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Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study

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Aims To obtain the normal ranges for 2D echocardiographic (2DE) measurements of left ventricular (LV) strain from a large group of healthy volunteers accounting for age and gender.

Methods and results A total of 549 (mean age: 45.6 ± 13.3 years) healthy subjects were enrolled at 22 collaborating institutions of the Normal Reference Ranges for Echocardiography (NORRE) study. 2DE data sets have been analysed with a vendor-independent software package allowing homogeneous measurements irrespective of the echocardiographic equipment used to acquire the data sets. The lowest expected values of LV strains and twist calculated as ± 1.96 standard deviations from the mean were -16.7% in men and -17.8% in women for longitudinal strain, -22.3% and -23.6% for circumferential strain, 20.6% and 21.5% for radial strain, and 2.2 degrees and 1.9 degrees for twist, respectively. In multivariable analysis, longitudinal strain decreased with age whereas the opposite occurred with circumferential and radial strain. Male gender was associated with lower strain for longitudinal, circumferential, and radial strain.

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Inter-vendor differences were observed for circumferential and radial strain despite the use of vendor-independent software. Importantly, no intervendor differences were noted in longitudinal strain.

Conclusion The NORRE study provides contemporary, applicable 2D echocardiographic reference ranges for LV longitudinal, radial, and circumferential strain. Our data highlight the importance of age- and gender-specific reference values for LV strain.

Keywords adult echocardiography • 2D echocardiography • deformation imaging • reference values

Introduction

Early detection of subclinical left ventricular (LV) dysfunction using strain plays a crucial role in the evaluation of many cardiac diseases.[1–7] Longitudinal, circumferential, and radial strain have been reported to detect LV dysfunction prior to a decline in LV ejection fraction. Therefore, global longitudinal strain is recommended as a routine measurement in patients undergoing chemotherapy.[7] Although normal range of LV strains has been derived from meta-analysis,[8] the inter-vendor variability, in particular, for circumferential and radial strain remain unknown.[9] In this study, we hypothesized that the use of vendor-independent software (VIS) for analysis of myocardial deformation could resolve in part the inter-vendor variability reported with these indices.

The NORRE (Normal Reference Ranges for Echocardiography) study is the first European, large, prospective, multicentre study performed in 22 laboratories accredited by the European Association of Cardiovascular Imaging (EACVI) and in 1 American laboratory, which has provided reference values for all 2D echocardiographic (2DE) measurements of the 4 cardiac chambers,[10] Doppler parameters,[11] aortic dimensions,[12] and 3D echocardiographic measurements of the LV volumes and strain.[13] The present study aimed to (i) establish normal reference limits, using VIS, for 2DE measurement of LV strains and twist in healthy adults and (ii) to examine the influence of age, sex, and vendor on the reference ranges.

Methods

Patient population

A total of 734 healthy European subjects constituted the final NORRE study population. The local ethics committees approved the study protocol. After the exclusion of patients that had incompatible image format and/or poor-image quality, the final study population consisted of 549 (75%) normal subjects.

Echocardiographic examination

A comprehensive echocardiographic examination was performed using state-of-the-art echocardiographic ultrasound systems (GE Vivid E9; Vingmed Ultrasound, Horten, Norway, and/or iE33; Philips Medical Systems, Andover, MA, USA) following recommended protocols approved by the EACVI.[14,15] All echocardiographic images were recorded in a digital raw-data format (native DICOM format) and centralized for further analysis, after anonymization, at the EACVI Central Core Laboratory at the University of Liège, Belgium.

