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Over all variability of mitral annular plane peak systolic velocity and peak global longitudinal strain rate in relation to age, body size, and sex: The HUNT Study

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Abstract

Background: Left ventricular (LV) systolic global function can be assessed by peak annular systolic velocity S'. Global longitudinal strain rate (GLSR) is relative LV shortening rate, equivalent to normalizing S' for LV length (S'_n). It has previously been shown that mitral annular plane systolic excursion (MAPSE) and global longitudinal strain (GLS) have similar biological variability, but GLS normalizes for one dimension only, inducing a systematic error, increasing body size dependence. The objective of this study was to compare S' with GLSR in the same way, comparing biological variability and body size dependence.

Methods and Results: A total of 1266 subjects from the third wave of Nord-Trøndelag Health Study (HUNT), without evidence of heart disease, were examined. Strain rate, S' and wall lengths were measured in the four walls of the two- and four-chamber views. Mean S' was 8.4 (1.4) cm/s, (S'_n) was 0.7 (0.14)s^{-1} and GLSR 1.02 (0.14)s^{-1}. All measures declined with age. Normalization of mitral annular velocities for LV length, or the use of GLSR, did not reduce overall biological variability compared with S'. S' did show a weak, positive correlation to BSA, while S'_n and GLSR a slightly stronger, negative correlation to BSA.

Conclusions: S', S'_n, and GLSR have similar biological variability, which is mainly due to age, not body size variation. Normalizing S' for LV length (as in S_n or GLSR) reverses correlation with BSA inducing a systematic error, due to the one-dimensional normalization for one dimension only.

KEYWORDS
mitral annular velocity, normalization, strain rate imaging, tissue Doppler echocardiography

1 | INTRODUCTION

Systolic left ventricular (LV) shortening can be assessed by peak mitral annular systolic velocity (S') by spectral Doppler,[1-3] which correlates

with EF in dilated heart disease,[1] although slightly less than mitral annular plane systolic excursion (MAPSE).[4] S' is reduced in pathological hypertrophy[2,3] and especially in heart failure with preserved EF,[5,6] shows better correlation with brain natriuretic peptide than

EF[7] and has prognostic predictive value in hypertension.[8] By tissue Doppler, both systolic and diastolic function can be measured by the same method, showing the interdependence between systolic and diastolic function.[2,3,9] Our group has previously published age and sex-specific normal values for S′ from the HUNT Study,[9] showing higher values in men, and lower velocities with increasing age. S′ shows differences between walls in healthy individuals, so for a global measure, measurements of S′ from different walls have to be averaged[9-11] as shown in Figure 1A.

Systolic strain rate is velocity difference per length unit[12] and has been validated as a measure of segmental systolic dysfunction[13-15] (Figure 1B). Peak global longitudinal strain rate (GLSR), being the mean of all segments is a global measure of LV function, the rate of LV shortening normalized for LV length. Normalizing annular velocity (S′$_n$) for wall length (WL) is also a measure of global strain rate as shown in Figure 2. Thus, both GLSR and S′$_n$ are measures of shortening rate, normalized for LV length. Normalized measures were supposed to compensate for differences due to heart, and thus, body size, reducing biological variability. However, recent data from the Nord-Trøndelag Health Study (HUNT) have shown that for MAPSE and global longitudinal strain (GLS) normalizing for LV length did not reduce biological variability, in fact normalizing for LV length induced a systematic error, with subsequently increased dependence on body size and sex.[16] The basic measures of S′, wall lengths and GLSR in this material, have all been published previously,[9,17,18] but the normalized values of S′$_n$, and the comparisons of variability and relation to body size are new. The aim of the present study was to ascertain the biological variability of S′ vs the normalized values S′$_n$ and GLSR in terms of the relations to age, body size and sex, and to see if the relations were similar to those of MAPSE and GLS.

