Prognostic value of early left ventricular ejection fraction reserve during regadenoson stress solid-state SPECT-MPI

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Background. **We hypothesized early post-stress left ventricular ejection fraction reserve (EFR) on solid-state-SPECT is associated with major cardiac adverse events (MACE).**

Methods. **151 patients (70 ± 12 years, male 50%) undergoing same-day rest/regadenoson stress ^{99m}Tc-sestamibi solid-state SPECT were followed for MACE. Rest imaging was performed in the upright and supine positions. Early stress imaging was started 2 minutes after the regadenoson injection in the supine position and followed by late stress acquisition in the upright position. Total perfusion deficit (TPD) and functional parameters were quantified automatically. EFR, Δend-diastolic volume (EDV), and end-systolic volume (ESV) were calculated as the difference between stress and rest values in the same position. EFR < 0%, ΔEDV ≥ 5 ml, or ΔESV ≥ 5 ml was defined as abnormal.**

Results. **During the follow-up (mean 3.2 years), 28 MACE occurred (19%). In Kaplan–Meier analysis, there was a significantly decreased event-free survival in patients with early EFR < 0% (P = 0.004). Similarly, there was a decreased event-free survival in patients with ΔESV ≥ 5 ml at early stress (P = 0.003). However, EFR, ΔEDV, and ΔESV at late stress were not associated with MACE-free survival. Cox proportional hazards model adjusting for clinical information and stress TPD demonstrated that EFR, ΔEDV, and ΔESV at early stress were significantly associated with MACE (P < 0.05 for all).**

Conclusions. **Reduced early post-stress EFR on vasodilator stress solid-state SPECT is associated with MACE. (J Nucl Cardiol 2022;29:1219–30.)**

Key Words: Ejection fraction reserve • solid-state SPECT • major cardiac adverse events

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Yuka Otaki and Mathews B. Fish have contributed equally to this work.

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Abbreviations	
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
ECG	Electrocardiogram
EF	Ejection fraction
MPI	Myocardial perfusion imaging
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
QPS	Quantitative perfusion SPECT
SPECT	Single-photon emission computed tomography
TPD	Total perfusion deficit

See related editorial, pp. 1231–1233

INTRODUCTION

Although evidence supporting the use of single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) for risk assessment and clinical decision making has accumulated over the last 30 years,[1] regional perfusion alone may underestimate the extent of coronary artery disease (CAD).[2,3] In particular, relative perfusion defects may not identify patients with left main or multi-vessel disease due to balanced ischemia.[2,3] However, such high-risk patients are the most important to identify since they have poor cardiac outcomes and may benefit from revascularization.[4–6] Traditionally, high-risk nonperfusion parameters such as transient ischemic dilation [7,8] and post-ischemic stunning [9] have been used as aids to identify patients with more severe CAD than would be predicted by relative perfusion alone on SPECT or positron emission computed tomography (PET) MPI.

One advantage of PET is the ability to rapidly measure LV function during peak hyperemia, which is not possible with conventional SPECT camera systems. Previous PET studies demonstrated that early post-stress EF reserve is a useful diagnostic and prognostic marker.[10–12]

The recent emergence of solid-state SPECT camera systems resulted in significant improvements in count sensitivity [13] and diagnostic accuracy for CAD [14–17] allowing shorter acquisition times to facilitate early post-stress imaging. Previously, our group evaluated a novel imaging protocol with early gated acquisitions after regadenoson stress using a solid-state SPECT camera system and demonstrated that patients with significant ischemia were more likely to have negative early post-stress EF reserve.[17] In the current study, we sought to establish if early post-stress EF reserve or change in end-systolic volume (ESV) and end-diastolic volume (EDV), measured using solid-state SPECT MPI, is associated with major adverse cardiac events (MACE).

METHODS

Study Population

Patients referred for clinically indicated rest/regadenoson stress SPECT MPI at the Nuclear Medicine Department, Sacred Heart Medical Center, Springfield, Oregon, between November 2013 and May 2016, were considered for the protocol. Final patient selection depended on the ability to accommodate additional imaging during this protocol and, in particular, the ability to have stress lab and nursing staff available during the entire procedure. Out of 1224 patients who underwent rest/regadenoson stress SPECT MPI during the above time period, a total of 151 patients were selected for the study protocol. The study protocol, including a waiver of informed consent, was approved by the PeaceHealth Institutional Review Board.

Rest/Early and Late Regadenoson Stress Imaging Protocol

The study protocol is shown in Figure 1. Rest and stress 1-day ^{99m}Tc-sestamibi imaging was performed using high -efficiency, solid-state SPECT camera system (D-SPECT, Spectrum-Dynamics, Haifa, Israel).[18] Patients were instructed to abstain from caffeine-containing drinks and foods for 24 hours before the study. Beta-blockers and calcium channel antagonists were discontinued for 24 hours and nitrates were withheld for 6 hours before the test.[19] During the pre-imaging stress lab evaluation and procedures, standard 12 leads for electrocardiogram (ECG) monitoring and leads for image gating were applied, and a venous catheter was inserted into an antecubital vein. Patients were injected with 222-333 MBq (6-9mci) of ^{99m}Tc-sestamibi, according to a body mass index (BMI)-related dose schedule (6-7 mCi for BMI $\leq$ 35, and 8-9 mCi for BMI range of 36-50) at rest. A 10-12 minute rest acquisition in the upright position was obtained 15-30 minutes after the rest injection, followed by a 10-12 minute rest acquisition in the supine position. After the rest acquisition, regadenoson 0.4 mg was injected over 10 seconds with 5 ml saline flush, and 10-20 seconds later followed by an IV bolus of 888-1332 MBq (24-36 mCi) 99mTc-sestamibi, according to the BMI-related dose schedule (24-28 mCi for BMI $\leq$ 35, 32-36 mCi for BMI range of 36-50) and 10 ml saline. A 6-8 minute early stress acquisition was obtained 2 minutes after the regadenoson injection in the supine position, followed by 6-8 minute late stress acquisition in the upright position. The perfusion results were derived from the late stress acquisitions since our previous work demonstrated that 96% of the stress images performed 5 minutes after

