Systolic Stretch Characterizes the Electromechanical Substrate Responsive to Cardiac Resynchronization Therapy

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ORIGINAL RESEARCH

Systolic Stretch Characterizes the Electromechanical Substrate Responsive to Cardiac Resynchronization Therapy

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ABSTRACT

OBJECTIVES In this study, the authors tested the hypotheses that the systolic stretch index (SSI) developed by computer modeling and applied using echocardiographic strain imaging may characterize the electromechanical substrate predictive of outcome following cardiac resynchronization therapy (CRT). They included patients with QRS width 120 to 149 ms or non-left bundle branch block (LBBB), where clinical uncertainty for CRT exists. They further tested the hypothesis that global longitudinal strain (GLS) has additional prognostic value.

BACKGROUND Response to CRT is variable. Guidelines favor patient selection by electrocardiographic LBBB with QRS width ≥150 ms.

METHODS The authors studied 442 patients enrolled in the Adaptive CRT 94-site randomized trial with New York Heart Association functional class III–IV heart failure, ejection fraction ≤35%, and QRS ≥120 ms. A novel computer program semiautomatically calculated the SSI from strain curves as the sum of posterolateral prestretch percent before aortic valve opening and the septal rebound stretch percent during ejection. The primary endpoint was hospitalization for heart failure (HF) or death, and the secondary endpoint was death over 2 years after CRT.

RESULTS In all patients, high longitudinal SSI (≥ group median of 3.1%) was significantly associated with freedom from the primary endpoint of HF hospitalization or death (hazard ratio [HR] for low SSI: 2.17; 95% confidence interval [CI]: 1.45 to 3.24, $p < 0.001$) and secondary endpoint of death (HR for low SSI: 4.06; 95% CI: 1.95 to 8.45, $p < 0.001$). Among the 203 patients with QRS 120 to 149 ms or non-LBBB, those with high longitudinal SSI (≥ group median of 2.6%) had significantly fewer HF hospitalizations or deaths (HR for low SSI: 2.08; 95% CI: 1.27 to 3.41, $p = 0.004$) and longer survival (HR for low SSI: 5.08; 95% CI: 1.94 to 13.31, $p < 0.001$), similar to patients with LBBB ≥150 ms. SSI by circumferential strain had similar associations with clinical outcomes, and GLS was additive to SSI in predicting clinical events ($p = 0.001$).

CONCLUSIONS Systolic stretch by strain imaging characterized the myocardial substrate associated with favorable CRT response, including in the important patient subgroup with QRS width 120 to 149 ms or non-LBBB. GLS had additive prognostic value. (J Am Coll Cardiol Img 2019;12:1741–52) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

aCRT = adaptive cardiac resynchronization

ARB = angiotensin II receptor blocker

AV = atrioventricular

AVC = aortic valve closure

AVO = aortic valve opening

CRT = cardiac resynchronization therapy

CI = confidence interval

EF = ejection fraction

GLS = global longitudinal strain

HF = heart failure

HR = hazard ratio

LBBB = left bundle branch block

LV = left ventricular

SSI = systolic stretch index

SPS = systolic prestretch

SRS = systolic rebound stretch

VV = interventricular

Cardiac resynchronization therapy (CRT) has provided major benefits to many patients with heart failure (HF) and reduced left ventricular (LV) ejection fraction (EF) and widened QRS complex (1). Current clinical guidelines most strongly favor CRT patient selection using electrocardiographic (ECG) criteria of left bundle branch block (LBBB) with QRS width ≥150 ms. CRT response is less predictable in patients with intermediate ECG criteria defined as QRS width 120 to 149 ms or non-LBBB morphology (2). Echocardiographic measures of regional mechanical delays, broadly defined as dyssynchrony, have failed to gain clinical acceptance to assist in CRT patient selection (3). The EchoCRT randomized clinical trial showed that CRT in HF patients with peak-to-peak dyssynchrony by tissue Doppler or radial strain and narrow QRS (width <130 ms) was not beneficial and could be potentially harmful (4). Accordingly, current guidelines do not advocate echocardiographic dyssynchrony to be used for patient selection for CRT.

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Computer modeling was more recently used to gain a deeper understanding of how regional mechanical dyssynchrony may exist in patients with narrow QRS width and to devise a new way to identify the myocardial substrate responsive to CRT (5). The systolic stretch index (SSI) was developed as a means to identify the mechanical pattern of electrical delay and properties of myocardial viability or absence of scar. The primary objective of the present study was to test the hypothesis that systolic stretch could predict CRT response in the large multicenter study, using the Adaptive CRT (aCRT) database (6). In particular, SSI was tested in a pre-specified subgroup of clinically challenging patients with QRS width 120 to 149 ms or non-LBBB morphology (7). This was a prospective study design with SSI analysis applied to the echocardiographic digital images of 478 patients from 94 sites by a blinded echo core lab. The secondary objective was to test the hypothesis that global longitudinal strain (GLS) would have additive prognostic value to systolic stretch (8,9). Pre-specified were the primary endpoint of HF hospitalization or death and secondary endpoint of all-cause mortality.

BACKGROUND

RATIONALE FOR SYSTOLIC STRETCH AS A MYOCARDIAL MARKER OF CRT RESPONSE. Computer model simulations of regional LV strain revealed that the combination of systolic pre-stretch in the lateral wall (SPS) and systolic rebound stretch in the septum (SRS), known as the SSI, is a specific marker of the electromechanical substrate amenable to CRT (5) (**Figure 1**). SPS is defined as stretch of the posterolateral wall resulting from early septal contraction before aortic valve opening (AVO). SPS reflects septal-to-lateral electrical activation delay (i.e., LBBB substrate), septal myocardium with sufficient contractility to stretch the late-activated lateral wall, and lateral myocardium with sufficient compliance (i.e., without scar) to be stretched by the early activated septum. SRS is defined as stretch of the septum following early systolic shortening and resulting from late posterolateral contraction before aortic valve closure (AVC). SRS reflects electrical activation delay of the posterolateral wall and increased contraction of the preloaded lateral wall to stretch the contracting septal tissue during ejection (10), resulting from length-dependent activation (i.e., the cellular basis of the Frank-Starling law) (11), and septal myocardium with sufficient compliance (i.e., without scar) in order to be stretched by the late activated posterolateral wall (12). In summary, SSI is a diagnostic index that detects the presence of both an electrical delay and of sufficiently contractile and nonscarred myocardium.