2 | METHODS

2.1 | Study subjects

The study population was recruited from 50 839 participants of the third wave of the Nord-Trøndelag Health Study (HUNT3) and has been extensively described in previous papers.[9,10,16,17,19] Briefly, a random sample restricted to two communities was invited to the echocardiographic study, excluding subjects with a history of heart disease, hypertension, or diabetes. A total of 1296 were included. After echocardiography, another 30 individuals with significant pathology on the echocardiogram were excluded. Thus, the study consisted of 1266 subjects aged 19-89 years. All subjects in the HUNT Study gave their written consent to participate in both main and substudies. The study was approved by the regional ethical committee (REK 4.2009.397 and 2018/929). Basic characteristics are given in Table 1. Echocardiographic measures were all normally distributed. Blood pressure was measured during the visit, as the mean of the two last of three automated measures. Despite excluding subjects with known hypertension, it is evident from Table 1 that some untreated

hypertension may be present in the material, although this was spot blood pressures on a single day. In the three age groups, <40, 40-60, and >60 years, respectively, 7%, 18%, and 44% had Systolic blood pressure (SBP) >140 mm Hg, and 3%, 9%, and 10% had diastolic blood pressure (DBP) >90 mm Hg. Both (SBP) and (DBP) correlated with age: $R = .40$ and $.24$, respectively (both $P < .001$).

2.2 | Echocardiography

One experienced echocardiographer (HD) conducted all the examinations. Subjects were examined in left lateral supine position with a Vivid 7 scanner (version BT06, GE Vingmed Ultrasound). Transducers were phased-array matrix transducers (M3S and M4S). The examination included apical four- and two-chamber and apical long-axis views. Mean B-mode frame rate was 44 FPS. Pulsed-wave tissue Doppler recordings of mitral annular velocities were acquired from the base of the septum and lateral wall in four-chamber, and anterior and inferior walls in the two-chamber views, S′ was measured by spectral tissue Doppler and averaged per patient for global measure in accordance with general usage.[1-3,6,9] Wall lengths (WL) were approximated by the straight line from the apex to the mitral ring at end-diastole in B-mode, as shown in Figure 1B. S′$_n$ was calculated as S′/WL and averaged for all four walls per patient for global value.

Color tissue Doppler images from the three standard apical planes were acquired separately with mean Doppler frame rate of 100 FPS, and B-mode images in the background. Peak systolic strain rate was measured by the combined segmental tissue Doppler and speckle tracking method described earlier [17,20] as shown in Figure 1B. Care was taken to avoid visible clutter areas. Global average (GLSR) was calculated of all six walls (16 segment model) from the three standard planes.[21] We also calculated the mean from the four walls of the four-chamber and two-chamber views, for comparison with S′ and S′$_n$. Longitudinal systolic strain rate is shortening, being negative, but the main objective was to compare with S′, so strain rate values are here referred as numerical values.

