Added prognostic value of left ventricular shape by gated SPECT imaging in patients with suspected coronary artery disease and normal myocardial perfusion

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Background. **Left ventricular (LV) remodeling is associated with adverse cardiovascular events. We evaluated the added prognostic value of LV shape index (SI) assessed by gated single-photon emission tomography (SPECT) in patients without known coronary artery disease (CAD).**

Methods and results. **We studied 674 patients with normal myocardial perfusion and normal LV ejection fraction (EF) on stress gated SPECT imaging. An automated software program was used to calculate end-diastolic and end-systolic LVSI. An LVSI ≤ 0.54 at end-systole was considered normal. Follow-up was 96% complete with a median follow-up of 37 months. During follow-up, 25 events occurred (3.8% cumulative event rate). Event-free survival was lower in patients with abnormal end-systolic LVSI ($P < .001$). Age ($P = .021$), diabetes ($P = .048$), and end-systolic LVSI ($P < .001$) were independent predictors of events. LVSI added prognostic information increasing the global chi-square of the model including age and diabetes from 15.15 to 25.97 ($P < .001$). The effect of diabetes on hazard ratio increased with increasing values of end-systolic LVSI. The probability of events at 48 months predicted by Weibull analysis progressively increased with increasing values of end-systolic LVSI and was higher in patients with diabetes as compared to those without. Decision curve analyses indicate that the model including end-systolic LVSI resulted in an increased net benefit between 5% and 30% threshold probability, indicating superior estimation of outcomes at low threshold probability levels.**

Conclusions. **The evaluation of LVSI may identify patients with early-stage LV remodeling and at higher risk of adverse cardiac events, even in the presence of normal myocardial perfusion. (J Nucl Cardiol 2019;26:1148–56.)**

Key Words: Cardiovascular risk factors • left ventricular shape index • gated SPECT • prognosis

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Abbreviations	
LV	Left ventricle
CAD	Coronary artery disease
EF	Ejection fraction
SPECT	Single-photon emission computed tomography
SI	Shape index
CI	Confidence interval

See related editorial, pp. 1157–1160

INTRODUCTION

Change in cardiac size, shape, and function determined by left ventricular (LV) remodeling is associated with adverse cardiovascular events.[1] Hence, early identification of LV remodeling might be of clinical value for risk stratification of patients with suspected coronary artery disease (CAD). Most studies evaluating the clinical implications of LV remodeling have focused on LV volumes and ejection fraction (EF), while only few studies analyzed LV shape, another measure of cardiac geometry.[2] Gated single-photon emission computed tomography (SPECT) is useful to assess both LV myocardial perfusion and function within a single study. In addition, endocardial and epicardial contours of LV can be obtained automatically using quantitative gated SPECT programs.[3] These items of information are useful for the assessment of LV function and to obtain quantitative indexes of three-dimensional LV geometry, such as the LV shape index (SI). LVSI provides highly repeatable ventricular shape assessment and might have useful clinical implications.[4] The aim of this study was to evaluate the added prognostic value of LVSI assessed by gated SPECT in patients with suspected CAD and normal myocardial perfusion.

METHODS

Study Population

The study population comprised 674 patients with suspected CAD undergoing stress gated SPECT between October 2010 and December 2014 who had normal myocardial perfusion. As part of the baseline examination, clinical teams collected information on traditional cardiovascular risk factors (including age, gender, body mass index, hypertension, diabetes, hypercholesterolemia, smoking, family history of CAD, chest pain symptoms). Patients with moderate to severe valvular dysfunction were excluded. Patients were classified as having diabetes if they were receiving treatment with oral hypoglycemic drugs or insulin. Hypertension was defined as a blood pressure $\geq$140/90 mm Hg or the use of antihypertensive medication. Hypercholesterolemia was defined as total cholesterol level $\geq$6.2 mmol/L or treatment with cholesterol-lowering medication. A positive family history of CAD was defined as the presence of disease in first-degree relatives younger than 55 years in men or 65 years in women. The pre-test probability of CAD was calculated by dedicated software (Cadenza, Advanced Heuristics Inc., Bainbridge Island, Washington) as aggregate descriptor of traditional cardiovascular risk factors.[5] The ethics committee of our institution approved the study and all patients gave informed consent.