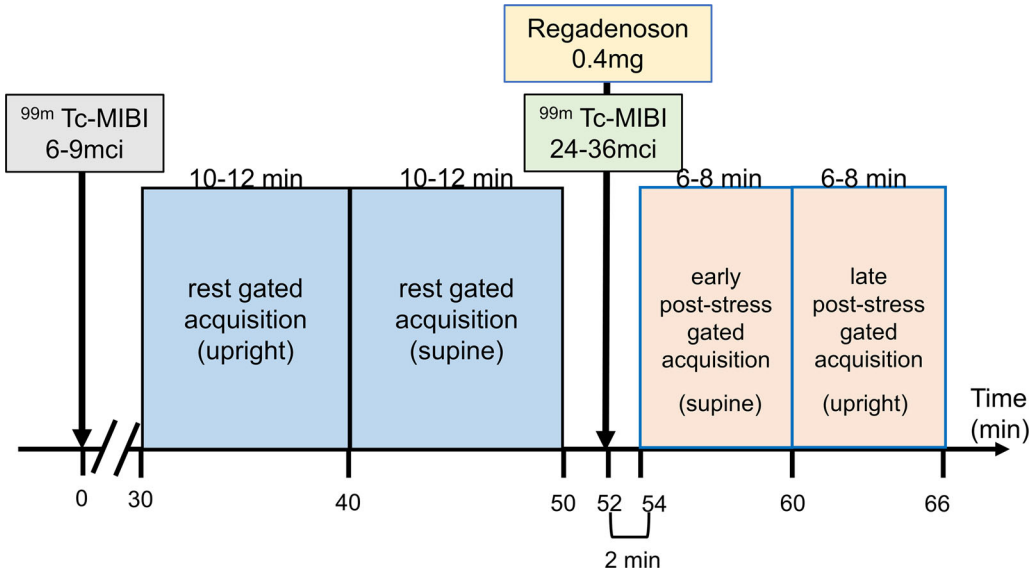

Figure 1. Early Post-Regadenoson Stress Solid-state SPECT MPI Protocol. Rest and stress 1-day ^{99m}Tc-sestamibi imaging was performed using high -efficiency, solid-state SPECT camera system (D-SPECT, Spectrum-Dynamics, Haifa, Israel).[18] Patients were injected with 6-9mci of ^{99m} Tc-sestamibi at rest. A 10-12 minute rest acquisition in the upright position was obtained 15-30 minutes after the rest injection, followed by a 10-12 minute rest acquisition in the supine position. After the rest acquisition, regadenoson 0.4 mg over 30 second was injected, immediately followed by an IV bolus of 24-36 mci ^{99m} Tc-MIBI and 10 ml saline. A 6-8 minute early stress acquisition was obtained 2 minutes after the regadenoson injection in the supine position, followed by 6-8 minute late stress acquisition in the upright position.

regadenoson/tracer injection demonstrated good, excellent, or fair quality with low or no extra-cardiac tracer activity, allowing for confident clinical interpretation.[17] The late post-stress images were performed at 8-10 minutes post-injection, and therefore would be of adequate quality, and were in the default position for this camera. Heart rate, blood pressure, and ECG were monitored and recorded during the imaging protocol for 10 minutes after stress injection.

Transaxial images were created by a reconstruction algorithm based on a maximum likelihood maximization method.[18] No attenuation or scatter correction was applied. Images were automatically re-oriented into short-axis, and vertical and horizontal long-axis slices with Quantitative Perfusion SPECT (QPS)/ Quantitative Gated SPECT (QGS) software (Cedars-Sinai Medical Center, Los Angeles, California).

Automated Quantification of Perfusion and Function Parameters

Automatically generated myocardial contours by QPS/QGS were evaluated, and when necessary, contours were adjusted to correspond to the myocardium by an experienced technologist. Rest and stress perfusion images were analyzed in the upright position (default position for this camera) as previously described using total perfusion deficit (TPD).[20,21] Functional parameters including EF, EDV, and ESV at rest and stress were quantified separately for each acquisition from 16 frames per cardiac cycle. EF reserve, ΔEDV, and ΔESV were calculated as the absolute difference between stress and rest values from the same position.[10] Abnormal post-stress functional parameters were defined as EF reserve $< 0\%$, ΔEDV $\geq$ 5 ml, or ESV $\geq$ 5 ml as previously reported.[12,22]

MACE

MACE consisted of all-cause mortality, nonfatal myocardial infarction, unstable angina, or coronary revascularization (PCI or CABG after SPECT MPI).[13] All-cause mortality was determined from the Social Security Death Index. All information related to myocardial infarction, unstable angina, and late revascularization including symptoms, ECG changes, cardiac biomarkers, and imaging modalities such as echocardiography, stress test, computed tomography angiography, and invasive angiography were obtained by reviewing medical records, a patient questionnaire, or patient interview. A board-

certified cardiologist adjudicated events based on all available information. The first event which occurred among the above components of MACE was considered as the main event for this analysis.

Statistical Analysis

All data were tested for normal distribution using the Kolmogorov–Smirnov test. Categorical variables are presented as frequencies and continuous variables as mean ± SD or median and interquartile ranges. Variables were compared using a $\chi 2$ statistic for categorical variables and Student's t test or Wilcoxon rank-sum test for continuous variables. Kaplan–Meier analysis and log-rank test were used to assess any differences in event risk between groups with and without EF reserve $< 0\%$, and ΔESV $\geq$ 5 ml and EDV $\geq$ 5 ml.