2.3 | Calculation and statistics

Calculations and statistics were done in SPSS (IBM, corp). Echocardiographic indices are presented as means and standard deviations (SD). Strain is given in numeric values. Differences between genders were tested by independent samples Student's *t*-test, differences between age groups by one-way ANOVA, with Bonferroni post hoc comparisons. As strain rate and velocity have different units, the relative SD (SD/mean) was used as variability measurement. Correlations were assessed by Pearson's correlation coefficient. Linear regression was used for assessing the interaction of BSA, age, and gender. Repeatability of the different measures has been extensively studied previously.[9,10,16-18] Shortly inter-observer variations in repeated acquisitions had a coefficient of repetition (CoR) of 1.7 cm/s and mean error (ME) of 8% for S′ averaged from four walls which increased to 11%
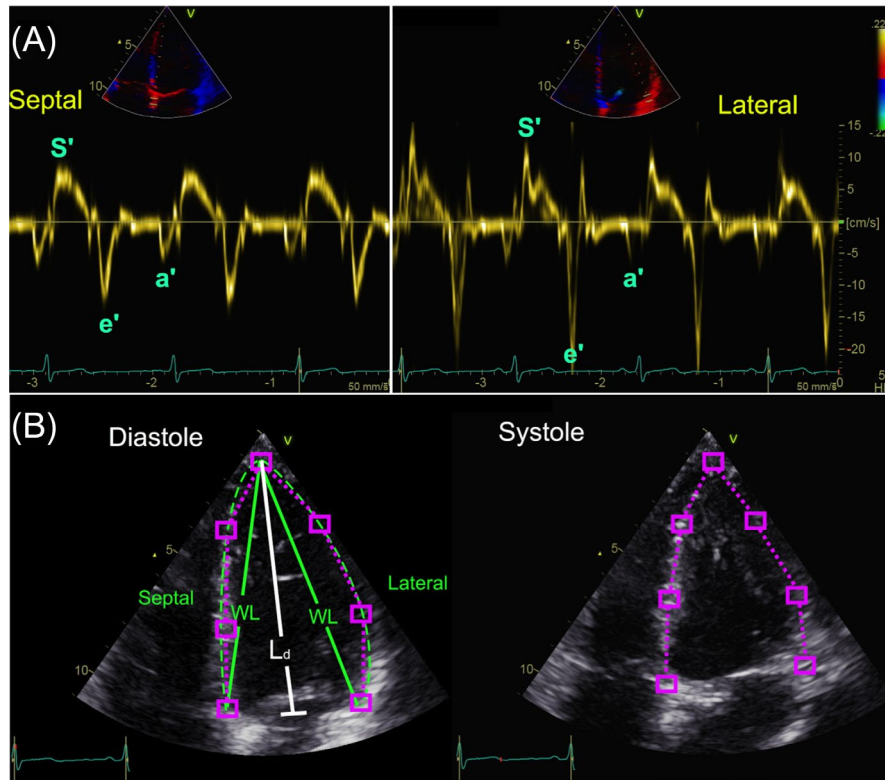
FIGURE 1 Measurements of peak mitral annular velocities, left ventricular wall lengths, and systolic longitudinal strain rate. A, Peak systolic mitral annular plane velocity (S′) by pulsed-wave spectral tissue Doppler curves from the septal and lateral points. Diastolic measures are obtained by the same method; e′ is peak early diastolic velocity (relaxation), a′ is peak late diastolic velocity (atrial contraction). It can be easily and robustly measured in the mitral annular points. It is evident that the lateral S′ is higher than the septal, so for global S′, at least two points have to be averaged. B: Wall lengths (WL) were approximated by the straight line from the apex to the mitral ring at end-diastole (green straight lines). Normalized S'_n was measured by S′/WL per wall. WL overestimates the LV diastolic length (Ld—white line), while underestimating the true wall length (green broken line). Segmental strain rate was measured with a combined tissue Doppler—speckle tracking method tracking kernels at the segmental borders (magenta squares), in the longitudinal direction by tissue Doppler, and in the lateral direction by speckle tracking. Strain rate was calculated as the temporal derivative of strain, converted from Lagrangian to Eulerian strain rate

when using mean of only two walls. The corresponding CoR and ME was 0.2 s^{-1} and 9% for GLSR and 1.6 mm and 4% for WL, respectively.

3 | RESULTS

Feasibility was 97% for global S′, 93% for S'_n, and 97% for GLSR. However, as segmental strain is susceptible to clutter, almost 40% of segments were rejected in order to obtain representative normal segmental values for SR and strain.[16] Feasibility per wall was 96%-97% for all four walls for S′, 93% for S'_n and 58%-90% for SR, lowest in anterior wall.

Distribution of measures are shown in Figure 3, panel A. GLSR was normally distributed, while S′ and S'_n showed significant, but modest skewness (near normal) of −0.24 and 0.35, respectively. As seen by Table 2, the relative SD was not very different between S′ and the two normalized measures S'_n and GLSR.

Sex- and age-related values are given in Table 2. For direct comparison, numerical values are given and discussed, even though the correct usage for GLSR and S_n should be negative systolic values as explained in Figure 2.

As pulsed-wave tissue Doppler conventionally is taken in four points from four- and two-chamber views, values for the mean of all four walls as well as for only septal and lateral walls (being a time-saving practice in everyday clinic) are given as secondary measures. Differences between two and four walls for S′ and S'_n were both significant, although differences are negligible in practice. GLSR was measured in all six walls, but for comparison, mean of the same four and two walls are also given. Again, differences were statistically significant, but in practice negligible. GLSR, however, was significantly higher than S'_n.

