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# Left ventricular strain-volume loops and diastolic dysfunction in suspected heart failure with preserved ejection fraction

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ABSTRACT

*Background:* Presence of left ventricular diastolic dysfunction (DD) is key in the pathogenesis of heart failure with preserved ejection fraction (HFpEF). However, non-invasive assessment of diastolic function is complex, cumbersome, and largely based on consensus recommendations. Novel imaging techniques may help detecting DD. Therefore, we compared left ventricular strain-volume loop (SVL) characteristics and diastolic (dys-)function in suspected HFpEF patients.

*Method and results:* 257 suspected HFpEF patients with sinus rhythm during echocardiography were prospectively included. 211 patients with quality-controlled images and strain and volume analysis were classified according to the 2016 ASE/EACVI recommendations. Patients with indeterminate diastolic function were excluded, resulting in two groups: normal diastolic function (control; $n = 65$) and DD ($n = 91$). Patients with DD were older (74.8 ± 6.9 vs. 68.5 ± 9.4 years, $p < 0.001$), more often female (88% vs 72%, $p = 0.021$), and more often had a history of atrial fibrillation (42% vs. 23%, $p = 0.024$) and hypertension (91% vs. 71%, $p = 0.001$) compared to normal diastolic function. SVL analysis showed a larger uncoupling i.e., a different longitudinal strain contribution to volume change, in DD compared to controls (0.556 ± 1.10% vs. -0.051 ± 1.14%, respectively, $P < 0.001$). This observation suggests different deformational properties during the cardiac cycle. After adjustment for age, sex, history of atrial fibrillation and hypertension, we found an adjusted odds ratio of 1.68 (95% confidence interval 1.19–2.47) for DD per unit increase in uncoupling (range: −2.95–3.20).

*Conclusion:* Uncoupling of the SVL is independently associated with DD. This might provide novel insights in cardiac mechanics and new opportunities to assess diastolic function non-invasively.

## 1. Introduction

Heart failure (HF) affects over 26 million people worldwide and is associated with high morbidity and mortality rates [1,2]. Echocardiography is traditionally used to quantify left ventricular ejection fraction (LVEF). Interestingly, despite having clinical complaints, a significant portion of all HF patients demonstrate a preserved LVEF (i.e., HFpEF) [3]. Etiology of HFpEF is not completely understood, but it is currently accepted that HFpEF is caused by pathophysiological processes affecting the myocardium (e.g. metabolic, ischemic, toxic, and genetic) and/or affecting the loading conditions of the heart (e.g. hypertension, atrial/ventricular cardiac arrhythmias, valvular or structural defects) [4].

Diagnosis of HFpEF is challenging [4,5]. The gold standard is invasive pressure measurements evaluating the presence of elevated pulmonary capillary wedge pressure as a measure for LV diastolic dysfunction (LVDD). Due to its invasive nature, several attempts have

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been made to establish alternative diagnostic means, including scoring-systems such as the HFA-PEFF or $H_2$FPEF algorithms that adopt a combination of echocardiographic markers, comorbidities, and (non-) invasive testing [4,6,7]. Due to the heterogeneity in the clinical presentation and incomplete understanding of the underlying pathophysiology of HFpEF, there is no clear consensus on methods to diagnose HFpEF [8,9]. Nonetheless, studies agree that LVDD plays a central role in HFpEF diagnosis, characterized by impaired myocardial relaxation during diastole, increased wall stiffness, and/or elevated filling pressures [10].

The strain(ε)-volume loop (SVL) is an echocardiography-based measure that evaluates the dynamic relationship between LV volume and global longitudinal strain across the total cardiac cycle [11–15]. We previously reported that the SVL can successfully detect changes in systolic and diastolic function upon alterations in pre- and afterload, an ability that is also present when using the invasive pressure-volume curve [16,17], whilst the SVL can also distinguish between various cardiac abnormalities [11], and has potential to provide additional predictive value in clinical populations [12,18]. Therefore, this study will evaluate the relation between the SVL characteristics and presence of diastolic dysfunction (DD) in patients suspected of having HFpEF. We hypothesized that SVL, and especially parameters related to the diastolic part of the loop, are associated with presence of DD.

## 2. Methods

### 2.1. Study design and population

In this cohort study, we prospectively included patients who were referred to the outpatient HFpEF clinic at the Maastricht University Medical Center (MUMC+) between January 2015 and July 2019 [7]. Patients underwent a diagnostic work-up at baseline and the diagnosis of HFpEF was based on the European Society of Cardiology HF guidelines (2016) [7,19]. Exclusion criteria were non-sinus rhythm during echocardiography examination, such as atrial fibrillation or ventricular pacing, and more than moderate mitral valve regurgitation or calcification, as these conditions hampered diastolic function assessment according to the 2016 ASE/EACVI recommendations. Additionally, patients with insufficient echocardiography image quality were excluded. We included all patients with normal diastolic function or DD according to the 2016 ASE/EACVI recommendations (Fig. 1 & Appendix Fig. 1) [20]. 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 (NL67997.068.18).