The annualized event rates based on events per patient per year were calculated and compared between patients with normal and abnormal EF reserve, ΔESV, and ΔEDV. Univariable Cox proportional hazards analysis was performed to assess associations with MACE. The baseline multivariable Cox proportional hazards analysis included age, history of prior PCI, and stress TPD (Model 1). Then, three multivariable Cox proportional hazards analyses were performed considering age, history of prior PCI, and stress TPD to determine the association between early post-stress functional parameters (Model 2: early EF reserve, Model 3: early Δ EDV, and Model 4: early Δ ESV) and MACE. A parsimonious multivariable model, including only significant predictors from the univariable analysis, was used to maintain statistical power.[23] A hazard ratio (HR) and 95% confidence interval (CI) were calculated from the Cox models. Global chi-square analyses utilized cox models and a likelihood ratios test to evaluate the incremental prognostic value of early post-stress functional parameters. Two-tailed P value < 0.05 was considered statistically significant. STATA version 13 was used for all analyses (Stata Corp, College Station, TX).

RESULTS

Outcome Events

During the mean follow-up of 3.2 ± 1.1 years, 28 MACE (19%) occurred including 13 deaths, 9 myocardial infarctions, and 6 coronary revascularizations.

Clinical Characteristics and Hemodynamic Results

Clinical characteristics and hemodynamic results are shown in Table 1. Patients with MACE were older (mean age 77 vs 68, $P = 0.0005$) and more likely to have a history of prior PCI (43% vs 17%, $P = 0.003$). There was no significant difference in hemodynamic results between patients with and without MACE.

Stress and Rest Quantitative MPI Results

SPECT imaging results are shown in Table 2. The automatic segmenting of the left ventricle was successful without need for manual adjustment of contours in 97%, 99%, 83%, 87%, 81%, and 91% on static stress, static rest, early stress gated, late stress gated, rest supine gated, and rest upright gated data. There was no significant difference in the need for manual adjustment between early stress gated and late stress gated data ($P = 0.26$). Stress and rest TPD were significantly higher in patients with MACE (median stress TPD: 12 vs 5, $P = 0.0005$) (median rest TPD:5 vs 3, $P = 0.03$). Compared to patients with no MACE, patients with MACE had higher ΔESV, and lower EF reserve at early stress ($P < 0.01$ for both). The frequencies of patients with abnormal functional parameters are shown in Table 3. Early EF reserve $< 0\%$ and ΔESV $\geq$ 5 ml were more frequent in patients who experienced MACE, while there was no significant difference in frequencies of abnormal late stress functional parameters between those with and without MACE.

Kaplan–Meier Analysis and Annualized MACE Rates

Kaplan–Meier analyses to compare MACE-free survival in patients with and without abnormal functional parameters at early and late stress are shown in Figures 2, 3, and 4 (Figures 2A and B: EF reserve, Figure 3A, and 3B: ΔESV and Figure 4A and 4B: ΔEDV). In the group with early EF reserve $< 0\%$, there was a significantly decreased event-free survival compared to patients with early EF reserve $\geq 0\%$ ($P = 0.004$, Figure 2A). Similarly, in the group with Δ ESV $\geq$ 5 ml at early stress, there was a significant decreased event-free survival ($P = 0.003$, Figure 3A) while there was no significant difference in the event risk between the group with ΔEDV $\geq$ 5 ml and those with ΔEDV $<$ 5 ml at early stress ($P = 0.24$, Figure 4A). At late stress, EF reserve, Δ EDV, and Δ ESV did not stratify MACE-free survival (P for all ≥ 0.41, Figures 2B, 3B, and 4B). Unadjusted annualized MACE rate was significantly higher in patients with early EF reserve < 0 compared to those with early EF reserve ≥ 0 (Figure 2C). Similarly, patients with Δ ESV $\geq$ 5 ml had higher annualized MACE rates compared to those with Δ ESV $<$ 5 ml at early stress (Figure 3C) while it was similar between patients with Δ

Table 1. Patient characteristics by MACE

	All (*n* = 151)	MACE (*n* = 28)	No MACE (*n* = 123)	*P*
Age, years	70 ± 12	77 ± 10	68 ± 12	**0.0005**
Male, %	50%	46%	51%	0.65
BMI, kg/m^2	32 ± 7	31 ± 7	32 ± 7	0.89
Hypertension, %	70%	75%	69%	0.54
Diabetes, %	29%	36%	28%	0.40
Dyslipidemia, %	65%	71%	63%	0.42
Smoking, %	23%	18%	24%	0.46
Family history of CAD, %	29%	25%	30%	0.59
Typical angina, %	5%	7%	4%	0.48
Prior MI	23%	36%	20%	0.08
Prior PCI	22%	43%	17%	**0.003**
Prior CABG	19%	32%	16%	0.05
Rest HR (bpm)	72 ± 13	74 ± 13	72 ± 13	0.45
Stress HR (bpm)	86 ± 19	84 ± 16	86 ± 19	0.52
Rest SBP (mmHg)	135 ± 23	139 ± 23	135 ± 23	0.38
Stress SBP (mmHg)	130 ± 24	126 ± 22	131 ± 24	0.31

Categorical value is expressed as frequency and continuous value is expressed as mean and standard deviation. *P* values showing significant differences are shown in bold
BMI body mass index, *CABG* coronary artery bypass graft, *CAD* coronary artery disease, *HR* heart rate, *MACE* major adverse cardiac events, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *SBP* systolic blood pressure