Mean S′ was highest in men (8.2 (women) vs 8.6 (men) cm/s, $P < .001$), while S_n (0.89 (women)s^{-1} vs 0.85 s^{-1}(men)) and GLSR (1.05 (women)s^{-1} vs 1.01 s^{-1} (men)) were highest in women, both $P < .001$.

S′ correlated with MAPSE ($R' = 0.55$). There was a weak positive univariate correlation of BSA with S′ of 0.13, while S_n and GLSR showed numerically slightly higher, but negative correlations with BSA as seen in Table 3. The relation between the three measures and BSA is shown in Figure 3, panel B. BSA was also significantly different between sexes (Table 1, $P < .001$). In linear regression with sex, age, and BSA, BSA was independently associated with S'_n, and sex was independently associated with S′ and GLSR as seen from Table 3.
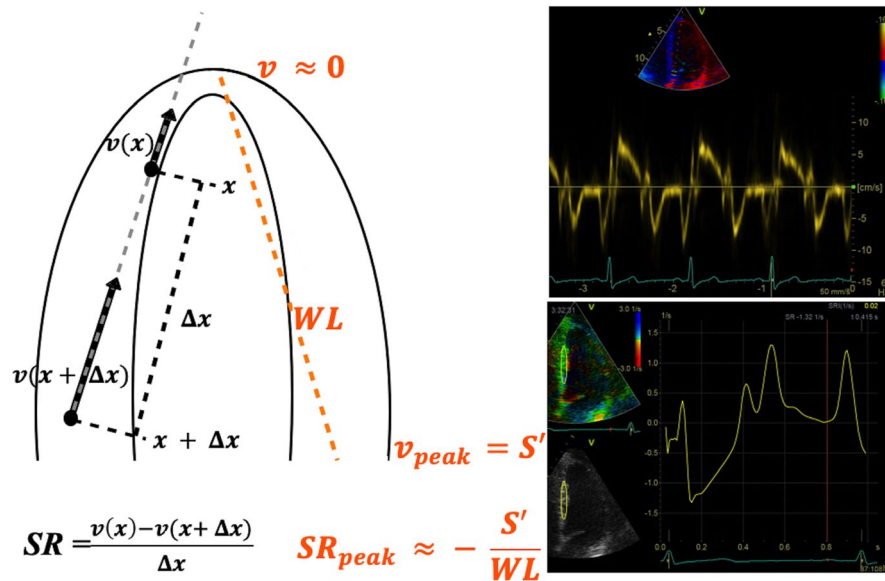
FIGURE 2 The relation of peak systolic mitral annular velocity and left ventricular systolic longitudinal strain rate. Left, the definition of strain rate $SR = \frac{v(x) - v(x+\Delta x)}{\Delta x}$ where $v(x)$ and $v(x+\Delta x)$ are velocities in two different points, and Δx is the distance between the points. As the apex is nearly stationary, v in apex is near zero. Peak systolic annular velocity (S') is the summed velocity of a whole wall. Wall length (WL) will then be Δx, and the strain rate formula will then give peak $SR \approx \frac{0 - S'}{WL} = \frac{-S'}{WL}$. Panels to the right show top: pulsed-wave spectral Doppler curve from the base of the septum, and bottom, a strain rate curve from most of the length of the septum of the same subject

