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ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2023) **00**, 1–9
https://doi.org/10.1093/ehjci/jead117

ORIGINAL PAPER

Association of left ventricular strain–volume loop characteristics with adverse events in patients with heart failure with preserved ejection fraction

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Received 15 March 2023; revised 24 April 2023; accepted 15 May 2023

Aims Patients with heart failure with preserved ejection fraction (HFpEF) are characterized by impaired diastolic function. Left ventricular (LV) strain–volume loops (SVL) represent the relation between strain and volume during the cardiac cycle and provide insight into systolic and diastolic function characteristics. In this study, we examined the association of SVL parameters and adverse events in HFpEF.

Methods and results In 235 patients diagnosed with HFpEF, LV-SVL were constructed based on echocardiography images. The endpoint was a composite of all-cause mortality and Heart Failure (HF)-related hospitalization, which was extracted from electronic medical records. Cox-regression analysis was used to assess the association of SVL parameters and the composite endpoint, while adjusting for age, sex, and NYHA class. HFpEF patients (72.3% female) were 75.8 ± 6.9 years old, had a BMI of 29.9 ± 5.4 kg/m^2, and a left ventricular ejection fraction of 60.3 ± 7.0%. Across 2.9 years (1.8–4.1) of follow-up, 73 Patients (31%) experienced an event. Early diastolic slope was significantly associated with adverse events [second quartile vs. first quartile: adjusted hazards ratio (HR) 0.42 (95%CI 0.20–0.88)] after adjusting for age, sex, and NYHA class. The association between LV peak strain and adverse events disappeared upon correction for potential confounders [adjusted HR 1.02 (95% CI 0.96–1.08)].

Conclusion Early diastolic slope, representing the relationship between changes in LV volume and strain during early diastole, but not other SVL-parameters, was associated with adverse events in patients with HFpEF during 2.9 years of follow-up.

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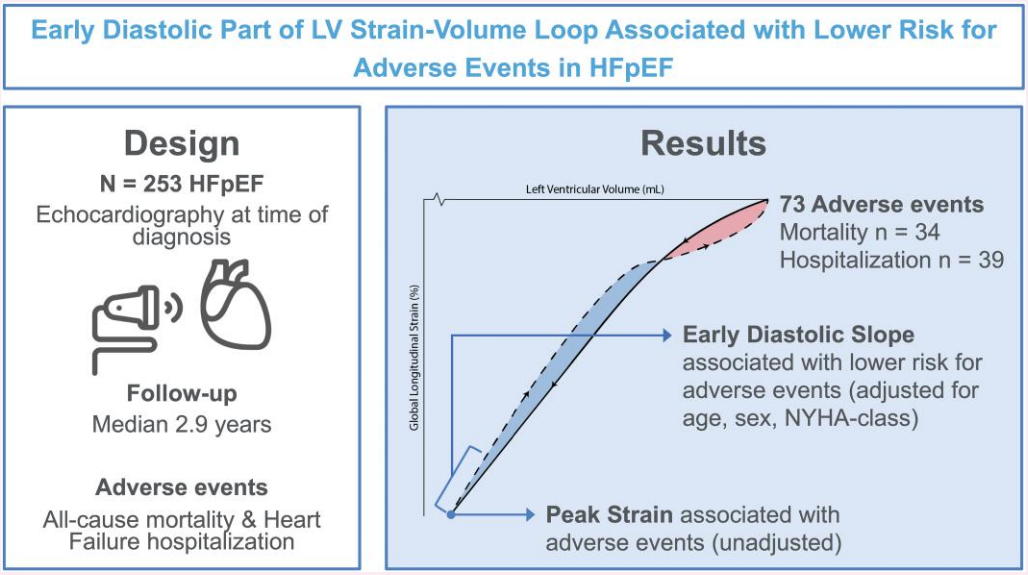
Graphical Abstract



Keywords strain–volume loop • HFpEF • survival • all-cause mortality • heart failure hospitalization

Introduction

Heart failure (HF) affects over 64 million people worldwide and is associated with high morbidity and mortality rates.[1,2] Traditionally, HF was diagnosed following an impaired ability of the left ventricle (LV) to eject blood into the systemic circulation, assessed by the ejection fraction. However, HF can also be present with preservation of LV ejection fraction, i.e. HF with preserved ejection fraction (HFpEF).[3] It is estimated that prevalence of HFpEF equals that of HF with reduced EF (HFrEF), with both groups of HF patients demonstrating comparable prognosis.[4] Nonetheless, therapeutic and diagnostic options for HFpEF patients are limited.[3,5,6] Studies exploring the mechanisms in patients with HFpEF have specifically focused on the diastolic phase and left atrial function.[7–10] Additionally, there is evidence that diastolic dysfunction and elevated LV filling pressure are a cornerstone in the diagnosis of HFpEF.[1,11] Moreover, elevated LV filling pressure is independently associated with worse clinical outcomes in HFpEF,[12] highlighting the central role of diastolic (dys)function in HFpEF disease progression and associated health outcomes.