Table 2. SPECT results

	All (*n* = 151)	MACE (*n* = 28)	No MACE (*n* = 123)	*P*
Stress TPD	6 [3,13]	12 [7,17]	5 [2.5,11]	**0.0005**
Rest TPD	3 [1, 7]	5[2,15]	3 [1,6]	**0.03**
Rest EDV (ml)	81 [63, 114]	106 [76, 124]	78 [62, 109]	**0.02**
Early stress EDV (ml)	87 [65, 116]	95 [81, 141]	83 [64, 112]	**0.02**
Late stress EDV (ml)	91 [66, 118]	110 [78, 144]	88 [65, 115]	**0.02**
Early delta EDV (ml)	− 2 [− 1, 6]	3[− 8, 12]	− 3 [− 13, 5]	0.09
Late delta EDV (ml)	6 [− 2, 13]	5 [− 1, 16]	6 [− 3, 13]	0.72
Rest ESV (ml)	27 [16, 51]	40 [24, 64]	23 [15, 46]	**0.03**
Early stress ESV (ml)	28 [14, 49]	41 [29, 66]	25 [13, 42]	**0.002**
Late stress ESV (ml)	29 [16, 47]	40 [26, 76]	28 [15, 44]	**0.01**
Early delta ESV (ml)	− 3 [− 8, 3]	1 [− 5, 12]	− 4 [− 8, 3]	**0.007**
Late delta ESV (ml)	1 [− 3, 7]	1 [− 3, 8]	1 [− 3, 6]	0.77
Rest EF (%)	68 [55, 75]	59 [43, 73]	68 [57, 76]	**0.05**
Early stress EF (%)	68 [58, 77]	61 [47, 68]	71 [60, 78]	**0.0012**
Late stress EF (%)	68 [53, 76]	62 [41, 72]	69 [59, 78]	**0.03**
Early EF reserve	1 [− 4, 6]	− 2[− 8, 3]	2 [− 3, 6]	**0.0035**
Late EF reserve	1 [− 4, 5]	0 [− 6, 3]	1 [− 3, 6]	0.29

Values are shown as median [interquartile range]. *P* values showing significant differences are shown in bold
CAD coronary artery disease, *EDV* end-diastolic volume, *EF* ejection fraction, *ESV* end-systolic volume, *HR* heart rate, *MACE* major adverse cardiac events, *SBP* systolic blood pressure, *TPD* total perfusion deficit

Table 3. Frequencies of abnormal functional parameters

	All (n = 151) (%)	MACE (n = 28) (%)	No MACE (n = 123) (%)	P
Early EF reserve < 0%	44	68	39	**0.006**
Early Δ ESV ≥ 5 ml	18	36	14	**0.006**
Early Δ EDV ≥ 5 ml	27	36	25	0.26
Late EF reserve < 0%	47	54	46	0.44
Late Δ ESV ≥ 5 ml	26	29	26	0.78
Late Δ EDV ≥ 5 ml	52	50	52	0.85

Values are shown as frequency (%). *P* values showing significant differences are shown in bold
EDV end-diastolic volume, *EF* ejection fraction, *ESV* end-systolic volume, *MACE* major adverse cardiac events

