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Left Ventricular Strain-Volume Loops in a Healthy Population: The Role of Sex and Age

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ABSTRACT

Background: By combining left ventricular (LV) global longitudinal strain (GLS) with LV volume during the cardiac cycle, LV strain-volume loops (SV-loops) can be generated. LV SV-loop derived parameters provide new insights into the interaction between cardiac contraction and volume in a variety of cardiac diseases and may even have prognostic value. The aim of this study is to describe SV-loops in a healthy adult population and investigate potential sex- and age-related differences of LV SV-loop characteristics.

Methods: In 125 healthy volunteers aged 18–72 years, apical 2-, 3- and 4-chamber views were acquired to measure GLS. Custom software was used to combine strain and volume data to construct SV-loops. Different parameters were derived: (i) linear slope of systolic strain-volume relation (S-Slope); (ii) linear slope of early-systolic strain-volume relation (ES-Slope); (iii) linear slope of early-diastolic strain-volume relation (ED-Slope); (iv) linear slope of late-diastolic strain-volume relation (LD-slope) and (v) uncoupling between systolic and diastolic strain-volume relation (UNCOUP).

Results: For systolic strain-volume relation, higher values were observed in females compared to males, with S-Slope values of 0.19 %/mL m^{-2} [0.17–0.22] and 0.13 %/mL m^{-2} [0.11–0.14], respectively ($p < 0.001$). Similarly, ED-Slope was higher in females than in males, with values of 0.18 %/mL m^{-2} [0.10–0.28] and 0.12 %/mL m^{-2} [0.06–0.18] respectively ($p = 0.003$). Low values for uncoupling between the systolic and diastolic strain-volume relation were observed, with a mean value of 0.34 ± 1.1. Additionally, UNCOUP was positively correlated with age ($r = 0.4$; $p < 0.05$).

Conclusions: Higher values observed in systolic and early-diastolic strain-volume relation in females may reflect sex-specific differences in LV contraction. While the exact mechanisms remain unclear, these findings suggest potential variations in myocardial deformation patterns that warrant further investigation. Consistent with previous work, relative coupling of the systolic and diastolic strain-volume relationship was identified in our cohort of healthy individuals. However, with increasing age, higher values for uncoupling were observed, suggesting age-related alterations in ventricular mechanics that may contribute to changes in cardiac function over time.

1 | Introduction

Echocardiography remains a cornerstone in the management of heart disease due to its ability to noninvasively evaluate ventricular function. It provides real-time visualization of left ventricular (LV) function while enabling the assessment of global function metrics, such as left ventricular ejection fraction (LVEF), which is essential for risk stratification and disease management [1]. Additionally, echocardiography is safe, cost-effective and widely accessible, making it preferable to alternative imaging modalities such as cardiac magnetic resonance (CMR) or ionizing radiation-based techniques.

The assessment of global longitudinal strain (GLS) using speckle-tracking echocardiography (STE) has emerged as a clinically feasible tool for evaluating myocardial function. Over the past decade, GLS has shown to be more sensitive than LVEF in detecting LV dysfunction, providing additional prognostic value [2, 3]. However, GLS only captures myocardial deformation at end-systole, failing to reflect dynamic cardiomechanical changes throughout the cardiac cycle.

To address this limitation, strain-volume loops (SV-loops) have been introduced as a novel parameter, integrating LV GLS with simultaneously measured LV volume across the entire cardiac cycle. By combining functional and volumetric information, SV-loops offer a more comprehensive representation of myocardial mechanics, providing new insights into the interplay between cardiac contraction and volume regulation. SV-loop-derived parameters have shown potential for characterizing cardiac dysfunction across various cardiovascular diseases and may hold prognostic value [4–9]. Despite its clinical potential, data on SV-loops in healthy individuals remain limited. Therefore, this study aims to describe LV SV-loop characteristics in a healthy adult population, and investigate potential sex- and age-related differences.

2 | Methods

2.1 | Study Population and Design

Study subjects were selected from a cohort of healthy adult volunteers (≥18 years) who visited the outpatient clinic of our tertiary center between 2014–2015 (Navigator study). Participants were stratified into five age groups: 18–29, 30–39, 40–49, 50–59 and 60–72 years, with equal representation of males and females in each group. All included subjects underwent physical examination, transthoracic echocardiography (TTE) and an electrocardiogram (ECG) at baseline. Details regarding the study design have been previously described [10]. Data were extracted for all eligible subjects, excluding those in whom strain measurements were not feasible in all three apical views. The study was conducted in accordance with the principles of the declaration of Helsinki and approved by the local medical ethical committee. Written informed consent was obtained from all participants.

