-MPI between March 2004 and October 2007 at Quanta Diagnostico Nuclear, Curitiba, Brazil. Reasons for SPECT-MPI referral included chest pain evaluation, systolic dysfunction investigation, surveillance of known IHD, diabetes mellitus workup, preoperative workup, and evaluation due to abnormal or inconclusive treadmill test. Clinical data were collected prospectively at study entrance. The only pre-specified exclusion criteria were sex and age, since males and older individuals have distinct IHD risk patterns and were out of the scope of the present investigation. The study was approved by the institutional review board, and all participants gave written informed consent.

Imaging acquisition protocol. All participants were submitted to stress (exercise or pharmacological protocols) and rest studies after intravenous injection of 20 to 25 mCi of ^{99m}Tc-sestamibi, based on patient weight. Conventional image protocol acquisition using standard energy windows for ^{99m}Tc in dual-head gamma cameras with a low-energy all-purpose collimator was performed. No attenuation or scatter correction was used. Images started 30 to 60 min after injection in the resting state and 15 to 30 min after injection at peak stress. An electrocardiography-gated SPECT acquisition was also performed.

Image interpretation. Semiquantitative visual interpretation of SPECT-MPI was performed by consensus of 2 experienced, board-certified observers using short-axis and vertical long-axis slices, divided into 17 standard segments for each patient (18). Each segment was scored based on the tracer uptake as: 0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; and 4, absent tracer uptake in rest and stress images. A summed rest score (SRS) and summed stress score (SSS) were obtained by adding the scores of the 17 segments of the rest and stress images, respectively. The summed difference score (SDS) was determined by subtracting the SRS from the SSS. Studies were classified as normal (SSS <4) or abnormal (SSS ≥ 4). Abnormal studies were further classified as having mild-to-moderate complete reversible perfusion defects (SSS = 4 to 12 and SRS <4), severe complete reversible perfusion defects (SSS ≥ 13 and SRS <4), partial reversible perfusion defects (SSS ≥ 4, SRS >4, and SDS ≥ 2), or only fixed perfusion defects (SSS ≥ 4 and SDS <2). The gated images were processed by quantified gated SPECT software (QGS, Cedars-Sinai, Los Angeles, California) to obtain post-stress LVEF.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
HR = hazard ratio
IDI = integrated discrimination index
IHD = ischemic heart disease
LVEF = left ventricular ejection fraction
NRI = net reclassification improvement
SDS = summed difference score
SPECT-MPI = single-photon emission computed tomography myocardial perfusion imaging
SRS = summed rest score
SSS = summed stress score

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Clinical data and patient follow-up. Clinical data including age, diabetes, hypertension, hyperlipidemia, body mass index, smoking status, symptoms, family history of premature IHD, and prior history of known IHD (prior myocardial infarction, revascularization, or IHD confirmed by coronary angiography) were collected prospectively at study entrance, before the SPECT-MPI study.

Follow-up was performed by blinded scripted telephone interviews. A minimum of 3 telephone contact attempts to patients and family members were made. If interview attempts failed, referring physicians were contacted, and the last office visit after the SPECT-MPI study was used as the censoring date.

The only outcome was all-cause mortality, which was confirmed by death certificate in government records in all cases. Subjects submitted to coronary revascularization after the SPECT-MPI were censored at the time of the procedure. Subjects not confirmed to be deceased by death certificate and without any follow-up information were considered lost to follow-up.

Statistical analysis. Statistical analyses were performed using Stata Statistical Software, release 11 (StataCorp, College Station, Texas). Comparisons between patient groups were performed using Kruskal-Wallis, chi-square, and ANOVA tests. Cumulative mortality rate curves were calculated using the Kaplan-Meier method and compared by log-rank test. A p value of <0.05 was considered statistically significant.