2D LV strain and twist analysis

Quantification of 2D strain was performed using commercially available VIS (2D Cardiac Performance Analysis, TomTec Imaging System, Munich, Germany). Analyses were performed in all three apical (LV four-chambers, two-chambers, and three-chambers view) and three short-axis views (LV basal, mid, and apical views). The most suitable cardiac cycle for each view was chosen. The reference point was set at the beginning of the QRS complex. End-systole was identified as the time point in which the LV cavity was the smallest. The endocardial border was traced in end-systole and the region of interest was adjusted to exclude the pericardium by attentively aligning the epicardial border. The integrity of tracking was visually confirmed as well as ascertained from the credibility of the strain curves, in addition to the automated tracking detection in the software. If necessary, the region of interest was readjusted. Segments with persistently inadequate tracking were excluded from analysis. Peak systolic longitudinal strain was determined from the apical views at the basal, midventricular, and apical levels in each wall and averaged into a global value for each direction. Peak systolic circumferential and peak systolic radial strain were measured at the basal, midventricular, and apical levels in each wall and averaged into a global value for each short-axis levels and strain type. All strains were calculated over the entire cardiac wall.[16] LV twist was defined as the net difference between apical and basal rotations. Peak twist was defined as the maximal value of twist during the cardiac cycle.

Statistical analysis

Continuous variables were expressed as means ± standard deviation (SD). The 95% confidence interval was calculated as ± 1.96 SDs from the mean. Differences between groups were analysed for statistical significance with the unpaired *t*-test. Comparison of continuous variables according to age groups was done with the one-way ANOVA test. When a significant difference was found, *post hoc* testing with Bonferroni comparisons for identified specific group differences was used. Correlation between continuous variables was performed using the Pearson correlation test. Multivariable linear regression analyses were performed to examine the independent correlates between LV strains/twist and baseline parameters including vendor. Intra-observer (T.S.), inter-observer (T.S. and R.D.), and inter-vendor (GE and Philips, T.S.) variability was assessed in 20 randomly selected subjects using Bland–Altman analyses. $P < 0.05$ was considered as statistically significant. Data were analysed using open source statistical software, R version 3.3.2 (R Foundation for Statistical Computing, www.R-project.org).

Results

Demographic data

Table 1 summarizes the demographic data of the NORRE population analysed in the present study. A total of 227 men (mean age 46 ± 14 years) and 322 women (mean age 45 ± 13 years) were included.

LV myocardial strains and twist—2DE LV strains and twist obtained from the study population are displayed in *Table 2*. All average strain components and twist were higher in women than in men,

Table 1 Characteristics of the population

Parameters	Total (*n* = 549)	Male (*n* = 227)	Female (*n* = 322)	*P*-value
Age, years	45.6 ± 13.3	46.2 ± 13.9	45.2 ± 12.9	0.4
Height, cm	170 ± 9	177 ± 7	164 ± 7	<0.001
Weight, kg	69 ± 11.8	77.5 ± 10	63 ± 9	<0.001
Body surface area, m^2	1.79 ± 0.19	1.94 ± 0.15	1.69 ± 0.13	<0.001
Body mass index, kg/m^2	23.9 ± 3.1	24.7 ± 2.7	23.3 ± 3.2	<0.001
Systolic blood pressure, mmHg	119 ± 13	123 ± 11	116 ± 14	<0.001
Diastolic blood pressure, mmHg	74 ± 9	76 ± 8	72 ± 9	<0.001
Glycaemia, mg/dL	92 ± 12	95 ± 12	89 ± 12	<0.001
Cholesterol level, mg/dL	185 ± 32	187 ± 30	183 ± 33	0.3