2.2 | Image Acquisition and Measurements

All echocardiographic examinations were performed by two dedicated sonographers. Two-dimensional greyscale harmonic images were acquired from a left lateral decubitus position, using an iE33 or EPIC7 ultrasound system (Philips Medical Systems, Best, the Netherlands) equipped with a transthoracic broadband X5-1 matrix transducer (composed of 3.040 elements with 1–5 MHz).

Guidelines of the American Society of Echocardiography and the Association of Cardiovascular Imaging were followed for chamber quantification [11]. For speckle tracking analysis, dedicated software was used (TomTec 2D Cardiac Performance Analysis; Image Arena version 4.6). All measurements were performed blinded for clinical outcome by two researchers. Cardiac cycles were defined based on the positioning of the R-waves on ECG. To define end-systole, timing of aortic valve closure was used. LV strain analysis was performed in the apical two-, three- and four-chamber (A2C, A3C, and A4C) views. The width of the segments was set to line up with the epicardial and endocardial border. The walls were automatically divided in segments based on the American Heart Association 17-segment model and were tracked on a frame-by-frame basis. When tracking was considered suboptimal, borders were adjusted manually.

2.3 | LV Strain-volume Loops

Data on LV strain and LV volume were exported from TomTec software to text-files. Subsequently, a MATLAB script (The Mathworks Inc, version 2019a, Massachusetts, USA) was used to combine strain and volume data to construct SV-loops, as has been described previously [5, 9]. 300-point cubic spline interpolation was used on systolic and diastolic parts of the temporal GLS and volume curves. Minimum and maximum values for the LV volume curve were identified and used as markers for end-systole and end-diastole, respectively.

Parameters that were obtained from the SV-loops to describe systolic LV function were:

i. Linear slope of the strain-volume relation During systole (S-slope)
ii. Linear slope of the strain-volume relation During the first 5% of volume change in systole (ES-slope)

To describe diastolic LV function the following parameters were evaluated:

i. Linear slope of the strain-volume relation During the first 5% of volume change in diastole (ED-slope)
ii. Linear slope of the strain-volume relation During the last 5% of volume change in diastole (LD-slope)
iii. Mean difference (i.e. uncoupling) Between systolic and diastolic strain for any given volume (UNCOUP)

Uncoupling was further divided into early uncoupling (UNCOUP-ED), which represents the first two-thirds of volume change during diastole, and late uncoupling (UNCOUP-LD), which represents the last one-third of volume change during diastole. (Figure 1) All strain-volume plots were manually assessed blinded for study results to evaluate the temporal