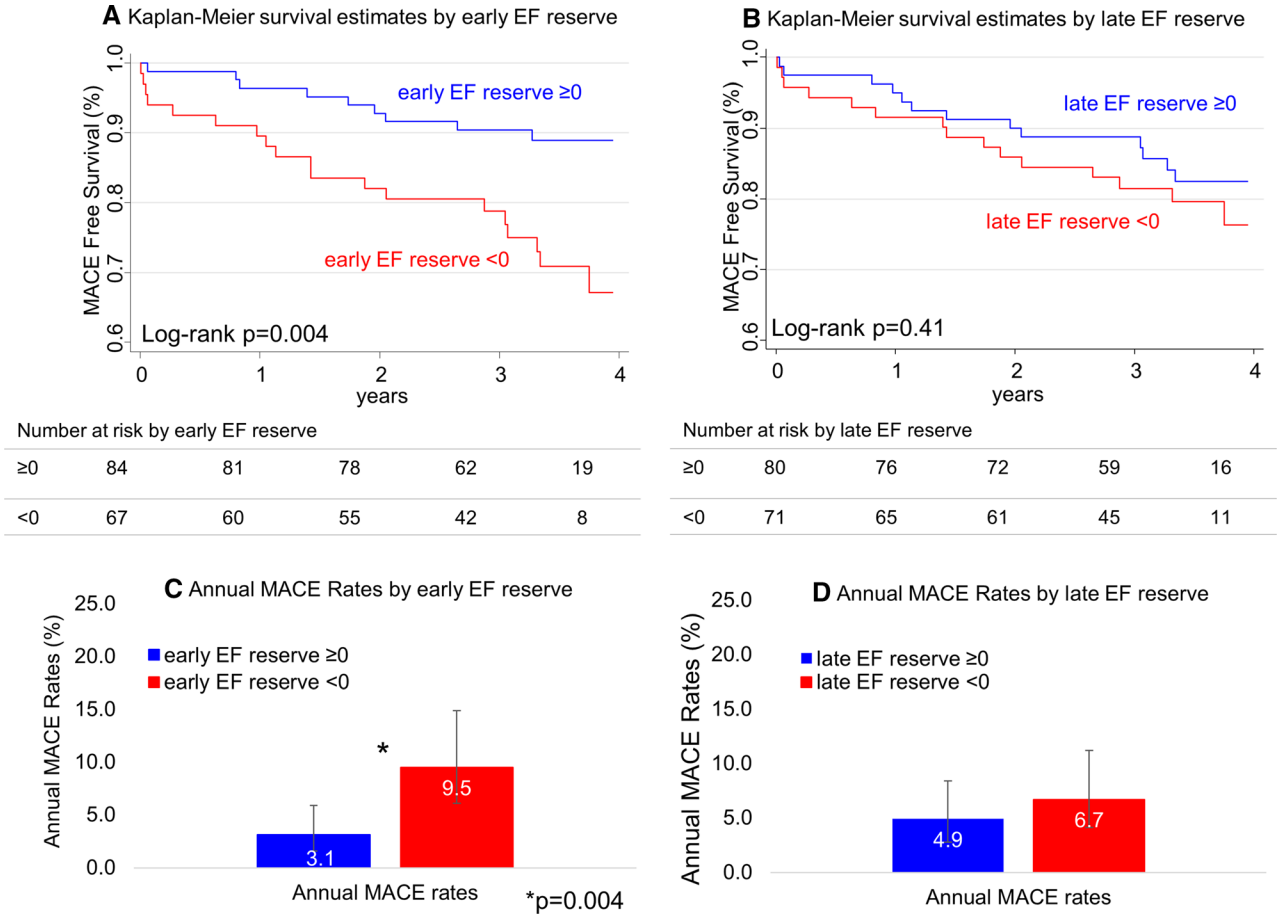

Figure 2. Survival Curves by EF Reserve at Early and Late Stress. Kaplan–Meier curves to compare MACE-free survival in patients with and without abnormal EF reserve and at early and late stress are shown in A (early EF reserve), and B (late EF reserve). Annual MACE rates in patients with and without abnormal EF reserve at early and late stress are shown in C (early EF reserve), and D (late EF reserve). *EF* ejection fraction, *MACE* major adverse cardiac events.

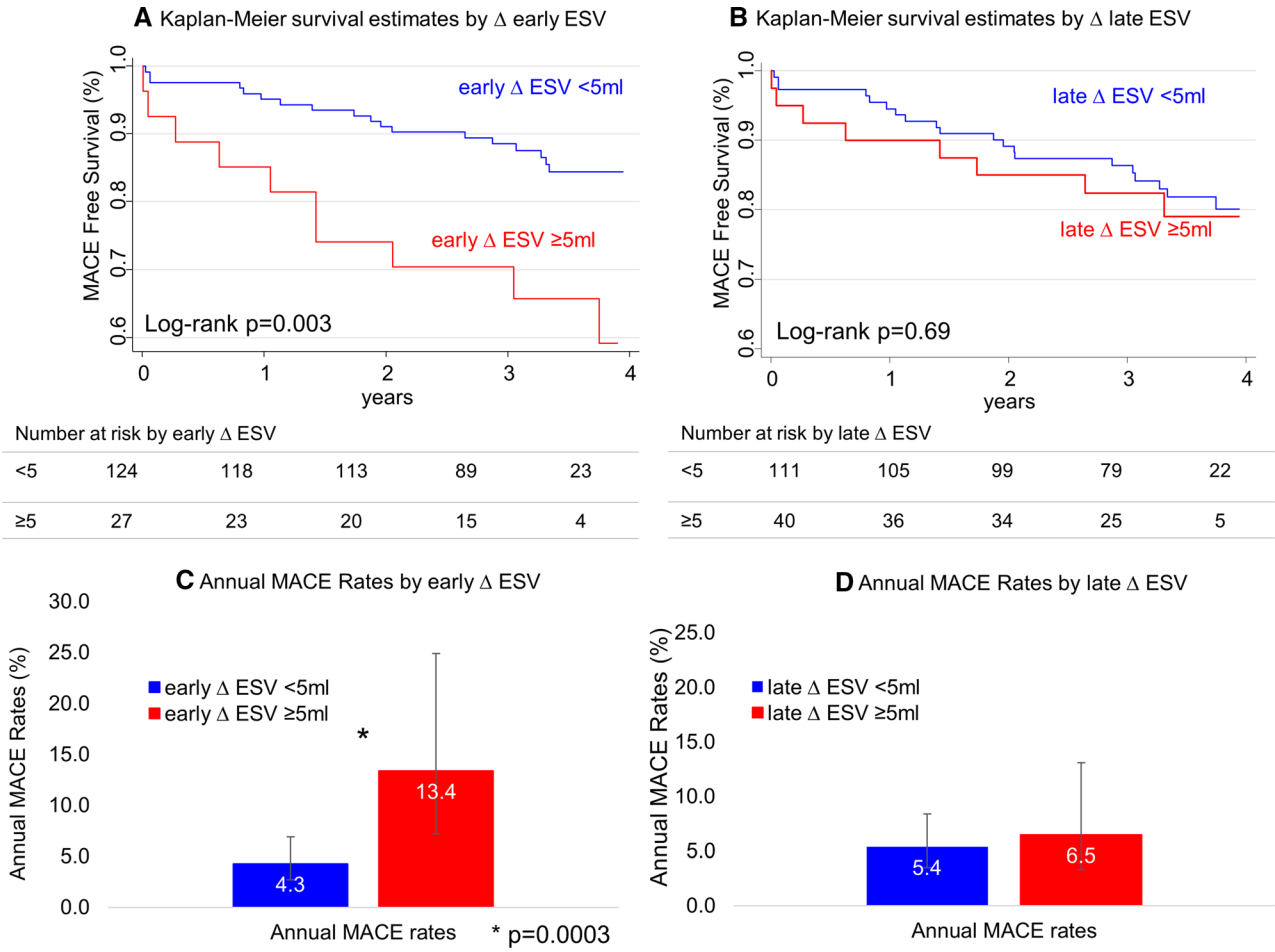

Figure 3. Survival Curves by ΔESV at Early and Late Stress. Kaplan–Meier curves to compare MACE-free survival in patients with and without abnormal EF reserve and at early and late stress are shown in A (early Δ ESV), and B (late Δ ESV). Annual MACE rates in patients with and without abnormal EF reserve at early and late stress are shown in C (early Δ ESV), and D (late Δ ESV). *ESV* end-systolic volume, *MACE* major adverse cardiac events.