Table 2 2D speckle tracking echocardiographic parameters

	Total Mean ± SD	Total 95% CI	Male Mean ± SD	Male 95% CI	Female Mean ± SD	Female 95% CI	*P*-value*
Longitudinal strain, %							
Apical 4-chamber	-22.6 ± 3	-16.6 to - 28.5	-21.6 ± 2.8	-16.1 to - 27.1	-23.2 ± 3	-17.3 to - 29.1	<0.001
Apical 2-chamber	-23.2 ± 3.3	-16.8 to - 29.7	-22.4 ± 3.1	-16.3 to - 28.5	-23.8 ± 3.3	-17.3 to - 30.3	<0.001
Apical three chamber	-21.6 ± 3.2	-15.3 to - 27.9	-21.1 ± 3.1	-15 to - 27.2	-22 ± 3.2	-15.7 to - 28.3	0.007
Average	-22.5 ± 2.7	-17.2 to - 27.7	-21.7 ± 2.5	-16.7 to - 26.7	-23 ± 2.7	-17.8 to - 28.2	<0.001
Circumferential strain, %							
Basal	-29.6 ± 3.9	-22 to - 37.2	-29.6 ± 4.1	-21.6 to - 37.6	-29.6 ± 3.8	-22.2 to - 37	0.9
Mid	-30.7 ± 4.6	-21.7 to - 39.7	-30.4 ± 4.8	-20.9 to - 39.7	-31 ± 4.4	-22.4 to - 39.6	0.2
Apical	-36.2 ± 6.4	-23.7 to - 48.7	-35.2 ± 6.6	-22.3 to - 48.1	-36.9 ± 6.1	-24.9 to - 48.9	0.02
Average	-31.9 ± 4.5	-23.1 to - 40.6	-31.4 ± 4.6	-22.3 to - 40.5	-32.2 ± 4.4	-23.6 to - 40.7	0.08
Radial strain, %							
Basal	39.3 ± 10.4	19 to 59.6	38.8 ± 9.2	20.8 to 56.8	39.8 ± 11.2	17.9 to 61.8	0.5
Mid	39.2 ± 9.9	19.8 to 58.6	38 ± 10	18.6 to 57.4	40 ± 9.8	20.8 to 59.2	0.04
Apical	33.5 ± 10.9	12.3 to 54.8	31.4 ± 9.6	12.6 to 50.2	35 ± 11.4	12.7 to 57.3	0.005
Average	37.4 ± 8.4	21.1 to 53.8	36.3 ± 8	20.6 to 52.1	38.2 ± 8.5	21.5 to 54.8	0.02
Twist, degrees	7.9 ± 3.1	2.9 to 13	7.4 ± 2.6	2.2 to 12.6	8.3 ± 3.3	1.9 to 14.8	0.03

CI, confidence interval; SD, standard deviation.
**P*-value differences between gender.

although the difference in circumferential strain was not significant ($P = 0.08$). The lowest expected values were -16.7% in men and -17.8% in women for longitudinal strain, -22.3% and -23.6% for circumferential strain, 20.6% and 21.5% for radial strain and 2.2 degrees and 1.9 degrees for twist, respectively.

Age and LV strains relationship

Relationships between age and LV strains and twist are shown in *Table 3* and *Figure 1*. Longitudinal strain decreased with age in women ($R^2 = 0.02$, $P = 0.01$) whereas circumferential strain increased with age in women ($R^2 = 0.05$, $P < 0.001$). In the three subgroups according to age (20–40, 40–60, and ≥60 years), longitudinal strain was higher in women than in men, respectively.

Repeatability and reproducibility

Intra-observer, inter-observer, and inter-vendor (GE to Philips) variability for LV strains and twist are summarized in *Table 4*. Intra-observer and inter-observer analysis showed excellent repeatability and good reproducibility in LV strains. Inter-vendor analysis also showed good reproducibility in LV strains (*Figure 2*) and significant difference in radial strain (GE 33.7 ± 7.5%, Philips 37.3 ± 5.9%, $P = 0.02$).

Vendor and LV strains relationship

Relationships between vendor and LV strains and twist are shown in *Figure 3*. Radial strain was lower with GE compared with Philips equipment for the total population (GE, 35.4 ± 7.7%, $n = 308$ vs.