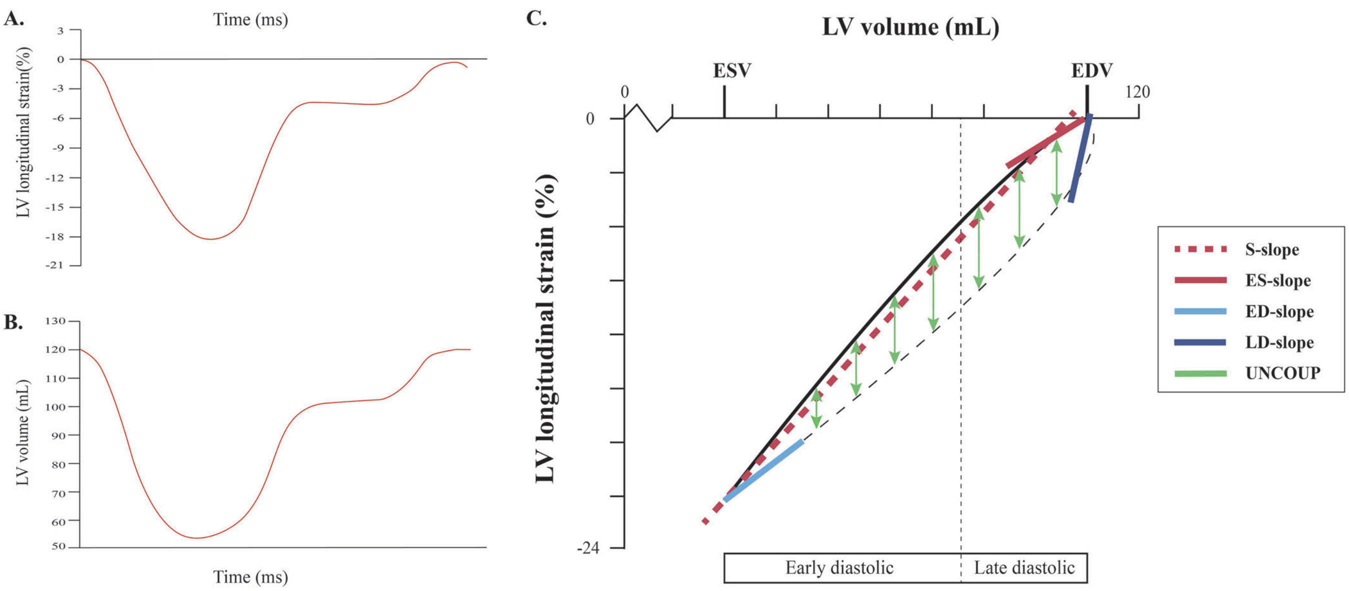

FIGURE 1 | Schematic overview of strain-volume loop analysis. Average LV longitudinal strain (A) and volume (B) from apical 2-, 3- and 4-chamber views during one cardiac cycle. (C) Schematic overview of strain-volume loop characteristics. Black lines represent the strain-volume curve with the bold line representing systole and the dashed line representing diastole.

volume and strain curves. If errors in interpolation were detected, the corresponding strain-volume loop parameter was excluded from analysis. To account for volumetric differences in parameters describing the linear slope of the strain-volume relation, parameters were indexed for body surface area (BSA).

2.4 | Statistical Analysis

Distribution of the data was examined through histograms and the Shapiro-Wilk test. When normally distributed, continuous data were presented as mean and standard deviation (SD) and compared between females and males using a Student's *t*-test. Non-parametric continuous data were presented as median and interquartile range and compared between females and males using a Mann–Whitney U test. Categorical data were presented as frequencies with percentages and compared between females and males using a chi-squared test. Associations of SV-loop parameters with age and other baseline characteristics were assessed using Pearson's or Spearman's correlation coefficient according to distribution. Reproducibility was assessed using intraclass correlation coefficients (ICCs) (Two Way Random – Absolute Agreement – Single Measures) and Bland-Altman analysis for intra- and inter-observer measurements. A p-value below 0.05 was considered statistically significant. Statistical analysis was performed in SPSS for Windows (Version 28.0, SPSS Inc., Chicago, IL, USA).

3 | Results

3.1 | Baseline Characteristics

A total of 125 subjects meeting the inclusion criteria were identified (median age 43 years, 50% female). Baseline characteristics are presented in Table 1. LV stroke volume (SV) was larger in males than in females (p <0.001), with end-diastolic and -systolic volumes of 129 mL [113–151] and 57 mL [48–68] in males and 103 mL [93–114] and 42 mL [37–50] in females, respectively. LV function was normal in all subjects, with higher LVEF (59 % ± 5 vs 56 % ± 4; $p < 0.001$) and GLS (−21 % ± 2 vs. −19 % ± 2; $p < 0.001$) observed in females compared to males.

3.2 | Strain-Volume Loop Characteristics

A total of 125 SV-loops were generated; however, in four subjects certain SV-loop characteristics could not be reliably calculated due to temporal variations in LV volumes or interpolation errors.

Table 2 presents the SV-loop characteristics stratified by sex. For systolic parameters (S-slope, ES-slope), higher values were observed in females after indexing for BSA ($p < 0.001$). Similarly, diastolic parameters (ED-slope, LD-slope) were higher in females, with values for ED-slope of 0.18 %/mL m^{-2} [0.10–0.28] and 0.12 %/mL m^{-2} [0.06–0.18], respectively (p = 0.003). (Figure 2) Low values for UNCOUP were observed for both females and males (p = 0.619) with a mean value of 0.34% ± 1.1.

Figure 3 illustrates the relation between UNCOUP and age, showing a trend toward higher values for UNCOUP in older age groups ($r = 0.40$; $p < 0.05$). No other significant relations between SV-loop parameters and age were found (Table S2).

An overview of the association between SV-loop parameters and conventional echocardiographic measurements can be found in Table S2. UNCOUP demonstrated a moderate correlation with e' and E/e', with values of −0.48 ($p < 0.05$) and 0.43 ($p < 0.05$), respectively.