METHODS

The aCRT trial was a multicenter randomized clinical trial of CRT-defibrillator patients enrolled from 94 international sites described elsewhere in detail (6). Each site obtained institutional review board approval, and all patients provided written informed consent. Briefly, 478 patients were included with routine CRT indications (New York Heart Association functional class III or IV HF on optimal medical therapy and LVEF ≤35%). All patients had QRS ≥120 ms of any morphology, although <10% of patients had right bundle branch block (RBBB) (**Table 1**). A novel aCRT algorithm for atrioventricular (AV) and interventricular (VV) delay optimization was found to be noninferior to routine echo-Doppler optimization. This substudy included all consecutive patients with baseline echocardiographic or electrocardiographic (ECG) data before CRT implantation and clinical follow-up regardless of optimization randomization (**Figure 2**).

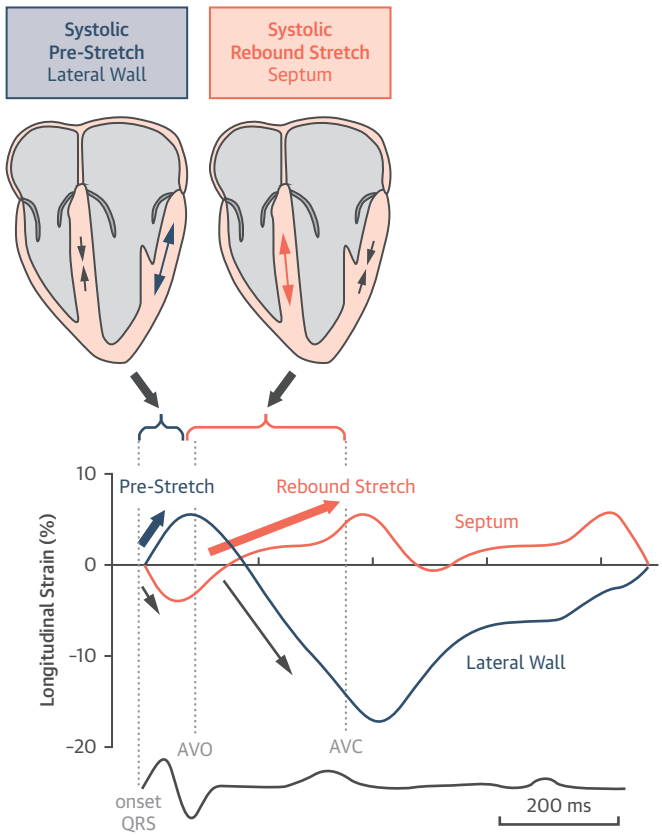
SPECKLE TRACKING ANALYSIS. Speckle tracking analysis was done on images in Digital Imaging and Communications in Medicine (DICOM) format using Research Arena version 4.6 software (TomTec, Munich, Germany) by the echo core lab, blinded to all clinical and follow-up data. Longitudinal strain was assessed in apical 4-chamber, 2-chamber, and long-axis views. Radial and circumferential strain were assessed in the mid-LV short-axis view. Pulsed-Doppler in the LV outflow tract determined AVO and AVC. Fully automated SSI was calculated by the biomedical engineering lab (Maastricht University, the Netherlands), using custom-made software (Matlab 7.11.0, MathWorks, Natick, Massachusetts) as detailed above (5) (**Figure 3**). Longitudinal SSI was calculated from basal and midventricular segments, excluding apical segments. Apical segments were excluded because systolic stretch of opposing walls was most pronounced in basal and mid-segments. Radial and circumferential SSI were calculated from the 2 septal and the 2 posterolateral segments. SPS was determined as stretch occurring from onset QRS to AVO, averaged over the 2 lateral or posterolateral wall segments. SRS was determined as the stretch occurring from onset QRS to AVC with the proviso that it followed early systolic shortening that occurred after onset of QRS.

SYSTOLIC STRETCH REPRODUCIBILITY ANALYSIS. Interobserver and intraobserver variability analysis for SSI was performed on 20 randomly selected studies with investigators blinded to all other measurements. The strain measurements were performed on the multiple beats from the image datasets available without prespecifying the same cycle. From the analysis on typically 3 beats, the user selected the beat with the highest-quality strain curves with the least noise. The SSI calculations fully automated by the same computer program described above using input of regional time-strain curves and times of onset of QRS AVO and AVC. Limits of agreement appear as ± 2 SDs. For longitudinal strain SSI, intraobserver mean bias was 0.1% with limits of agreement 4.5%, and interobserver mean bias was 0.6% with limits of agreement 4.4%. For circumferential strain SSI, intraobserver mean bias was 0.4% with limits of agreement 6.2%, and interobserver mean bias was 1.7% with limits of agreement 6.4%. For radial strain SSI, intraobserver mean bias was 2.3% with limits of agreement 10%, and interobserver mean bias was 4.5% with limits of agreement 17%.

GLOBAL LONGITUDINAL STRAIN. GLS was determined using the maximal number of longitudinal strain segments available: a 16-segment model was used for patients with 3 apical views and a 12-segment model in patients with 2 apical views available. GLS was not calculated if only 1 apical view was available. Our laboratory's interobserver and intraobserver reproducibility for GLS was 0.97 (95% confidence interval [CI]: 0.93 to 0.99) and 0.92 (95% CI: 0.72 to 0.98), respectively, as previously reported (9).

OUTCOME ANALYSIS. The primary pre-specified endpoint was HF hospitalization or death. The secondary endpoint was all-cause death. All events were adjudicated by an independent clinical events committee and recorded in the clinical trial database. Hospitalization for worsening HF was defined as a nonelective admission of at least 1 overnight stay for administration or augmentation of

FIGURE 1 Systolic Stretch Index from Computer Modeling



A schematic representation of the systolic stretch index (SSI) from computer modeling that identifies the myocardial substrate responsive to cardiac resynchronization therapy from longitudinal strain curves. SSI combines the systolic prestretch of the lateral wall **(blue upward arrow)** caused by early septal contraction **(black downward arrow)** and systolic rebound stretch of the septum **(orange upward arrow)** caused by late lateral wall contraction **(black downward arrow)**. AVC = aortic valve closure; AVO = aortic valve opening.