The primary purpose of our study was to explore the association between SVL characteristics and presence of diastolic function in HFpEF. For this purpose, patients who fulfilled the inclusion criteria were allocated according to expert consensus on diastolic function assessment into I) normal diastolic function (*control*) or II) DD (*dysfunction*) [20].

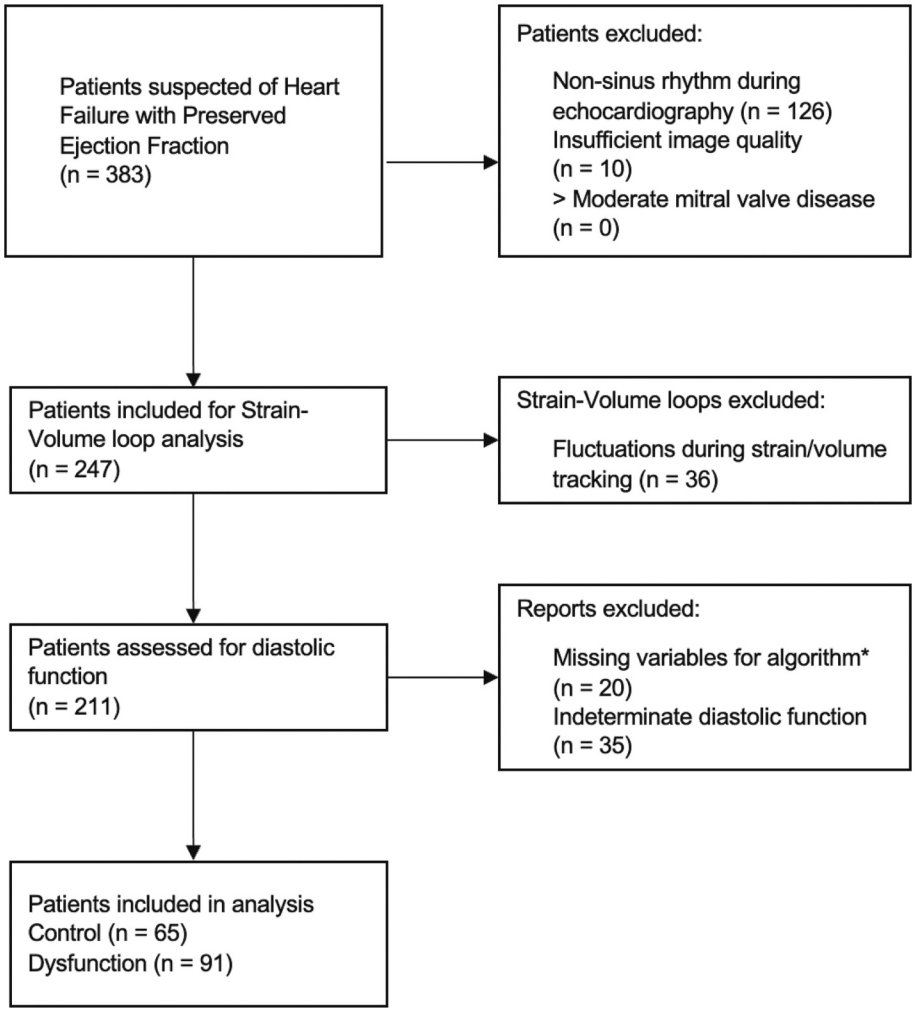


**Fig. 1.** Flow diagram of patient selection for this study. Control, normal diastolic function; Dysfunction, diastolic dysfunction. *Algorithm as used in the 2016 ASE/EACVI recommendations.

### 2.2. Transthoracic echocardiography and strain analyses

Echocardiography was performed as part of clinical routine according to guideline recommendations [21] and was subsequently analyzed with speckle-tracking echocardiography, as described in detail earlier [22]. Briefly, temporal LV global longitudinal strain (GLS) on 2D ultrasound cine-loops was obtained by manual endocardial and myocardial tracing of the apical two-, three-, and four-chamber according to current consensus recommendations using dedicated speckle-tracking method (TomTec, 2D Cardiac Performance Analysis v1.4, ImageArena v4.6); all investigators were blinded to all other clinical data [23]. Images were excluded for analysis if apical views were missing or image quality was insufficient according to a standard operating 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).