TABLE 1 | Baseline characteristics.

Demographic	All (n = 125)	Female (n = 63)	Male (n = 62)	p-value
Age, years	43 [31–56]	45 [36–56]	43 [30–55]	0.435
BSA, m^2	1.9 ± 0.2	1.8 ± 0.1	2.0 ± 0.1	<0.001
Systolic blood pressure, mmHg	126 [115–133]	122 [114–129]	128 [122–138]	0.001
Diastolic blood pressure, mmHg	80 ± 9	77 ± 9	82 ± 8	<0.001
Heart rate, bpm	69 [63–77]	70 [65–78]	68 [60–77]	0.289
Sinus rhythm, n (%)	125 (100)	63 (100)	62 (100)	
Echocardiographic				
LVEDD, mm	46 ± 4	45 ± 3	47 ± 4	0.004
LVESD, mm	28 [26–30]	27 [25–30]	29 [27–31]	0.023
LVEDV, mL	113 [100–132]	103 [93–114]	129 [113–151]	<0.001
LVESV, mL	49 [40–61]	42 [37–50]	57 [48–68]	<0.001
LV SV, mL	67 ± 14	61 ± 11	73 ± 14	<0.001
LVEF, %	57 ± 5	59 ± 5	56 ± 4	<0.001
GLS, %	−20 ± 2	−21 ± 2	−19 ± 2	<0.001
E-wave, m/s	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.1	0.002
A-wave, m/s	0.5 [0.4–0.6]	0.5 [0.4–0.6]	0.5 [0.4–0.5]	0.283
Deceleration time, ms	183 [165–210]	180 [165–201]	190 [162–217]	0.234
E', cm/s	9.6 ± 2.5	9.7 ± 2.7	9.5 ± 2.3	0.639
E/A ratio	1.4 [1.2–2.0]	1.5 [1.2–2.1]	1.4 [1.0–1.9]	0.527
E/e' ratio	7.2 [6.3–8.5]	7.4 [6.5–9.3]	7.0 [6.1–8.1]	0.037
LAVI, mL/m^2	28 [23–33]	29 [24–33]	27 [22–32]	0.162
LAVI>34 mL/m^2, n (%)	24 (40)	12 (20)	12 (20)	

Abbreviations: BSA, body surface area; GLS, global longitudinal strain; LAVI, left atrial volume index; LV SV, left ventricular stroke volume; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume.

3.3 | Reproducibility

Reproducibility was assessed in 20 subjects. Intra-observer variability values were in general moderate to good across SV-loop parameters. Inter-observer analysis revealed moderate to good agreement for systolic parameters; however, greater variability was observed for the diastolic parameters (ED-slope, LD-slope and UNCOUP) (Table 3). Figure S1 provides an overview of the Bland-Altman analysis.

4 | Discussion

The aim of this study was to describe novel SV-loop derived parameters in a healthy adult population and to explore the influence of sex- and age-related differences. Our findings demonstrate higher values for both systolic and early-diastolic strain-volume relationships in females, even after correction for differences in LV dimensions, highlighting sex-related differences in LV mechanics. Moreover, healthy individuals exhibited relative coupling of the systolic and diastolic strain-volume relationship, whereas a significant shift toward uncoupling was observed with increasing age. Together these findings underscore the sensitivity of SV-loops in detecting subtle differences in contraction mechanics.

4.1 | Sex-Related Differences

Sex is a well-known factor influencing reference ranges for strain analysis, and current echocardiographic guidelines recommend incorporating sex-specific considerations when assessing myocardial deformation [12–14]. In our study, higher values for S-slope and ES-slope were observed in females, indicating a relatively smaller volume displacement after longitudinal shortening. Persistence of these differences after adjustment for LV dimensions, suggests intrinsic sex-related differences in LV contraction mechanics, underscoring the need for sex-specific reference values for interpretation of these novel parameters.

For the diastolic strain-volume relation, early filling was characterized by higher ED-slope values in females compared to males. A previous study by Kerstens et al. [7]. hypothesized that higher values in the early diastolic strain-volume relation could indicate more pronounced longitudinal deformation before LV volume increases. This pattern may be analogous to diastolic

TABLE 2 | Strain-volume loop characteristics.

