ORIGINAL RESEARCH

Early Systolic Lengthening in Patients With ST-Segment–Elevation Myocardial Infarction: A Novel Predictor of Cardiovascular Events

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Background—Early systolic lengthening (ESL) may occur in ischemic myocardial segments with reduced contractile force. We sought to evaluate the prognostic potential of ESL in patients with ST-segment–elevation myocardial infarction treated with primary percutaneous coronary intervention.

Methods and Results—We prospectively enrolled 373 patients with ST-segment–elevation myocardial infarction treated with primary percutaneous coronary intervention. All patients underwent a speckle tracking echocardiographic examination a median of 2 days (interquartile range, 1–3 days) after the percutaneous coronary intervention. We assessed a novel viability index, the ESL index, defined as follows: [−100×(peak positive systolic strain/peak negative strain in cardiac cycle)]. We also calculated ESL duration, defined as time from onset of QRS complex on the ECG to time of peak positive systolic strain. Both parameters were averaged from 18 myocardial segments. During a median follow-up of 5.3 years (interquartile range, 2.5–6.0 years), 145 (39%) experienced major adverse cardiovascular events, a composite of incident heart failure, new myocardial infarction, and all-cause mortality. The ESL index and ESL duration were significantly increased in culprit lesion areas (6.7±6.2% versus 5.0±4.1% and 43±33 ms versus 33±24 ms, respectively; $P<0.001$ for both). In Cox proportional hazard models, the ESL index (hazard ratio, 1.27 per 1% increase; 95% CI, 1.13–1.43; $P<0.001$) and ESL duration (hazard ratio, 1.49 per 1-ms increase; 95% CI, 1.15–1.92; $P=0.002$) yielded prognostic information on major adverse cardiovascular events. Both associations remained significant after adjusting for clinical, echocardiographic, and invasive confounders.

Conclusions—Assessment of ESL after primary percutaneous coronary intervention in patients with ST-segment–elevation myocardial infarction yields independent and significant prognostic information on the future risk of cardiovascular events. **(*J Am Heart Assoc*. 2020;9:e013835. DOI: 10.1161/JAHA.119.013835.)**

Key Words: 2-dimensional speckle tracking echocardiography • deformation • early systolic lengthening • echocardiography • myocardial infarction • revascularization

Patients with ST-segment–elevation myocardial infarction (STEMI) face an elevated risk of subsequent cardiovascular events.[1–4] Prospective risk stratification remains a core challenge in this group of patients and is important for both decision making and risk factor management.[5] An echocardiographic examination is useful to visualize significant changes in the left ventricular (LV) function after STEMI. However, changes in conventional echocardiographic parameters, such as LV ejection fraction (LVEF) and the wall motion score index (WMSI), are not necessarily present when myocardial scarring is limited. By contrast, 2-dimensional speckle tracking echocardiography (STE), a novel method for assessment of LV function, may offer information on subtle changes associated with myocardial ischemia.[6–8] Recent studies have demonstrated how STE may be useful for evaluating the benefit of cardiovascular drugs[9] and also can predict prognosis in acute heart failure[10] (HF) and after cardiac surgery.[11]

Asynchronous myocardial contraction may occur in response to myocardial ischemia and infarction and is believed to interfere with systolic and diastolic cardiac function.[12] A feature of LV dyssynergy is lengthening of ischemic myocardial segments before onset of systolic

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Clinical Perspective

What Is New?

- Early systolic lengthening (ESL) occurs in ischemic myocardial segments. Using speckle tracking echocardiography, we assessed the prognostic value of a novel viability index, the ESL index, and duration of ESL in patients with ST-segment–elevation myocardial infarction.
- We demonstrate that assessment of ESL in this population is associated with regional myocardial changes and offers independent prognostic information on the future risk of major adverse cardiovascular events.

What Are the Clinical Implications?

- Assessment of ESL may constitute a useful tool to identify ischemic changes.
- Information on ESL is quick and easily obtained by speckle tracking echocardiography and may complement routine risk stratification of patients with ST-segment–elevation myocardial infarction.

shortening. This may occur because of a reduced ability to generate active force when the LV pressure increases during early systole. Other proposed mechanisms involve electrical dyssynchrony and disparity between myocardial segments.[13,14] The duration of early systolic lengthening (ESL) has been shown to correlate with final infarct size in patients with STEMI, and it was coined a predictor of significant coronary artery disease in patients with stable angina pectoris (Figure 1).[15,16] However, the prognostic potential of ESL has not previously been assessed in any study cohort. In this study, we hypothesized that assessment of ESL after primary percutaneous coronary intervention (PCI) in patients with STEMI may provide prognostic information on future cardiovascular events.

Methods

Population

We prospectively enrolled 391 patients with STEMI from September 2006 to December 2008 who were treated with primary PCI at Gentofte University Hospital, Copenhagen, Denmark. The study population has previously been described.[7,17] Patients were enrolled and treated if they (1) had presence of chest pain >30 minutes and <12 hours, (2) demonstrated persistent ST-segment elevation ≥2 mm in a minimum of 2 contiguous precordial leads or ≥1 mm in a minimum of 2 contiguous limb leads, or (3) had a significant increase in troponin I (>0.5 μg/L). All baseline data were collected on inclusion, and troponin I was measured at baseline and after 6 and 12 hours. Patients were categorized as hypertensive if they received blood pressure–lowering drugs. We defined diabetes mellitus as nonfasting plasma glucose ≥11.1 mmol/L, fasting glucose ≥7 mmol/L, or use of antidiabetic medication. We excluded patients with atrial fibrillation (n=14) and inadequate image quality for STE (n=4). Hence, a total of 373 patients were included. All patients provided written informed consent, and the study applied to the principles in the second Declaration of Helsinki. Because of the sensitive nature of the data collected for this study, requests to access the data set should be sent to the Danish Ministry of Health, the Danish Data Protection Agency, the Steering Committee of the CCHS (Copenhagen City Heart Study), and the corresponding author. T.B.S. and P.B. have full access to the data and take full responsibility for their integrity and the data analysis.

Echocardiography

Two-dimensional echocardiographic examinations were performed using Vivid 7 equipment with a 3.5-MHz transducer (GE Healthcare, Horten, Norway). Echocardiographic examinations were performed a median of 2 days (interquartile range [IQR], 1–3 days) after the primary PCI. Echocardiograms were stored externally and later analyzed off-line using echocardiographic software (EchoPac 12; GE Medical, Horten, Norway) by a single investigator, who was blinded to all clinical information and end point events (T.B.S.).