### 2.3. Strain(ε)-volume loop analysis

Temporal myocardial global longitudinal strain values and temporal LV volume values were exported from the dedicated software (2D Cardiac Performance Analysis v1.4, Image Arena v4.6) to text-files. Using an in-house developed MATLAB script (The Mathworks Inc., version 2019a, Massachussetts, USA) we imported the volume and GLS curves values to construct SVL adapted from earlier work [11,24]. Firstly, markers for end diastole and end systole were adjusted based on the maximum and minimum of the LV volume curve, respectively [23]. Secondly, 300-point cubic spline interpolations were applied to both the systolic, and diastolic parts of the curves to obtain equidistant sampling for differential analysis. Next, drift compensation was applied on both the volume and strain curves to achieve closed SV-loops. The longitudinal strain-volume relationship was assessed using the following parameters (Appendix Fig. 2): (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 longitudinal strain (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, and (f) uncoupling (UNCOUP), defined as the average difference in strain between systole and diastole (systolic strain – diastolic strain) for any given volume during these phases. Uncoupling is also divided in uncoupling during the lower two-thirds of the total volume and the final third of total volume to represent the early and the active mitral inflow phase, i.e., (g) early (UNCOUP ED) and (h) late (UNCOUP LD) uncoupling [11,25]. Individual SVL plots were manually assessed blinded from other results to detect fluctuations in temporal strain or volume tracking. The obtained SVL parameters including the patient ID and other measurement and analysis information, were automatically transferred into a Microsoft Access database using a local Open DataBase Connectivity (ODBC) connection.

### 2.4. Statistical analysis

Statistical analysis was performed using R-studio version 1.4.1106 (RStudio, PBC) [26]. All parameters were visually inspected for normality using histograms, Q-Q plots, and the Shapiro-Wilk test. Continuous variables were reported as mean ± standard deviation (SD) or median [interquartile range] and categorical variables as proportions. Differences between groups were assessed using a *t*-test or a non-parametric equivalent. Proportions were tested using chi-squared tests or Fisher's exact tests. To assess the association between SVL parameters and DD, backward stepwise logistic regression was used. The first model included the SVL parameters, i.e., UNCOUP, S slope, ES slope, Peak Strain, ED slope, and LD slope. Based on the Wald test, independent variables were excluded from the model until all independent variables remained significant. Collinearity was detected for UNCOUP, UNCOUP ED and UNCOUP LD. Therefore, backward selection was repeated replacing UNCOUP with UNCOUP ED and UNCOUP LD separately, resulting in three models with the different uncoupling parameters. Based on the lowest Akaike information criterion (AIC) the model with UNCOUP was selected for subsequent multivariable analysis. Additionally, for the final model the association was assessed for each of 2000 bootstrapped samples, and the 95% confidence interval was computed determining the odds ratio at the 2.5th and 97.5th percentiles. *P*-values of <0.05 were considered significant.

## 3. Results

A total of 383 patients enrolled in this cohort were initially eligible for analysis (Fig. 1). We excluded 126 (33%) patients because of non-sinus rhythm during echocardiograph. Moreover, we excluded an additional 10 (2.6%) patients due to insufficient image quality for speckle-tracking imaging, whilst we did not have to additionally exclude patients based on mitral valve disease. Of these remaining 247 patients, we excluded 36 (14%) due to fluctuations in temporal volume tracking after evaluating the SVL. This resulted in 211 patients to be classified according to 2016 ASE/EACVI recommendations. Due to missing parameters used in the 2016 ASE/EACVI algorithm ($n = 20$) and classification of diastolic function as indeterminate ($n = 35$), 156 patients were available for statistical analyses and were classified as: control ($n = 65$, 42%) or DD ($n = 91$, 58%).

Patients with DD were significantly older, more frequently female, and had higher NT-proBNP levels compared to controls (Table 1). We

**Table 1**
Clinical baseline characteristics.

| | Control ($N = 65$) | Dysfunction ($N = 91$) | P- Value |
|---|---|---|---|
| Age (years) | 68.5 ± 9.44 | 74.8 ± 6.85 | <0.001 |
| Female sex, n (%) | 47 (72.3%) | 80 (87.9%) | 0.021 |
| Body mass index (kg/m$^2$) | 30.5 ± 6.30 | 31.0 ± 5.63 | 0.577 |
| Systolic blood pressure (mmHg) | 150 ± 18.2 | 156 ± 30.1 | 0.147 |
| Diastolic blood pressure (mmHg) | 79.0 ± 10.3 | 75.2 ± 12.9 | 0.045 |
| Laboratory values | | | |
| *NT-proBNP (pg/ml)* | 163 [85.6–417] | 420 [217–945] | <0.001 |
| Medical History, n (%) | | | |
| *Hypertension* | 46 (70.8%) | 83 (91.2%) | 0.001 |
| *Significant CAD* | 7 (10.8%) | 19 (20.9%) | 0.130 |
| Missing | 4 (6.2%) | 2 (2.2%) | |
| *Acute coronary syndrome* | 5 (7.7%) | 6 (6.6%) | 1.000 |
| *Atrial fibrillation* | 15 (23.1%) | 38 (41.8%) | 0.024 |
| *Valve Replacement* | 1 (1.5%) | 7 (7.7%) | 0.140 |
| *Hypercholesterolemia* | 28 (43.1%) | 40 (44.0%) | 1.000 |
| *Kidney disease* | 10 (15.4%) | 23 (25.3%) | 0.167 |
| *Sleep apnea* | 16 (24.6%) | 18 (19.8%) | 0.559 |
| *Pulmonary embolism* | 3 (4.6%) | 2 (2.2%) | 0.650 |
| *COPD* | 11 (16.9%) | 14 (15.8%) | 0.827 |
| *Anemia* | 7 (10.9%) | 18 (19.8%) | 0.184 |
| *Transient ischemic attack* | 1 (1.5%) | 8 (8.8%) | 0.087 |
| Missing | 5 (7.7%) | 0 (0%) | |
| *Stroke* | 4 (6.2%) | 6 (6.6%) | 1.000 |
| *Peripheral artery disease* | 2 (3.1%) | 12 (13.2%) | 0.058 |
| *Diabetes Mellitus* | 13 (20.0%) | 30 (33.0%) | 0.101 |
| Symptoms, n (%) | | | 0.297# |
| NYHA class | | | |
| 1 | 5 (7.7%) | 3 (3.3%) | |
| 2 | 28 (43.1%) | 39 (42.9%) | |
| 3 | 26 (40.0%) | 42 (46.2%) | |
| 4 | 1 (1.5%) | 6 (6.6%) | |
| Missing | 5 (7.7%) | 1 (1.1%) | |
| Expert diagnosis, n (%) | | | |
| HFpEF | 37 (56.9%) | 74 (81.3%) | <0.001 |