Studies adopting echocardiography have increasingly used measures of LV peak global longitudinal strain (GLS) and revealed its potential to independently predict outcomes in HFrEF patients.[13] Previously, we have introduced the strain(ε)–volume loop (SVL), which not only examines peak strain, but allows for evaluation of the dynamic relation between changes in LV volume and GLS across the cardiac cycle.[14–18] SVL is sensitive to detect changes in systolic and diastolic function when manipulating pre- and afterload,[19] can detect cardiac abnormalities,[14,20] and, most importantly, has potential to aid risk stratification in patient populations.[15,21] To expand on these observations, the present study investigated whether LV-SVL parameters are associated with adverse events (all-cause mortality and HF hospitalization) in HFpEF patients during follow-up. Based on our earlier work,[15,21] we hypothesized that, independent of existing and established cardiovascular risk factors (e.g. age, New York Heart Association (NYHA)-class), left ventricular SVL parameters are associated with clinically relevant outcomes in HFpEF.

Methods

Study design and population

In this prospective cohort study, patients who were referred to the outpatient HFpEF clinic at the Maastricht University Medical Centre between January 2015 and July 2019 were included.[22] Patients underwent a diagnostic work-up at baseline, and HFpEF was diagnosed based on the European Society of Cardiology HF guidelines (2016) by consensus of a panel of experienced HF cardiologists, as described earlier.[22,23] We excluded patients with insufficient echocardiography image quality according to a standardized procedure including poor myocardial wall visibility or traceability during the cardiac cycle in more than two segments in a single view, or a too low frame rate (<50 frames per second). Additionally, individual SVL plots were manually assessed, blinded from other results, to detect non-physiological errors in temporal volume tracking, which were excluded from analysis. Patients provided written informed consent, and the cohort complies with the Declaration of Helsinki. The Medical Ethics Review Committee of the Maastricht University Medical Center approved the initial cohort study (NL69779.068.18).

Transthoracic echocardiography and strain analyses

Echocardiography was performed as part of clinical routine according to guideline recommendations[24] and was analysed with speckle-tracking echocardiography, as described in detail earlier.[8] Briefly, temporal LV GLS on 2D echocardiographic cine-loops was obtained by manual endocardial and myocardial tracing of the apical two-, three-, and four-chamber views according to current consensus recommendations using dedicated speckle-tracking method (TomTec, 2D Cardiac Performance Analysis v1.4, ImageArena v4.6).[25] All investigators were blinded to all other clinical data.

Strain(ε)–volume loop analysis

Temporal myocardial GLS values and temporal LV volume values were exported from the dedicated software (2D Cardiac Performance Analysis

v1.4, Image Arena v4.6). LV Volume and GLS have been shown to be reproducible measurements.[24,26,27] Moreover, when combining both measures into the SVL, previous work showed good reproducibility for the SVL characteristics.[14,21] Using an in-house-developed MATLAB script (The MathWorks Inc, version 2019a, Massachusetts, USA), we imported the temporal volume and GLS values to construct the SVL adapted from earlier work by our lab.[14,28] Firstly, markers for end diastole and end systole were adjusted based on the maximum and minimum of the LV volume curve, respectively.[25] Secondly, 300-point cubic spline interpolations were applied to both the systolic and diastolic parts of the curves to obtain equidistant sampling for subsequent analysis. The longitudinal strain–volume relationship was assessed using the following parameters (*Figure 1*): (a) early systolic slope during the first 5% of volume ejection (ES slope), (b) strain(ε)–volume slope during systole (S slope), (c) end-systolic GLS (peak strain), (d) strain(ε)–volume slope during the first 5% of volume increase (ED slope) and (e) last 5% of volume increase (LD slope) during diastole. Slopes were calculated using a least-squares fit method for the entirety of the defined segments. Furthermore, (f) uncoupling (UNCOUP) is defined as the average difference in strain between systole and diastole (systolic strain–diastolic strain) for any given volume within the stroke volume. Uncoupling was divided in uncoupling during the lower two-thirds of the stroke volume and the final third of stroke volume, i.e. (g) early (UNCOUP ED) and (h) late (UNCOUP LD) uncoupling.[14,29] In line with recommendations, all references to strain increase or decrease apply to the absolute value of strain.[25]

Clinical outcome

The composite endpoint was defined as all-cause mortality or HF hospitalization. Events during follow-up were assessed using electronic medical records and municipality records, which were reviewed through September 2021. Patients were censored on the last day of follow-up if lost-to-follow-up occurred before the event of interest.

Statistical analysis

Statistical analysis was performed using R version 4.0.4.[30] All parameters were visually inspected for normality using histograms, Q–Q plots, and the Shapiro–Wilk test and compared between the groups with and without events to identify possible confounders. Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range) and categorical variables as numbers (percentages). Student's *t*-test or non-parametric equivalent was used to test continuous variables; categorical variables were tested with chi-squared test or fisher's exact test.