The effect of the myocardial perfusion result by SPECT-MPI on mortality and the 3-year estimated incident mortality risk were determined using Cox regression models. Three models were created in the order in which they would actually be considered in clinical practice: 1) clinical model; 2) clinical + LVEF model, adding LVEF; and 3) clinical + LVEF + perfusion model, including SPECT-MPI results. The risk estimates were categorized as $<3\%$, 3% to 6%, and $>6\%$ risk of mortality in 3 years, corresponding to low, intermediate, and high risk ($<1\%$, 1% to 2%, $>2\%$ event rate per year).

Discrimination was assessed comparing the areas under the receiver-operator characteristics curves of each model using the DeLong method for correlated curves (19). We also calculated the integrated discrimination index (IDI) and the net reclassification improvement (NRI) between models following the methodology of Pencina et al. (20,21).

In an attempt to project potential misleading results due to the loss of follow-up patients missing data, we conducted a sensitivity analysis using a multiple imputation for missing data approach (22,23).

RESULTS

Clinical characteristics and SPECT-MPI results. The study population included 2,427 women. Follow-up information was not available for 202 individuals (8.3%), leaving a final study cohort of 2,225 participants. The final cohort mean population age was 64.5 ± 5.6 years, with a mean LVEF of 64.4 ± 10.9%. Four hundred and fifty (20.2%) had past history of known IHD, with prior myocardial infarction in 182 (8.2%). The stress testing method was treadmill exercise in 1,626 (73.1%) and pharmacological in 599 (26.9%) patients. Interestingly, 999 (44.9%) participants were asymptomatic and were referred for SPECT-MPI due to surveillance of known IHD (18.5%), diabetes mellitus workup (20.7%), and largely due to abnormal or inconclusive treadmill test (42.7%). Table 1 shows the baseline clinical characteristics stratified by the SPECT-MPI result.

From the 548 (24.6%) subjects with abnormal scans, 443 (80.8%) had complete reversible perfusion defects, 53 (9.7%) had only fixed perfusion defects, and 52 (9.5%) had partial reversible perfusion defects.

Survival analysis by the presence, severity, and type of perfusion defects on SPECT-MPI. During the mean follow-up period of 3.7 ± 1.4 years, there were 139 deaths with an event rate of 6.2%. Overall survival was 96.0% and 86.9% among the cohort when grouped according to the absence or presence of perfusion defects, respectively ($p < 0.001$) (Fig. 1A). The unadjusted hazard ratio (HR) for mortality was 4.53 (95% confidence interval [CI]: 3.25 to 6.32). After adjustment for clinical IHD risk factors and LVEF, the multivariable model showed that the presence of any perfusion defect (SSS ≥ 4) was an independent predictor of mortality (HR: 3.02, 95% CI: 2.06 to 4.44).

Considering subgroups with abnormal SPECT-MPI results stratified by the type and extent of perfusion defects, survival rates and adjusted HRs are presented in Tables 1 and 2. Adjusted survival analysis curves are shown in Figure 1B.

Conventional risk factors, LVEF, and myocardial perfusion defect as predictors of all-cause mortality. Univariate analysis demonstrated that known IHD

Table 1. Clinical Characteristics, LVEF, SSS, and SRS, Absolute Mortality Incidence, and Survival Rate Stratified by the SPECT-MPI Results