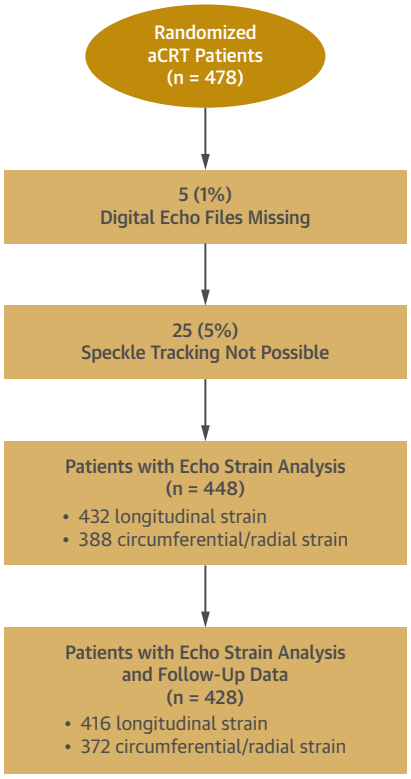
TABLE 1 Baseline Characteristics of All 428 Patients Grouped by Longitudinal Systolic Stretch Above or Below Median Values

	All Patients (N = 428)	Patients With High Systolic Stretch (n = 214)	Patients With Low Systolic Stretch (n = 214)	p Value
Age (yrs)	65 ± 11	65 ± 10.4	66 ± 11	0.33
Male	67 (280)	58 (120)	77 (160)	<0.0001
BMI (kg/m^2)	29 ± 6	29 ± 6	29 ± 6	0.93
NYHA functional class I	0.2 (1)	0.5 (1)	0 (0)	0.44
NYHA functional class II	1.2 (5)	1.9 (4)	0.5 (1)	0.44
NYHA functional class III	94 (391)	93 (194)	95 (197)	0.44
NYHA functional class IV	4.6 (19)	4.3 (9)	4.8 (10)	0.44
LVEF (%)	24.6 ± 6.6	24.5 ± 6.7	24.8 ± 6.6	0.73
Ischemic disease	47 (197)	42 (87)	53 (110)	0.03
QRS width (ms)	155 ± 21	157 ± 20	153 ± 21	0.09
LBBB	77 (321)	77 (161)	77 (160)	1.00
Hypertension	66 (273)	65 (136)	66 (137)	1.00
Renal dysfunction	20 (84)	18 (37)	23 (47)	0.27
COPD	17 (71)	18 (38)	16 (33)	0.60
CABG (previous)	26 (110)	23 (48)	30 (62)	0.14
ACEI/ARBs	87 (363)	90 (188)	84 (175)	0.08
Beta-blockers	91 (380)	89 (185)	94 (195)	0.11
Previous device	21 (88)	18 (38)	24 (50)	0.19

Values are mean ± SD or % (n).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; Previous device = pacemaker or defibrillator implant.

FIGURE 2 Flow Chart of Echocardiograms



Flow chart of patients with baseline echocardiographic strain data and clinical follow-up from the aCRT (Adaptive Cardiac Resynchronization Trial). The study cohort was 442 total patients, including an additional 14 patients with no echo data available and only ECGs of left bundle branch block and QRS ≥150 ms for comparison.

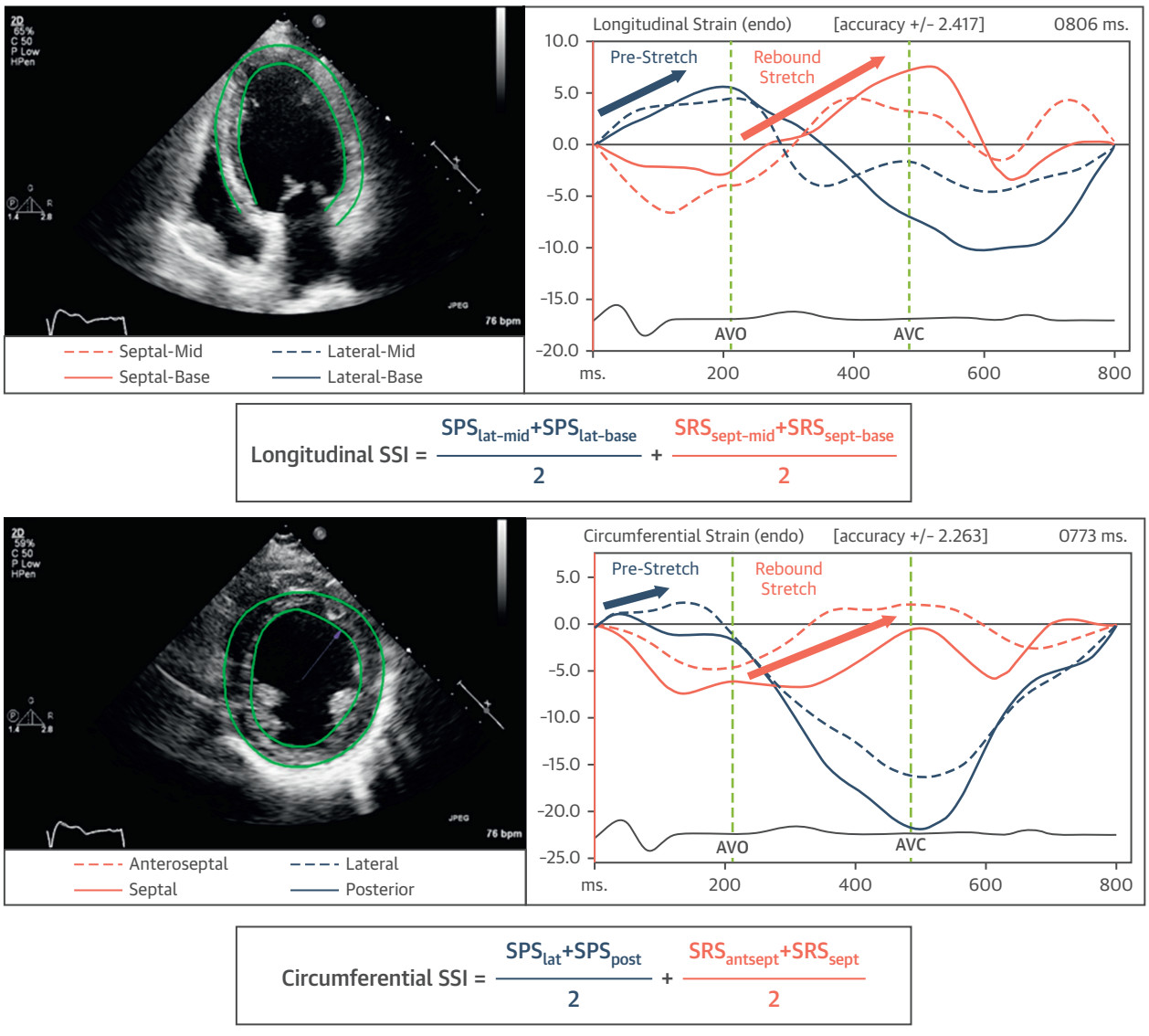
intravenous or oral HF therapy, including inotropes, diuretics, and/or vasodilators. Time to first event was counted from the time of CRT implantation.