#*P*-value for trend. Data are given as n (%), mean ± standard deviation, or median [interquartile range]. CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide; NYHA, New York Heart Association. Percentage missing values below 5% was discarded in this table.

found no differences between groups in BMI or systolic blood pressure. Patients with DD more often had a history of atrial fibrillation and hypertension than controls, whilst no differences in the prevalence of other cardiovascular diseases were found between the groups. In line with current DD algorithms, we found significantly higher LV mass, left atrial volume indexes, E- and A-peak velocities, RV systolic pressure, and lower lateral/septal e' velocities in DD compared to controls (Table 2). We found no significant differences between groups in LVEF, end-diastolic/systolic diameters or E/A-ratio.

*Strain(ε)-volume loop, SVL.* We found no significant differences between groups in the early/late systolic and diastolic slopes or in peak strain (Table 3). A significantly higher uncoupling (total, early diastolic, late diastolic) was found in DD compared to control (Fig. 2, Fig. 3). Subsequently, we performed multivariable logistic regression to identify SVL characteristics that are independently associated with DD. Backward, stepwise selection resulted in a model with total uncoupling as the sole independent variable. The odds of DD increased with 63% (odds ratio (OR) 1.63. 95% confidence interval (CI) [1.21–2.25]) per one-unit increase in uncoupling (bootstrapped OR 1.67, 95%CI [1.24–2.30]), while values for uncoupling ranged from −2.95 to 3.20 in this cohort. Total uncoupling remained independently associated with presence of DD when adjusting for age, sex, history of hypertension and history of atrial fibrillation (adjusted OR 1.68, 95% CI [1.19–2.47], bootstrapped OR 1.79, 95% CI [1.20–2.81]). Additional correction for NT-pro-BNP resulted in an adjusted OR 1.81 (95%CI [1.26–2.70]) with complete case analysis and $n = 1$ missing in DD. When using endocardial global longitudinal strain instead of myocardial strain, uncoupling remained independently associated with diastolic dysfunction (OR 1.54 [95%CI 1.14–2.13]). Additionally, we explored the trend in SVL parameters over different sub-groups. Fig. 4 shows the distribution of SVL parameters for patients diagnosed with HFpEF and non-heart failure in both the control and DD group. No visual clustering was observed for SVL parameters, nor were differences found for HFpEF compared to non-heart failure patients.