Myocardial Perfusion Imaging

All patients underwent ^{99m}Tc sestamibi exercise or pharmacological stress gated SPECT according to the recommendations of the European Association of Nuclear Medicine [6] as previously described in detail.[7] In all patients, beta-blocking medications and calcium antagonists were withheld for 48 hours and long-acting nitrates for 12 hours before testing. Imaging was performed using a dual-head rotating gamma camera (E.CAM, Siemens Medical Systems, Hoffman Estates, IL, USA) equipped with a low-energy, high-resolution collimator and connected with a dedicated computer system. No attenuation or scatter correction was used. For gating, a cardiac cycle was divided into sixteen frames. The R-R interval and heart rate histogram were recorded to monitor arrhythmia. An average R-R interval of ±15% was accepted for gating.

An automated software program (e-soft 2.5, QGS/QPS, Cedars-Sinai Medical Center, Los Angeles, CA) was used to calculate LV volumes, EF, and the scores incorporating both the extent and severity of perfusion defects, using standardized segmentation of 17 myocardial regions.[3] This commercial package determines reconstruction limits for the projection dataset, reconstructs the projection images into transaxial images using standard filtered backprojection, and then reorients the transaxial images into short-axis images. LV contours were checked visually and manually adjusted if the computer-generated automatic contours were found to be incorrect. Quantitative defect extent and severity were defined from gender-specific normal limits, and a summed stress score was obtained by adding the scores of the 17 segments (0 = normal to 4 = absent perfusion) of the stress images. A post-stress LVEF >45% and a summed stress score <3 were considered normal.[8,9] LVSI was calculated as the ratio of the maximum three-dimensional short- and long-axis LV dimension, at end-diastole and at end-systole as proposed by Abidov et al.[4] Briefly, endocardial (and epicardial) three-dimensional LV surfaces were determined from the maximal count mid-myocardial surfaces via asymmetrical Gaussian fitting, as previously described.[10] Of note, surfaces can usually be determined even in the apparent absence of perfusion, as the algorithm seeks to preserve the continuity of the three-dimensional myocardial surface gradients by extrapolating the gradients of points immediately adjacent to the non-perfused area.[11] The algorithm, based on the regional search for the maximal distance between endocardial surface points, assumes that the LV shape may be estimated using the major and minor axes of the prolate ellipsoid that best fits it. The closer the axes in size, the closer the ellipsoid becomes to a

sphere and the higher its LVSI value. An LVSI ≤0.54 at end-systole was considered normal.[4]

Follow-up Data

Patient follow-up was prospectively obtained by use of a questionnaire that was assessed by a phone call to all patients and general practitioners or cardiologists and by review of hospital or physicians' records by individuals blinded to the patient's test results. The outcome was a composite end point of cardiac death, non-fatal myocardial infarction, or unstable angina requiring coronary revascularization, whichever occurred first. The cause of death was confirmed by review of death certificate, hospital chart, or physician's records. Death was considered to be of cardiac origin if the primary cause was defined as acute myocardial infarction, congestive heart failure, valvular heart disease, sudden cardiac death, and cardiac interventional/surgical procedure related. Myocardial infarction was defined when 2 or more of the following 3 criteria were met: chest pain or equivalent symptom complex, positive cardiac biomarkers, or typical electrocardiographic changes. The date of the last examination or consultation was used to determine the length of follow-up.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and categorical data as percentages. Differences between groups were analyzed by t test and χ^2 analysis, as appropriate. A two-tailed P value <.05 was considered statistically significant. Annualized event rates, expressed as % person-years, were calculated as the cumulative number of events divided by person-time. This latter is an estimate of the actual time-at-risk that all persons contribute to the study, i.e., the sum of each individual follow-up period. Event-free survival curves were obtained by the Kaplan-Meier method and compared with the log-rank test. Hazard ratios with 95% confidence intervals (CI) were calculated by univariable and multivariable Cox regression analysis. The proportional hazard assumption was assessed by visual inspection of the log[−log(survival function)] for categorical variables and with statistical tests based on Schoenfeld residuals for continuous variables. The proportional hazard assumption was not rejected for any one of the covariates included in the Cox model. Variables showing a P value <.05 at univariable analysis were considered for multivariable analysis. Cox models of different complexity were compared using the log likelihood statistics.[12] Parametric Weibull survival analysis was performed to evaluate the probability of events at specified time.[13] The adequacy of the Weibull model was checked by stratified Kaplan-Meier curves (Figure 1). The added value of LVSI was also evaluated comparing the net benefit curves obtained by decision curve analysis.[14] The net benefit is calculated as true positive rate - false positive rate × weighting factor. Specifically, the false positive rate is multiplied by the ratio of the threshold probability divided by 1 - the threshold probability. Statistical analysis was performed with STATA 15.0 for Windows (StataCorp LP, College Station, TX).