Characteristics	Valid cases *n* (%)	All (*n* = 125)	Female (*n* = 63)	Male (*n* = 62)	*p*-value
S-slope, %/mL m^{-2}	125 (100)	0.16 [0.13–0.19]	0.19 [0.17–0.22]	0.13 [0.11–0.14]	<0.001
ES-slope, %/mL m^{-2}	125 (100)	0.14 [0.10–0.19]	0.17 [0.12–0.23]	0.12 [0.10–0.15]	<0.001
ED-slope, %/mL m^{-2}	125 (100)	0.15 [0.07–0.22]	0.18 [0.10–0.28]	0.12 [0.06–0.18]	0.003
LD-slope, %/mL m^{-2}	125 (100)	0.13 [0.08–0.17]	0.15 [0.11–0.21]	0.11 [0.07–0.16]	<0.001
UNCOUP, %	121 (97)	0.34 ± 1.1	0.29 ± 1.1	0.39 ± 0.95	0.619
UNCOUP-ED, %	125 (100)	0.39 ± 1.2	0.31 ± 1.3	0.47 ± 1.1	0.462
UNCOUP-LD, %	121 (97)	0.23 ± 0.92	0.23 ± 1.0	0.23 ± 0.82	0.998

Abbreviations: ED-slope, linear slope of the early-diastolic strain-volume relation; ES-slope, linear slope of the early-systolic strain-volume relation; LD-slope, linear slope of the late-diastolic strain-volume relation; S-slope, linear slope of the systolic strain-volume relation; UNCOUP, difference between systolic and diastolic strain-volume relation; UNCOUP-ED, difference between the systolic and diastolic strain-volume relation in early-diastole; UNCOUP-LD, difference between the systolic and diastolic strain-volume relation in end-diastole.

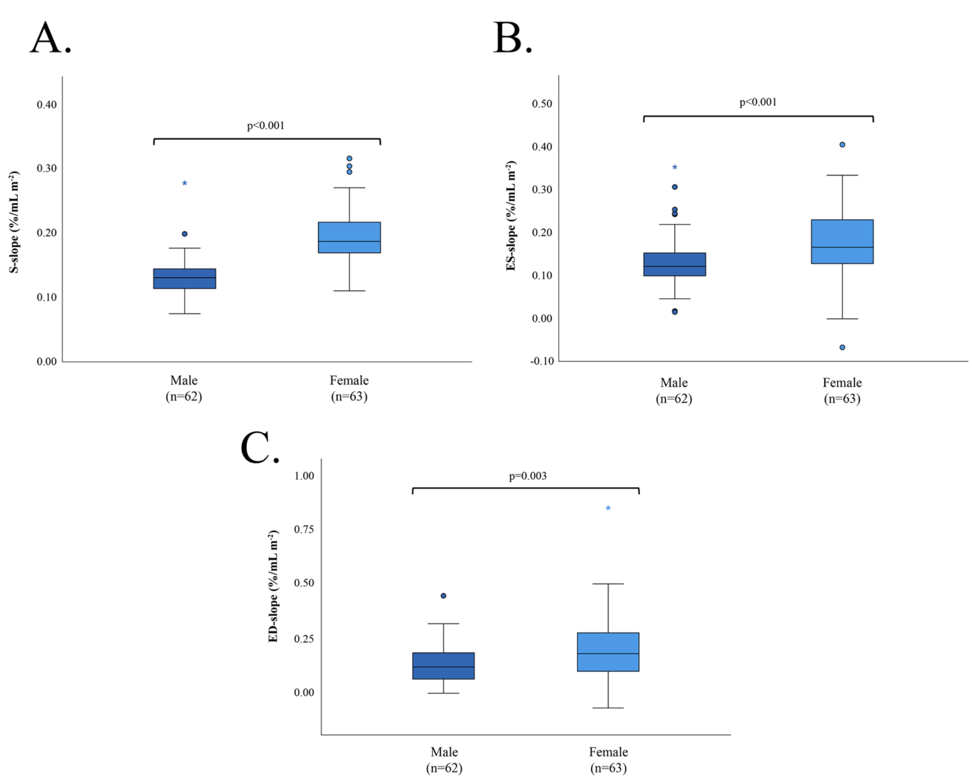

FIGURE 2 | Sex-related differences in strain-volume relation. Boxplots showing the differences between sex and S-slope (A), ES-slope (B) and ED-slope (C).

untwisting of the LV, facilitating a more pronounced negative LV pressure gradient in females, which could enhance early diastolic filling [15, 16]. Although these findings suggest intrinsic sex-related differences in LV diastolic mechanics, further investigation is needed to assess whether these variations translate into functional advantages or disadvantages in long-term cardiac performance. Future studies incorporating circumferential and radial strain analysis, as well as pressure-volume relationships, could provide a more comprehensive understanding of sex-specific myocardial mechanics.