STATISTICAL ANALYSIS. Baseline characteristics were reported as means and standard deviations for continuous variables and counts and percentages for categorical variables. Group comparisons were based on 2-sample Student's *t*-tests (or Mann-Whitney tests) and Fisher's exact tests, as appropriate. In time to event analyses, follow-up was censored at study closure, date of death, withdrawal from the study, or loss to follow-up, whichever came first. We divided the sample into high and low SSI groups at the overall or subgroup medians for time to event outcomes with Kaplan-Meier plots. Hazard ratios (HRs) and 95% CIs were calculated from Cox proportional hazards models. Multivariate Cox proportional hazards models were also used to adjust for important covariates (including gender, etiology, QRS width, and treatment with angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB) when estimating the association between SSI and clinical outcomes. Harrell's C statistic with 95% CIs was used to determine associations of SSI by strain calculation methods. To produce a strain metric based on SSI and GLS that was optimized for predicting HF hospitalization and death, we derived weights for the component parts from coefficients obtained using multivariable Cox regression (with LBBB/QRS status as a covariate). One-year and 18-month risks were estimated using logistic regression. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) except for derivation of Harrell's C, which used the survC1 package for R 3.3.0 (R Core Team, Vienna, Austria) (13).

RESULTS

SYSTOLIC STRETCH AND CLINICAL OUTCOMES. The overall study cohort consisted of 442 patients

FIGURE 3 **Examples of Systolic Stretch Index From Echocardiographic Images**



Echocardiographic strain imaging examples from a patient in the study with left bundle branch block and favorable response to cardiac resynchronization therapy. Segmental longitudinal strain from the apical 4-chamber view **(top)** and segmental circumferential strain from midventricular short axis view **(bottom)** are shown. The systolic prestretch (SPS) **(upward blue arrows)** in lateral and posterolateral segments related to early septal shortening occurring before aortic valve opening (AVO). The systolic rebound stretch (SRS) **(upward orange arrows)** in septal segments occurred after initial shortening during the ejection interval until aortic valve closure (AVC) and relates to delayed posterolateral contraction. The systolic stretch index is the sum of SPS and SRS. lat = lateral; sept = septum; post = posterior; antsept = anteroseptum.

with available baseline strain imaging, ECG, and follow-up data. There were 416 patients with longitudinal strain, 372 patients with circumferential/radial strain, and 14 patients with LBBB ≥150 ms with no strain data available (3%). There were 107 patients who reached an endpoint: 63 (15%) with HF hospitalizations and 44 (11%) who died with or without a preceding HF hospitalization. Results of associations of SSI with clinical outcome in all patients appear in Table 2 and Figures 3 and 4. Results of associations of SSI with clinical outcome in the 208 patients with intermediate ECG criteria (QRS 120 to 149 ms or non-LBBB) also appear in Table 2 and Figures 5 and 6. When compared with the patients with the class I

TABLE 2 Univariate Associations of Baseline Systolic Stretch Index With Clinical Outcomes

Strain Data	n	Median SSI	Endpoint	Hazard Ratio	95% CI	p Value
All CRT patients (QRS width ≥120 ms)						
Longitudinal	416	3.1	Survival free from HF hospitalization	2.17	1.45–3.24	<0.001
			Survival	4.06	1.95–8.45	<0.001
Circumferential	372	3.5	Survival free from HF hospitalization	2.25	1.45–3.47	<0.001
			Survival	3.18	1.55–6.51	<0.001
Radial	372	8.9	Survival free from HF hospitalization	1.90	1.24–2.91	0.003
			Survival	2.71	1.35–5.42	0.005
CRT patients with QRS width 120–149 ms or non-LBBB						
Longitudinal	203	2.6	Survival free from HF hospitalization	2.08	1.27–3.42	0.004
			Survival	5.08	1.94–13.31	<0.001
Circumferential	181	3.2	Survival free from HF hospitalization	2.13	1.24–3.67	0.006
			Survival	3.00	1.26–7.13	0.013
Radial	181	7.3	Survival free from HF hospitalization	1.36	0.81–2.29	0.25
			Survival	1.90	0.85–4.27	0.12

Median SSI for each subgroup was used for cutoff of high SSI and low SSI, with associations of high SSI with favorable clinical outcomes. Hazard ratio (HR) refers to increased risk with low SSI.

CRT = cardiac resynchronization therapy; CI = confidence interval; HF = heart failure; HR = hazard ratio for low SSI; LBBB = left bundle branch block; SSI = systolic stretch index.

indication for CRT of LBBB and QRS ≥150 ms, patients with intermediate ECG criteria and high longitudinal SSI had similar clinical outcomes of survival free from HF hospitalizations and nearly identical survival after CRT.

SYSTOLIC STRETCH AND CLINICAL OUTCOMES AFTER ADJUSTMENT FOR BASELINE CHARACTERISTICS. Overall baseline characteristics were balanced in subjects grouped by low and high longitudinal SSI (Table 1), with only 5 variables identified as potential confounders: male gender (associated with lower SSI), ischemic disease (associated with lower SSI), previous coronary artery bypass (trend toward association with lower SSI), ACEi/ARB use (associated with higher SSI), and beta-blocker use (associated with higher SSI in the QRS 120 to 149 ms or non-LBBB subgroup). Only ACEi/ARB use and ischemic disease were significantly associated with the clinical outcomes in univariate regression models ($p = 0.043$ and $p = 0.035$, respectively), and none of them were significantly

TABLE 3 Comparison of Associations of Baseline Strain Parameters With Primary Outcome of Heart Failure Hospitalization or Death