Conventional echocardiography

Conventional echocardiography was done at rest and according to contemporary guidelines from the American Society of Echocardiography.[18] In the parasternal long-axis view at the tip of the mitral valve leaflets, LV end-diastolic dimensions were obtained. LV mass was calculated using the Devereux formula, and the LV mass index was obtained by dividing LV mass with the body surface area. Pulsed-wave Doppler was used to measure inflow between the mitral valve leaflets, allowing us to obtain peak velocity of early (E) and atrial (A) diastolic filling and deceleration time. Accordingly, we calculated the E/A ratio. Simpson's biplane method was used to derive LVEF. Color tissue–Doppler imaging loops were obtained from the 3 apical projections, where the peak early diastolic longitudinal mitral annular velocity (e′) was averaged from the 6 mitral annular sites. We then calculated the E/e′ ratio. Furthermore, WMSI was obtained from the 16–myocardial segment model and was available in 95% (n=355). The motion of segments was graded as follows: normal, 1; hypokinesia, 2; akinesia, 3; and dyskinesia, 4.

Speckle tracking echocardiography

Two-dimensional STE was performed in the apical 2-, 3-, and 4-chamber views at an average of 86 frames/s (SD,

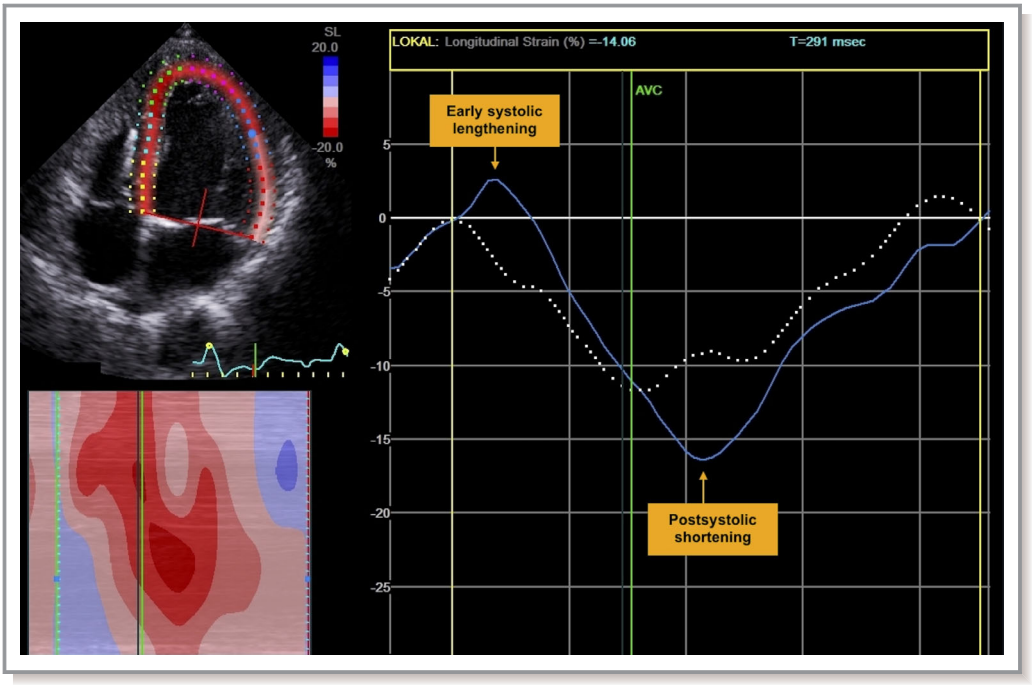

Figure 1. Speckle tracking profile. The blue myocardial wall segment displays early systolic lengthening and postsystolic shortening. AVC indicates aortic valve closure; SL, strain longitudinal.

±23 frames/s), providing longitudinal strain measurements in 18 myocardial segments.[6] In addition, we analyzed circumferential and radial strain at the level of the papillary muscles in the short-axis view. In each view, the responsible investigator defined a region of interest, which allowed the software to automatically track the gray-scale speckles. If the region of interest did not cover the entire myocardial wall or speckles were inadequately visualized, it was manually readjusted to ensure correct tracking. According to software protocol, we adjusted regional and temporal smoothing settings to improve regional fidelity of trackings. In each myocardial segment, we obtained information on ESL duration and longitudinal strain parameters: peak positive systolic strain (indicating maximum systolic lengthening), peak negative systolic strain (indicating maximum systolic shortening), and peak negative strain in the cardiac cycle (describing maximum shortening). We defined ESL duration as time from onset of the Q wave in the QRS complex on the ECG to the time of peak positive systolic strain. If the Q wave was absent, we used the R wave. We assessed a novel myocardial viability index, the ESL index, which was calculated as follows: [−100×(peak positive systolic strain/peak negative strain in cardiac cycle)] (Figure 2). If no systolic lengthening was present, the ESL index was zero, by definition. This index has previously been investigated as the "lengthening/shortening ratio."[16,19] We calculated the postsystolic index, defined as the difference between peak negative systolic strain and peak negative strain in cardiac cycle divided by peak negative strain in cardiac cycle.[20] All of the above-mentioned parameters (including ESL duration and index) were calculated as the average value obtained from all 18 myocardial segments, hence allowing us to obtain a single value for each patient. Circumferential and radial strain were averaged from 6 myocardial segments at the level of the papillary muscles.

Culprit Lesion

The left anterior descending artery was assigned to myocardial segments from the anterior and anteroseptal wall and furthermore the apical and midventricular segments of the septal wall. The right coronary artery was assigned to the inferior wall and the basal segment of the septal wall. The left circumflex artery was assigned to the posterior and lateral wall.[18]

Revascularization

We performed primary PCI with a preassigned treatment regimen that involved 300 mg acetylsalicylic acid, 600 mg clopidogrel, and 10 000 IU of unfractioned heparin. TIMI (Thrombolysis in Myocardial Infarction) flow was obtained before and after revascularization. Treatment during and after hospitalization was in accordance to contemporary guidelines and involved antianginal, antithrombotic, and lipid-lowering medication.