The association between SVL parameters and outcome was assessed using Cox regression analysis resulting in hazards ratios (HR) and their 95% confidence intervals (CI). Firstly, univariable analysis of the separate SVL parameters was performed, and covariates with $P < 0.1$ were included for multivariable analysis. Secondly, we corrected for age, sex, and NYHA class >II in a multivariable model. For both univariable and multivariable models, the proportional hazards assumption was tested; moreover, non-linearity was assessed using Martingale residuals and restricted cubic spline

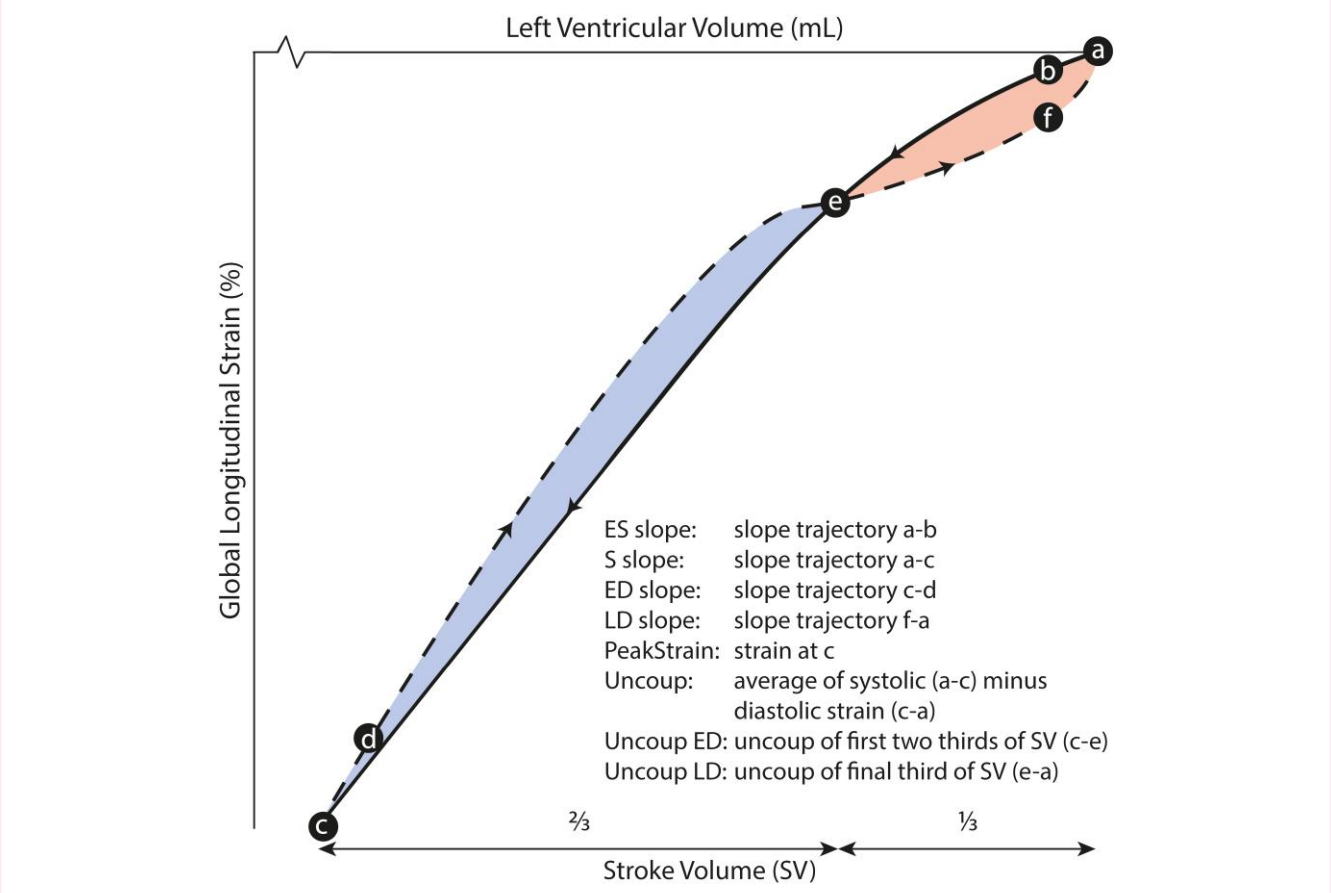


Figure 1 A schematic overview of the strain–volume loop and the derived characteristics. Solid line: systolic strain–volume relation; dashed line: diastolic strain–volume relation. (a) end diastolic volume; (b) after ejecting 5% of stroke volume; (c) end systolic volume; (d) filling at 5% of stroke volume; (e) filling at two thirds of stroke volume; (f) filling at 95% of stroke volume. ES: early systolic; S: systolic; ED: early diastolic; LD: late diastolic; Uncoup: uncoupling.

interpolation. If non-linearity was confirmed after restricted cubic spline interpolation, covariates were categorized in quartiles with the first quartile being the reference quartile for Cox regression analysis. All other continuous variables were added to the model as is, resulting in a HR per unit increase of the continuous variable. Unadjusted Kaplan–Meier curves were constructed for significant categorical variables after multivariable analysis, mainly for visualization purposes. In a sensitivity analysis, only patients with sinus rhythm during echocardiography were included since we hypothesized that presence of arrhythmia or pacing may affect the quality or validity of the SVL. Significance levels were set at $P < 0.05$.