Table 3 2D speckle tracking echocardiographic parameters according to gender and age

	Age 20–40 (*n* = 202)		Age 40–60 (*n* = 252)		Age ≥60 (*n* = 95)		*P*-value		Male		Female	
	Male Mean ± SD	Female Mean ± SD	Male Mean ± SD	Female Mean ± SD	Male Mean ± SD	Female Mean ± SD	Male	Female	*R*	*P*-value	*R*	*P*-value
Longitudinal strain, %												
Apical four chamber	-21.7 ± 3	-23.4 ± 2.9*	-21.5 ± 3.1	-23.3 ± 3.1*	-21.7 ± 1.9	-22.7 ± 2.9	0.5	0.5	0.01	0.9	0.11	0.054
Apical two chamber	-22.9 ± 2.8	-24.7 ± 3*	-22.3 ± 3.2	-23.6 ± 3.4*	-21.8 ± 3.2	-22.6 ± 3.5	0.2	0.004	0.12	0.1	0.26	<0.001
Apical three chamber	-21.4 ± 3.5	-21.7 ± 3.2	-21.1 ± 2.7	-22.1 ± 3.2*	-20.4 ± 3.3	-22.5 ± 3.4*	0.4	0.5	0.09	0.3	-0.04	0.6
Average	-22 ± 2.7	-23.3 ± 2.7*	-21.6 ± 2.6	-23 ± 2.6*	-21.4 ± 2.2	-22.4 ± 2.9*	0.4	0.2	0.07	0.3	0.15	0.01
Circumferential strain, %												
Basal	-29.3 ± 4.1	-29 ± 3.7	-30 ± 4.2	-30 ± 3.8	-29.8 ± 3.9	-30.4 ± 3.2	0.6	0.2	-0.06	0.5	-0.18	0.02
Mid	-29.8 ± 4.2	-29.8 ± 4.1	-30.8 ± 5.4	-31.4 ± 4.3	-30.9 ± 4.9	-32.4 ± 5.2	0.4	0.003	-0.14	0.08	-0.21	<0.001
Apical	-35.7 ± 7	-36.3 ± 6.4	-34.7 ± 6.4	-36.5 ± 5.9	-35.1 ± 6.2	-39.8 ± 5.8*	0.8	0.04	0.01	0.9	-0.13	0.07
Average	-31.1 ± 4.3	-31.1 ± 4	-31.6 ± 5	-32.4 ± 4.4	-31.6 ± 4.6	-34 ± 4.5*	0.7	0.001	-0.07	0.3	-0.22	<0.001
Radial strain, %												
Basal	37.2 ± 8.6	38.2 ± 10.9	39.3 ± 10.7	40.8 ± 11	41.7 ± 6.2	41.5 ± 135	0.2	0.4	0.19	0.05	0.19	0.03
Mid	36.6 ± 10.3	38.4 ± 8.5	39.7 ± 10.2	41.4 ± 10.5	37.1 ± 7.6	39.5 ± 10.3	0.2	0.08	0.09	0.3	0.1	0.1
Apical	31.9 ± 8.9	36.9 ± 13.2*	30.3 ± 10.5	34.2 ± 9.5*	32.7 ± 9.2	32.5 ± 12.5	0.6	0.2	-0.03	0.8	-0.16	0.04
Average	35.6 ± 8.1	37.5 ± 8.1	37 ± 8.6	38.8 ± 8.6	36.5 ± 6.1	37.6 ± 9.1	0.5	0.5	0.07	0.4	0.05	0.4
Twist, degrees	7.7 ± 2.9	7.8 ± 3.3	6.9 ± 2.3	8.6 ± 3.2*	7.6 ± 2.5	9.6 ± 3.4	0.4	0.2	-0.07	0.5	0.18	0.058

SD, standard deviation.
*$P < 0.05$ vs. male.