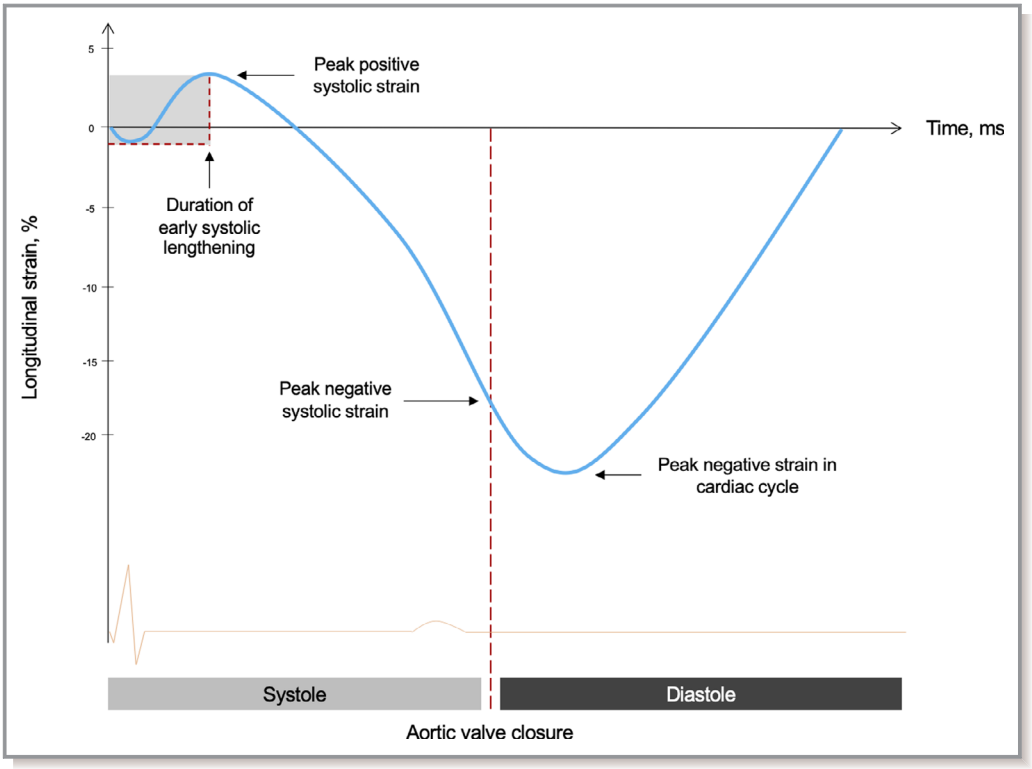

Figure 2. Schematic drawing of early systolic lengthening. During early systole, the strain curve (blue line) displays early systolic lengthening, as indicated by peak positive systolic strain before the aortic valve closure. Duration of early systolic lengthening is indicated on the curve. The ECG is displayed (orange line).

Follow-Up

Data on incident HF and myocardial infarction (MI) were determined from 2 sources by the use of the *International Classification of Diseases, Tenth Revision* (*ICD-10*): (1) review of local medical records and (2) the Danish National Board of Health's National Patient Registry. A recent study reported that the diagnosis of HF in Danish registries had high specificity.[21] All-cause mortality was determined from the National Person Identification Registry. In time to first event analyses, we examined a prespecified end point, major adverse cardiovascular events (MACEs), defined as the composite of incident HF, new MI, and all-cause mortality. Follow-up was 100%.

Statistical Analyses

All statistical analyses were performed using STATA, version 14.2 (StataCorp LP, College Station, TX). Patients were categorized according to tertiles of the ESL index (cutoff, 5.5% and 16%) and ESL duration (cutoff, 24.6 and 40.2 ms). We calculated *P* for trend using linear regression models and Cuzick's nonparametric test for trend. The postsystolic index, ESL index, and ESL duration displayed nongaussian distributions that were successfully converted to a normal distribution using a natural logarithmic transformation. Differences between culprit and nonculprit areas were compared using Wilcoxon signed-rank tests. The same test was used to assess differences in deformational parameters according to wall motion categories of myocardial segments. Differences between groups with gaussian distributed variables were compared using Student *t* test. Correlations between deformational parameters were assessed using Spearman's ρ. Logistic regression models were used to assess associations with preprocedural TIMI flow. These models were prespecified and adjusted for the following: age, sex, hypertension, heart rate, LV mass index, E/e′, and WMSI. Cumulative survival curves were constructed using the Kaplan-Meier method. Prespecified Cox proportional hazard models were used to calculate univariable and multivariable hazard ratios (HRs) that we adjusted as follows: model 1: age, sex, hypertension, and heart rate; and model 2: the same as model 1 and postprocedural TIMI flow, troponin I, LV mass index, E/e′, WMSI, LVEF, and the postsystolic index. Multicollinearity was assessed using Spearman's correlation and variance inflation factors. All values are reported in Table S1, and no variables in the multivariable model 2 exhibited a variance inflation factor >2.1. We also conducted a sensitivity analysis, excluding new MI from the composite end point. Using univariable survival models, Harrel's C-statistic was used to assess the prognostic performance of ESL index, ESL duration, and global

longitudinal strain (GLS), and these variables were compared using the Somers'D method. Unadjusted restricted cubic spline models were constructed to assess the association between ESL index and ESL duration and the incidence of MACEs in Figure 3A and 3B. The number of knots was determined according to the lowest Akaike information criterion value. Reproducibility was assessed using Bland-Altman analyses in 25 randomly selected patients from our laboratory. We regarded $P<0.050$ as significant.

Results

A total of 373 patients were included in the study cohort. More than 90% of the population had a significant stenosis (≥90% luminal narrowing) in ≥1 coronary vessels. The mean±SD WMSI was 1.6±1.4 (range, 1–3), and no patients displayed dyskinetic segments. Median values of the ESL index and ESL duration were 9% (IQR, 4%–28%) and 32 ms (IQR, 21–46 ms), respectively. Patients in the highest tertile of the ESL index were more frequently women, had occluded left anterior descending artery, and presented with higher levels of peak troponin I (Table 1). As well, they had affected echocardiographic parameters in terms of lower LVEF, GLS, and circumferential and radial strain and increased values of LV mass index, WMSI, E/e′, and the postsystolic index. The same characteristics applied to patients in the third tertile of ESL duration (Table S2).

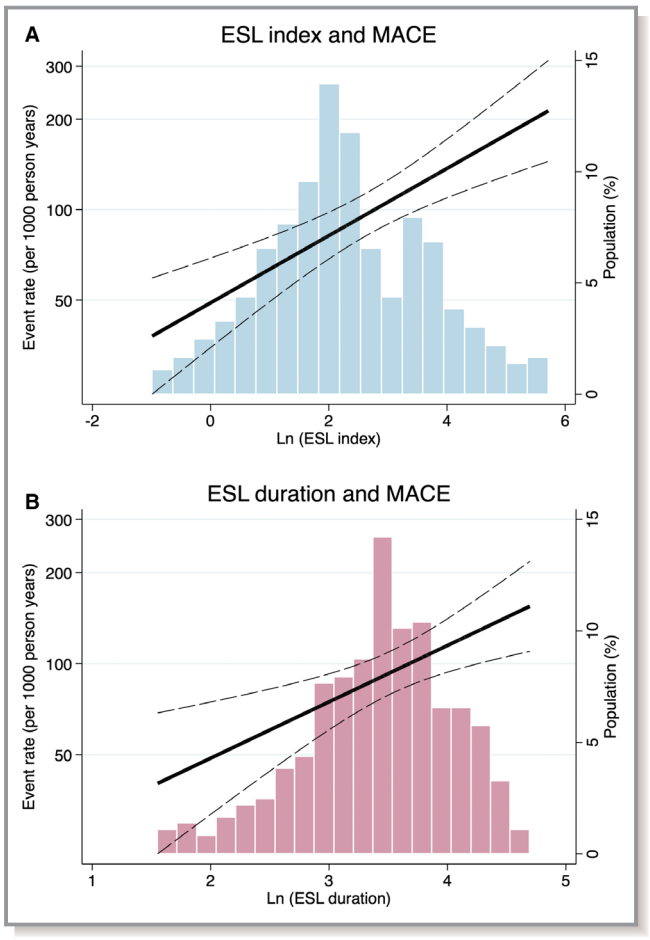

Figure 3. Association between major adverse cardiovascular events (MACEs) and early systolic lengthening. Cubic spline models of the association between MACEs and the early systolic lengthening (ESL) index (**A**) and ESL duration (**B**). Black line indicates the unadjusted incidence rate of MACEs, and dotted lines indicate 95% CIs. Histograms display the distribution of the predictor variable in the population.