4.2 | Age-Related Differences

SV-loops offer new insights into the dynamic interplay between longitudinal strain and LV volume changes throughout the cardiac cycle. Previous literature has demonstrated relative coupling of the strain-volume relation in healthy individuals and relative uncoupling in patients with impaired LV function during the early filling phase in a variety of diseases [5–8]. Our study reinforces these findings, demonstrating low UNCOUP values in healthy individuals, indicating relative

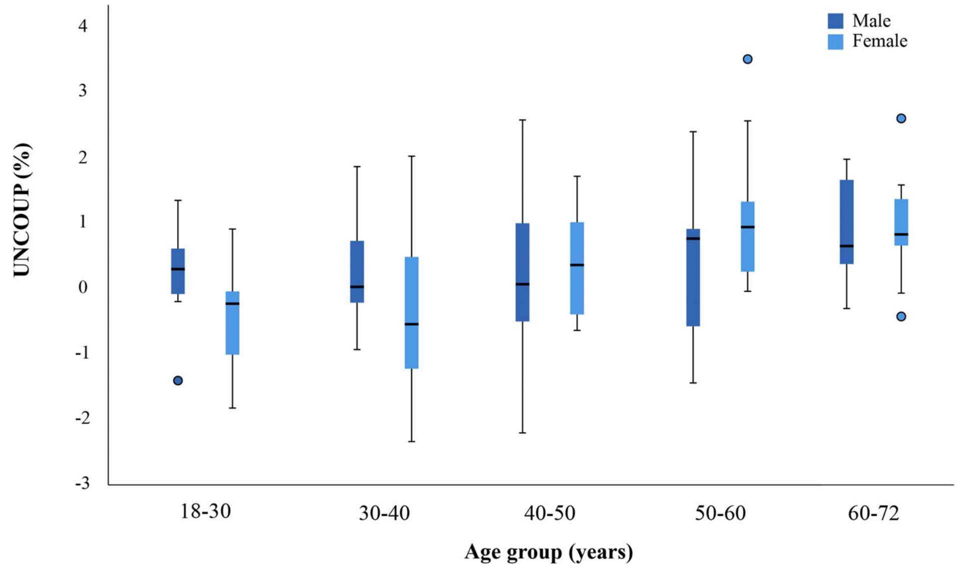

FIGURE 3 | Uncoupling of strain-volume relation between age groups. Distribution of UNCOUP for different age groups, stratified for sex. Males are represented in dark blue, females in light blue.

TABLE 3 | Observer variability.

	Intra-observer		Inter-observer	
Variable	**Valid cases *n* (%)**	**ICC (95% CI)**	**Valid *n* (%)**	**ICC (95% CI)**
Peak strain	20 (100)	0.73 (0.09–0.91)	20 (100)	0.78 (0.49–0.91)
LVEDV	20 (100)	0.86 (0.00–0.97)	20 (100)	0.87 (0.60–0.96)
LVESV	20 (100)	0.97 (0.65–0.99)	20 (100)	0.85 (0.49–0.95)
S-slope	20 (100)	0.95 (0.24–0.99)	20 (100)	0.93 (0.71–0.98)
ES-slope	20 (100)	0.78 (0.53–0.91)	20 (100)	0.75 (0.47–0.89)
ED-slope	20 (100)	0.87 (0.72–0.95)	20 (100)	0.58 (0.21–0.81)
LD-slope	20 (100)	0.78 (0.52–0.91)	20 (100)	0.45 (0.00–0.74)
UNCOUP	17 (85)	0.78 (0.49–0.91)	17 (85)	0.46 (0.03–0.76)
UNCOUP-ED	18 (90)	0.81 (0.56–0.93)	18 (90)	0.55 (0.12–0.81)
UNCOUP-LD	19 (95)	0.68 (0.35–0.86)	19 (95)	0.36 (−0.09–0.69)

Abbreviations: ED-slope, linear slope of the early-diastolic strain-volume relation; ES-slope, linear slope of the early-systolic strain-volume relation; LD-slope, linear slope of the late-diastolic strain-volume relation; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; S-slope, linear slope of the systolic strain-volume relation; UNCOUP, difference between systolic and diastolic strain-volume relation; UNCOUP-ED, difference between the systolic and diastolic strain-volume relation in early-diastole; UNCOUP-LD, difference between the systolic and diastolic strain-volume relation in end-diastole.

coupling of the strain-volume relationship compared to the diseased LV.