Variable	Normal (N = 1,677)	Mild/Moderate Reversible Defect (N = 382)	Fixed Defect (N = 53)	Severe Reversible Defect (N = 61)	Partial Reversible Defect (N = 52)	p Value
Age, yrs	64.1 (5.6)	65.5 (5.4)	64.6 (5.1)	66.3 (5.5)	66.0 (5.5)	0.0001
BMI, kg/m^2	27.6 (4.8)	28.4 (5.7)	27.4 (5.1)	28.5 (5.8)	27.7 (5.7)	0.31
Hypertension	71.9%	81.3%	88.2%	86.7%	85.7%	<0.001
Diabetes mellitus	17.5%	28.7%	25.5%	46.7%	26.8%	<0.001
Hyperlipidemia	57.0%	62.6%	64.7%	66.7%	64.3%	0.12
Smoking	10.1%	12.1%	11.8%	5.0%	19.7%	0.08
Known IHD	13.3%	33.4%	78.4%	28.3%	76.8%	<0.001
Symptoms						<0.001
Typical Angina	6.3%	11.6%	7.8%	27.6%	12.5%	
Atypical Angina	46.8%	51.8%	43.1%	38.0%	35.7%	
Asymptomatic	46.8%	36.6%	49.0%	34.5%	51.8%	
LVEF, %	66.7 (8.5)	60.7 (12.6)	51.0 (13.1)	50.4 (13.6)	46.0 (13.9)	0.0001
SSS	0.05 (0.4)	6.5 (2.6)	10.6 (8.1)	18.8 (6.0)	16.8 (7.8)	0.0001
SRS	0.01 (0.2)	0.02 (0.2)	10.6 (7.9)	0.01 (0.2)	8.1 (6.3)	0.0001
All-cause mortality	67	38	10	12	12	0.0001
Survival rate	96.0%	89.8%	81.1%	80.3%	78.8%	0.0001

Values are presented as means (SD), %, or N.
BMI = body mass index; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; SPECT = single-photon emission computed tomography; SSS = summed stress score; SRS = summed rest score.

(HR: 1.65, 95% CI: 1.14 to 2.40) and older age (HR: 1.06, 95% CI: 1.03 to 1.10) were the only significant clinical variables for the prediction of death. Lower LVEF and presence of any perfusion defect were also highly predictive of death, with HRs of 0.95 (95% CI: 0.94 to 0.96) and 4.53 (95% CI: 3.25 to 6.32), respectively. In multivariate analysis (Table 2), only older age remained a clinical predictor of all-cause mortality after inclusion of LVEF and SPECT-MPI results to the model. According to a realistic clinical approach, adding LVEF and SPECT-MPI results to the clinical model resulted in significant incremental prognostic information, measured by the improvement in the global chi-square (Table 2).

Perfusion defects and all-cause mortality discrimination. Measures of discrimination showed a significant improvement with the inclusion of LVEF and SPECT-MPI results to the prediction model. In our cohort of patients, the areas under the receiver-operator characteristic curves for the prediction of all-cause death significantly increased with addition of both variables (Table 2).

Also, the IDI was 0.031 ($p < 0.001$) when LVEF was added to the clinical model (relative IDI of 3.7), and 0.009 ($p = 0.02$) when SPECT-MPI results were added to the clinical + LVEF model (relative IDI of 0.24).

Perfusion defects and risk category reclassification. The addition of LVEF to the clinical predictive model reclassified 45% of the sample, mostly due to downward reclassification (33.9%) of individuals that were subsequently free of mortality during follow-up, achieving an NRI of 0.26 (95% CI: 0.14 to 0.37, $p < 0.001$). The further addition of SPECT-MPI results reclassified 28% of the sample, also mostly due to downward reclassification (17%) of individuals that were subsequently outcome free. Upward reclassification of patients that subsequently had a fatal event was achieved in only 1% of the cohort. The NRI for event was 0.03 and the NRI for non-event was 0.09, achieving an NRI of 0.12 (95% CI: 0.04 to 0.21, $p = 0.005$). Cross-tabulations of the 3-year estimated risk and Kaplan-Meier event rates for the last 2 models are shown in Table 3.

The risk stratification capacity of the models is shown in Figure 2. The left panel shows that including myocardial perfusion to the model with clinical factors and LVEF places 61% of the overall population into either the highest or lowest risk categories, compared with 46% in the clinical model and 53% in the clinical + LVEF model. With the addition of the SPECT-MPI results, an additional 8.5% of those who did not experience events were reclassified as low risk (Fig. 2, right panel) and an additional 3.6% of those who experience events were reclassified as high-risk (Fig. 2, center panel) when compared with the model including clinical risk factors and LVEF.