Relationship With Deformational Parameters

The ESL index and ESL duration were moderate to highly correlated with both the postsystolic index (ESL index: ρ=0.48, $P<0.0001$; and ESL duration: ρ=0.66, $P<0.0001$) and GLS (ESL index: ρ=0.45, $P<0.0001$; and ESL duration: ρ=0.57, $P<0.0001$). Although significant, the correlations with circumferential (ESL index: ρ=0.23, $P=0.0003$; and ESL duration: ρ=0.26, $P<0.0001$) and radial strain (ESL index: ρ=−0.18, $P=0.004$; and ESL duration: ρ=−0.30, $P<0.0001$) were markedly lower.

Regional Changes

The ESL index and ESL duration were significantly increased in culprit lesion areas compared with nonculprit lesion areas (6.7±6.2% versus 5.0±4.1% and 43±33 ms versus 33±24 ms, respectively; $P<0.001$ for both). Akinetic wall segments had significantly higher values of all examined deformational parameters, including ESL index and ESL duration, compared with normal and hypokinetic segments ($P<0.0001$ for all; Table 2). More important, akinetic segments were more prevalent in the culprit lesion areas (647 versus 420 segments; $P<0.001$). In logistic regression models, we found that the ESL index (odds ratio, 0.79 per 1% increase; 95% CI, 0.68–0.93; $P=0.003$) and duration of ESL (odds ratio, 0.71 per 1-ms increase; 95% CI, 0.51–0.97; $P=0.031$) were associated with low preprocedural TIMI flow. A similar association was found for GLS ($P=0.018$). However, in the adjusted model only, the ESL index remained a significant predictor of low TIMI flow before revascularization (odds ratio, 0.83 per 1% increase; 95% CI, 0.70–0.99; $P=0.044$).

Prognostic Value

During a median follow-up time of 5.3 years (IQR, 2.5–6.0 years), 145 patients (39%) reached the composite end point, MACE: 69 had incident HF, 51 experienced MI, and 59 died. The ESL index (HR, 1.27 per 1% increase; 95% CI, 1.13–1.43; $P<0.001$) and ESL duration (HR, 1.49 per 1-ms increase; 95% CI, 1.15–1.92; $P=0.002$) were significantly associated with

Table 1. Baseline Characteristics According to Tertiles of ESL Index

Characteristics	ESL Index			*P* Value
	First Tertile (<5.4%) (n=125)	Second Tertile (5.5%–15.9%) (n=124)	Third Tertile (>16.0%) (n=124)	
Clinical				
Age, y	63±11	61±12	63±11	0.701
Men, n (%)	97 (77.6)	96 (77.4)	87 (70.2)	0.176
Hypertension, n (%)	40 (32.0)	39 (31.5)	40 (32.3)	0.966
Smoking status, n (%)				0.940
Present	59 (47.2)	66 (53.2)	56 (45.2)	
Never	24 (19.2)	18 (14.5)	16 (12.9)	
Previous	32 (25.6)	34 (27.4)	38 (30.6)	
Mean arterial pressure, mm Hg	96.7±18.9	100.8±18.5	101.5±18.3	0.044
Heart rate, bpm	75.1±56.1	73.9±14.9	79.7±15.5	0.304
Diabetes mellitus, n (%)	10 (8.0)	10 (8.1)	12 (9.7)	0.638
eGFR, mL/min per 1.73 m^2	73.5 (61.2–87.6)	73.0 (59.1–85.1)	73.7 (60.2–86.0)	0.870
Peak TnI, μg/L	52 (20–177)	117 (35–216)	203 (56–313)	<0.001
Invasive procedure				
Symptom to balloon, min	245.0±206.2	233.3±177.8	280.1±196.7	0.155
Location of stenosis, n (%)				<0.001
Left anterior descending artery	46 (37.1)	55 (44.4)	77 (62.1)	
Right circumflex artery	64 (51.6)	53 (42.7)	36 (29.0)	
Left circumflex artery	14 (11.3)	16 (12.9)	11 (8.9)	
TIMI flow before PCI, n (%)				<0.001
0–1	82 (65.2)	90 (72.5)	107 (86.3)	
2–3	42 (33.6)	33 (26.6)	17 (13.7)	
TIMI flow after PCI, n (%)				0.970
0–1	12 (9.6)	6 (4.8)	12 (9.7)	
2–3	111 (88.8)	116 (93.5)	109 (87.9)	
Echocardiography				
LV ejection fraction, %	47.6±9.1	46.5±7.9	43.3±9.7	<0.001
LV mass index, g/m^2	85.4 (68.9–103.9)	91.8 (78.2–110.8)	92.8 (78.0–113.5)	0.008
Wall motion score index	1.5±0.4	1.5±0.4	1.8±0.4	<0.001
E, cm/s	8.0±2.1	7.7±1.7	7.4±1.9	0.014
A, cm/s	7.4±1.8	7.5±2.1	7.5±2.1	0.610
e′, cm/s	0.8±0.2	0.7±0.2	0.7±0.2	<0.001
E/e′ ratio	10.5±3.9	11.2±3.4	11.9±5.0	0.007
Left atrial volume index, mL/m^2	25.0±7.1	24.9±6.9	24.0±6.6	0.274
Global longitudinal strain, %	−14.4±3.7	−12.2±3.1	−10.5±3.2	<0.001
Circumferential strain, %	−16.2±5.3	−16.1±6.2	−13.1±4.6	<0.001
Radial strain, %	32.6±21.4	25.4±18.1	22.1±14.3	<0.001
Postsystolic index, %	8.2 (4.3–18.7)	15.2 (10.2–22.9)	27.6 (17.4–41.3)	<0.001
ESL index, %	2.5 (1.4–3.9)	8.8 (7.1–11.4)	41.5 (27.9–77.2)	<0.001
ESL duration, ms	20.8 (11.0–30.4)	30.6 (21.6–42.1)	46.6 (33.5–63.3)	<0.001

Continued

Table 1. Continued

Characteristics	ESL Index			*P* Value
	First Tertile (<5.4%) (n=125)	Second Tertile (5.5%–15.9%) (n=124)	Third Tertile (>16.0%) (n=124)	
Outcome				
MACE, n (%)	36 (28.8)	45 (36.3)	64 (51.6)	<0.001

Data are given as mean±SD, unless otherwise indicated. Nongaussian distributed variables are listed as median (interquartile range). *P* values were assessed as *P* for trend by the use of linear regression models and Cuzick's nonparametric test for trend. A, transmitral peak velocity of atrial diastolic filling; bpm, beats per minute; E, transmitral peak velocity of early diastolic filling; e′, average peak early diastolic longitudinal mitral annular velocity; eGFR, estimated glomerular filtration rate; ESL, early systolic lengthening; LV, left ventricular; MACE, major adverse cardiovascular event; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; TnI, troponin I.