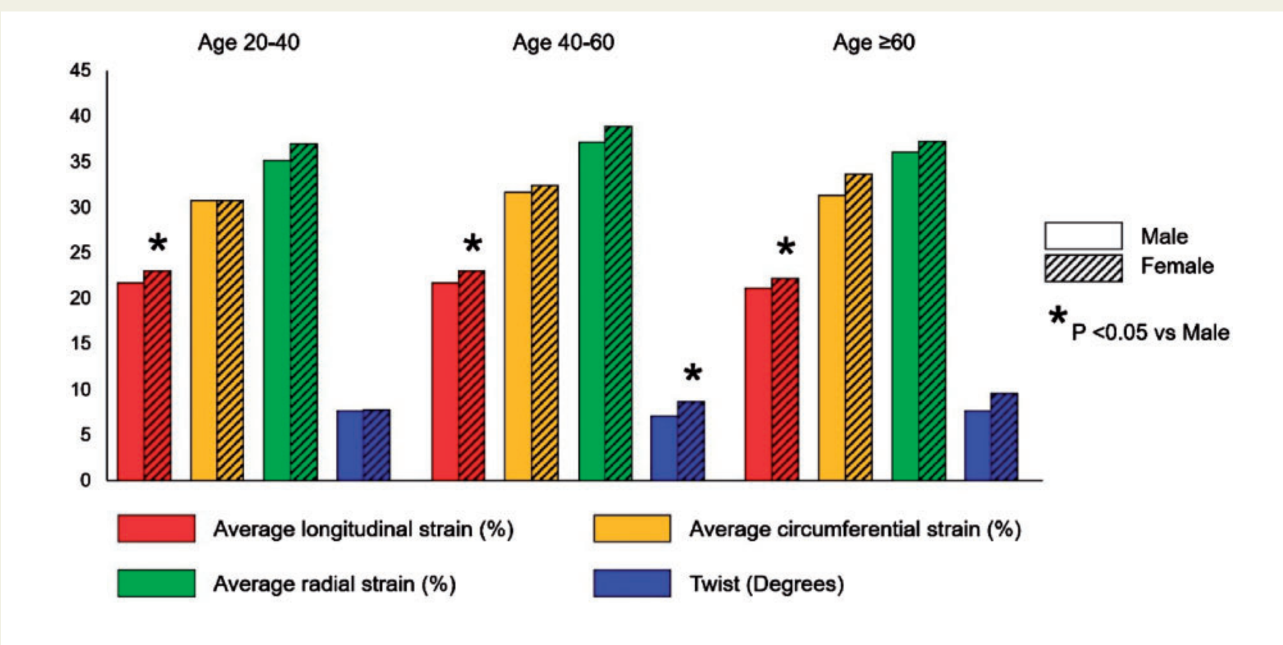

Figure 1 Bar graphs showing average longitudinal, circumferential and radial strain and twist obtained by 2D echocardiography analysis according to gender and age categories. **P*-value differences between gender.

Table 4 **Repeatability and reproducibility of 2D echocardiographic data**

Variables			Bias	*P*-value	95% LOA	Relative difference (%)
Intraobserver						
Average longitudinal strain, %	-21.9 ± 1.3	-21.5 ± 1.3	-0.4	0.09	-2.2 to 1.6	2 ± 5
Average circumferential strain, %	-33.8 ± 3	-32.2 ± 3.3	-1.6	<0.01	-4.6 to 1.4	5 ± 5
Average radial strain, %	37 ± 6.6	36.5 ± 5.8	0.5	0.6	-8.7 to 9.7	1 ± 14
Twist, degrees	7.1 ± 3.6	7 ± 3.1	0.1	0.9	-4.5 to 4.7	7 ± 33
Interobserver						
Average longitudinal strain, %	-21.5 ± 1.3	-20.7 ± 1.7	-0.8	0.09	-4.9 to 3.2	4 ± 10
Average circumferential strain, %	-32.2 ± 3.3	-30.6 ± 3.3	-1.6	0.03	-7.5 to 4.2	5 ± 10
Average radial strain, %	36.5 ± 5.8	38.3 ± 5.4	-1.8	0.3	-13.3 to 17	5 ± 21
Twist, degrees	7 ± 3.1	7.7 ± 4.3	-0.7	0.4	-6.4 to 7.7	9 ± 49
GE vs. Philips						
Average longitudinal strain, %	-23 ± 2.3	-22.3 ± 2.5	-0.8	0.2	-5.5 to 4	3 ± 11
Average circumferential strain, %	-32.1 ± 4.1	-30.7 ± 3.4	-1.4	0.1	-9 to 6.2	4 ± 12
Average radial strain, %	33.7 ± 7.5	37.3 ± 5.9	-3.6	0.02	-15.4 to 8.3	10 ± 17
Twist, degrees ($n = 7$)	7.8 ± 3.9	7.5 ± 2.4	0.3	0.8	-2.5 to3.2	4 ± 51

LOA, limits of agreement.