Examples of normal and abnormal SPECT-MPI images from 2 patients with multiple risk factors

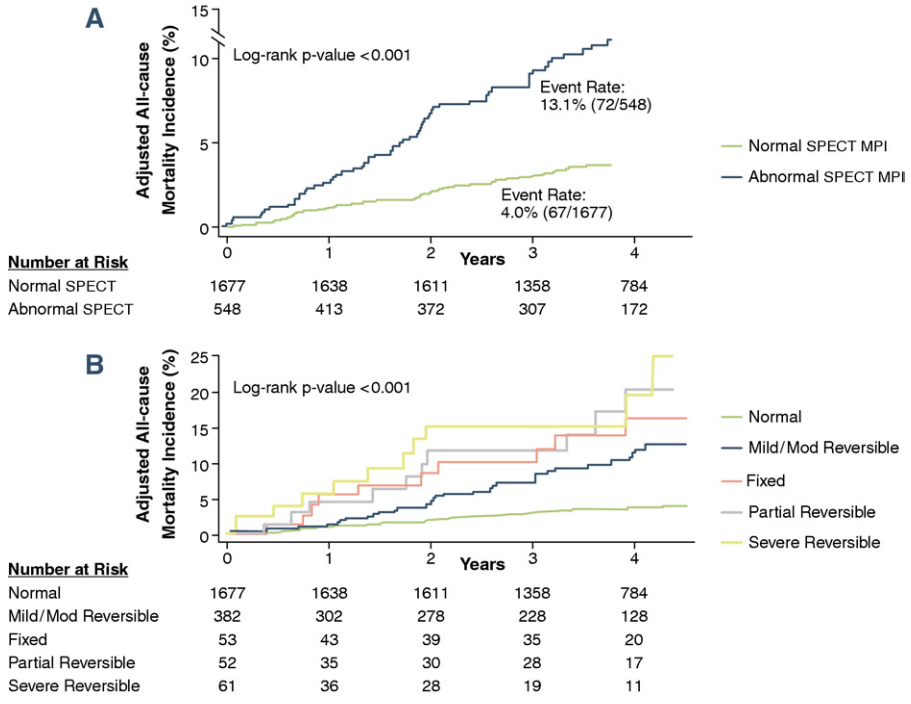

Figure 1. Risk-Adjusted Cumulative Incidence of All-Cause Mortality

(A) All-cause mortality is shown according to the presence or absence of perfusion defects by single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) and **(B)** according to the presence of mild/moderate complete reversible, severe complete reversible, partial reversible, or only fixed perfusion defects by SPECT-MPI. Mild/Mod = mild and moderate.

and atypical angina classified as high risk for all-cause mortality (>2%/year) by the model with clinical factors and LVEF, but with distinct outcomes during the follow-up are presented in Figure 3.

Sensitivity analysis. Although the clinical and SPECT-MPI variables were similar between the included and lost to follow-up populations, the LVEF was slightly but significantly higher in the followed cohort (64.4 ± 10.9% vs. 61.2 ± 13.4%; $p < 0.001$), and a sensitivity analysis was conducted. Applying mortality rates of 6.2%, 10%, 50%, and 100% on the lost to follow-up population, the multivariate HRs variation for abnormal SPECT, mild/moderate complete reversible perfusion defects, severe complete reversible perfusion