MACEs (Table 3; Figure 3A and 3B). In the fully adjusted model, both the ESL index (HR, 1.21 per 1% increase; 95% CI, 1.06–1.39; *P*=0.007) and ESL duration (HR, 1.63 per 1-ms increase; 95% CI, 1.12–2.36; *P*=0.010) remained predictors of MACEs. In sensitivity analyses, excluding new MI from the end point, all results remained significant (Table S3). When assessing the 1-year prognostic value, all associations with MACEs remained significant and the HRs increased (Table 4).

The risk of MACEs increased incrementally with increasing tertiles of the ESL index (HR, 1.53 per 1-tertile increase; 95% CI, 1.24–1.88; *P*<0.001) and ESL duration (HR, 1.61 per 1-tertile increase; 95% CI, 1.31–1.97; *P*<0.001). The highest tertile of the ESL index (Figure 4A) and ESL duration (Figure 4B) yielded the highest risk of MACEs, and both associations remained significant throughout multivariable models (Table S4). Tertiles of both parameters remained significant predictors of MACEs when assessing the 1-year prognostic value (Table S5).

No difference in terms of C-statistics was observed between ESL index (C-statistic, 0.62; 95% CI, 0.56–0.67) and ESL duration (C-statistic, 0.59; 95% CI, 0.54–0.64) versus GLS (C-statistic, 0.64; 95% CI, 0.58–0.69) or WMSI (C-statistic, 0.65; 95% CI, 0.61–0.70) (*P* difference >0.050 for all).

Reproducibility

Reproducibility analyses showed only little bias for the ESL index (mean difference, ±1.96 SDs was 0.07±1.58% for intraobserver variability and 0.02±1.56% for interobserver variability). The reproducibility was lower for ESL duration (2.47±6.28 ms for intraobserver variability and −1.50±9.23 ms for interobserver variability). Bland-Altman plots are shown in Figure S1A through S1D.

Discussion

In the present study, we introduce the ESL index and duration of ESL, assessed by STE, as novel and independent predictors of long-term cardiovascular events in patents with STEMI treated with primary PCI. Despite cardiovascular events mainly occur within the first month after primary revascularization, patients with STEMI still face a substantial risk of long-term cardiovascular events.[1,2,4,22] Registry data have indicated that the relative risk of cardiac events is 30% higher compared with the general population, suggesting prolonged surveillance and novel tools for risk stratification.[3]

The rationale for investigating ESL as a prognostic marker is that the degree of passive movement in the myocardium is correlated with the extent of future scarring tissue.[16,23] Ischemic, but viable, myocardial segments have a reduced ability to generate active force compared with nonischemic myocardial segments and, therefore, exhibit reduced systolic strain. By contrast, ischemic segments with no viable components remain passive throughout the cardiac cycle. When the LV pressure increases, these segments undergo passive lengthening during the early systole, referred to as

Table 2. Distribution of the ESL Index and ESL Duration According to Normal, Hypokinetic, and Akinetic Segments, Assessed by Wall Motion Scoring

Variable	Normal Segments	Hypokinetic Segments	Akinetic Segments
ESL index (%), median (IQR)	3.2 (1.3–7.8)	6.0 (1.2–19.0)*	16.6 (3.4–47.7)*†
ESL duration (ms), median (IQR)	20.3 (10.1–34.9)	32.2 (12.3–51.0)*	51.3 (29.0–73.8)*†
Postsystolic index (%), median (IQR)	7.5 (3.9–13.9)	15.8 (6.9–29.3)*	39.7 (19.7–71.4)*†
Global longitudinal strain (%), median (IQR)	15.9 (13.5–18.0)	12.3 (10.0–14.5)*	9.5 (7.0–11.7)*†

ESL indicates early systolic lengthening; IQR, interquartile range.
**P* difference <0.0001 when compared with normal segments.
†P difference <0.0001 when compared with hypokinetic segments.

Table 3. ESL Index and ESL Duration as Predictors of MACEs

Risk of MACE	ESL Index per 1% Increase, HR (95% CI)	*P* Value	ESL Duration per 1-ms Increase, HR (95% CI)	*P* Value
Unadjusted	1.27 (1.13–1.43)	<0.001	1.49 (1.15–1.92)	0.002
	C-statistic, 0.62		C-statistic, 0.59	
Model 1*	1.29 (1.15–1.44)	<0.001	1.47 (1.14–1.89)	0.003
Model 2†	1.21 (1.06–1.39)	0.007	1.63 (1.12–2.36)	0.010

ESL indicates early systolic lengthening; HR, hazard ratio; MACE, major adverse cardiovascular event.
*Model 1 adjusted for age, sex, hypertension, and heart rate.
†Model 2 adjusted for model 1 and TIMI (Thrombolysis in Myocardial Infarction) flow, peak troponin I, left ventricular mass index, left ventricular ejection fraction, ratio between peak transmitral early diastolic inflow velocity and average peak early diastolic mitral annular velocity, wall motion score index, and postsystolic index.

ESL.[19] The role of ESL as marker of viability was examined in a study of patients with acute MI, in whom ESL duration was able to reliably differentiate between viable and nonviable segments with a sensitivity and specificity >90%.[16] A similar finding was done by Kahyaoglu et al,[24] who suggested that ESL may be useful for identifying ischemic but viable myocardial tissue.

Only few studies have investigated ESL in patients with cardiac ischemia. Zahid et al investigated patients with non-STEMI and found that among echocardiographic parameters (ESL, LVEF, GLS, and WMSI), ESL duration had the best accuracy for detecting minimal myocardial damage determined by magnetic resonance imaging.[23] We found that regions supplied by a culprit vessel had significantly increased ESL index and ESL duration compared with nonculprit regions ($P<0.001$) and that akinetic segments also displayed significantly higher values of both ESL parameters. As expected, akinetic segments were more prevalent in culprit lesion areas ($P<0.001$). These findings suggest ESL is a phenomenon that occurs in ischemic myocardial segments with a reduced contractile function.