EDV ≥ 5 ml and those with Δ EDV < 5 ml at early stress (Figure 4C).

Cox Proportional Hazards Analyses

Univariable Cox proportional hazards analysis are shown in Table 4. By univariable analysis, age, history of prior PCI, stress TPD, rest TPD, and early post-stress functional parameters were significantly associated with MACE (*P* for all < 0.05, Table 4). Multivariable Cox proportional hazards models are shown in Table 5. Model 1 demonstrated that stress TPD was significantly associated with MACE adjusting for age and history of prior PCI. Models 2 to 4 demonstrated that EFR, and change in EDV and ESV at early stress were significantly associated with MACE adjusting for age, history of prior PCI, and stress TPD. Figure 5 shows that the addition of EFR and change in EDV and ESV at early stress (Models 2 to 4) incrementally enhanced the combined model of age, prior history of percutaneous coronary intervention, and stress TPD (p for all < 0.05 compared to Model 1). Multivariable Cox proportional hazards models adjusting for age, history of prior PCI, and rest TPD are shown in Supplemental Materials.

DISCUSSION

This is the first study to evaluate the utility of early post-stress imaging for MACE on vasodilator stress solid-state SPECT MPI. Abnormal early post-stress EF reserve and change in ESV were more commonly observed in patients who experienced MACE and stratified MACE-free survival, while late post-stress imaging did not. Multivariable analysis demonstrated

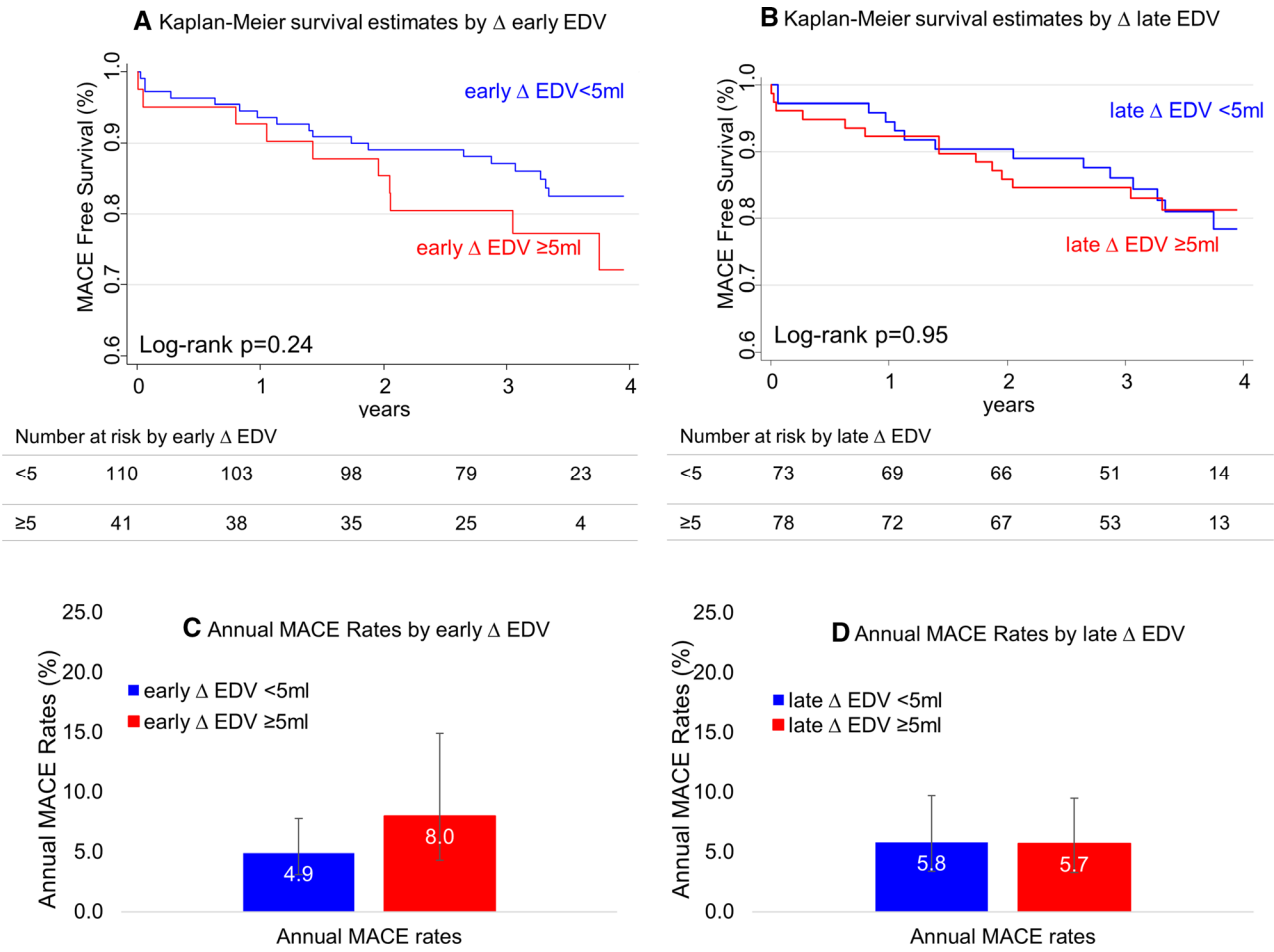

Figure 4. Survival Curves by ΔEDV at Early and Late Stress. Kaplan–Meier curves to compare MACE-free survival in patients with and without abnormal EF reserve and at early and late stress are shown in A (early Δ EDV), and B (late Δ EDV). Annual MACE rates in patients with and without abnormal EF reserve at early and late stress are shown in C (early Δ EDV), and D (late Δ EDV). *EDV* end-diastolic volume, *MACE* major adverse cardiac events.

that early post-stress functional parameters were independently associated with MACE after adjusting for clinical and perfusion variables. The addition of early post-stress functional parameters improved risk stratification compared to a model considering other important SPECT MPI variables. The proposed protocol includes all image acquisitions used clinically and could potentially be modified to also allow myocardial blood flow estimation.