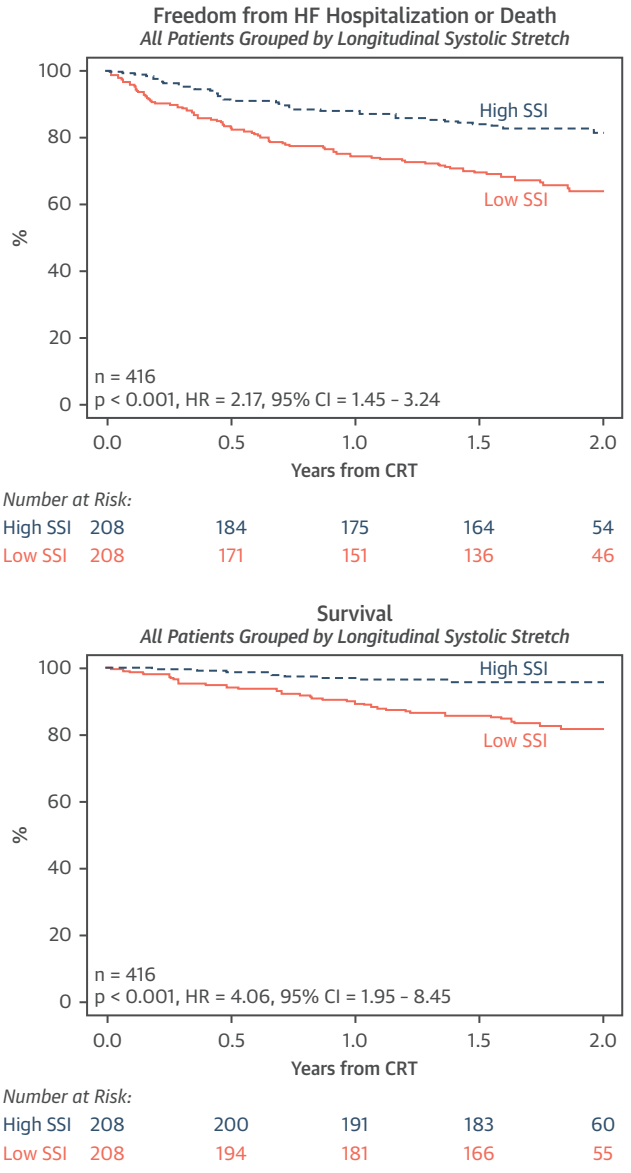
	Harrell's C	Lower 95%	Upper 95%
All patients			
Radial strain SSI alone	0.597	0.511	0.683
Circumferential strain SSI alone	0.628	0.557	0.699
Longitudinal strain SSI alone	0.651	0.581	0.721
Longitudinal and radial strain SSI	0.666	0.599	0.733
Longitudinal and circumferential strain SSI	0.675	0.610	0.740
GLS alone	0.589	0.515	0.663
GLS and longitudinal strain SSI	0.681	0.618	0.745
GLS and longitudinal and circumferential strain SSI	0.699	0.619	0.780
Patients with intermediate ECG criteria (QRS 120–149 ms or non-LBBB)			
Radial strain SSI alone	0.551	0.433	0.669
Circumferential strain SSI alone	0.621	0.521	0.722
Longitudinal strain SSI alone	0.651	0.576	0.725
Longitudinal and radial strain SSI	0.656	0.571	0.742
Longitudinal and circumferential strain SSI	0.670	0.581	0.759
GLS alone	0.588	0.506	0.671
GLS and longitudinal strain SSI	0.678	0.601	0.755
GLS and longitudinal and circumferential strain SSI	0.701	0.611	0.791

Comparative associations with clinical outcomes of different strain methods for systolic stretch index (SSI) at baseline and clinical outcomes after cardiac resynchronization therapy. Associations of SSI and when combined with global longitudinal strain (GLS) are shown. The larger Harrell's C statistic indicates closer associations.

associated with survival in multivariate Cox regression models. After adding SSI by longitudinal strain to the multivariate models for HF hospitalization or death, SSI remained significantly and independently associated with freedom from HF hospitalization or death (HR: 0.84 per unit increase of SSI; 95% CI: 0.77 to 0.92; $p < 0.001$) and significantly and independently associated with survival (HR: 0.83 per unit increase of SSI; 95% CI: 0.71 to 0.96; $p = 0.001$). Furthermore, the addition of SSI to multivariable models did not affect the lack of association that was previously observed with the other covariates ($p > 0.10$ for all). Similar patterns were observed when adjusting SSI by circumferential strain for covariates: for freedom from HF hospitalization or death (HR: 0.89 per unit increase of SSI; 95% CI: 0.82 to 0.96; $p = 0.002$) and for survival (HR: 0.87; 95% CI: 0.77 to 0.98; $p = 0.028$). Comparison of associations with clinical outcomes of longitudinal, circumferential, and radial strain parameters and GLS appears in **Table 3** and the Supplemental Appendix. Multivariate proportional hazards models to investigate the effect of SSI on primary and secondary endpoints were repeated with models that feature QRS morphology as predictors for longitudinal and circumferential SSI with similar results. In each case, the weight of evidence favored the conclusion that SSI was at least as strongly associated with clinical outcomes as any other variable including QRS morphology. In addition, this association was independent of the associations that all other examined predictors may have with outcomes (gender, ischemic origin, ACE inhibitor/ARB or beta-blocker use, ischemic origin, previous coronary bypass, LBBB, or RBBB) and was maintained in the subgroup of patients with intermediate ECG criteria.

ADDITIVE PROGNOSTIC VALUE OF GLOBAL LONGITUDINAL STRAIN TO SYSTOLIC STRETCH. GLS measurements were possible in 370 patients overall. Significant associations of GLS at baseline dichotomized by the median value of 7.4% (in absolute values) were demonstrated with the primary endpoint of HF hospitalization or death: HR for low SSI: 1.55; 95% CI: 1.02 to 2.35; $p = 0.040$ and secondary endpoint of all-cause mortality: HR for low SSI: 2.25; 95% CI: 1.10 to 4.59; $p = 0.026$. GLS had a highly significant additive relationship with longitudinal strain SSI in patients with QRS 120 to 149 ms or non-LBBB. The highest risk quartile had a >6-fold increased risk of HF hospitalization or death compared with the lowest risk quartile (HR: 6.31; 95% CI: 2.41 to 16.56; $p < 0.001$) (**Figure 7**).