Smedsrud et al studied patients with suspected coronary artery disease referred for coronary angiography and showed that duration of ESL, assessed by tissue-Doppler imaging, was significantly prolonged in patients with significant coronary artery disease (76 ms versus 38 ms).[15] By contrast, the median ESL duration in the present study was markedly lower (median, 32 ms). This could potentially be accounted for by differences in choice of modality (TDI versus STE) and timing of assessment of ESL, as ESL has been shown to decrease over time after ischemic events. We showed that the ESL index was an independent predictor of low TIMI flow assessed before revascularization. Considering that preprocedural TIMI flow has been associated with greater risk of transmural infarcts and increased infarct size,[25,26] this strengthens ESL as a phenomenon related to ischemic changes and, potentially, also a marker of the ischemic burden. Consequently, a greater amount of ischemic damage may lead to reduced regional contractility of the LV, hence explaining why ESL provides prognostic information on future cardiovascular events.

More important, we found that patients with the lowest risk of MACEs still had increased values of ESL index (range of first tertile, 0–5.4%) and prolonged ESL duration (range of first tertile, 0–24.5 ms). In both of the first tertiles, LVEF remained within normal range, and although the average GLS was reduced, some patients still displayed GLS >18%. This suggests that ESL may represent a novel and sensitive measure of subclinical LV damage. As Lyseggen and colleagues have suggested, the small amount of ESL in the

Table 4. Prognostic Value of the ESL Index and ESL Duration as Predictors of MACEs at 1 Year

1-y Risk of MACEs	ESL Index per 1% Increase, HR (95% CI)	*P* Value	ESL Duration per 1-ms Increase, HR (95% CI)	*P* Value
Unadjusted	1.51 (1.26–1.82)	<0.001	1.87 (1.22–2.88)	0.004
	C-statistic, 0.66		C-statistic, 0.62	
Model 1*	1.51 (1.26–1.82)	<0.001	1.96 (1.26–3.04)	0.003
Model 2†	1.42 (1.10–1.83)	0.006	2.40 (1.19–4.86)	0.014

ESL indicates early systolic lengthening; HR, hazard ratio; MACE, major adverse cardiovascular event.
*Model 1 adjusted for age, sex, hypertension, and heart rate.
†Model 2 adjusted for model 1 and TIMI (Thrombolysis in Myocardial Infarction) flow, peak troponin I, left ventricular mass index, left ventricular ejection fraction, ratio between peak transmitral early diastolic inflow velocity and average peak early diastolic mitral annular velocity, wall motion score index, and postsystolic index.

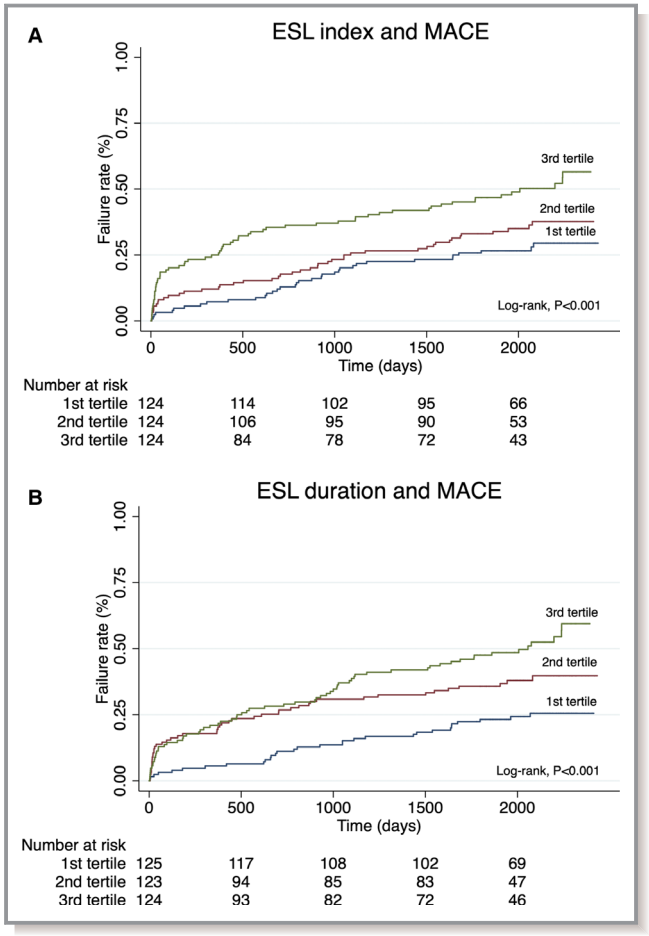

Figure 4. Survival curves of the end point, according to tertiles of early systolic lengthening (ESL). Kaplan-Meier curves displaying the risk of major adverse cardiovascular events (MACEs), according to tertiles of the ESL index (**A**) and ESL duration (**B**). Log-rank values are displayed.

first tertiles could be caused by the "tug-of-war" effect, in which LV segments with different rates of force development exhibit ESL.[27,28]

Our results indicate that assessment of ESL, after revascularization in patients with STEMI, might constitute a useful tool to identify, and potentially also quantify, ischemic changes and obtain prognostic information. In particular, the highest tertiles of the ESL index (cutoff, 16%) and ESL duration (cutoff, 40 ms) were significant and independent predictors of the composite end point. Although ESL was not superior to GLS or WMSI, it could potentially complement these parameters in risk stratification of patients after myocardial ischemia. With reference to Zahid et al,[23] some of the first signs from small myocardial infarcts may lead to occurrence of ESL, even when conventional echocardiographic parameters are preserved. On a hypothesis-generating basis, identification of ESL could strengthen the suspicion of myocardial ischemia in patients with chest pain and facilitate more rapid intervention; however, this should be confirmed in future studies. Information on ESL is quick and easily obtained in a clinical setting by STE and could be implemented in the routine management and risk stratification after revascularization. As well, we found that the reproducibility of the ESL index was good with only little bias, whereas ESL duration had lower reproducibility, a finding in line with that of Minamisawa et al.[29] More important, the present results indicating that ESL may useful for risk stratification should be validated and confirmed in larger and future cohorts.

Strengths and Limitations

As this was a prospective study, we applied a rigorous study design to lower the risk of unmeasured confounders and to create a homogeneous population of patients with STEMI. Assessment of ESL parameters is dependent on resolution of the echocardiographic images. Our resolution was 12 ms; and considering the median duration of ESL was 23 ms (IQR, 21–46 ms), the resolution should be sufficient. Had we used TDI to assess ESL, we would have attained a much higher temporal resolution, potentially reducing the impact of resolution on ESL measures; however, our results would have been influenced by angle dependency. Unfortunately, data on ESL obtained by TDI were not available. Considering ESL is a short-lived event with minor magnitude, the use of older software could have affected our trackings. We performed the echocardiographic examination a median of 2 days after revascularization. Systolic dysfunction may not be fully manifested during this period; and measurements of ESL are known to change after ischemic events, which could have impacted the estimated values of ESL.[30] Assignment of the right coronary artery and left circumflex artery to predetermined myocardial segments may be influenced by coronary dominance. As HF was a part of the composite end point, it is a major limitation that we did not assess the Killip classification[31] and hence could not examine the relationship of the Killip classification with the ESL index/duration of ESL at the time of echocardiography. Unfortunately, we had no information available to compare the predictive value of ESL with ECG criteria, such as ventricular ectopy or autonomic criteria.[32,33] Similarly, it remains unknown if interventricular conduction disturbances may affect the occurrence of this phenomenon. We performed STE in an 18-segment model, which may result in an overweighting of the apical region.[6]

Conclusions

Assessment of ESL after primary PCI in patients with STEMI was associated with regional myocardial changes and provided independent prognostic information on the future risk of MACEs.