Results

Patient characteristics

A total of 383 patients were enrolled in the initial cohort, followed by exclusion of 4% ($n = 17$) due to image quality and 15% ($n = 59$) due to temporal strain or volume tracking issues. Of the remaining 307 patients, diagnosis of HFpEF was confirmed in $n = 235$. Clinical characteristics of the cohort are summarized in *Table 1*. A total of 73 events, i.e. 39 HF hospitalizations (53%) and 34 deaths (47%), were recorded across 2.9 (1.75–4.11) years of follow-up. HFpEF patients with an event were older (77.1 ± 6.7 vs. 75.2 ± 6.9, $P = 0.048$), more frequently male (39.7% vs. 22.2%, $P = 0.009$), and had more often comorbidities such as a history of coronary artery disease (30.1% vs. 12.3%, $P = 0.002$) and chronic kidney disease (38.4% vs. 24.7%, $P = 0.047$) compared with patients without events (*Table 1*). Left ventricular ejection fraction did not significantly differ in patients with event vs. without event (59.2%±7.2% vs. 60.3%±7.0, $P = 0.306$). However, amongst others, LV mass index (85.2 g/m^2 ± 22.8 vs. 78.1 g/m^2 ± 17.3, $P = 0.019$), *E*-wave peak velocity [97.0 cm/s (73.0–119.0) vs. 82.0 cm/s (64.0–102.0), $P = 0.004$], and estimated right ventricular systolic pressure [40.0 mmHg (30.0–50.0) vs. 33.0 mmHg (25.0–40.0), $P = 0.001$] were higher in patients with events (*Table 2*). SVL parameters are summarized in *Table 3*, where only peak strain was significantly different in patients with vs. without events (−16.2 ± 4.1 vs. −17.4 ± 3.6, $P = 0.040$). Sex-stratified cohort characteristics are summarized in Supplementary data online, *Tables S1–S3*.

Table 1 Clinical characteristics of HFpEF cohort stratified by observed composite endpoint

	Event free ($n = 162$)	Event ($n = 73$)	Overall ($n = 235$)	*P*-value
Age (years)	75.2 ± 6.91	77.1 ± 6.86	75.8 ± 6.94	0.048
Female sex, *n* (%)	126 (77.8%)	44 (60.3%)	170 (72.3%)	0.009
Medical History, *n* (%)				
Hypertension	140 (86.4%)	55 (75.3%)	195 (83.0%)	0.059
Coronary artery disease	20 (12.3%)	22 (30.1%)	42 (17.9%)	0.002
Missing	3 (1.9%)	1 (1.4%)	4 (1.7%)	
Acute coronary syndrome	7 (4.3%)	11 (15.1%)	18 (7.7%)	0.009
Atrial fibrillation	89 (54.9%)	50 (68.5%)	139 (59.1%)	0.070
Valvular disease repair	6 (3.7%)	6 (8.2%)	12 (5.1%)	0.198
Hypercholesterolemia	70 (43.2%)	27 (37.0%)	97 (41.3%)	0.451
Chronic kidney disease	40 (24.7%)	28 (38.4%)	68 (28.9%)	0.047
Sleep apnoea	30 (18.5%)	14 (19.2%)	44 (18.7%)	1.000
Missing	1 (0.6%)	0 (0%)	1 (0.4%)	
Pulmonary embolism	9 (5.6%)	3 (4.1%)	12 (5.1%)	0.759
COPD	17 (10.5%)	20 (27.4%)	37 (15.7%)	0.002
Anaemia	21 (13.0%)	19 (26.0%)	40 (17.0%)	0.023
Transient ischaemic attack	14 (8.6%)	8 (11.0%)	22 (9.4%)	0.747
Stroke	14 (8.6%)	10 (13.7%)	24 (10.2%)	0.341
Peripheral artery disease	10 (6.2%)	9 (12.3%)	19 (8.1%)	0.179
Diabetes mellitus	34 (21.0%)	31 (42.5%)	65 (27.7%)	0.001
NYHA classification				0.009
I–II	87 (53.7%)	24 (32.9%)	111 (47.2%)	
III–IV	75 (46.3%)	49 (67.1%)	124 (52.8%)	
Body mass index (kg/m^2)	29.7 ± 5.39	30.5 ± 5.47	29.9 ± 5.42	0.272
Systolic blood pressure (mmHg)	155 ± 23.3	145 ± 23.4	152 ± 23.8	0.002
Missing	0 (0%)	1 (1.4%)	1 (0.4%)	
Diastolic blood pressure (mmHg)	78.8 ± 13.1	75.7 ± 12.6	77.8 ± 13.0	0.084
Missing	0 (0%)	1 (1.4%)	1 (0.4%)	
NT-proBNP (pg/mL)	504 (238–1330)	1250 (566–1970)	677 (279–1590)	<0.001
Missing	2 (1.2%)	2 (2.7%)	4 (1.7%)	

COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Table 2 Echocardiographic parameters of HFpEF cohort, stratified by observed composite endpoint

	Event free (*n* = 162)	Event (*n* = 73)	Overall (*n* = 235)	*P*-value
LVEF (%)	60.3 ± 7.01	59.2 ± 7.16	60.0 ± 7.06	0.306
LVMI (g/m^2)	78.1 ± 17.3	85.2 ± 22.8	80.3 ± 19.4	0.019
Missing	1 (0.6%)	0 (0%)	1 (0.4%)	
LV end-systolic diameter (mm)	31.7 ± 3.91	32.3 ± 5.09	31.9 ± 4.31	0.376
Missing	1 (0.6%)	0 (0%)	1 (0.4%)	
LV end-diastolic diameter (mm)	47.2 ± 4.84	47.3 ± 6.37	47.2 ± 5.35	0.875
Missing	1 (0.6%)	0 (0%)	1 (0.4%)	
LA volume index (mL/m2)	46.8 (37.3–58.8)	48.8 (41.4–58.5)	47.3 (37.8–58.8)	0.415
Missing	1 (0.6%)	1 (1.4%)	2 (0.9%)	
E-wave peak velocity (cm/s)	82.0 (64.0–102)	97.0 (73.0–119)	85.0 (67.8–108)	0.004
Missing	3 (1.9%)	4 (5.5%)	7 (3.0%)	
A-wave peak velocity (cm/s)	78.2 ± 24.1	88.1 ± 23.4	80.7 ± 24.2	0.339
Missing	53 (32.7%)	37 (50.7%)	90 (38.3%)	
Lateral e′ (cm/s)	8.90 (7.00–10.6)	9.20 (6.85–10.6)	8.90 (7.00–10.6)	0.927
Missing	10 (6.2%)	18 (24.7%)	28 (11.9%)	
Septal e′ (cm/s)	6.40 (5.20–7.83)	6.40 (5.45–7.65)	6.40 (5.30–7.85)	0.928
Missing	10 (6.2%)	18 (24.7%)	28 (11.9%)	
E/A ratio	0.900 (0.700–1.30)	0.800 (0.700–1.30)	0.900 (0.700–1.30)	0.562
Missing	53 (32.7%)	37 (50.7%)	90 (38.3%)	
E/e′ average	10.8 (8.40–13.5)	12.6 (10.5–16.4)	11.2 (8.53–14.1)	0.004
Missing	15 (9.3%)	19 (26.0%)	34 (14.5%)	
Tricuspid insufficiency (m/s)	2.60 (2.30–2.90)	2.70 (2.50–3.30)	2.65 (2.30–3.00)	0.005
Missing	9 (5.6%)	2 (2.7%)	11 (4.7%)	
Estimated RV systolic pressure (mmHg)	33.0 (25.0–40.0)	40.0 (30.0–50.0)	35.0 (26.8–43.1)	0.001
Missing	9 (5.6%)	2 (2.7%)	11 (4.7%)	
Good RV function, *n* (%)	136 (84.0%)	53 (72.6%)	189 (80.4%)	0.062
Missing	20 (12.3%)	13 (17.8%)	33 (14.0%)	
Rhythm during echocardiography				0.016*
Sinus rhythm	114 (70.4%)	37 (50.7%)	151 (64.3%)	
Atrial fibrillation	43 (26.5%)	32 (43.8%)	75 (31.9%)	
Atrial flutter	0 (%)	1 (1.4%)	1 (0.4%)	
Ventricular pacing	5 (3.1%)	2 (2.7%)	7 (3.0%)	
Biventricular pacing	0 (0%)	1 (1.4%)	1 (0.4%)	

LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LV, left ventricular; LA, left atrial; RV, right ventricular.
**P*-value for trend.

Strain–volume loop and adverse events

Non-linearity was detected for S slope and ED slope in Cox regression analysis; therefore, these variables were categorized based on quartiles. Univariable analysis showed that a lower peak strain (i.e. less negative) was associated with adverse events during follow-up (HR 1.07, 95% CI 1.00–1.13) per unit increase in strain. Moreover, the second and third ED slope quartiles were associated with lower risk for adverse events [HR 0.34 (95% CI 0.17–0.71) and HR 0.54 (95% CI 0.30–0.99), respectively] compared with the first quartile. Whereas the fourth quartile was not significantly associated compared with the first quartile [HR 0.66 (95% CI 0.36–1.19), *Figure 2*]. ED slope values ranged from −0.88 to 4.39 with a median of 0.60. The 25th and 75th percentiles were at 0.38 and 1.03, respectively. Unadjusted Kaplan–Meier curves for the quartiles of ED slope are shown in *Figure 3*.