Due to the short half-life of PET radiotracers, PET stress images are routinely collected during peak hyperemia. In comparison, ^{99m}Tc-sestamibi anger SPECT imaging in a standard protocol is performed 15-45 minutes after the stress tracer injection.[20] Therefore, PET imaging is able to capture early functional changes during the post-stress period. In a cohort of 510 patients who underwent vasodilator stress ^{82}Rubidium PET MPI, Dorbala et al. demonstrated that patients with severe ischemia and those with 3 vessel/left main disease had significantly lower EF during peak vasodilator stress and a lower EF reserve.[10] Similarly, Brown et al. found that the magnitude of ischemia on ^{82}Rubidium PET MPI was inversely correlated with EF Reserve.[11] The results of these studies suggest that the EF reserve during vasodilator ^{82}Rubidium PET is inversely related to the extent of myocardium at risk. Furthermore, in a cohort of 985 patients followed for 1.7 years, patients with EF reserve < 0 had a higher risk of annualized cardiac events compared to patients with an EF reserve ≥ 0 after accounting for differences in clinical factors and perfusion findings.[12] Similarly, reduced EF reserve provided incremental prognostic information in patients with systolic dysfunction.[24] Our findings suggest that SPECT measurement of early EF reserve provides the

Table 4. Univariable cox proportional hazards model predicting MACE

	HR	95% CI	*P*
Age (per year)	1.07	1.03-1.11	**<0.001**
Male	0.84	0.40-1.77	0.65
Prior PCI	3.34	1.58-7.07	**0.002**
Prior CABG	2.20	0.96-4.87	0.05
Stress TPD (per 1%)	1.04	1.01-1.07	**0.004**
Rest TPD (per 1%)	1.05	1.01-1.08	**0.009**
Rest EF (per 1%)	0.98	0.96-1.00	0.07
Rest ESV (per 1 ml)	1.01	1.00-1.02	0.07
Rest EDV (per 1 ml)	1.01	1.00-1.01	0.05
Early EF reserve (per 1%)	0.93	0.89-0.97	**0.001**
Early Δ ESV (per 1 ml)	1.03	1.02-1.05	**<0.001**
Early Δ EDV (per 1 ml)	1.02	1.00-1.04	**0.03**
Late EF reserve (per 1%)	0.98	0.94-1.03	0.41
Late Δ ESV (per 1 ml)	1.01	0.98-1.04	0.70
Late Δ EDV (per 1 ml)	1.00	0.98-1.02	0.99

P values showing significant differences are shown in bold
CI confidence interval, *EF* ejection fraction, *HR* hazard ratio, *PCI* percutaneous coronary intervention, *TPD* total perfusion deficit

capability for detecting this potentially useful prognostic parameter.

Recently, Gomez et al. [25] demonstrated that LVEF reserve following regadenoson stress was not associated with increased risk of adverse cardiac events in 929 patients who underwent conventional Anger SPECT. The most important difference from our study is that peak stress imaging was not performed by Gomez et al. In our study, late post-stress functional parameters were not associated with MACE but early post-stress parameters were. Therefore, it seems that early post-stress gated acquisitions may yield valuable additional diagnostic and prognostic information. We previously demonstrated that significantly lower EF reserve was obtained 5 to 9 minutes after regadenoson injection in patients with significant ischemia compared to patients without ischemia, while with later post-stress imaging this difference was no longer significant.[17] In the current study, we demonstrated that early post-stress EF reserve and change in ESV were independently associated with increased MACE. Additionally, both parameters significantly improved upon a prognostic model with other important SPECT variables. Conversely, late post-stress functional variables were not associated with MACE.

The current study also suggests that early ΔESV may be a stronger predictor of cardiac events than early

Table 5. Multivariable cox proportional hazards model predicting MACE

	HR	95% CI	*P*
Model 1 (Baseline model)			
Age (per year)	1.08	1.04-1.13	**<0.001**
Prior PCI	2.38	1.10-5.16	**0.03**
Stress TPD (per 1%)	1.06	1.02-1.09	**0.001**
Model 2 (Age + prior PCI + stress TPD + early EF reserve)			
Age (per 1 year)	1.08	1.04-1.13	**<0.001**
Prior PCI	2.71	1.25-5.88	**0.012**
Stress TPD (per 1%)	1.06	1.02-1.09	**0.002**
Early EF reserve (per 1%)	0.94	0.90-0.98	**0.001**
Model 3 (Age + prior PCI + stress TPD + early ΔEDV)			
Age (per year)	1.08	1.04-1.13	**<0.001**
Prior PCI	2.61	1.20-5.64	**0.02**
Stress TPD (per 1%)	1.06	1.02-1.09	**0.001**
Early ΔEDV (per 1 ml)	1.02	1.00-1.04	**0.03**
Model 4 (Age + prior PCI + stress TPD + early ΔESV)			
Age (per 1 year)	1.08	1.04-1.13	**<0.001**
Prior PCI	3.07	1.38-6.78	**0.006**
Stress TPD (per 1%)	1.05	1.01-1.08	**0.02**
Early ΔESV (per 1 ml)	1.03	1.01-1.05	**0.002**

P values showing significant differences are shown in bold
CI confidence interval, *EF* ejection fraction, *EDV* end-diastolic volume, *ESV* end-systolic volume, *HR* hazard ratio, *MACE* major adverse cardiac events, *PCI* percutaneous coronary intervention, *TPD* total perfusion deficit