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Disclosures

None.

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Supplemental Material

Table S1. Variance inflation factors for covariates.

Variable	Variance inflation factor	Tolerance
Age	1.16	0.86
Sex	1.15	0.87
Hypertension	1.16	0.86
Heart rate	1.13	0.88
Postprocedural TIMI flow	1.10	0.91
TnI	1.23	0.81
LVMI	1.23	0.81
E/e’	1.36	0.74
WMSI	2.08	0.48
LVEF	1.48	0.68
Postsystolic index	1.39	0.72

TnI: troponin I, LVMI: left ventricular mass index, LVEF: left ventricular ejection fraction, E/e’: ratio between peak transmitral early diastolic inflow velocity and average peak early diastolic mitral annular velocity, WMSI: wall motion score index

Table S2. Baseline characteristics according to tertiles of duration of early systolic lengthening.

ESL duration	1st tertile (n=125)	2nd tertile (n=124)	3rd tertile (n=124)	P-value
	[<24.5ms]	[24.6-40.1ms]	[>40.2ms]	
Clinical				
Age, years	62 ± 11	61 ± 12	64 ± 11	0.105
Male, n(%)	103 (82.4%)	96 (77.4%)	81 (65.3%)	0.002
Hypertension, n(%)	33 (26.4%)	42 (33.9%)	44 (35.5%)	0.124
Smoking status, n(%)				0.240
Present	70 (56.0%)	47 (37.9%)	64 (51.6%)	
Never	21 (16.8%)	22 (17.7%)	15 (12.1%)	
Previous	25 (20.0%)	42 (33.9%)	37 (29.8%)	
Mean arterial pressure, mmHg	98.8 ± 18.2	97.8 ± 18.3	102.5 ± 19.2	0.112
Heart rate, bpm	76.8 ± 56.3	74.8 ± 14.5	77.1 ± 15.8	0.945
Diabetes, n(%)	11 (8.8%)	6 (4.8%)	15 (12.1%)	0.357
eGFR, mL/min/1.73m^2	73.3 [61.6, 85.7]	75.5 [62.6, 89.4]	70.8 [55.8, 84.5]	0.247
Peak TnI, µg/L	54 [21, 160]	140 [40, 259]	163 [43, 268]	<0.001
Invasive procedure				
Symptom to balloon, min	244.2 ± 195.7	252.9 ± 212.5	261.4 ± 174.5	0.488
Location of stenosis, n(%)				0.046
Left anterior descending artery	47 (37.6%)	64 (51.6%)	67 (54.5%)	
Right circumflex artery	67 (53.6%)	45 (36.3%)	41 (33.3%)	
Left circumflex artery	11 (8.8%)	15 (12.1%)	15 (12.2%)	
TIMI flow before PCI, n(%)				0.012
0-1	84 (67%)	94 (76%)	101 (81%)	
2-3	40 (32%)	29 (23%)	23 (19%)	
TIMI flow after PCI, n(%)				0.009
0-1	6 (5%)	7 (6%)	17 (14%)	
2-3	117 (94%)	115 (93%)	104 (84%)	
Echocardiography				
LV ejection fraction, %	48.6 ± 8.6	45.6 ± 8.3	43.2 ± 9.5	<0.001
LV mass index, g/m^2	85.1 [70.5, 99.3]	95.4 [78.5, 113.0]	92.1 [76.2, 113.0]	0.010
Wall motion score index	1.4 ± 0.3	1.6 ± 0.4	1.8 ± 0.4	<0.001
E, cm/s	8.0 ± 1.8	7.8 ± 2.1	7.3 ± 1.8	0.003
A, cm/s	7.3 ± 1.9	7.6 ± 2.2	7.4 ± 2.0	0.889
e', cm/s	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	<0.001
E/e' ratio	10.3 ± 3.7	11.4 ± 3.7	11.9 ± 4.9	0.003
Left atrial volume index, mL/m^2	24.2 ± 6.7	25.6 ± 7.3	24.1 ± 6.4	0.895
Global longitudinal strain, %	-14.8 ± 3.4	-12.2 ± 3.0	-10.1 ± 3.0	<0.001
Circumferential strain, %	-17.5 ± 5.9	-14.4 ± 5.3	-13.3 ± 4.7	<0.001
Radial strain, %	33.8 ± 20.9	24.0 ± 16.8	21.1 ± 14.8	<0.001
Postsystolic index, %	8.6 [4.4, 13.5]	17.7 [10.6, 25.9]	33.1 [22.3, 56.3]	<0.001
ESL index, %	3.6 [1.8, 7.6]	9.3 [5.5, 22.7]	26.6 [9.6, 47.1]	<0.001
ESL duration, ms	17.1 [10.9, 20.6]	31.8 [29.0, 35.6]	57.2 [46.5, 72.2]	<0.001
Outcome				
MACEs, n(%)	32 (25.6%)	47 (37.9%)	66 (53.2%)	<0.001

ESL: early systolic lengthening, eGFR: estimated glomerular filtration rate, TnI: troponin I, TIMI: Thrombolysis In Myocardial Infarction, PCI: percutaneous coronary intervention; LV: left ventricle, E: peak transmitral early diastolic inflow velocity, A: peak transmitral late diastolic inflow velocity, e': average peak early diastolic mitral annular velocity, MACEs: major adverse cardiovascular events. Non-gaussian distributed variables are listed as median [interquartile range].

Table S3. Sensitivity analysis of the ESL index and ESL duration as predictors of a composite endpoint including only heart failure and all-cause mortality. Both parameters are assessed continuously.

Risk of MACE (heart failure and all-cause mortality)	**ESL index** Per 1% increase HR (95%CI)	P-value	**ESL duration** Per 1ms increase HR (95%CI)	P-value
Unadjusted	1.29 (1.13-1.43)	<0.001	1.54 (1.15-2.06)	0.004
Model 1*	1.29 (1.14-1.47)	<0.001	1.50 (1.13-2.00)	0.005
Model 2†	1.18 (1.01-1.39)	0.036	1.62 (1.06-2.47)	0.026

*Model 1 adjusted for age, sex, hypertension and heart rate.