RESULTS

Patient Characteristics and Outcome

Of the 674 patients enrolled, follow-up data were not available in 28 patients (4%), leaving 646 subjects available for the analysis, with a median follow-up of 37 months. During follow-up, 25 events occurred (3.8% cumulative event rate), with an event rate of 1.25 % person-years (95% confidence interval 0.85 to 1.85). The events were cardiac death in 13 patients, non-fatal myocardial infarction in 8, and unstable angina requiring revascularization in 4. Clinical characteristics of patients with and without events are reported in Table 1. Patients who experienced events were older and showed higher prevalence of diabetes as compared to patients without events. Pharmacological stress test was performed in 267 subjects, 13 (52%) with and 254 (41%) without events ($P = .27$). In 379 patients undergoing exercise

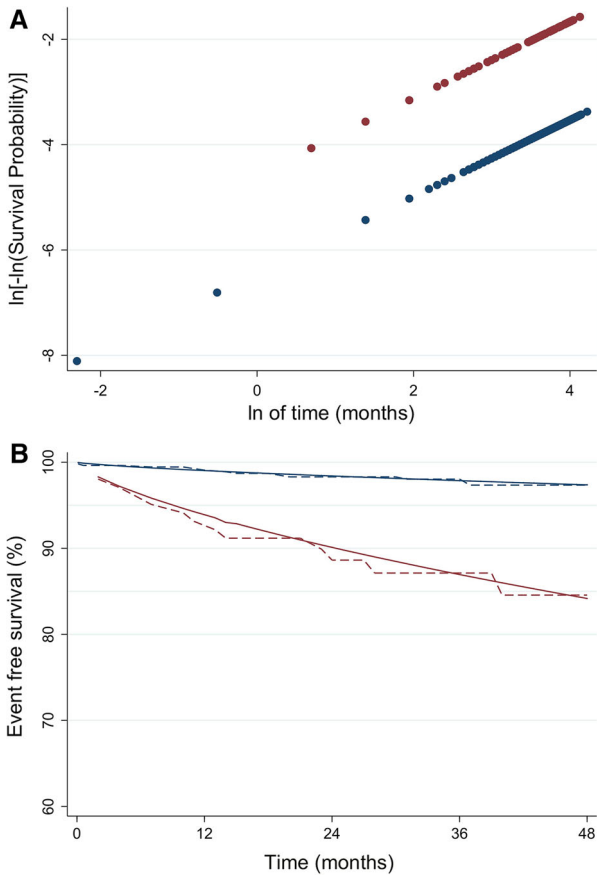

Figure 1. A Weibull regression diagnostic plot for patients with normal (*navy dots*) or abnormal (*maroon dots*) end-systolic LVSI. Both plots look reasonably straight suggesting that the Weibull assumption is reasonable. **B** Weibull (*solid lines*) and Kaplan-Meier (*dashed lines*) estimated survival curves for patients with normal (*navy lines*) or abnormal (*maroon line*) end-systolic LVSI.

stress test, exercise workload was 9.56 ± 2.57 METS, comparable in those with and without events (8.44 ± 2.24 vs. 9.59 ± 2.55 METS, $P = .32$).

Imaging findings of patients with and without events are reported in Table 2. Patients who experienced event showed a significantly higher end-diastolic and end-systolic LVSI values as compared to patients without event. Patients with events also showed a higher prevalence of abnormal end-systolic LVSI ($P < .001$). Representative examples of patients with normal and increased LVSI are depicted in Figure 2. End-systolic LVSI demonstrated a weak albeit statistically significant correlation with LVEF (Figure 3) and with EDV and ESV (Figure 4). The event-free survival curves according to end-systolic LVSI are reported in Figure 5. Event-free survival was lower in patients with abnormal end-systolic LVSI ($P < .001$). In particular, the event rate was 0.70% person-years in patients with normal and 4.66% person-years in those with abnormal end-systolic LVSI ($P < .001$). To eliminate redundancy and avoid model over fitting, only end-systolic LVSI was considered for Cox analysis.