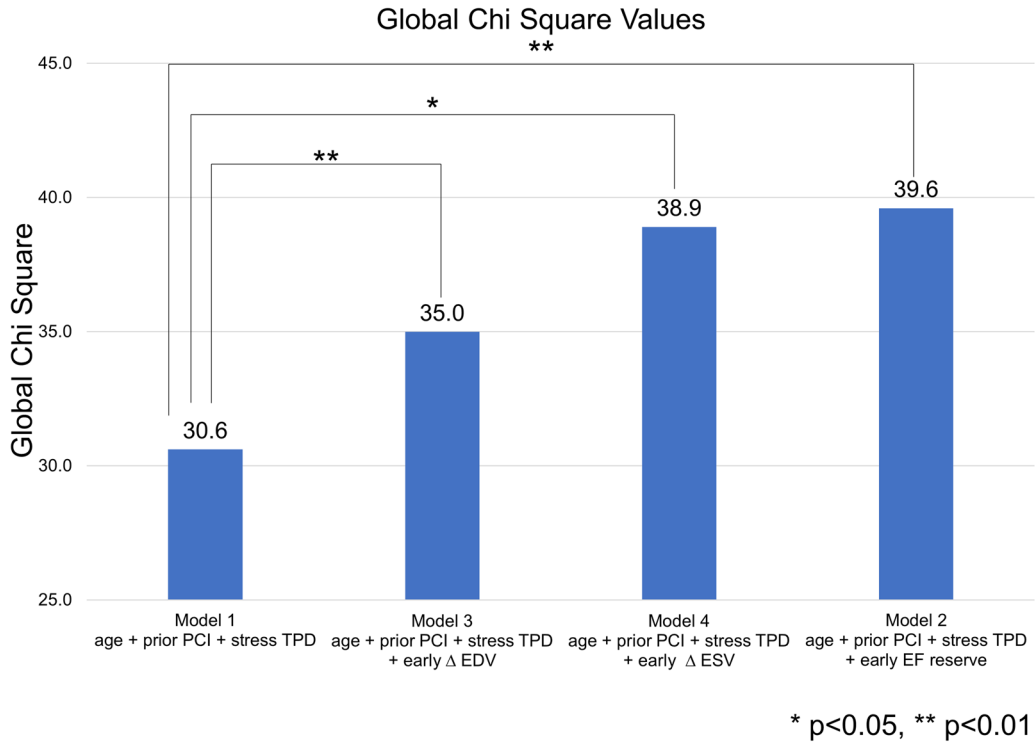

Figure 5. Incremental MACE Prediction by the Addition of Early Post-stress Functional Parameters. The addition of each early stress functional parameter (Models 2: early EF reserve, Model 3: early ΔEDV and Model 4: early Δ ESV) incrementally enhanced the combined model (Model 1) of age, prior history of percutaneous coronary intervention, and stress TPD (p for all < 0.05, compared to Model 1). *EDV* end-diastolic volume, *EF* ejection fraction, *ESV* end-systolic volume, *PCI* percutaneous coronary intervention, *TPD* total perfusion deficit.

EF reserve and ΔEDV. This is consistent with a previous stress echocardiogram study demonstrating an independent association between ΔESV and all-cause mortality in 934 patients with stable CAD after accounting for rest imaging variables.[26] The authors of the echocardiogram study concluded that ESV may more accurately assess contractile reserve since it is less sensitive to cardiac loading and varies greatly in response to changes in contractility.

The early post-stress imaging could potentially be a dynamic acquisition in order to add the ability to estimate absolute MBF (33). SPECT MBF estimates correlate well with values from PET (33) and have high diagnostic accuracy for obstructive CAD.[24,26] Therefore, implementing early post-stress imaging could allow centers to improve disease diagnosis and risk stratification by assessing both EF reserve and MBF; markers which have dramatically improved the clinical utility of PET. Larger studies are required to determine if there is additive diagnostic or prognostic value to considering both early post-stress EF reserve and ΔESV from MPI, in combination with other perfusion parameters.

Study Limitations

There were several limitations to this study. This was a retrospective study with a small sample size from a single center; however, early post-stress SPECT MPI imaging is not currently a routine clinical protocol. The sample size limited our ability to adjust for other SPECT MPI variables in multivariable modeling. The analysis of incremental prognostic value in specific perfusion categories was not possible due to limited statistical sample and larger prospective studies are needed. Similar to previous studies,[27–29] we relied on all-cause mortality rather than cardiovascular mortality which may be more closely related to post-stress EF reserve. All-cause mortality is often chosen as an endpoint in cardiovascular studies because physician determined cause-of-death is frequently discrepant with autopsy findings and methods to determine cardiovascular mortality retrospectively may underestimate the true proportion of events.[30] Lastly, since the acquisition time for rapid stress was limited, only supine imaging could be performed at rapid stress.

CONCLUSION

Ejection fraction reserve, Δ EDV, and ESV measured after early post-stress by solid-state SPECT MPI provide significant, independent, and incremental value for predicting the risk of adverse cardiovascular events. The measurement of LVEF reserve is possible using a solid-state SPECT system and prospective validation of the potential value of this information is warranted.

NEW KNOWLEDGE GAINED

Early ejection fraction reserve, measured using solid-state SPECT MPI, was significantly decreased in patients who experienced MACE. Early post-stress (but not late) ejection fraction reserve was independently associated with MACE and improved risk stratification compared to a model with other important SPECT MPI variables.

Disclosure

Dr. Slomka participates in software royalties for QPS software at Cedars-Sinai Medical Center and has received research grant support from Siemens Medical Systems. All other authors have nothing to disclose.

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