Despite this general coupling of the strain-volume relation in our cohort, we observed a shift toward uncoupling with advancing age, coinciding with increased markers of diastolic dysfunction, such as e' and E/e'. It is well established that LV diastolic function declines with age, even in the absence of overt cardiovascular disease [17]. Early diastolic filling is driven by LV untwisting, which involves not only longitudinal but also circumferential and radial motion. Therefore, age-related uncoupling of the early-diastolic strain-volume relation may indicate subtle cardiomechanical adaptations, where increased circumferential relaxation could compensate to maintain adequate cardiac filling. Although circumferential strain data were not available in this study, previous work of Skaarup et al. [18]. who used STE to measure layer specific circumferential strain, supports this hypothesis. Their findings demonstrated higher circumferential strain values with advancing age, suggesting a compensatory shift in contraction mechanics.

4.3 | Reproducibility

The assessment of GLS from speckle-tracking analysis of two-dimensional echocardiography has become a widely available tool for evaluating myocardial function. Although the technology is considered reliable within an acceptable range, its accuracy and consistency remain influenced by image quality, temporal resolution and user expertise. In our study, SV-loops were feasible in all included subjects. However, after manual review of SV-loops and independent temporal strain and volume curves, interpolation errors during the late-diastolic phase were observed in four subjects, which led to exclusion of the corresponding parameters from analysis. As these interpolation errors may be attributed to the relatively minimal change of strain and volume in diastasis, future research should optimize current approach in a manner that more closely reflects physiology.

Despite moderate to good intra-observer agreement, a relatively wide confidence interval was observed, which may in part be attributed to the small sample size but may also reflect inaccuracies in tracking strain and volume. Inter-observer agreement was less favorable, with discrepancies in the late diastolic phase. These inconsistencies were primarily due to less accurate strain-volume measurement over relatively short sections, emphasizing the challenges of tracking strain and volume over the full cardiac cycle. These findings highlights the critical role of good temporal resolution in strain analysis, especially when assessing strain-volume relationships dynamically rather than at a single time point such as end-systole. Future studies should focus on optimizing temporal resolution and tracking of strain and volume across the entire cardiac cycle to enhance the reliability of SV-loop-derived parameters.

4.4 | Limitations

This study was conducted at a single center with a relatively small sample size, which warrants caution in interpreting the findings. Additionally, participants aged 73 years and older were not included, despite this age group comprises a substantial proportion of the current patient population. Consequently, the applicability of these results to older individuals remains uncertain.

5 | Conclusions

This study provides an overview of SV-loop derived parameters in a healthy adult population. The technique identified higher systolic and early-diastolic strain-volume relationships in females, offering new insights into sex-related differences in myocardial mechanics. Furthermore, relative coupling of the systolic and diastolic strain-volume relation was observed, with a shift toward uncoupling in older individuals. As cardiac filling involves not only longitudinal motion but also circumferential and radial components, these finding highlight potential compensatory mechanisms between deformation planes. Future studies integrating circumferential and radial strain analysis may further elucidate sex- and age-specific remodeling patterns, enhancing our understanding of cardiac function across the lifespan and between sexes.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supplemental Figure 1: Bland-Altman analysis for intra- and inter-observer variability. Bland-Altman plots for S-slope (A) and UNCOUP (B) of the intra-observer analysis are displayed. No evidence of proportional bias was observed for any SV-loop parameter. However, considerable measurement variability was evident, which may reflect the known inherent variability of the underlying volume and strain measurements. Notably, S-slope (A), along with several other SV-loop parameters, shows evidence of systematic variation, which may reflect operator-dependent variability, as systematic variation was also observed in underlying measurements (left ventricular end-diastolic volume, left ventricular end-systolic volume and peak-strain). Limit of agreement (LoA) is defined as bias ± 1.96 x standard deviation. Mean bias is represented by the red line, whereas the green lines represent the upper and lower LoAs. **Supporting Information**: echo70534-sup-0002-tablesS1-S2.docx