After adjustment for age, sex, and NYHA class, the association between peak strain and adverse outcomes was attenuated [adjusted HR 1.02 (95% CI 0.96–1.08)]. In contrast, the second quartile of ED slope remained significantly associated with adverse events [adjusted HR 0.42 (95% CI 0.20–0.88)]. However, the association between the third quartile and adverse outcomes was also attenuated [adjusted HR 0.55 (95 CI% 0.30–1.00)]. Sensitivity analyses among patients with sinus rhythm during echocardiography (*n* = 151) largely confirmed these outcomes (see Supplementary data online, *Table S4*).

Table 3 Strain–volume loop characteristics stratified by observed composite endpoint

	Event free (*n* = 162)	Event (*n* = 73)	Overall (*n* = 235)	*P*-value
S slope (%/mL)	0.431 (0.356–0.531)	0.411 (0.323–0.509)	0.425 (0.345–0.523)	0.140
ES slope (%/mL)	0.367 (0.215–0.604)	0.373 (0.218–0.597)	0.371 (0.215–0.602)	0.884
ED slope (%/mL)	0.757 ± 0.538	0.734 ± 0.739	0.749 ± 0.606	0.812
LD slope (%/mL)	0.333 ± 0.258	0.292 ± 0.320	0.320 ± 0.279	0.333
UNCOUP (%)	−0.0898 ± 1.28	−0.250 ± 1.15	−0.139 ± 1.24	0.343
UNCOUP ED (%)	−0.179 ± 1.42	−0.304 ± 1.36	−0.218 ± 1.40	0.522
UNCOUP LD (%)	0.0889 ± 1.13	−0.141 ± 1.01	0.0174 ± 1.10	0.122
Peak strain (%)	−17.4 ± 3.60	−16.2 ± 4.07	−17.0 ± 3.79	0.040

S, systolic; ES, early systolic; ED, early diastolic; LD, late diastolic; UNCOUP, uncoupling.

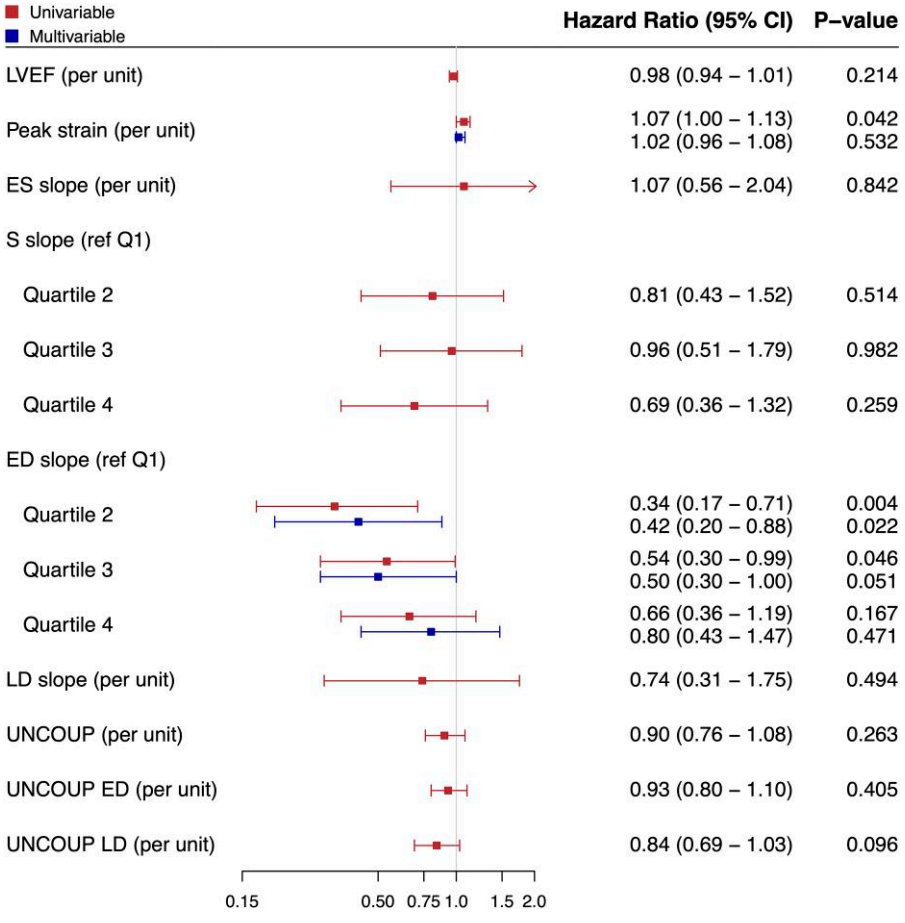


Figure 2 Forest plot and hazard ratios for univariable (red) and multivariable (blue) Cox regression analysis. Hazard ratios are plotted on a logarithmic scale. LVEF, left ventricular ejection fraction; ES, early systolic; S, systolic; ED, early diastolic; LD, late diastolic; UNCOUP, uncoupling; ref, reference; Q1, first quartile; CI, confidence interval.