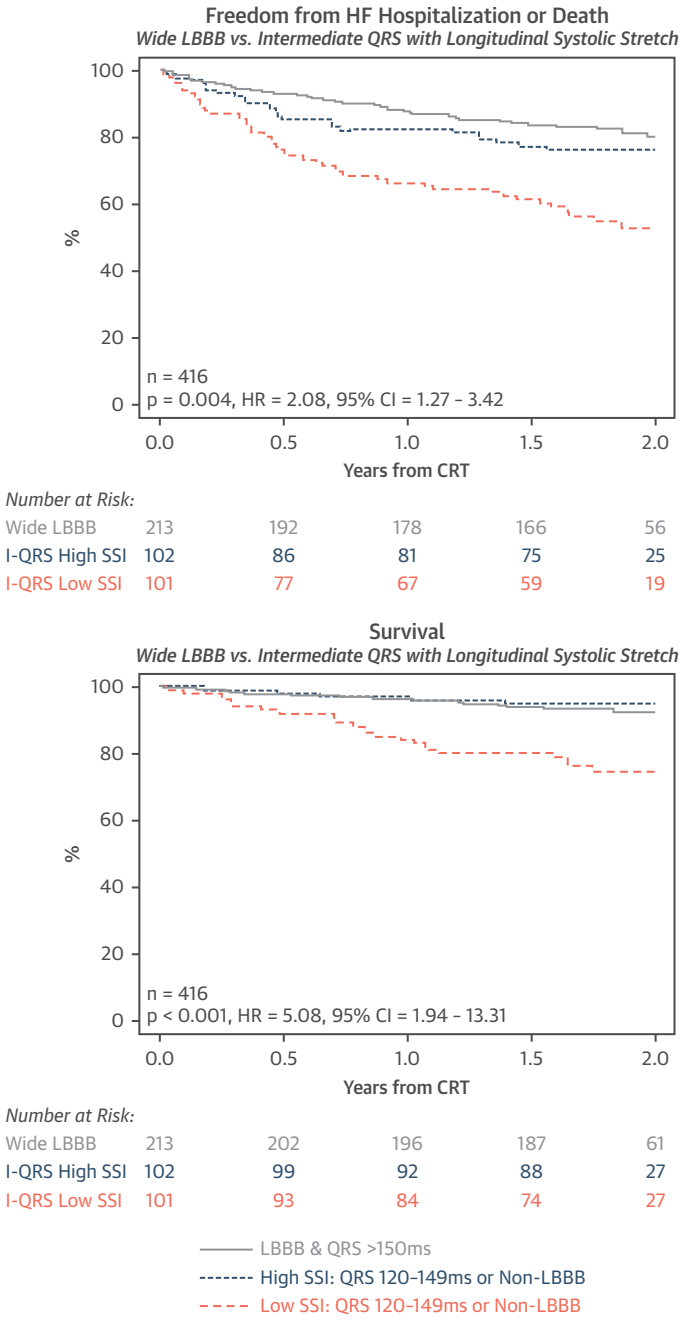
FIGURE 4 Associations of Longitudinal Systolic Stretch With Clinical Outcomes in All Patients



Kaplan-Meier plots of all 416 patients with longitudinal strain available at baseline, demonstrating significant associations of a high systolic stretch index (SSI) with favorable clinical outcomes of the combined endpoint of heart failure (HF) hospitalization or death **(top)** or survival alone **(bottom)** after cardiac resynchronization therapy (CRT). Plots were grouped above and below the median SSI value for all patients. CI = confidence interval; HR = hazard ratio.

Incremental risk of reaching the primary endpoint over 12 and 18 months was estimated using a combined hazard model of GLS and SSI (**Figure 8**). Grouping longitudinal SSI and GLS by quintiles, risk was additive over the entire range of values. As

FIGURE 5 Associations of Longitudinal Systolic Stretch With Clinical Outcomes in Patients With Intermediate ECG Criteria



Kaplan-Meier plots of 416 patients including 213 with QRS width >150 ms and left bundle branch block (LBBB) and 203 with QRS 120 to 149 ms or non-LBBB stratified by high or low longitudinal strain systolic stretch index (SSI) above or below the group median value, respectively. Patients with QRS 120 to 149 ms or non-LBBB and high SSI had more favorable clinical outcomes, similar to those with QRS width >150 ms and LBBB. Abbreviations as in Figure 4.

examples, over 12 months, patients with the highest SSI (>5.8%) and highest absolute GLS (10.4% to 21.5%) had the lowest 3.7% risk of HF hospitalization or death, and patients with the lowest SSI (<1.3%) and lowest absolute GLS (<4.7%) had the highest 37.7% risk of HF hospitalization or death.

DISCUSSION

This analysis of 442 patients from the aCRT randomized trial is the first large multicenter study to demonstrate that echocardiographic SSI at baseline was strongly associated with subsequent clinical outcome after CRT. Although previous studies focused on echocardiographic dyssynchrony and CRT response have had varied success in a multicenter setting (3), the current study included quantitative SSI analysis from 94 international sites and reflects a "real-world" multicenter clinical experience. These data were further strengthened by both the echo core lab and investigators doing the SSI calculation blinded from all clinical and outcome data and the clinical endpoints being rigorously adjudicated as part of a randomized clinical trial. In particular, SSI was able to identify the CRT patients with intermediate ECG criteria (QRS 120 to 149 ms or non-LBBB) who had favorable clinical outcomes similar to those with LBBB >150 ms, known to be the best responders to CRT (14). GLS was found to be additive to SSI in its predictive value for clinical outcomes, which, from a practical point of view, can be easily incorporated into the same longitudinal strain data.

IMPROVED PREDICTION OF CLINICAL OUTCOMES AFTER CRT OVER ECG CRITERIA. The large randomized clinical trials for CRT used either a QRS width ≥120 ms or ≥130 ms, regardless of morphology where 30% to 50% of patients were nonresponders (1,15–17). Post hoc analyses demonstrated that patients with LBBB morphology and QRS width ≥150 ms had the best CRT response, and these ECG criteria became the Class I indication for CRT (2). There is less certainty about CRT response in patients with intermediate ECG criteria of QRS 120 to 149 ms or non-LBBB: at present, Class IIa or IIb indications (2). Furthermore, patients with narrow QRS do not benefit from CRT and may be harmed with an increased mortality (4). Accordingly, the key observations in the current study—that SSI, either when considered alone or combined with GLS, may provide important information about CRT response in patients with intermediate ECG criteria—are of practical clinical relevance.