TABLE 1 Basic measurements of the study population

	Women	Men	Total
Numbers	663	603	1266
Age (years)	47.8 (13.5)	50.5 (13.7)	49.1 (13.7)
Height (m)	1.65 (0.11)	1.79 (0.07)	1.72 (0.12)
Weight (kg)	71.6 (14.0)	87.1 (30.7)	79.0 (24.7)
BSA (m^2)	1.97 (0.16)	2.05 (0.16)	1.91 (0.20)
BMI (kg/m^2)	25.9 (4.2)	26.8 (3.5)	26.3 (3.9)
BP systolic/diastolic (mm Hg)	127/71 (17/10)	133/77 (14/10)	130/74 (16/10)
Present or ex smokers (%)	54.8%	49.6%	52.4%
Total cholesterol (mmol/L)	5.5 (1.1)	5.6 (0.9)	5.5 (1.1)
HDL cholesterol (mmol/L)	1.5 (0.3)	1.2 (0.3)	1.4 (0.4)
IVSd (mm)	8.1 (1.4)	9.5 (1.5)	8.7 (1.6)
LVIDd (mm)	48.8 (4.5)	52.9 (5.6)	50.8 (5.4)
LVPWd (mm)	8.2 (1.4)	9.6 (1.4)	8.9 (1.6)

Note: Measurements are mean (SD).

Abbreviations: BMI = body mass index; BP = blood pressure; BSA = body surface area; IVSd = diastolic intraventricular septal thickness; LVIDd = diastolic left ventricular diameter; LVPWd = diastolic left ventricular posterior wall thickness.

Differences between age groups were highly significant (post hoc $P < .001$ overall and for difference between all age groups) as seen in Table 2. Relations with age are shown in Figure 3, panel C. There was almost no correlation between age and BSA ($R = -.06$, $P = .04$), not significant if multiple correlations were taken into account. In line with this, there was little difference between univariate and multivariate correlations of the echocardiographic measures and age as seen from Table 3.

Age correlated with BP, in linear regression against age and blood pressure, age had the strongest association with S', S'_n, and GLSR with β of -0.39, -0.245, and -0.25, respectively (all $P < .001$), SBP was not significant, while DBP was also associated with all three (β of -0.1, -0.19, and -0.12, all $P < .005$).

4 | DISCUSSION

The main findings in this study were as follows:

- Normalization of mitral annular velocities for LV length, or the use of GLSR, do not reduce overall variability compared with S'.
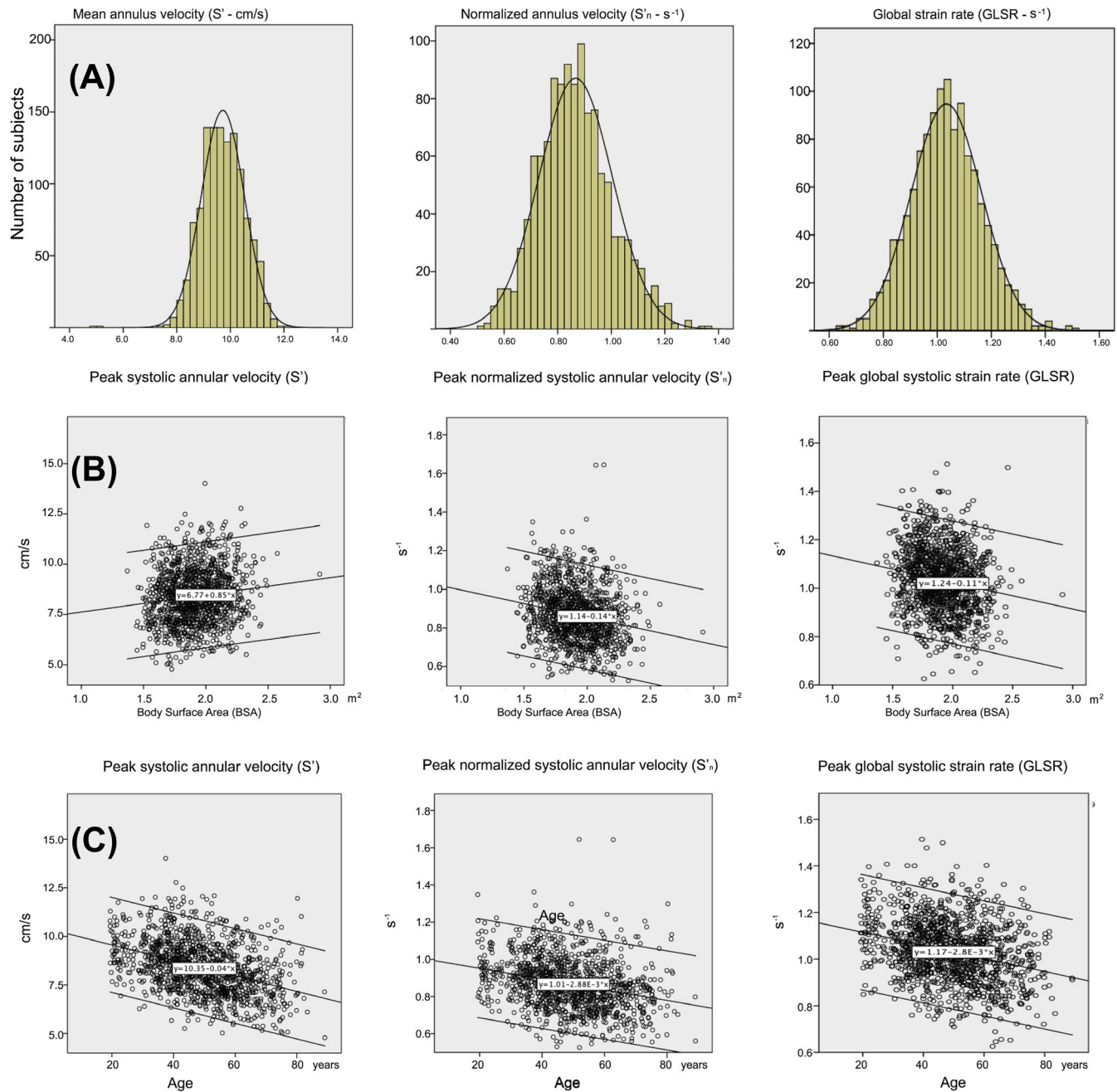
FIGURE 3 Peak systolic mitral annular velocity and global strain rate. Distributions and relation with body surface area and age.. A: Distribution of both S′, normalized S′ (S′$_n$) and GLSR values, showing near normal distribution of all measures. B: Relation of S′, S′$_n$, and GLSR with body surface area, showing a modest positive relation of S′, a more pronounced negative relation of S′$_n$ and GLSR. C: Relation of S′, S′$_n$, and GLSR with age, showing decrease of all measures with increasing age. Abbreviations: BSA; body surface area, GLSR; global strain rate, S′; peak mitral annular systolic longitudinal velocity, S′$_n$; peak mitral annular systolic longitudinal velocity normalized for wall length, e′; peak mitral annular early diastolic longitudinal velocity, e′; peak mitral annular late diastolic longitudinal velocity, WL; wall length

- All measures are age dependent.
- S′ shows a weak, positive correlation to BSA, while S′$_n$ and GLSR are somewhat stronger, negatively correlated to BSA.

The findings mainly confirm what was recently found for MAPSE vs GLS in the same material.[16] Both GLSR and S′n are measures of global strain rate by different methods, and both are included to show that findings about strain rate are general, not method

dependent. Biological variability (relative SD) is similar for both GLSR, S′$_n$, and S′, as age is the greatest source of biological variability of all three (Tables 2 and 3, and Figure 3). Age correlated with BP, and linear regression showed a negative independent association with DBP as well. However, this was similar for all three measures, and less important for the relation between the measures.

Global longitudinal strain rate and S′$_n$ normalize for length only. Both LV length and diameter are proportional to BSA, while the ratio

TABLE 2 Normal values for left ventricular shortening according to gender and age