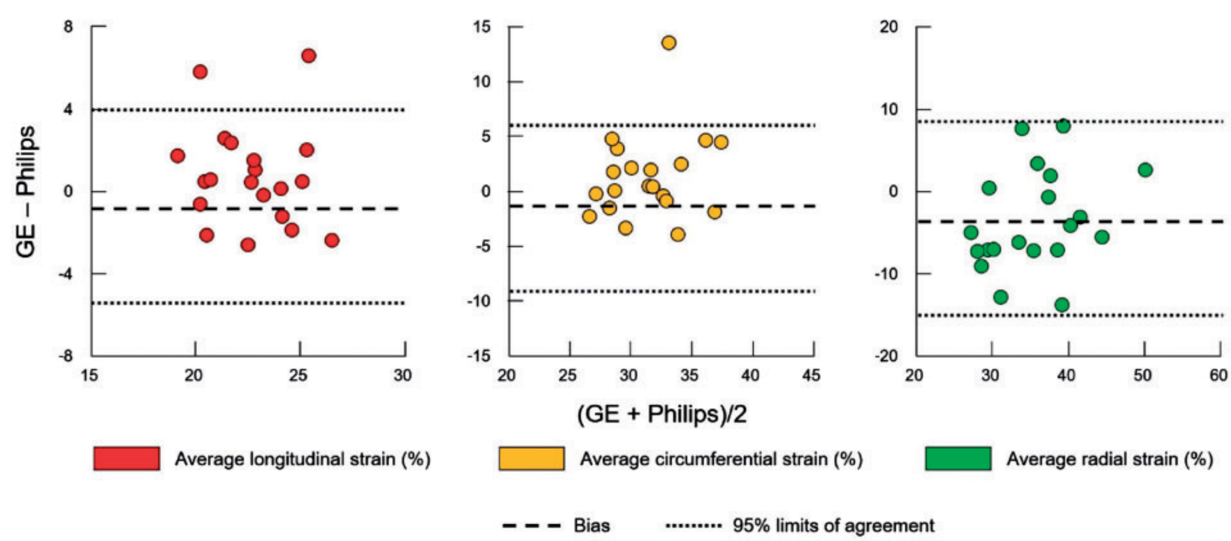

Figure 2 Bland–Altman plots for average longitudinal, circumferential, and radial strain between GE and Philips using a VIS. Dotted lines represent bias and 95% limits of agreement for measurements performed in 20 patients.

Philips, 40.4 ± 8.4%, $n = 241$, $P < 0.001$) including both men (34.2 ± 7.9% vs. 39.3 ± 7.3%, $P < 0.001$) and women (36.2 ± 7.5% vs. 41.2 ± 9.1%, $P < 0.001$). The same tendency was observed for the basal (37.8 ± 9.7% vs. 41.6 ± 10.9%, $P = 0.006$), mid (36.7 ± 8.8% vs. 43.1 ± 10.3%, $P < 0.001$), and apical (31.4 ± 10% vs. 36.6 ± 11.3%, $P < 0.001$) levels of radial strain.

Multivariable analysis for LV strains showed that longitudinal strain decreased whereas circumferential and radial strain increased with age and that all strain components were higher in women than in men after adjusting for variables including basic parameters and vendor (*Table 5*). Furthermore, circumferential strain was higher (β-coefficient = 1.6, $P = 0.009$) and radial strain was lower (β-