Predictors of Events

Univariable and multivariable Cox regression analyses are reported in Table 3. Age, diabetes, and end-systolic LVSI were univariable and multivariable predictors of events. End-systolic LVSI added prognostic information increasing the global chi-square of the model including age and diabetes from 15.15 to 25.97 ($P < .001$).

Effect of Diabetes

The effect of diabetes on hazard ratio at different values of end-systolic LVSI is depicted in Figure 6. As shown, the effect of diabetes increases with increasing values of end-systolic LVSI, without significant interaction between diabetes and end-systolic LVSI

Table 1. Baseline characteristics of patients with and without events

	All patients ($n = 646$)	Events ($n = 25$)	No events ($n = 621$)	P value
Age (years)	62.1 ± 11	67.64 ± 8.2	61.84 ± 11.02	.01
Male gender	334 (52)	16 (59)	318 (52)	.21
Body mass index (kg/m^2)	28.1 ± 5.2	27.1 ± 4	28.2 ± 5.3	.64
Hypertension	510 (84)	21 (84)	489 (79)	.53
Diabetes	205 (32)	15 (53.1)	190 (30.4)	.002
Hypercholesterolemia	377 (58)	10 (40)	367 (59)	.06
Smoking	216 (36)	5 (28)	211 (36)	.15
Family history of CAD	335 (52)	11 (43)	324 (52)	.42
Chest pain symptoms	246 (37.2)	5 (22)	241 (38)	.06
Pre-test likelihood of CAD	0.18 ± 0.2	0.24 ± 0.3	0.19. ± 0.2	.27

Values are expressed as mean value ± standard deviation or as number (percentage) of subjects
CAD, coronary artery disease

Table 2. Left ventricle imaging findings of patients with and without events

	All patients ($n = 646$)	Events ($n = 25$)	No events ($n = 621$)	P value
End-diastolic volume (mL)	94 ± 26	95 ± 25	94 ± 26	.79
End-systolic volume (mL)	33 ± 16	34 ± 12	33 ± 15	.57
LV ejection fraction (%)	67 ± 12	66 ± 14	67 ± 12	.63
End-diastolic LVSI	0.65 ± 0.08	0.69 ± 0.09	0.64 ± 0.08	.002
End-systolic LVSI	0.47 ± 0.08	0.53 ± 0.10	0.46 ± 0.08	<.0001

Values are expressed as mean value ± standard deviation
LV, left ventricular; *LVSI*, left ventricular shape index