Table 2. Multivariate Models of All-Cause Mortality

Variable	Clinical	p Value	Clinical + LVEF	p Value	Clinical + LVEF + Perfusion	p Value
Age	1.07 (1.03–1.10)	<0.001	1.07 (1.03–1.10)	<0.001	1.06 (1.03–1.10)	<0.001
Smoking	1.74 (1.10–2.75)	0.02	1.47 (0.93–2.33)	0.1	1.57 (0.99–2.50)	0.055
Known IHD	1.55 (1.06–2.25)	0.02	1.21 (0.83–1.78)	0.3	0.78 (0.51–1.20)	0.27
LVEF	—	—	0.95 (0.94–0.96)	<0.001	0.97 (0.96–0.98)	<0.001
SPECT-MPI result Normal					1.0	
Mild/moderate reversible defects	—	—	—	—	2.52 (1.64–3.85)	<0.001
Fixed defects	—	—	—	—	4.42 (2.07–9.44)	<0.001
Partial reversible defects	—	—	—	—	5.29 (2.53–11.03)	<0.001
Severe reversible defects	—	—	—	—	6.01(3.08–11.71)	<0.001
Global chi-square	27.4		87.7	<0.001*	127.1	<0.001‡
Area under the ROC curve (95% CI)	0.61 (0.56–0.66)		0.69 (0.65–0.74)	0.0004*	0.73 (0.68–0.77)	0.02‡

Values are presented as hazard ratios with 95% confidence intervals (CI). *p value for the difference between clinical and clinical + LVEF models; †p value for the difference between clinical + LVEF and clinical + LVEF + perfusion models.
Abbreviations as in Table 1.

Table 3. Three-Year Risk of All-Cause Mortality Predicted by the Clinical + LVEF and Clinical + LVEF + Perfusion Models

3-Year Risk in Clinical + LVEF Model	3-Year Risk in Clinical + LVEF + Perfusion Model*					
	<3%	3%–6%	>6%	Overall	Reclassified Higher Risk	Reclassified Lower Risk
<3%						
Participants	585	67	7	272		
With events	11	4	0	8	4 (50%)	NA
Without events	574	63	7	264	70 (26.5%)	NA
Kaplan-Meier 3-yr risk (95% CI)	1.6 (0.8–3.0)	1.6 (0.2–10.9)	0	1.5 (0.6–4.0)		
3%–6%						
Participants	236	640	142	1,201		
With events	4	29	26	66	26 (39.4%)	11 (16.7%)
Without events	232	611	116	1,135	116 (10.2%)	408 (35.9%)
Kaplan-Meier 3-yr risk (95% CI)	1.7 (0.6–4.6)	3.5 (2.3–5.4)	14.2 (9.2–21.7)	4.2 (3.2–5.6)		
>6%						
Participants	0	339	385	752		
With events	0	21	44	65	NA	21 (32.3%)
Without events	0	318	341	687	NA	346 (50.4%)
Kaplan-Meier 3-yr risk (95% CI)	NA	3.8 (2.2–6.6)	10.4 (7.6–14.2)	6.9 (5.3–9.2)		
Overall						
Participants	821	1,046	534	2,225		
With events	15	54	70	139	30 (21.6%)	32 (23%)
Without events	806	992	464	2,086	186 (8.9%)	754 (36.2%)
Kaplan-Meier 3-yr risk (95% CI)	1.6 (0.9–2.8)	3.5 (2.5–4.8)	11.1 (8.6–14.2)	4.8 (3.9–5.8)		

*The net reclassification improvement is 0.12 (95% CI: 0.04 to 0.21, p = 0.005).
CI = confidence interval; LVEF = left ventricular ejection fraction; NA = not applicable.

defects, only fixed perfusion defects, and partial reversible perfusion defects were 2.96 to 3.01, 2.55 to 2.84, 4.84 to 5.33, 3.10 to 4.46, and 4.16 to 5.13, respectively. Even in the worst scenario tested, the log-rank test comparing the cumulative mortality curves had a $p < 0.001$.