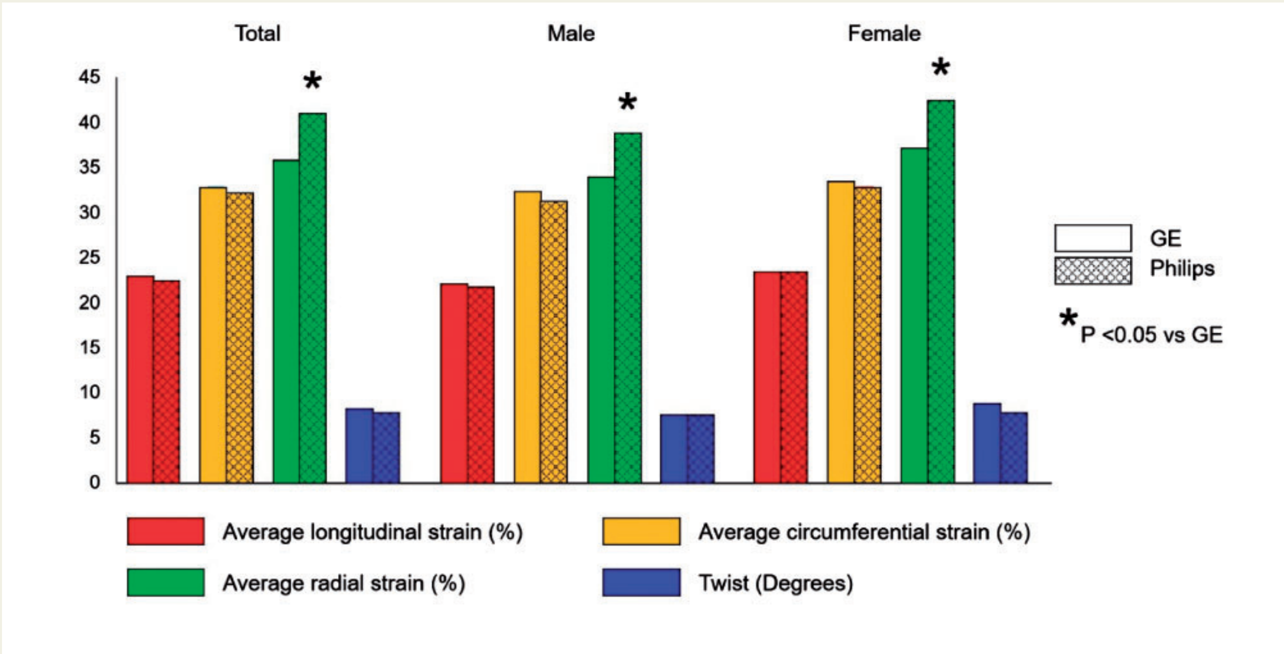

Figure 3 Bar graphs showing average longitudinal, circumferential, and radial strain and twist obtained by 2D echocardiography analysis according to vendor and gender categories. **P*-value differences between vendor.

coefficient = 4.6, $P = 0.001$) with GE equipment compared with Philips group. There was a significant difference in twist among gender in univariable analysis but no association was observed after adjustment for confounders. The lowest expected values for circumferential strain were -23.4% (GE) and -21.1% (Philips) in men and -24.1% (GE) and -22.9% (Philips) in women and those for radial strain were 18.7% (GE) and 25% (Philips) in men and 21.5% (GE) and 23.5% (Philips) in women.

Discussion

The present prospective, EACVI, multicentre study provides contemporary normal references values for 2DE measurements of LV strains and twist in a large cohort of healthy volunteers over a wide range of ages. 2DE analyses were performed using a VIS in order to obtain homogeneous measurements irrespective of the echocardiographic equipment used to acquire the data. LV strains correlated with age and gender after adjusting for variables. Longitudinal strain decreased with age while circumferential and radial strain increased. All strains were lower in men than in women. Interestingly, inter-vendor differences were observed in circumferential and radial strain despite the use of VIS software.