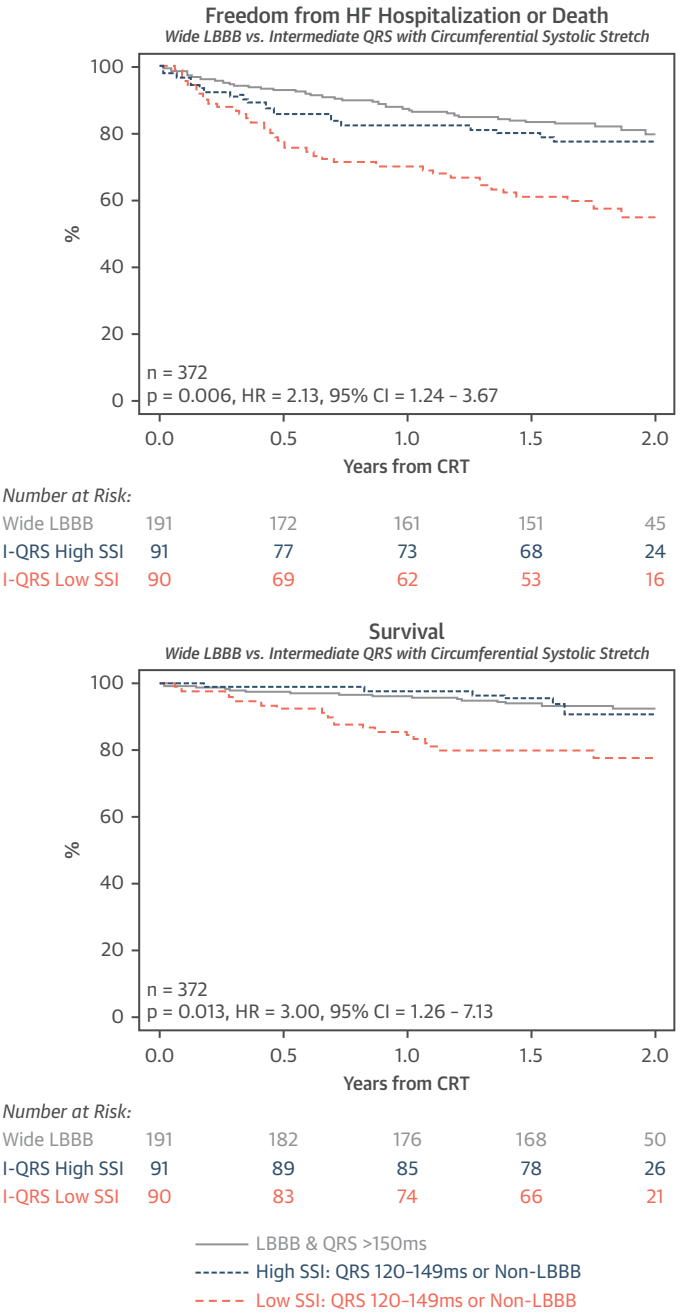
SYSTOLIC STRETCH CHARACTERIZING THE ELECTROMECHANICAL SUBSTRATE OF CRT RESPONSE. The concept of the pathophysiology of systolic stretch and CRT response is supported by the experimental work of Tangney et al. in an isolated mouse papillary muscle model (18). They showed that dyssynchronous regional activation led to abnormal regional systolic stretch and that the timing of systolic stretch affected regional tension and external work development. By performing quick stretches to dissociate cross-bridges, they demonstrated alterations in the force-velocity relation occurring before the peak of the calcium transient. They suggested that stretch near the start of cardiac tension development substantially increased twitch tension and mechanical work production as seen experimentally in late activated regions of the paced canine heart, whereas late stretches decreased external work as seen in early activated regions (19). The decreased work in muscles stretched after the peak of the calcium transient was thought to be due to myofilament deactivation.

Multiple interacting factors may influence response to CRT, including the presence of an appropriate electromechanical substrate amenable to CRT, global scar burden, and LV lead position both anatomically and in relation to regional scar (5,20,21). SSI was introduced as a quantitative assessment of septal-to-posterolateral systolic mechanical interactions caused by LBBB using radial strain (5). The results of the current study extend the use of SSI to longitudinal and circumferential strain, which were found to be more closely associated with clinical outcomes than radial SSI, using vendor-independent speckle tracking software. Although a septal-to-posterolateral electrical activation delay is essential for SSI to occur, SSI also includes myocardial properties of viability and stiffness and is likely to be attenuated by fibrotic remodeling related to scar. Accordingly, SSI enables noninvasive electromechanical profiling that is additive to the conventional ECG parameters currently used for CRT patient selection.

PROGNOSTIC VALUE OF GLOBAL LONGITUDINAL STRAIN IN CRT

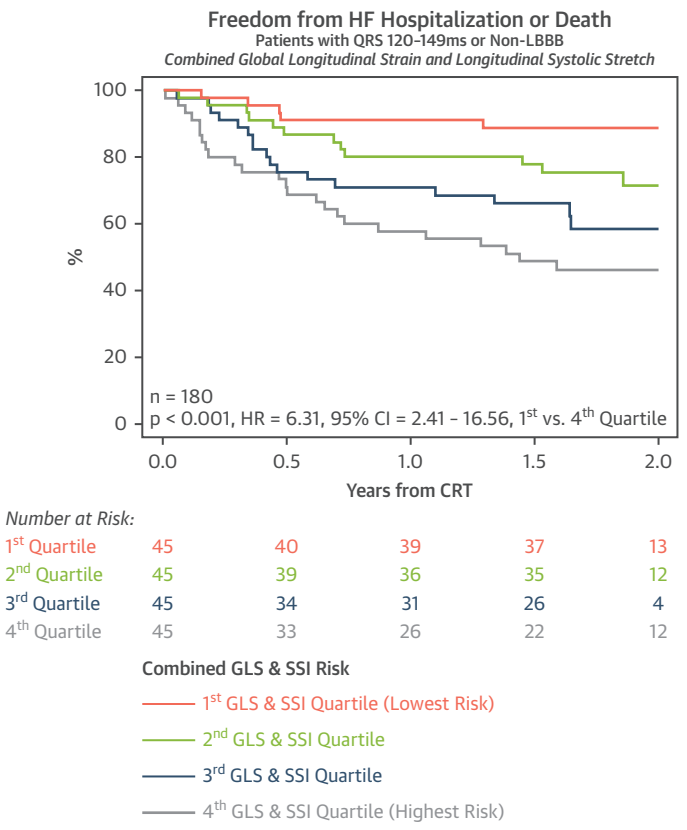
Several studies have shown that GLS can provide valuable prognostic information beyond routine LVEF in CRT candidates (8,22). Although chamber deformation is related to LVEF, GLS provides additive information on wall properties such as hypertrophy

FIGURE 6 Associations of Circumferential Systolic Stretch With Clinical Outcomes in Patients With Intermediate ECG Criteria



Kaplan-Meier plots of 372 patients including 213 with QRS width >150 ms and left bundle branch block (LBBB) and 181 with QRS 120 to 149 ms or non-LBBB stratified by high or low circumferential strain systolic stretch index (SSI) above or below the group median value, respectively. Patients with QRS 120 to 149 ms or non-LBBB and high SSI had more favorable clinical outcomes, similar to those with QRS width >150 ms and LBBB. Abbreviations as in Figure 4.

FIGURE 7 Associations of Combined Longitudinal Systolic Stretch and GLS With Clinical Outcomes in Patients With Intermediate ECG Criteria



Kaplan-Meier plots of 370 patients combining longitudinal strain systolic stretch index (SSI) and global longitudinal strain (GLS) stratified by quartiles. The addition of GLS strengthened the association of SSI with the primary endpoint of heart failure hospitalization or death after cardiac resynchronization therapy. Abbreviations as in Figure 4.

or fibrosis (23-25). It appears that GLS may further characterize the myocardial substrate that is not responsive to CRT by reflecting the myocardial scar burden in patients with ischemic cardiomyopathy and profound myocardial dysfunction in patients with nonischemic cardiomyopathy (5,9). A substudy of the EchoCRT randomized trial reported that GLS had important prognostic value in patients with narrow QRS (9). When patients were stratified by GLS in the worst quartile (GLS of <6.2% in absolute values), patients randomized to CRT-On had a significantly higher mortality than those randomized to CRT-Off ($p = 0.007$) (9). This finding was observed similarly in patients classified as having ischemic or nonischemic cardiomyopathies. These data suggest that the increased mortality with CRT observed in the EchoCRT trial occurred in patients with the most impaired LV function and that low absolute GLS may potentially serve as a marker of risk for CRT treatment, although this remains to be proved (8,9).