**Table 2**
Conventional echocardiographic characteristics of cohort.

| | Control (N = 65) | Dysfunction (N = 91) | P- Value |
|---|---|---|---|
| LV Ejection fraction (%) | 61.9 ± 7.0 | 60.7 ± 7.2 | 0.330 |
| LV Mass Index (g/m$^2$) | 73.9 ± 13.1 | 85.2 ± 21.2 | <0.001 |
| LV End Systolic Diameter (mm) | 32.0 ± 3.5 | 32.0 ± 5.5 | 0.971 |
| LV End Diastolic Diameter (mm) | 48.0 ± 4.3 | 47.1 ± 6.3 | 0.252 |
| LA volume index (mL/m$^2$) | 32 [27–39] | 44 [36–53] | <0.001 |
| Missing | 0 (0%) | 3 (3.3%) | |
| E peak (cm/s) | 63.0 [55–83] | 83.0 [63–108] | <0.001 |
| A peak (cm/s) | 77.3 ± 18.8 | 86.2 ± 28.9 | 0.024 |
| Missing | 3 (4.6%) | 5 (5.5%) | |
| Lateral e' (cm/s) | 8.6 [7.7–10.1] | 6.90 [6.0–9.1] | <0.001 |
| Missing | 0 (0%) | 10 (11.0%) | |
| Septal e' (cm/s) | 7.5 [6.9–8.6] | 5.6 [4.8–6.2] | <0.001 |
| Missing | 0 (0%) | 10 (11.0%) | |
| E/A ratio | 0.85 [0.70–1.00] | 0.90 [0.70–1.38] | 0.440 |
| Missing | 3 (4.6%) | 5 (5.5%) | |
| E/e' average | 8.5 [7.0–10.3] | 13.9 [10.8–16.4] | <0.001 |
| Missing | 0 (0%) | 11 (12.1%) | |
| Tricuspid regurgitation peak velocity (m/s) | 2.5 [2.2–2.7] | 2.9 [2.5–3.3] | <0.001 |
| Missing | 3 (4.6%) | 10 (11.0%) | |
| Estimated RV systolic pressure (mmHg) | 30.0 [25.0–35.0] | 40.0 [30.0–46.3] | <0.001 |
| Missing | 3 (4.6%) | 11 (12.1%) | |
| Good RV function, n (%) | 60 (92.3%) | 77 (84.6%) | 0.391 |
| Missing | 4 (6.2%) | 10 (11.0%) | |
| LV Hypertrophy, n (%) | | | <0.001# |
| None | 65 (100%) | 25 (27.5%) | |
| Concentric remodeling | 0 (0%) | 36 (39.6%) | |
| Concentric left ventricular hypertrophy | 0 (0%) | 8 (8.8%) | |
| Eccentric left ventricular hypertrophy | 0 (0%) | 22 (24.2%) | |
| Grade Diastolic Dysfunction, n (%)* | | | |
| Grade I | 0 (0%) | 30 (33.0%) | <0.001# |
| Grade II | 0 (0%) | 40 (44.0%) | |
| Grade III | 0 (0%) | 11 (12.1%) | |
| Missing E/A ratio | 0 (0%) | 5 (5.5%) | |
| Cannot determine | 0 (0%) | 5 (5.5%) | |

*Based on classification according to guidelines [20]. #P-value for trend. Data are given as n (%), mean ± standard deviation, or median [interquartile range]. LA, left atrial; LV, left ventricular; RV right ventricular.

**Table 3**
Strain volume loop characteristics.

| | Control (N = 65) | Dysfunction (N = 91) | P- Value |
|---|---|---|---|
| S slope (%/ml) | 0.432 ± 0.125 | 0.458 ± 0.175 | 0.284 |
| ES slope (%/ml) | 0.426 ± 0.281 | 0.399 ± 0.341 | 0.599 |
| ED slope (%/ml) | 0.764 ± 0.617 | 0.591 ± 0.513 | 0.067 |
| LD slope (%/ml) | 0.295 ± 0.249 | 0.357 ± 0.285 | 0.153 |
| UNCOUP (%) | −0.0506 ± 1.14 | 0.556 ± 1.10 | 0.001 |
| UNCOUP ED (%) | −0.0999 ± 1.27 | 0.572 ± 1.89 | 0.002 |
| UNCOUP LD (%) | 0.0480 ± 1.02 | 0.525 ± 0.976 | 0.004 |
| Peak Strain (%) | −18.0 ± 3.54 | −17.7 ± 3.13 | 0.657 |

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

## 4. Discussion

The purpose of our study was to explore the association between the strain(ε)-volume loop (SVL) and DD in patients suspected of HFpEF. We present the following findings: first, patients with DD were slightly older, more often female, and more often had a medical history of hypertension and atrial fibrillation compared to controls. Secondly, we found significant differences in SVL characteristics between both groups, with patients with DD demonstrating a significantly larger early and late diastolic 'uncoupling' compared to control. This finding means that, compared to systole, the diastolic relationship between longitudinal strain and volume is altered. In other words, early in diastole the LV shows less longitudinal deformation for a given change in volume. Such differences in loop characteristics were specifically observed during diastole, with no differences between groups for systolic characteristics (e.g., peak strain, S slope). Finally, upon correcting for age, sex, medical history, and NT pro-BNP, we reinforced that uncoupling of the SVL remained independently associated with presence of DD. Taken together, this means that the SVL provides additional information to identify presence of DD in suspected HFpEF patients.

Our finding that the SVL can detect abnormalities in different cardiac pathologies is in line with earlier studies. Specifically, in previous work we found uncoupling to be higher in both patients with aortic regurgitation and aortic stenosis, whilst changes in uncoupling were also significantly related to cardiac remodeling after aortic valve replacement [11,12]. Pagourelias et al. detected a greater uncoupling in potentially stiffer hearts in hypertrophic cardiomyopathy [27]. Interestingly, Hubert et al. found a smaller area enclosed by the SVL in patients with HFpEF and amyloidosis compared to healthy controls [15]. However, this smaller area could be partly attributed to a difference in stroke volume between the groups, whereas the definition of DD involved single echocardiographic parameters and cardiac pathologies rather than the 2016 ASE/EACVI recommendations [28,29]. Our study, therefore, adds the novel insight that the association between systolic-diastolic uncoupling and presence of DD remained present when normalizing for stroke volume.