Age (years)	N	S′ (cm/s) 4 walls	S′ (cm/s) 2 walls	S′$_n$ (s^{-1}) 4 walls	S′$_n$ (s^{-1}) 2 walls	GLSR (s^{-1})	GLSR (s^{-1}) (4 walls)	GLSR (s^{-1}) (2 walls)
Women								
<40	208	8.9 (1.1)	8.8 (1.1)	0.94 (0.12)	0.94 (0.13)	1.09 (0.12)	1.01 (0.16)	1.02 (0.18)
40-60	336	8.2 (1.2)	8.1 (1.2)	0.88 (0.13)	0.88 (0.14)	1.06 (0.12)	1.02 (0.15)	1.02 (0.16)
>60	119	7.2 (1.2)	7.3 (1.2)	0.81 (0.13)	0.82 (0.12)	0.98 (0.14)	1.01 (0.13)	1.01 (0.15)
All	663	8.2 (1.3)	8.2 (1.3)	0.89 (1.3)	0.89 (0.14)	1.05 (0.13)	1.02 (0.15)	1.02 (0.16)
Men								
<40	126	9.4 (1.4)	9.3 (1.4)	0.90 (0.14)	0.90 (0.14)	1.06 (0.13)	1.01 (0.12)	1.02 (0.14)
40-60	327	8.6 (1.3)	8.6 (1.3)	0.84 (0.13)	0.84 (0.15)	1.01 (0.12)	1.04 (0.14)	1.03 (0.15)
>60	150	8.0 (1.3)	8.1 (1.3)	0.82 (0.14)	0.83 (0.13)	0.97 (0.14)	1.03 (0.15)	1.03 (0.16)
All	603	8.6 (1.4)	8.6 (1.4)	0.85 (0.14)	0.85 (0.14)	1.01 (0.13)	1.03 (0.14)	1.03 (0.15)
Total	1266	8.4 (1.4)	8.4 (1.3)	0.87 (0.14)	0.87 (0.14)	1.03 (0.13)	1.02 (0.14)	1.02 (0.16)
Relative SD (%)		16.7	15.5	16.1	16.1	12.6	13.7	15.6

Note: Values are mean (SD). All differences between sex and age were significant; all $P < .001$. Overall standard deviations are given as % of mean in the bottom line, to compare the biological variations between normalized and non-normalized measures. MAPSE^n and S$'^n$ MAPSE and S′ normalized for LV mean diastolic wall length, respectively. MAPSE^{n2} and S$'^{n2}$ normalized for both mean LV diastolic wall length and LV diastolic external diameter, respectively.

Abbreviations: GLS = global longitudinal strain; GLSR = global longitudinal strain rate; MAPSE = mitral annular plane systolic excursion; S′ = peak mitral annular systolic longitudinal velocity.

TABLE 3 Linear regression coefficients for S′, S′$_n$, and GLSR vs BSA, sex, and age

Measure		R (univariate)	β	P
S′	BSA	.13	−0.02	NS
	Age	−.40	−0.42	<.001
	Sex		0.20	<.001
S′$_n$	BSA	−.22	−0.29	<.001
	Age	−.29	−0.31	<.001
	Sex		0.08	<.03
GLSR	BSA	−.17	−0.17	<.001
	Age	−.29	−0.30	<.001
	Sex		0.03	NS

between them remains constant across the BSA range.[18] As the main contribution to the stroke volume is the AV-plane motion,[22] this means that with larger BSA and larger hearts, the main SV increase is related to the cross-sectional LV area, and the square of the radius. Thus, a larger heart generates a larger SV even without the effect of increased AV-plane motion, as illustrated in Figure 4, meaning that even with a higher SV, there is very little increase in MAPSE with increasing BSA. This is thus also the case for S′, which correlates strongly with MAPSE, and thus changes very little with heart size, despite change in SV. The weak correlation between S′ and BSA, however, is sufficient to give a statistically significant sex difference, although for practical purposes the difference is negligible as seen in Table 2, the mean sex differences are small compared with the prediction interval.

As previously shown for global strain,[16] GLSR and S′$_n$ show a slightly stronger, negative correlation with BSA, due to the systematic error that they are normalized for LV length only as explained in Figure 4. As S′ is nearly unchanged with larger heart size, GLSR and S′$_n$ will decrease by the larger denominator (length), as seen by the numerically higher, but negative correlations with BSA.

The diagnostic discriminatory capability of a parameter is related to both the variability of the parameter and the separation of means between normalcy and disease. As normalization for length does not reduce overall biological variability compared to S′, there seems to be no advantage of using global strain rate as a global LV contractility measure compared to S′. Basically, strain rate is a method to assess regional dysfunction and differences in timing, while regional S′ is not.[4] This is important in diseases with regional uneven function, as coronary artery disease and conduction abnormalities. Here, GLSR may still be important in assessing global function. The diagnostic accuracy in specific patient populations must be assessed in direct comparative studies.