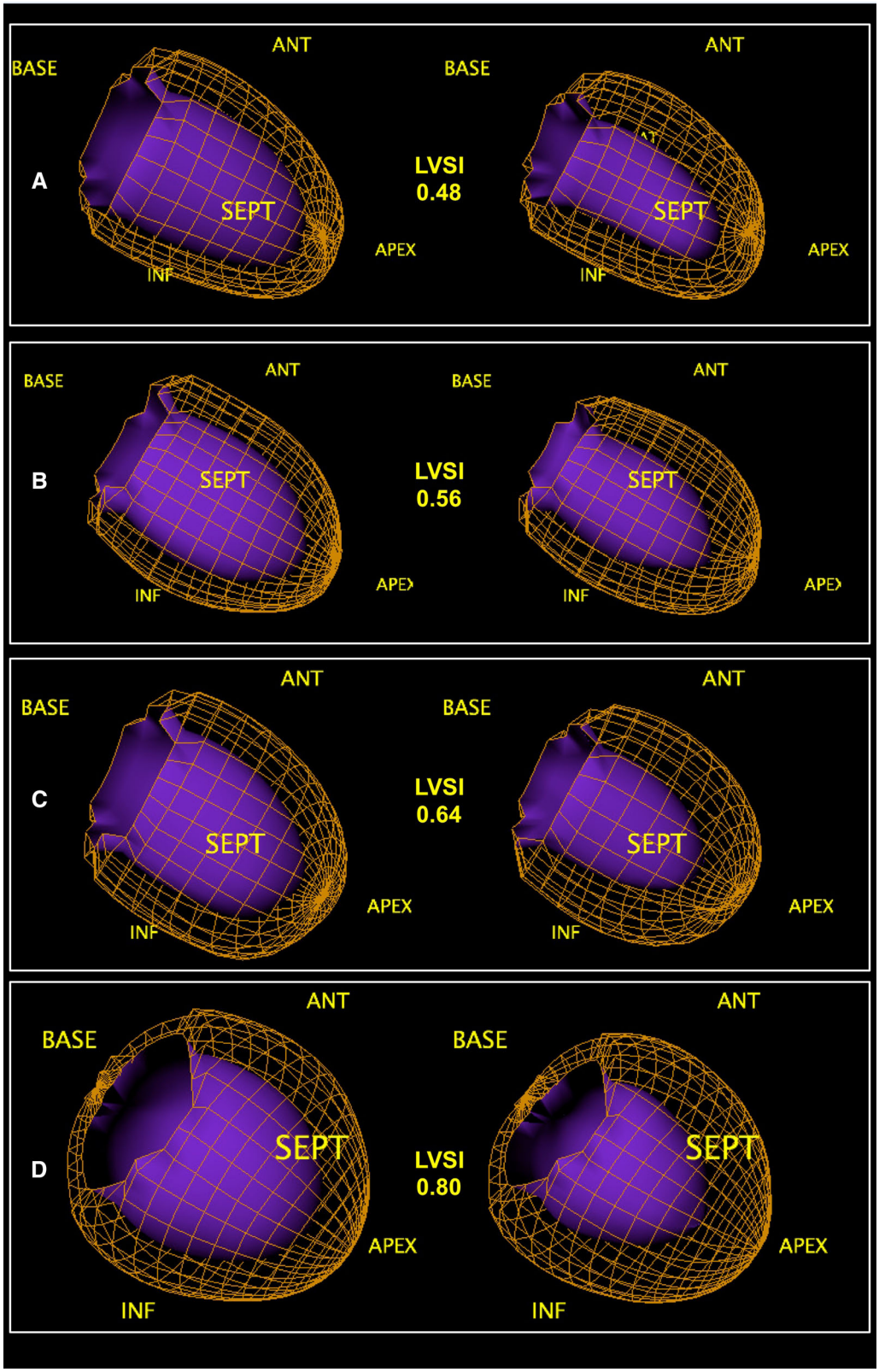

Figure 2. End-diastolic and end-systolic gated SPECT images in patients with normal (**A**), mildly increased (**B**), moderately increased (**C**), and severely increased (**D**) LVSI.

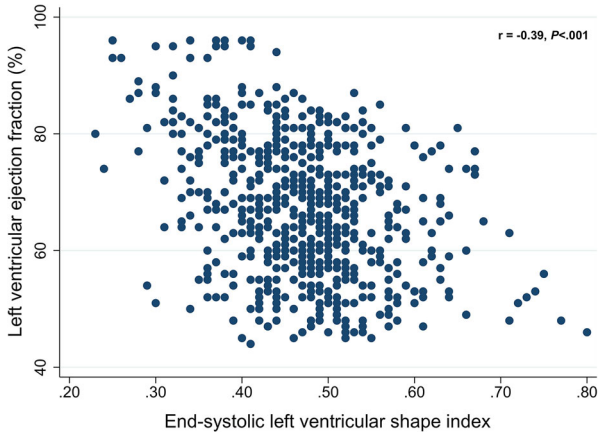

Figure 3. Scatter plot demonstrating the relationship of end-systolic LVSI with left ventricular ejection fraction.