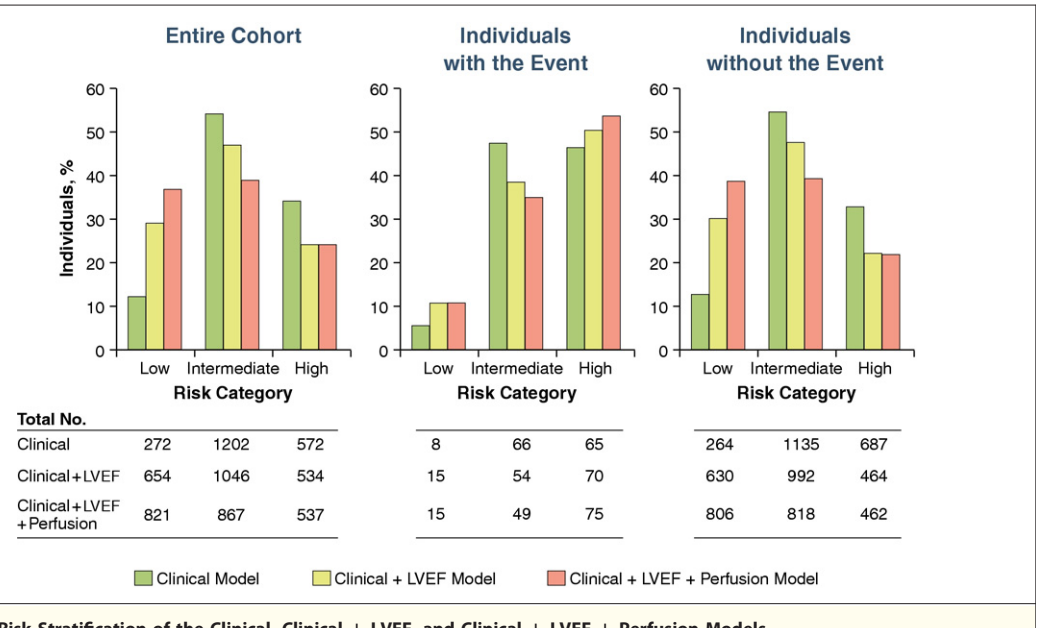

Figure 2. Risk Stratification of the Clinical, Clinical + LVEF, and Clinical + LVEF + Perfusion Models

LVEF = left ventricular ejection fraction.

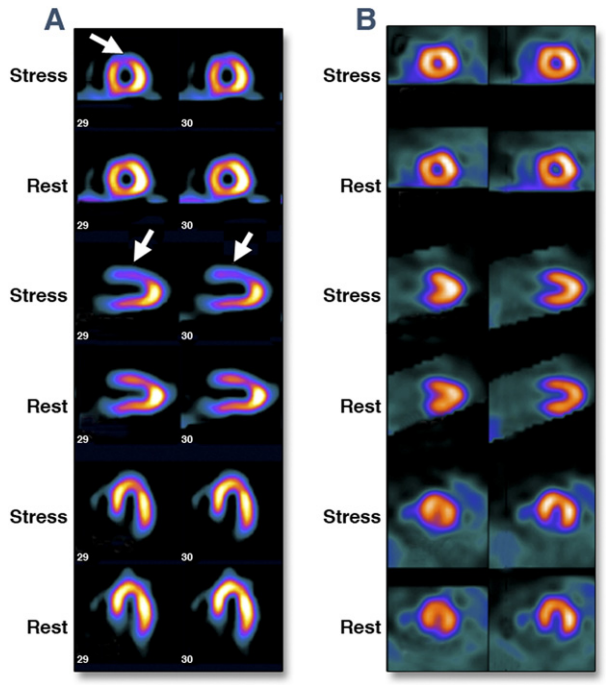

Figure 3. Examples of SPECT-MPI

Examples of single-photon emission computed tomography myocardial perfusion images (SPECT-MPI) of patients with multiple risk factors and atypical angina classified as high risk for all-cause mortality (>2%/year) by the clinical + left ventricular ejection fraction model. **(A)** Patient with significant anteroseptal perfusion defect **(white arrows)**. After adding the SPECT-MPI results to the model, the patient probability of all-cause mortality increased from 2.8% to 4.5%/year, remaining in the higher-risk range of >2%/year. The patient died after 2.1 years of follow-up. **(B)** Patient with normal myocardial perfusion. After adding the SPECT-MPI results to the model, the patient was reclassified from high risk (2.3%/year) to low risk (0.9%/year) and survived after 3.5 years of follow-up.