STUDY LIMITATIONS. All patients in the aCRT trial received CRT. Several randomized clinical trials of CRT in patients with widened QRS complexes demonstrated benefit previously, and no control group of patients without CRT was included (1,2). Accordingly, this study could not determine the prognostic benefit from the CRT intervention or an interaction term associating SSI and GLS with outcomes by comparing patients who received CRT with those who did not receive CRT. It may be considered a limitation that a particular cutoff value for SSI was not tested prospectively. SSI was dichotomized by the median values observed in each subgroup in order to allow the use of Kaplan-Meier curves for data visualization. We note that both GLS and SSI are continuous variables that indicate a risk gradient and that it will often be preferable in both practice and analysis to consider these quantities as such. Accordingly, specific cutoff values from risk predictions of SSI and GLS deserve future prospective study to make an impact on patient selection for CRT, in particular for patients with intermediate ECG criteria. Because this was a substudy of the aCRT trial, the interaction of the A-V and V-V optimization scheme on our observations is unknown. However, the SSI measures were performed on baseline echocardiograms of patients with routine CRT indications before randomization to AV and VV optimization algorithms and included all consecutive patients with data available for our study. The variability in SSI calculations is a limitation and appeared to be least for longitudinal strain and greatest for radial strain. This variability is believed to be due to operator placement of regions of interest and will likely decrease with improvements in software design. It would be of interest to have an alternate imaging technique to quantify scar burden, such as late gadolinium enhancement with CMR, but this will have to be part of future study. LV lead placement has been shown to influence CRT response, especially in patients with intermediate ECG criteria (26), but lead placement information was not available. A known limitation of speckle tracking is that it cannot be applied to all consecutive patients, but in this "real-world" large multicenter study, we needed to exclude only 9% of routine digital echocardiograms in which speckle tracking was not possible. Finally, the potential influence of aCRT randomization versus routine echo Doppler AV and VV delay optimization after CRT was not part of this study,

which focused on SSI and GLS, and future investigation is warranted.

CONCLUSIONS

A high value of systolic stretch as measured by speckle tracking strain imaging prior to CRT was strongly associated with favorable clinical outcomes after CRT. In patients with high systolic stretch and QRS 120 to 149 ms or non-LBBB—currently a class II indication for CRT—clinical outcomes were similar and survival was nearly identical to patients with the class I indication for CRT of LBBB with QRS width >150 ms. GLS using the same longitudinal strain dataset provided additional prognostic information to systolic stretch. Measurements of both global and regional myocardial function that reflect the electromechanical substrate responsive to CRT can therefore provide additional benefit on top of ECG selection criteria. We stress the need for external validation in a future randomized controlled clinical trial, particularly in patients with intermediate ECG criteria that are class II indications for CRT.

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FIGURE 8 Risk Prediction Using Longitudinal Systolic Stretch and Global Longitudinal Strain in Patients With Intermediate ECG Criteria

12-Month Risk of HF Hospitalization or Death after CRT (%)

	Global Longitudinal Strain (%)				
SSI (%)	*0 - 4.7*	*4.7 - 6.8*	*6.8 - 8.4*	*8.4 - 10.4*	*10.4 - 21.5*
0 - 1.3	48.4	42.4	37.6	32.5	25.8
1.3 - 2.3	41.8	36.1	31.6	27.0	21
2.3 - 3.7	34.6	29.3	25.3	21.4	16.4
3.7 - 5.8	25.8	21.5	18.3	15.2	11.4
>5.8	13.8	11.2	9.4	7.6	5.6

18-Month Risk of HF Hospitalization or Death after CRT (%)

	Global Longitudinal Strain (%)				
SSI (%)	*0 - 4.7*	*4.7 - 6.8*	*6.8 - 8.4*	*8.4 - 10.4*	*10.4 - 21.5*
0 - 1.3	54.4	46.8	40.6	34.1	25.5
1.3 - 2.3	49.3	41.8	35.8	29.7	21.9
2.3 - 3.7	43.5	36.2	30.6	25.0	18.1
3.7 - 5.8	35.8	29.2	24.3	19.5	13.8
>5.8	23.6	18.6	15.1	11.8	8.2

This is a table for prediction of risk of heart failure hospitalization or death after cardiac resynchronization therapy (CRT) in patients with QRS 120 to 149 ms or non-LBBB. Risk was calculated from measures of baseline longitudinal strain systolic stretch index (SSI) and global longitudinal strain (GLS) in absolute values stratified by quintiles. SSI is a strong predictor of risk of clinical events and GLS is additive in prognostic predictive value.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study focuses on improvement in patient selection for CRT in heart failure patients with widened QRS and reduced ejection fraction. Current guidelines recommend selecting patients by ECG criteria alone, favoring QRS duration >150 ms and LBBB morph-ology. However, there remains a significant number of CRT nonresponders, and there is clinical uncertainty for use of CRT in those patients with QRS width 120 to 149 ms or non-LBBB morphology. This research study used mechanistic knowledge obtained from previous computer modeling work to characterize the electromechanical substrate of CRT response by determining the SSI from echocardiographic strain imaging. SSI was shown to improve prediction of CRT response above ECG criteria alone. In particular, SSI was able to improve prediction of response in patients with QRS width 120 to 149 ms or non-LBBB, where those with high SSI had similar clinical outcomes of heart failure hospitalizations or death after CRT as patients with QRS width >150 ms and LBBB. Furthermore, GLS was additive to SSI in predicting risk and clinical response. These data provide the opportunity for improvement of patient selection for CRT in the future, and further investigation is warranted.

TRANSLATIONAL OUTLOOK: Applying the concept of cardiac mechanical function, specifically systolic stretch, to electrocardiographic criteria for response to cardiac resynchronization therapy is a potential translation from whole organ physiology to individual patient selection. These data extracted from a large multicenter randomized clinical trial echocardiographic database provide evidence that systolic stretch may identify the electromechanical substrate that is responsive to cardiac resynchronization therapy. These findings may translate to the care of the individual patient with further study.

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APPENDIX For supplemental statistical methods and results sections, please see the online version of this article.