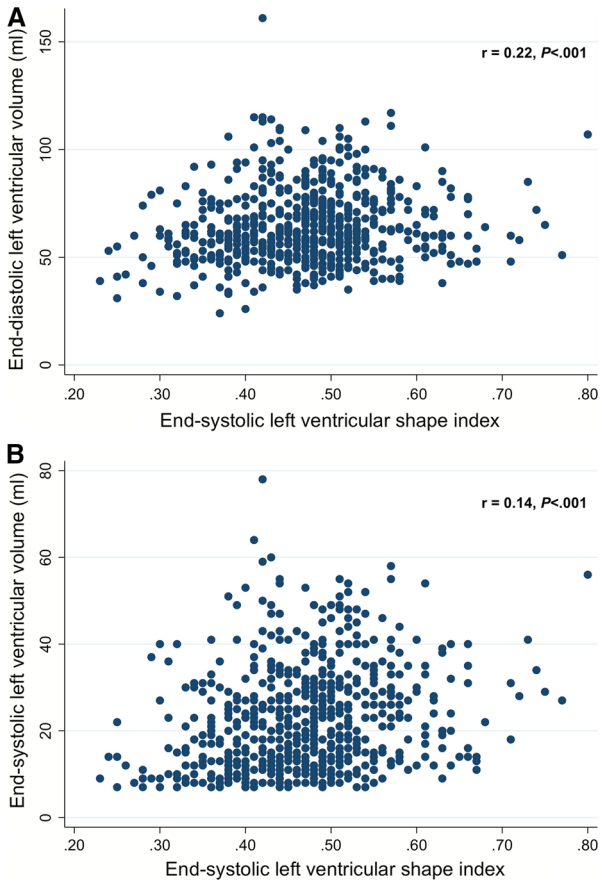

Figure 4. Scatter plot demonstrating the relationship of end-systolic LVSI with end-diastolic (**A**) and end-systolic (**B**) left ventricular volume.

($P = .89$). The probability of events at 48 months predicted by Weibull analysis progressively increases with increasing values of end-systolic LVSI and is higher in patients with diabetes as compared to those without (Figure 7). The predicted hazard ratio as a function of age, according to the presence of diabetes and normal or abnormal end-systolic LVSI, is showed in Figure 8.

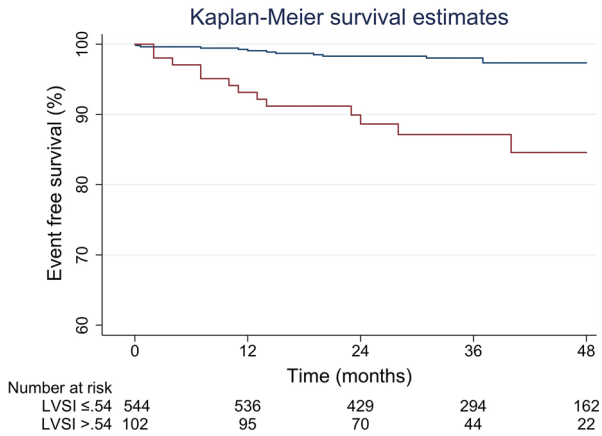

Figure 5. Event-free survival curves by Kaplan-Meier analysis in patients with normal (*navy line*) or abnormal (*maroon line*) end-systolic LVSI.

Decision Curve Analysis

In our study population, on decision curve analysis the addition of end-systolic LVSI to the prognostic model including age and diabetes shows an increased net benefit in the 5 to 30% threshold probability range, indicating superior estimation of outcomes at low-intermediate threshold probability levels (Figure 9). Net benefit has a straightforward interpretation. At 48 months of follow-up, the value of 0.02 at a threshold probability of 5% using the full prognostic model is equivalent to a strategy that identifies 2 events per hundred patients as compared to assuming that no patient will experience an event, without increasing the false positive rate.

DISCUSSION

To our knowledge, this is the first study evaluating the prognostic value of LV geometry indices obtained by gated SPECT in patients with normal stress myocardial perfusion imaging and preserved LVEF. In our study population, end-systolic LVSI was an independent predictor of cardiac events and added prognostic information over traditional cardiac risk factors. Therefore, the evaluation of LVSI may have a potential role in risk stratification even in patients without known CAD.

LV remodeling is associated with progressive worsening of cardiac function and increased cardiovascular morbidity and mortality in many cardiovascular diseases.[15,16] Of note, evaluation of LV geometry may enhance risk stratification even in patients with

Table 3. Univariable and multivariable predictors of cardiac events in the overall study population