DISCUSSION

Over 80% of cardiovascular deaths occur in low- and middle-income countries and occur almost equally in men and women (17). Although women with IHD have more adverse outcomes as compared with men (24), physicians still often underestimate their IHD prevalence, and studies have reported a gender bias in the management of IHD, even in contemporary practice (2,3). With the new paradigms where MPI may be used to guide IHD patient decision making regarding target intervention or clinical treatment, the prognostic implication of different types and severity of perfusion defects must be completely defined in the previously underrepresented female population (25,26).

Our results show that women with abnormal SPECT-MPI results had a 3.02 times higher incidence of all-cause death during the follow-up period, when compared with women with normal results. Additionally, by assessing the extent and severity of defect size and its degree of reversibility, SPECT-MPI provided a continuum of risk stratification (12,14).

In developed nations, SPECT-MPI has been shown to have a powerful predictive value regarding cardiac death, myocardial infarct, or the need of coronary revascularization in a multitude of clinical studies with more than 15,000 women (27) and has also been shown to risk stratify and add incremental prognostic value to clinical and exercise variables (28). Elhendy et al. (29) evaluated SPECT-MPI for predicting all-cause mortality in 503 women with known or suspected coronary IHD. The annual mortality rate was 1.4% with normal and 4% with abnormal perfusion ($p < 0.01$) during a median follow-up of 3.5 years. Comparatively, our results show an annualized mortality rate of 0.94% in patients with normal SPECT-MPI and 7.2% in patients with severe complete reversible perfusion defects during a similar follow-up period, indicating a slightly lower death rate in patients with normal myocardial perfusion, but a higher rate in patients with severe defects.

Finally, the presence of myocardial perfusion defect was incremental and led to a more refined estimation of mortality risk. An important strength of a diagnostic test is the number of patients identified as having higher and lower risk and, consequently, becoming eligible or not to receive different therapy (usually more intensive and expensive). Almost 7.5% of the total cohort was reclassified as high risk and 10.6% as low risk with the SPECT-MPI results. Importantly, 54% of the events (75 of 139) occurred in individuals classified as high risk, and 73% (1,624 of 2,086) of the patients classified as low or intermediate risk by the final model were alive at the last follow-up. Inspection of relative contribution of correct reclassification for event or non-event also reveals important strengths and weakness of SPECT-MPI. When adding myocardial perfusion data to the model, the NRI for events was 0.03, whereas the NRI for non-events was 0.09, suggesting that SPECT-MPI may identify more individuals who do not experience events than individuals who do. Another metric of a test's utility is the ability to separate individuals into more clinically relevant risk categories. When myocardial perfusion was added to the final model, almost 16% of the intermediate-risk group were reclassified as high risk, whereas 22.6% were reclassified as low risk,

where treatment strategies may be better defined (Fig. 2).

Radiation dose of cardiac imaging is always a concern, and therefore, the ALARA ("As Low As Reasonably Achievable") principle should be applied. Our standard myocardial perfusion imaging protocol has an effective dose near 10 mSv.

Approximately 8.3% of the initial population was lost to follow-up. Sensitivity analysis concluded that inclusion of data from this missing group would not have affected the overall study results.

This study has some other limitations. Results are based on a female population between 55 and 75 years old referred to cardiac SPECT-MPI who may have more severe disease than a nonreferral population. A final consensus of 2 readers was used as the final SPECT-MPI result instead of blinded interpretations. Also, the study was not designed to evaluate management strategies, and no conclusions can be made in this regard. However, the performance of angioplasty or surgical coronary revascularization may have altered the total mortality of the population, despite censoring at the time of the procedure when the information was available.

CONCLUSIONS

SPECT-MPI added significant incremental prognostic information to clinical and left ventricular functional variables. Myocardial perfusion data also substantially enhances the ability to classify this Brazilian female population with known or suspected IHD into low- and high-risk categories of all-cause mortality.

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