Discussion

The aim of this study was to explore the association between LV-SVL characteristics and adverse events in HFpEF patients, using a composite endpoint of all-cause mortality and HF hospitalization. Across a 2.9-year follow-up, univariable analysis revealed that both peak strain and early diastolic slope, but none of the other SVL parameters, were significantly related to adverse events. After adjustment for age, sex, and NYHA class, only early diastolic slope was significantly associated with adverse events in HFpEF patients. These findings were confirmed in a sensitivity

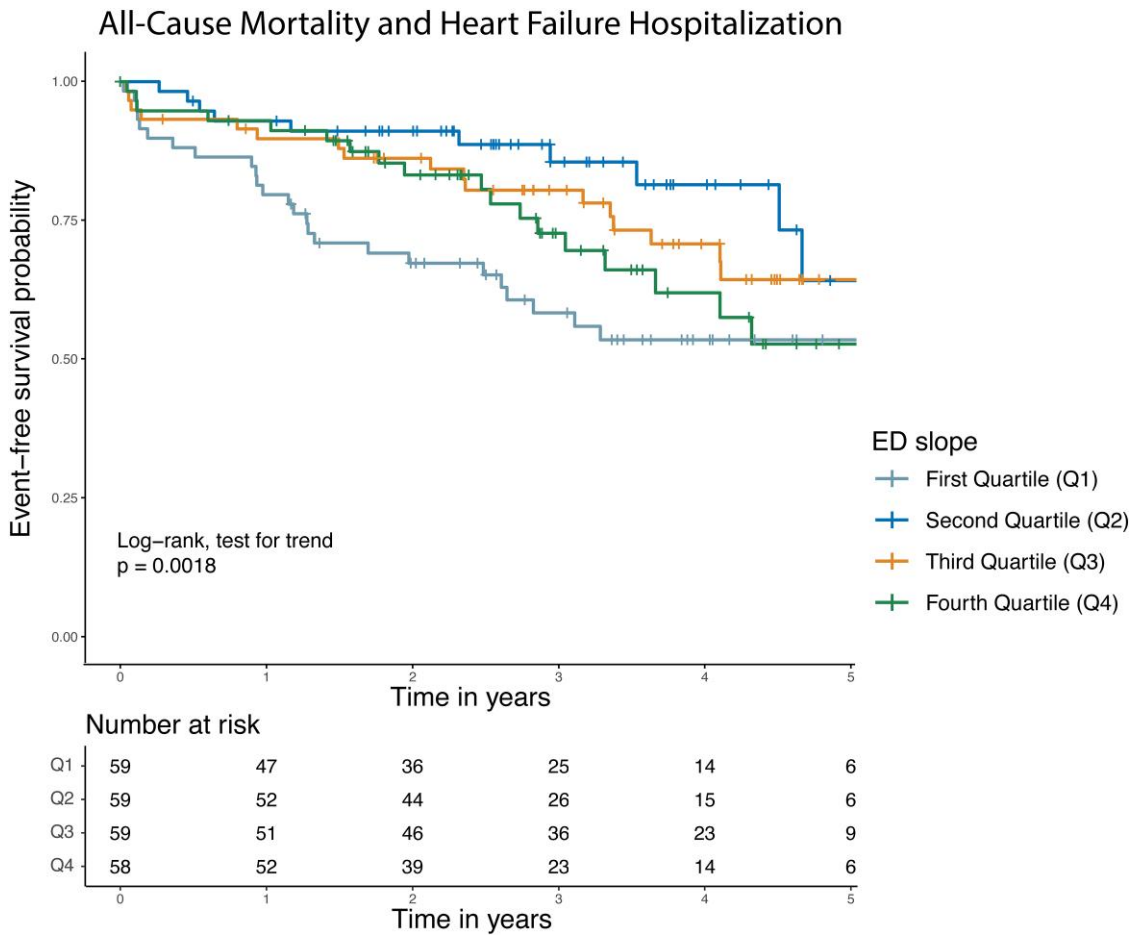


Figure 3 Kaplan–Meier curve for composite endpoint to ED slope divided in quartiles. Vertical lines represent censored patients. ED, early diastolic.

analysis including only patients with sinus rhythm during echocardiography. Taken together, this study suggests that measures reflecting diastolic (dynamic) function, rather than parameters during the systolic phase only, are associated with survival in patients with HFpEF. This supports future studies to explore the impact and role of measures of diastolic (dynamic) function in predicting future clinical events and/or personalizing or evaluating treatment.