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age	1.05 (1.01-1.09)	.008	1.05 (1.01-1.09)	.021
Male gender	0.58 (0.26-1.32)	.19		
Body mass index	0.98 (0.91-1.06)	.63		
Hypertension	1.42 (0.49-4.13)	.52		
Diabetes	3.33 (1.50-7.42)	<.005	2.26 (1.01-5.20)	.048
Hypercholesterolemia	0.48 (0.22-1.07)	.07		
Smoking	1.99 (0.75-5.30)	.17		
Family history of CAD	1.32 (0.60-2.91)	.49		
Chest pain symptoms	2.63 (0.98-7.01)	.05		
LV ejection fraction	0.99 (0.96-1.03)	.65		
End-systolic LVSI	1.09 (1.05-1.13)	<.0001	1.07 (1.03-1.12)	<.001
Pharmacological stress test	1.47 (0.67-3.23)	.33		

CAD, coronary artery disease; *LV*, left ventricular; *LVSI*, left ventricular shape index

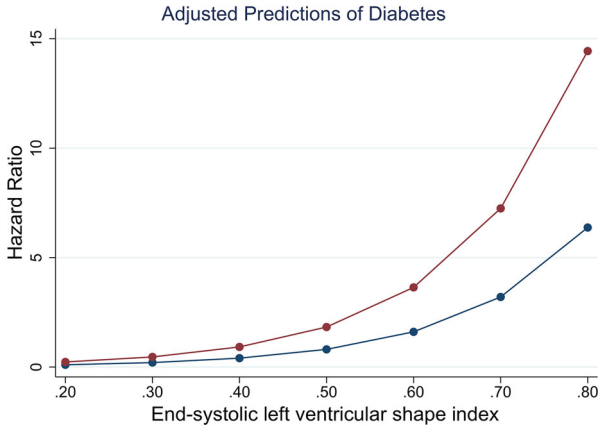

Figure 6. Predicted hazard ratio at different values of end-systolic LVSI in diabetic (*maroon line*) and non-diabetic (*navy line*) patients.

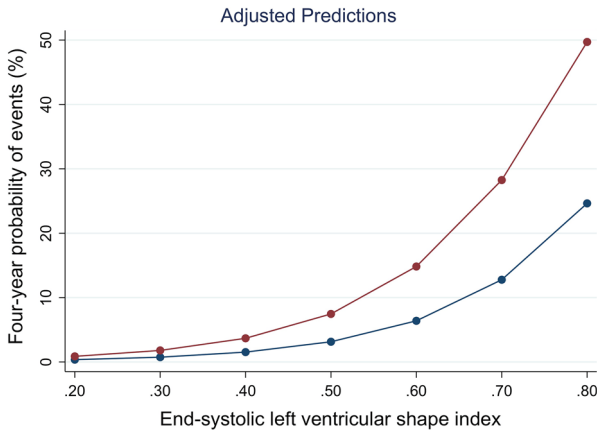

Figure 7. Probability of events at 48 months by Weibull analysis with increasing values of end-systolic LVSI in diabetic (*maroon line*) and non-diabetic (*navy line*) patients.

preserved LVEF.[17] Diabetes mellitus is an independent risk factor for the development of LV remodeling.[18,19] The alterations in LV structure and function decrease cardiac performance, finally resulting in heart failure and may occur independently from CAD.[20] In a prior study, we compared LV shape parameters obtained by gated SPECT in a propensity score-matched cohort of diabetic and non-diabetic patients with normal myocardial perfusion and normal LVEF.[21] The results of that study indicated that diabetic patients have abnormal indices of LV geometry independently of other coronary risk factors and stress-induced myocardial ischemia. Although the difference in LVSI between diabetic and non-diabetic patients was relatively small, the percentage of diabetic subjects with abnormal end-systolic LVSI was about 2-fold larger. In addition, diabetes was an independent predictor of high end-systolic LVSI even after matching for demographic characteristics and risk factors.[21] The present investigation extends these findings, showing that age, diabetes, and end-systolic LVSI are independent predictors of cardiac events during follow-up even in patients with normal stress myocardial perfusion imaging. Noteworthy, event-free survival decreased with worsening of end-systolic LVSI, particularly in diabetic patients. Accordingly, the probability of events increases with increasing values of end-systolic LVSI and is higher in patients with diabetes as compared to those without.