A possible explanation regarding underlying causes for higher uncoupling in those with DD could be a difference in the contribution of longitudinal and circumferential deformation in relation to volume

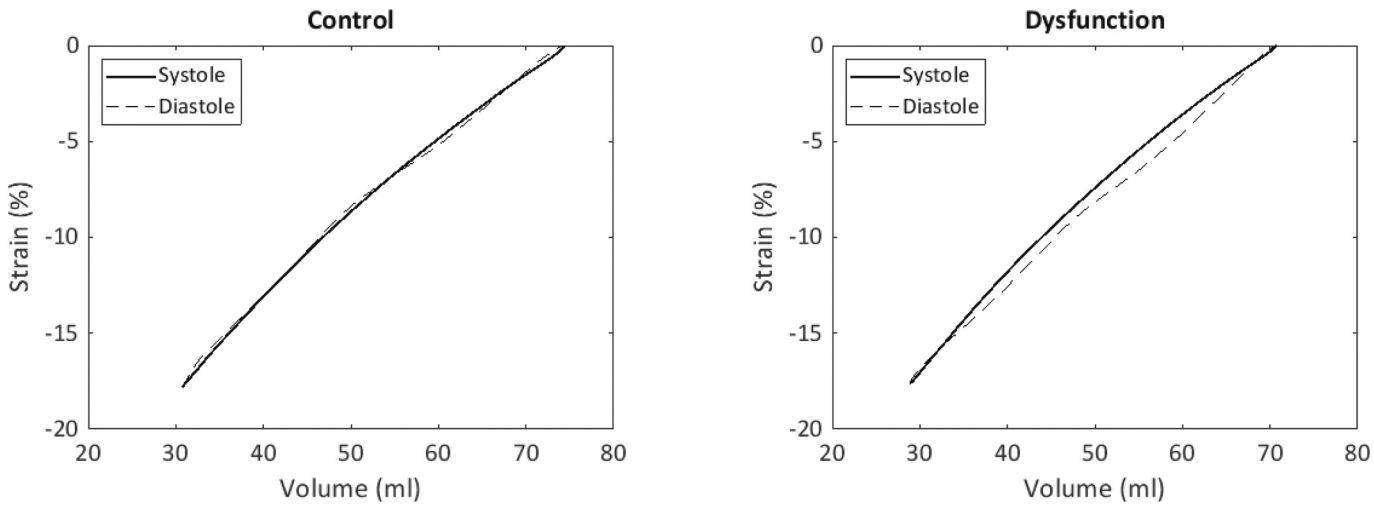


**Fig. 2.** Average Strain-Volume relationship for both normal diastolic function ($n = 65$) and diastolic dysfunction ($n = 91$). Bold line represents systolic strain-volume relationship, thin line represents diastolic strain-volume relationship. Higher uncoupling is represented by the average distance between the systolic and diastolic line, i.e., for most of the strain-volume relationship the diastolic strain is more negative for any given volume then the systolic strain for that same volume. No standard bars were added for visualization purposes. Control, normal diastolic function; dysfunction, diastolic dysfunction.