Previous research in healthy controls revealed a steep ED slope, suggesting pronounced longitudinal deformation in early diastole in a healthy heart may facilitate efficient LV filling.[14,31] Our finding that ED slope, a parameter assessed during early diastole, is associated with adverse events is in line with other studies. Specifically, previous work also observed early diastolic parameters, such as E/e′, to be associated with adverse events in HFpEF.[32–34] From a mechanistical point of view, studies evaluating diastolic function typically assessed myocardial relaxation [e.g. LV systolic pressure decay or mitral annulus early diastolic velocity (e′)] and LV stiffness (e.g. LV late diastolic pressures or deceleration time).[35] LV stiffness, often measured late in diastole, is known to be affected in HFpEF.[1,36,37] To underline the importance of early diastole and LV relaxation, previous studies showed a prolonged LV pressure decay in HFpEF.[36,38,39] Moreover, echocardiographic markers of early diastole were shown to be significant predictors for diagnosis of HFpEF.[40] Additionally, our data suggest that abnormalities in cardiac dynamics during early diastole, which may be related to LV relaxation and consequently LV filling, are relevant for clinical progression in patients with HFpEF. Possible mechanisms underlying these altered cardiac dynamics could be related to inflammation and mitochondrial function,[41] structural changes (e.g. myocardial fibrosis and steatosis),[42,43] altered titin phosphorylation,[44] and/or altered calcium hemostasis.[45] Although the (combination of) mechanisms underlying the observed changes in early diastole remain to be elucidated in future research, our data suggest that the SVL, especially during early diastole, might be of added prognostic value in HFpEF.

An unexpected observation was the non-linear relation between the early diastolic slope and HR. Whilst the second quartile showed a reduced risk compared with the first quartile, we did not observe this for the third and fourth quartile, although a trend could be observed for the former, which might suggest the presence for a physiological optimal range for the relation between strain change and volume change during early diastole. This observation is in line with other parameters, such as E/A ratio, for which a reference-range rather than a single cut-off is determined.[46] An alternative explanation for this observation is related to the wide range of the 95% CI of mainly the fourth quartile. Altogether, this finding warrants future research with a larger sample size to explore this observation in more detail.

In addition to diastolic markers, previous prognostic research in HFpEF also focused on systolic function in relation to adverse events.[38,47] In our study, peak strain was not significantly associated with long-term adverse events after correcting for potential confounders. Our findings are in line with some,[48] but not all, previous

studies.[49–51] A potential explanation for these discrepant findings may relate to the heterogeneity in study protocols. Firstly, Buggey *et al.*[48] assessed GLS during hospitalization, whereas the studies observing an association, assessed strain at the time of admission for acute HF. Strain may be more impaired during the acute episode than when HF is stable, and patients admitted for HF are at higher risk for future adverse events compared with stable ambulant patients. This may contribute to the differences between studies. Of these studies, only Shah *et al.*[49] included mortality, albeit using a predefined cut-off value for impaired strain, whilst other studies focused on readmission or change in EF with strain as a continuous variable.[50,51] As a result, a definitive conclusion pertaining to the association of peak strain and future outcomes in HFpEF cannot be drawn.

Strengths and limitations. Our data underline the importance of the assessment of diastolic function analysis in HFpEF and highlight the potential for (combining) measurements across the cardiac cycle that go beyond the currently accepted (systolic) parameters, such as peak measurements. Nevertheless, some limitations apply to our study. Firstly, although patients were not evaluated with the gold standard for diastolic function, diagnosing HFpEF is done in line with guidelines, not solely focusing on invasive measurements.[3,52] Secondly, due to the small number of events during follow-up, we were restricted in the correction for potential confounders. Specifically, we were unable to explore the value of the SVL in addition to current markers of diastolic function and investigate possible confounders [e.g. right ventricular (RV) function and indices of pulmonary vasculature (e.g. RV systolic pressure)]. Similarly, comorbidities are likely to affect adverse events or possibly the SVL through altered cardiac dynamics. Consequently, the generalizability of our results to specific subgroups remains to be elucidated, especially since, based on previous studies, different phenotype-groups might exist.[53] However, we have selected the most important potential factors.[5] Thirdly, SVL analysis is labour-intensive, potentially hampering both future scientific and clinical applications. However, our MATLAB tool automated part of the process, making it more widely applicable in future research and in large cohorts. Hence, external validation of our findings can be applied to routine clinical care data, enhancing possible clinical utility of SVL parameters.

In conclusion, we found an association between the magnitude of the early diastolic slope of the LV-SVL and adverse events in HFpEF patients visiting a tertiary outpatient clinic. These results provide further support for the importance of measures reflecting (early) diastolic function in HFpEF related to the association with future clinical events.

Acknowledgements

T.K. received a personal grant for his research at the Radboudumc.

Supplementary data

Sex-stratified cohort characteristics can be found in Supplementary data online, *Table S1–S3*. Results of univariable and multivariable Cox regression for patients with sinus rhythm during echocardiography can be found in Supplementary data online, *Table S4*.

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Funding

T.K. was supported by a personally obtained grant from the Radboud University Medical Center.

Conflict of interest: None declared.

Data availability

The analysed dataset, underlying this manuscript, will be shared on reasonable request to the corresponding author.

Author contributions

T.K., A.v.D., G.W., and T.E., D.T. designed the study idea. Data collection and acquisition were done by J.W., V.v.E., and C.K. Analysis and interpretation of the results were carried out by all authors. T.K., T.E., and D.T. drafted the manuscript. All authors reviewed and revised it critically for important intellectual content, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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