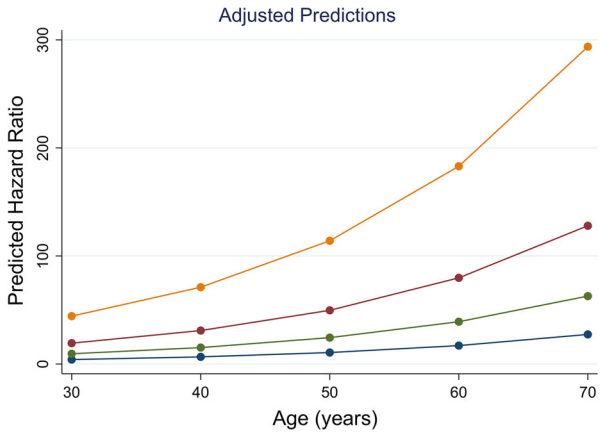

Figure 8. Predicted hazard ratio at different ages according to diabetes and normal or abnormal end-systolic LVSI. *Navy line*, no diabetes and normal end-systolic LVSI; *green line*, diabetes and normal end-systolic LVSI; *maroon line*, no diabetes and abnormal end-systolic LVSI; *orange line*, diabetes and abnormal end-systolic LVSI.

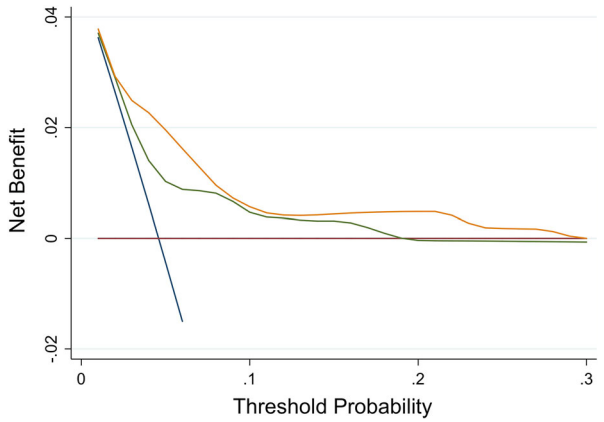

Figure 9. Decision curve analysis depicts the clinical net benefit of the model including age and diabetes (*green line*) and end-systolic LVSI (*orange line*) in terms of 4-year event-free survival across a range of threshold probabilities. The horizontal maroon line represents the assumptions that no patients will experience events, and the navy line the assumption that all patients will experience events. The model including LVSI shows superior net benefit across a range of threshold probabilities from 5% to 30%.

In the present investigation, LVSI added prognostic information to a multivariable model including clinical variables. Interestingly, LVSI also led to an improvement in the decision curve analysis over a realistic range of threshold probabilities. The decision curve is a graphical summary useful to illustrate potential clinical impact of risk models for recommending treatment or intervention. In this analysis, prediction models are compared to two default strategies: (1) assume that all patients will experience the event of interest and therefore treat everyone, or (2) assume that no patients will experience the event and offer treatment to no one. Treatment is considered in the widest possible sense: not only drugs, radiotherapy, or surgery, but advice, further diagnostic procedures, or more intensive monitoring.[22] Using decision curve analysis, we have shown that measures of LV remodeling may improve clinical decision making in patients with normal myocardial perfusion, avoiding further unnecessary testing in low-risk patients, and identifying those at higher risk that may benefit from a more aggressive approach. This finding seems particularly relevant in low-risk patients, such as most of the patients with normal stress myocardial perfusion imaging, included in the present investigation.

This study has some limitations. First, the potential role of epicardial stealing should be considered together with the possible confounding factors such as age and hypertension. The application of our findings to clinical practice needs further clarification and more studies are required to confirm the results of the present investigation also in patients with abnormal myocardial perfusion.

NEW KNOWLEDGE GAINED

Our study adds new knowledge on clinical value of LV remodeling showing that LVSI by gated SPECT provides additional prognostic information in patients without overt CAD.

CONCLUSION

The results of this study indicate that the evaluation of LVSI may identify patients with early-stage LV remodeling and at higher risk of adverse cardiac events, even in the presence of normal myocardial perfusion.

Disclosure

V. Gaudieri, C. Nappi, W. Acampa, E. Zampella, R. Assante, T. Mannarino, A. Genova, G. De Simini, M. Klain, M. Petretta and A. Cuocolo declare that they have no conflict of interest. Cedars-Sinai Medical Center receives royalties for the quantitative assessment of function, perfusion, and viability, a minority portion of which is distributed to one of the authors of this manuscript (G. Germano).

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