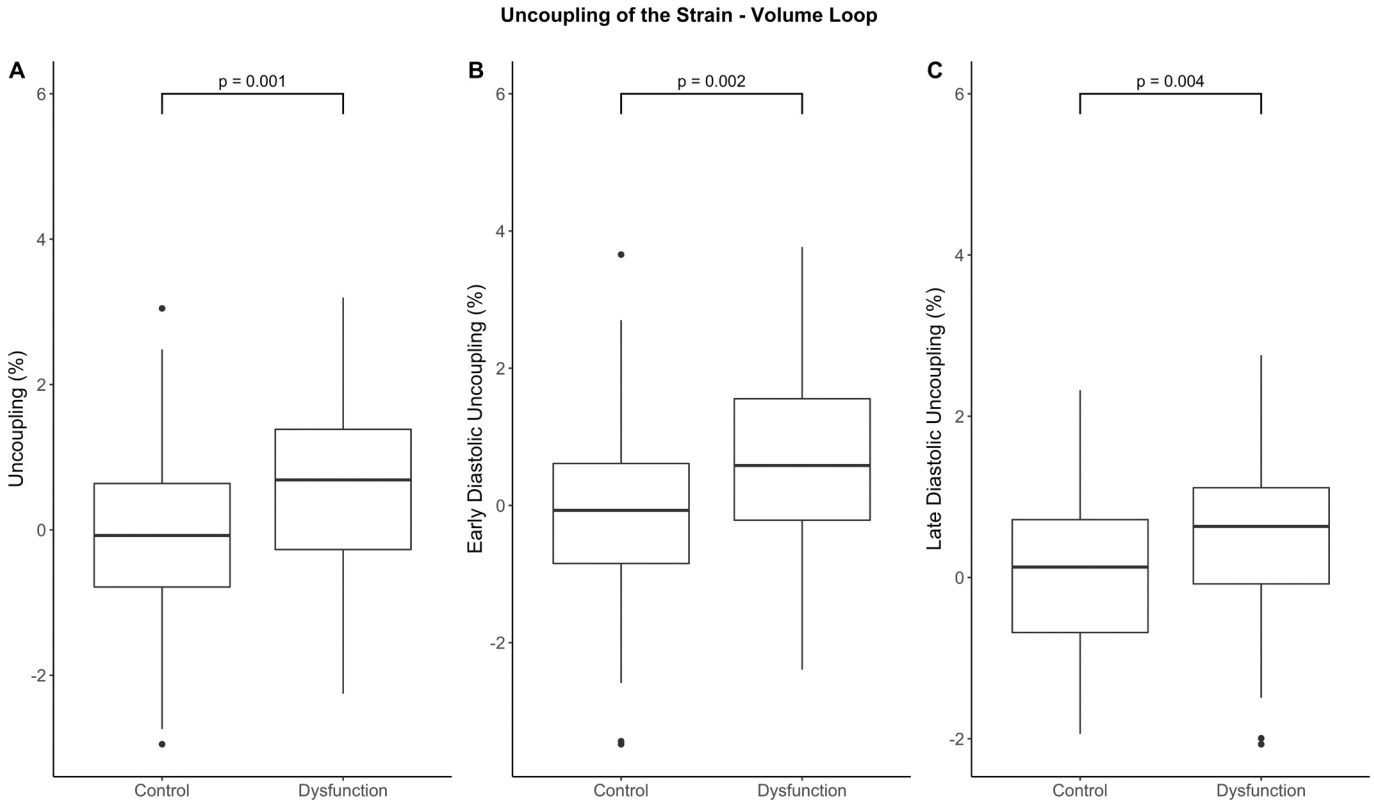


**Fig. 3.** Uncoupling of the Strain – Volume Loop. (A) Uncoupling averaged during entire cardiac cycle, (B) early diastolic uncoupling, and (C) late diastolic uncoupling for patients with normal diastolic function and diastolic dysfunction. Control, normal diastolic function; Dysfunction, diastolic dysfunction.

change since deformation in both directions contributes to LV volume changes [30]. In healthy individuals, we have repeatedly observed a pronounced decrease in deformation in early diastole before LV volume increases [11]. This pronounced longitudinal deformation of the LV might facilitate a negative LV pressure during early diastole, comparable to the diastolic untwist, as a driving force for passive LV filling [31,32]. Interestingly, these changes in early diastole were not observed in our study. Moreover, those with DD even demonstrated a further attenuated longitudinal deformation in early diastole, resulting in an uncoupling between the systolic and diastolic strain-volume relation. Despite the absence of (marked) changes in longitudinal strain, volume increased. Possibly, changes in circumferential strain compensate for this change in LV volume. Altogether, this might suggest mitigation of passive relaxation and the accompanying pressure gradient in the LV during early diastole, potentially caused by altered hemodynamics, in DD. An alternative explanation for the difference in uncoupling between both groups may relate to metabolic changes in DD. Several studies have found changes in cardiac metabolism in patients with DD, including altered