2D LV strains—recent 2D and 3D speckle tracking echocardiography (STE) studies in healthy population[13,17–20] have shown that LV longitudinal strain is higher in women and tends to decrease with age although a study using 2D STE showed no relationship between longitudinal strain and both age and sex, respectively.[21] Although a few 2D STE studies have shown no age-related changes of LV strains,[17,21] a large population study using 2D STE and recent studies using 3D STE have detected age-related changes of longitudinal,[13,18,20] circumferential,[13,19,20] and radial strain.[13] In this study, univariable analysis denoted age-related changes in longitudinal and circumferential strains in women and higher longitudinal and radial strains in women. Multivariable analysis revealed age- and gender-related differences in all strains. This finding is consistent with the previous findings of 3D STE.[13,19,20]

Our data demonstrate that the best concordance between the two major vendors is in LV longitudinal strain whereas the major discordance between vendors is noted in radial strain even after dividing the data by gender and/or three short-axis views. These results are different to those reported in a recent study assessing concordance between the same two vendors using the same VIS.[22] Our results is consistent with a previous study showing good concordance between the two major vendors for longitudinal strain[9] and support the good reproducibility in LV strains using VIS and the possibility of using comparable values independently of the machine used to acquire longitudinal strain in clinical practice.

Limitations

This study presents several limitations. First, only 75% of the patients included in the study have been available for strain analysis, and this in the context of image acquisition according to a dedicated protocol, indicating that dependency on image quality is still one of the main limitations of strain analysis by speckle tracking. Second, whether the NORRE study results can be extrapolated to non-Caucasian European individuals is still unknown.

Table 5 Univariable and multivariable analysis for 2D speckle tracking echocardiographic parameters

Variable	Univariable		Multivariable basic parameters		Multivariable basic parameters + vendor	
	Coefficients	*P*-value	β-coefficients	*P*-value	β-coefficients	*P*-value
Longitudinal strain, %						
Age, years	0.12	0.006	0.03	0.004	0.03	0.03
Male gender (=1)	0.24	<0.001	1	<0.001	0.8	0.02
Body mass index, kg/m^2	0.14	0.001				
Systolic blood pressure, mmHg	0.13	0.005				
Diastolic blood pressure, mmHg	0.14	0.002	0.05	0.02	0.05	0.03
Glycaemia, mg/dL	0.01	0.8				
Cholesterol level, mg/dL	-0.05	0.3	-0.01	0.02	-0.01	0.007
Vendor (GE = 0, Philips = 1)	0.07	0.2				
Circumferential strain, %						
Age, years	-0.16	<0.001	-0.05	0.02	-0.05	0.03
Male gender (=1)	0.09	0.07	1.5	0.006	2.9	<0.001
Body mass index, kg/m^2	-0.04	0.3				
Systolic blood pressure, mmHg	-0.11	0.02			-0.08	0.01
Diastolic blood pressure, mmHg	-0.02	0.7				
Glycaemia, mg/dL	-0.03	0.6			0.06	0.03
Cholesterol level, mg/dL	-0.08	0.2				
Vendor (GE = 0, Philips = 1)	0.09	0.2			1.6	0.009
Radial strain, %						
Age, years	0.06	0.2			0.12	0.04
Male gender (=1)	-0.11	0.02			-3.5	0.03
Body mass index, kg/m^2	-0.15	0.002	-0.44	0.01		
Systolic blood pressure, mmHg	-0.07	0.2				
Diastolic blood pressure, mmHg	-0.06	0.2				
Glycaemia, mg/dL	-0.18	0.001	-0.1	0.03	-0.15	0.03
Cholesterol level, mg/dL	0.01	0.9				
Vendor (GE = 0, Philips = 1)	0.34	<0.001			4.6	0.001
Twist, degrees						
Age, years	0.06	0.4				
Male gender (=1)	-0.16	0.03				
Body mass index, kg/m^2	0.07	0.3				
Systolic blood pressure, mmHg	0.02	0.8				
Diastolic blood pressure, mmHg	-0.12	0.1				
Glycaemia, mg/dL	-0.01	0.9				
Cholesterol level, mg/dL	0.02	0.8				
Vendor (GE = 0, Philips = 1)	-0.08	0.3				

Conclusion

The NORRE study provides applicable 2DE reference ranges for LV strains. Multivariable analysis showed that age and gender, respectively, are independently associated with all strain components. Our data highlight the importance of age-gender-specific assessment for LV strains.

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