†Model 2 adjusted for model 1 and TIMI-flow, peak TnI, LVMI, LVEF, E/e', WMSI and postsystolic index

ESL: early systolic lengthening, MACE: major adverse cardiovascular events, HR: hazard ratio, TnI: troponin I, LVMI: left ventricular mass index, LVEF: left ventricular ejection fraction, E/e': ratio between peak transmitral early diastolic inflow velocity and average peak early diastolic mitral annular velocity, WMSI: wall motion score index

Table S4. Tertiles of the ESL index and ESL duration as predictors of major adverse cardiovascular events.

ESL index	MACE HR (95%CI)	P-value	**ESL duration**	MACE HR (95%CI)	P-value
Unadjusted			Unadjusted		
1st tertile	Ref.		1st tertile	Ref.	
2nd tertile	1.36 (0.87-2.11)	0.174	2nd tertile	1.83 (1.16-2.88)	0.009
3rd tertile	2.29 (1.51-3.45)	<0.001	3rd tertile	2.66 (1.74-4.08)	<0.001
Model 1*			Model 1*		
1st tertile	Ref.		1st tertile	Ref.	
2nd tertile	1.47 (0.94-2.29)	0.089	2nd tertile	1.85 (1.18-2.92)	0.008
3rd tertile	2.36 (1.56-3.58)	<0.001	3rd tertile	2.65 (1.72-4.10)	<0.001
Model 2†			Model 2†		
1st tertile	Ref.		1st tertile	Ref.	
2nd tertile	1.17 (0.71-1.93)	0.540	2nd tertile	1.80 (1.08-3.00)	0.023
3rd tertile	1.90 (1.16-3.11)	0.011	3rd tertile	2.78 (1.61-4.80)	<0.001

*Model 1 adjusted for age, sex, hypertension and heart rate.

†Model 2 adjusted for model 1 and TIMI-flow, peak TnI, LVMI, LVEF, E/e', WMSI and postsystolic index

ESL: early systolic lengthening, MACE: major adverse cardiovascular events, HR: hazard ratio, TnI: troponin I, LVMI: left ventricular mass index, LVEF: left ventricular ejection fraction, E/e': ratio between peak transmitral early diastolic inflow velocity and average peak early diastolic mitral annular velocity, WMSI: wall motion score index

Table S5. One-year prognostic value for tertiles of the ESL index and ESL duration as predictors of major adverse cardiovascular events.

ESL index	1-year risk of MACE HR (95%CI)	P-value	**ESL duration**	1-year risk of MACE HR (95%CI)	P-value
Unadjusted			Unadjusted		
1st tertile	Ref.		1st tertile	Ref.	
2nd tertile	1.73 (0.76-3.96)	0.193	2nd tertile	3.48 (1.49-8.15)	0.004
3rd tertile	3.83 (1.83-8.06)	<0.001	3rd tertile	4.03 (1.75-9.29)	0.001
Model 1*			Model 1*		
1st tertile	Ref.		1st tertile	Ref.	
2nd tertile	1.79 (0.78-4.10)	0.166	2nd tertile	3.66 (1.56-8.59)	0.003
3rd tertile	3.87 (1.84-8.15)	<0.001	3rd tertile	4.25 (1.83-9.87)	0.001
Model 2†			Model 2†		
1st tertile	Ref.		1st tertile	Ref.	
2nd tertile	1.38 (0.54-3.55)	0.475	2nd tertile	3.10 (1.22-7.92)	0.018
3rd tertile	2.59 (1.07-6.23)	0.034	3rd tertile	3.77 (1.28-11.13)	0.016

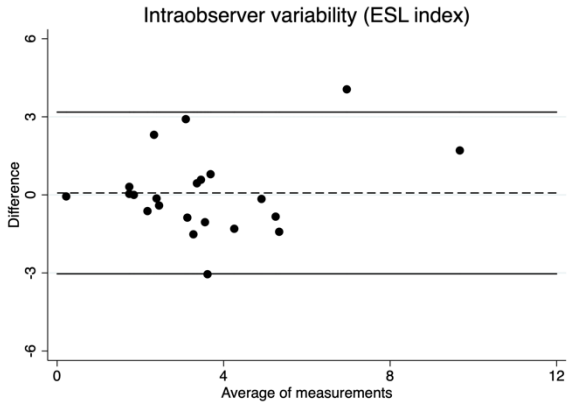
*Model 1 adjusted for age, sex, hypertension and heart rate.

†Model 2 adjusted for model 1 and TIMI-flow, peak TnI, LVMI, LVEF, E/e', WMSI and postsystolic index

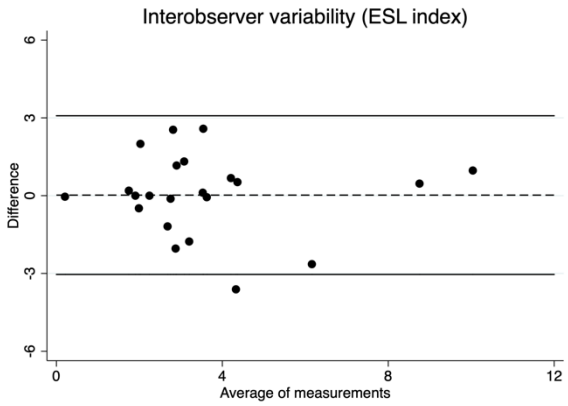
ESL: early systolic lengthening, MACE: major adverse cardiovascular events, HR: hazard ratio, TnI: troponin I, LVMI: left ventricular mass index, LVEF: left ventricular ejection fraction, E/e': ratio between peak transmitral early diastolic inflow velocity and average peak early diastolic mitral annular velocity, WMSI: wall motion score index

Figure S1. Bland-Altman analyses.
(A) Intraobserver variability for the ESL index.
(B) Interobserver variability for the ESL index.
(C) Intraobserver variability for ESL duration.
(D) Interobserver variability for ESL duration.

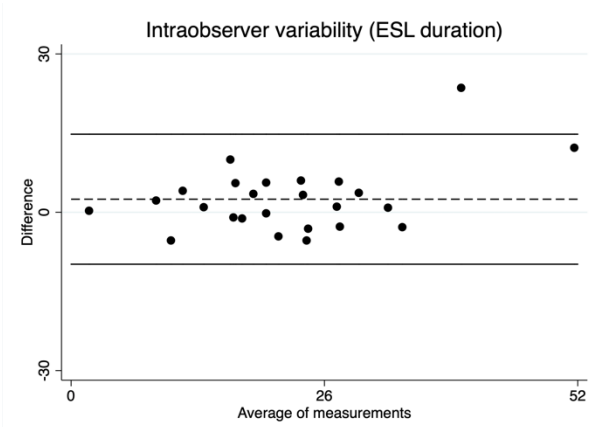
(A)



(B)



(C)



(D)