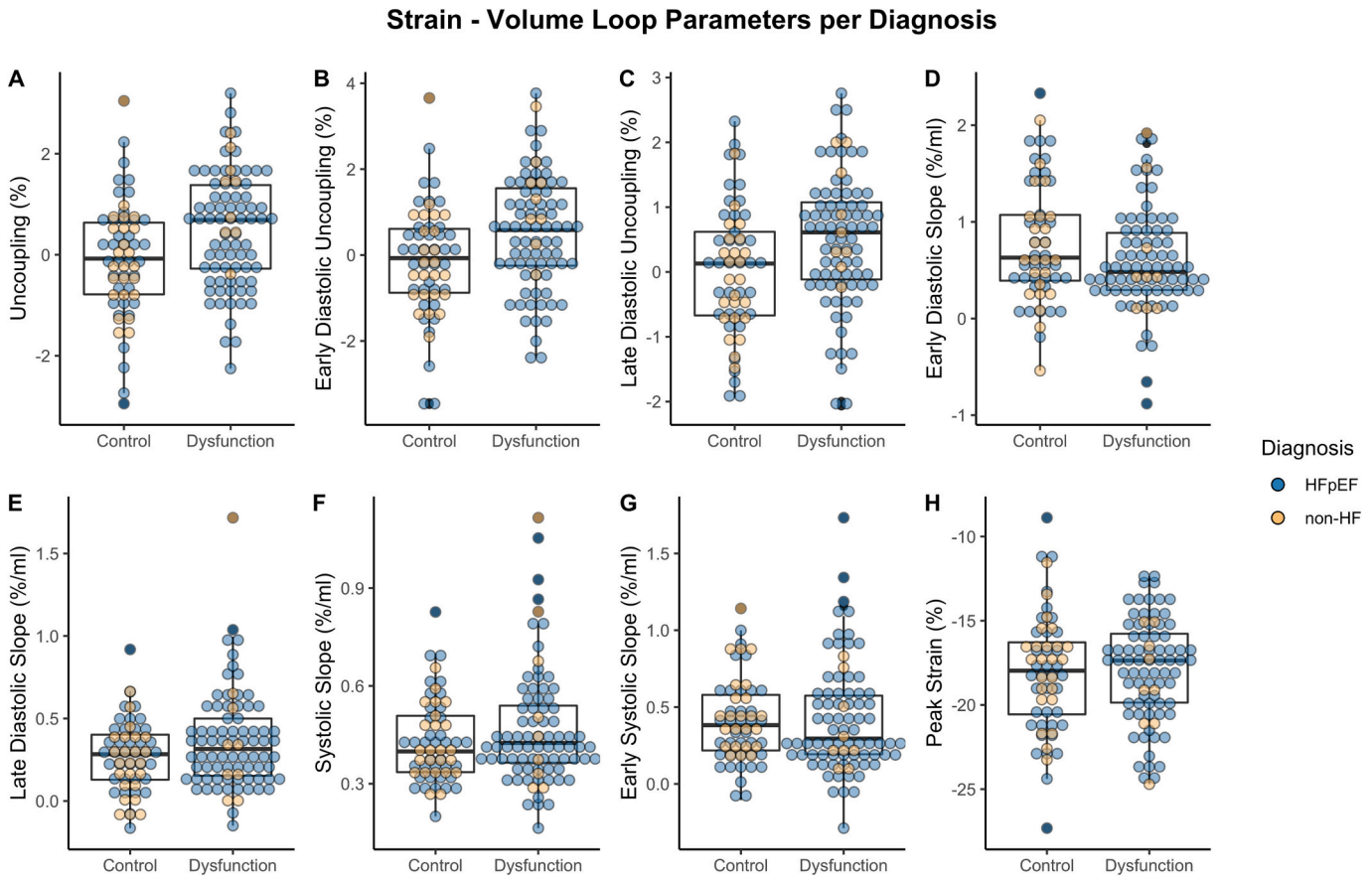


**Fig. 4.** Different Strain – Volume Loop parameters for a subset of patients with normal diastolic function and diastolic dysfunction. Colored dots represent the final diagnosis for each individual patient, i.e. heart failure with preserved ejection fraction (HFpEF) or a non-heart failure (non-HF) diagnosis. Normal, normal diastolic function; Dysfunction, diastolic dysfunction.

calcium reuptake, impaired myocardial energetics, mitochondrial function, or myocardial steatosis, of which some have been shown to cause abnormalities in both active relaxation and stiffness [2,33–37]. These alterations may lead to a distinct pattern of cardiac dynamics, throughout the cardiac cycle, as observed with the SVL. Future studies are warranted to further explore the mechanism of cardiac metabolism and dynamics.

We explored the SVL parameters for patients with asymptomatic DD i.e., non-heart failure, compared with HFpEF patients, since these are considered different entities. Previous research showed different (hemodynamic) characteristics, which also applies to different grades of diastolic dysfunction [38–41]. However, we did not (visually) detect distinctive clustering of SVL parameters between HFpEF and non-heart failure patients in this cohort (Fig. 4).

*Limitations.* Diastolic function was assessed using the 2016 ASE/EACVI recommendations, but we recognize that invasive pressure measurements remain the gold standard. Moreover, a substantial number of patients had indeterminate diastolic function and were therefore excluded from analysis, emphasizing the difficulties in diastolic function assessment. Nonetheless, our data provide additional support for using SVL to detect changes during the cardiac cycle that are not simply detected using the more widely adopted and accepted echocardiographic parameters, peak values or ejection fraction. Secondly, using 2D-echocardiography we could only assess longitudinal strain in relation to volume, and therefore the known role of circumferential strain remains uncovered [30]. Thirdly, since the effects of arrhythmias on the SVL are yet to be elucidated, we excluded patients with atrial fibrillation paced rhythm, limiting the possible clinical applicability of the SVL.

In conclusion, this exploratory study found an association between uncoupling of the SVL and presence of DD as determined by the ASE/EACVI-algorithm in suspected HFpEF patients. These measurements of the SVL provide more insight in the hemodynamic consequences of DD and might aid in future work to detect DD non-invasively. Future research should focus on the SVL in relation to invasive pressure measurements and pressure gradients to further explore the hemodynamic explanation for increased uncoupling. Additionally, for its clinical potential it is of importance to investigate the (additional) discriminative capabilities for specific diagnostic purposes and its value in predicting future cardiovascular events or evaluate response to (non)pharmacological therapy.

## Author contributions

TK, AvD, GW, TE, and DT were involved in the conceptualization. All authors were involved in analysis and interpretation of the results. TK, AvD, TE, and DT were involved in writing the draft of the manuscript. All authors reviewed the results, revised it critically for important intellectual content, and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

## Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

## Data availability

The analyzed dataset, underlying this manuscript, will be shared

upon reasonable request to the corresponding author.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.01.084.

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