Global longitudinal strain rate and S′, on the other hand, have been shown to have about the same reproducibility, where image quality is good.[10] However, spectral tissue Doppler is much more robust in the presence of clutter.[23] Also, tissue Doppler has an additional advantage of measuring systolic and diastolic function with the same method, while diastolic strain rate indices so far lack similar documentation.

The correlation between MAPSE and S′ in this material were 0.55, indicating that they are relatively interchangeable as global function measures. However, this again is limited to the normal range seen in this study. S′ has a slightly lower reproducibility than
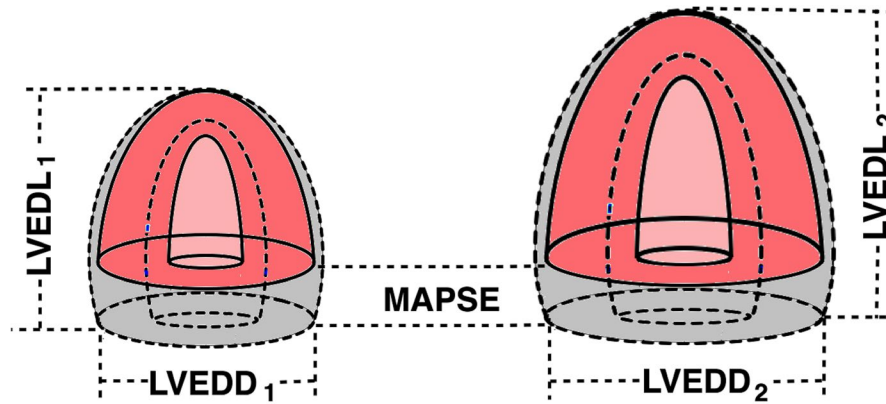
FIGURE 4 Relation between stroke volume and mitral annular plane systolic excursion (MAPSE) in ventricles of different size. It has been shown that while heart size increases with body size, the ratio between length (LVEDL) and external diameter (LVEDD) does not. As the stroke volume is mainly determined by the systolic shortening (MAPSE), a larger ventricle has a larger radius, and thus, a larger stroke volume (increasing proportional to the square of the radius) even without any differences in MAPSE, as shown by the very low correlations between MAPSE and BSA. Thus, in the ventricle to the right, for the same MAPSE, the SV is far higher. As length increases proportional to the diameter, GLS being MAPSE/ LVEDL, GLS actually decreases with increasing heart size. This is a systematic error that occurs due to the one-dimensional normalization. As there is a strong correlation between S′ and MAPSE, this is also the case for S′ vs GLSR, even if those measures are more closely related to contractility than stroke volume

MAPSE,[10] partly related to the width of the spectrum. An important point is also that values obtained by color tissue Doppler and spectral tissue Doppler differ, and are not interchangeable.[9] Color tissue Doppler values based on this material and automated analysis are published recently.[24]

4.1 | Limitations

The HUNT study is among the largest normal studies but is limited by the lack of ethnic and geographical differences. This limits the generalizability of the normal values. However, for the main issue of comparing GLSR and S′ with relation to BSA and age, this is less important. As the conventional LV dimensions and FS in this material are in line with other M-mode studies,[25,26] the population seems to be fairly representative.

As this is a cross-sectional study, the age differences are between cohorts and not true aging. However, it reflects the age relations as seen today.

The present study only discusses the variability of the indices within normal ranges. In conditions with reduced regional function, the diagnostic performance of global strain rate may still be better than S′, although this needs to be established in studies by direct comparison.

5 | CONCLUSION

Systolic annular velocity shows similar biological variation as global strain rate in normal adults, despite global strain rate are normalized for LV length. Further, the normalization for LV length actually increases the body size dependence. Age is the main determinant

of LV shortening. Thus, it is dubious that strain rate adds diagnostic information about global function, compared to mitral annular peak velocity, although strain rate being important for assessing regional function.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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