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3D echocardiographic reference ranges for normal left ventricular volumes and strain: results from the EACVI NORRE study

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Aim

To obtain the normal ranges for 3D echocardiography (3DE) measurement of left ventricular (LV) volumes, function, and strain from a large group of healthy volunteers.

Methods and results

A total of 440 (mean age: 45 ± 13 years) out of the 734 healthy subjects enrolled at 22 collaborating institutions of the Normal Reference Ranges for Echocardiography (NORRE) study had good-quality 3DE data sets that have been analysed with a vendor-independent software package allowing homogeneous measurements regardless of the echocardiographic machine used to acquire the data sets. Upper limits of LV end-diastolic and end-systolic volumes were larger in men (97 and 42 mL/m^2) than in women (82 and 35 mL/m^2; $P < 0.0001$). Conversely, lower limits of LV ejection fraction were higher in women than in men (51% vs. 50%; $P < 0.01$). Similarly, all strain components were higher in women than in men. Lower range was −18.6% in men and −19.5% in women for 3D longitudinal strain, −27.0% and −27.6% for 3D circumferential strain, −33.2% and −34.4% for 3D tangential strain and 38.8% and 40.7% for 3D radial strain, respectively. LV volumes decreased with age in both genders ($P < 0.0001$), whereas LV ejection fraction increased with age only in men. Among 3DE LV strain components, the only one, which did not change with age was longitudinal strain.

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Conclusion The NORRE study provides applicable 3D echocardiographic reference ranges for LV function assessment. Our data highlight the importance of age- and gender-specific reference values for both LV volumes and strain.

Keywords adult echocardiography • three-dimensional echocardiography • left ventricular function • deformation imaging • reference values

Introduction

Impressive technological advancements have made 3D echocardiography (3DE) a fundamental tool for the assessment of left ventricular (LV) volumes and function.[1] As 3DE does not rely on geometric assumptions about LV shape and allows assessment of LV volumes, LV ejection fraction, and all strain components within a single data set acquisition, it has overcome most of the 2D echocardiographic limitations. Accuracy of 3DE is similar to that of cardiac magnetic resonance.[2] Compared with conventional 2D echocardiography, 3DE has better intra-observer, inter-observer reproducibility and test–retest variability. Accordingly, the recent guidelines on chamber quantification recommend assessing and monitoring LV volumes and function with 3DE when feasible depending on image quality and the experience of the laboratory.[3,4]

Normal values for 3D echocardiographic measurement of LV volumes and function have been proposed in the latest recommendations on chamber quantification.[3] However, the upper limits of the normal ranges proposed rely on weighted averages of three national studies.[5–7] These studies, however, showed disparate normal ranges that might be because of population differences and analysis software.[3]

The NORRE (Normal Reference Ranges for Echocardiography) Study is the first European, large, prospective, multicenter study performed in 22 laboratories accredited by the European Association of Cardiovascular Imaging (EACVI) and in one American laboratory, which has provided reference values for all 2D echocardiographic measurements of the four cardiac chambers,[8] for Doppler parameters[9] and for aortic dimensions.[10]

The present study aimed to establish normal reference limits for 3D echocardiographic measurement of LV volumes, function, and strain in healthy adults and to examine the influence of age, sex, and body size on the reference ranges.

Methods

Patient population

A total of 734 healthy European subjects constituted the final NORRE study population. After the exclusion of patients that lacked 3D volume acquisition or had incompatible image format ($n = 242$) and/or poor image quality ($n = 50$), the final 3D study population consisted of 440 normal subjects with a mean age of 45 ± 13 years (range: 19–75). The local ethics committees approved the study protocol.

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.[11,12] The 3D echocardiographic data set was acquired at the end of the standard 2D echocardiographic study. The 3D full-volume LV data set was obtained by stitching together four or six consecutive ECG-gated subvolumes taking care to include all LV segments in the data set. All Doppler-echocardiographic images were recorded in a digital raw-data format (native DICOM format) and analysed, after anonymization, at the EACVI Central Core Laboratory at the University of Liège, Belgium.

3D LV volume and strain analysis

At the Core Lab, two EACVI observers (A.B., K.A.), blinded to the age and sex of each subject, performed an image quality check and analysis. Image quality was judged considering the signal-to-noise ratio (good or bad), the blood-tissue contrast and the completeness of LV wall visualization. It was then categorized as excellent, good, or fair.

Quantification of 3D LV volumes, ejection fraction, and 3D strain was performed using commercially available, vendor-independent software that has been previously validated against cardiovascular MRI (4D LV-Function, TomTec Imaging Systems version 2.0, Unterschleissheim, Germany). To begin, the 3D full-volume data sets of the LV were transferred to a workstation equipped with the software. When the data set was selected in this environment, orthogonal cut planes of the four-, two-, and three-chamber views are automatically displayed. These cut-planes were then manually adjusted if necessary to optimize the views (*Figure 1A*). Completion of this step triggered a semi-automated border detection algorithm, which generated end-diastolic and end-systolic contours of the LV in each of the above cut-planes and in the short-axis view. The proposed LV contour is estimated based on US volume data in combination with a statistical model of the LV. A large database of healthy and pathological data sets has been used to establish a detection algorithm covering a wide range of LV shapes and sizes. End-diastole was identified automatically by the software as the time point in which the LV cavity is the largest and end-systole as the time point at which the cavity was smallest. These contours were then manually edited by the user, when required, while studying the dynamic motion of the LV cavity during the cardiac cycle (*Figure 1B*). The LV outflow tract, papillary muscles, and trabeculae were included within the LV cavity. Finally, the program generated an endocardial surface shell from which volumes, ejection fraction, and strain parameters were derived. Because the software does not provide an automated evaluation of the adequacy of image tracking capabilities, the accuracy of tracking was visually evaluated on the 2D images extracted from 3D data sets. When tracking was judged as suboptimal, the endocardial surface was manually adjusted as necessary. For strain evaluation, a 3D speckle-tracking algorithm is applied that follows the endocardium over time. The strain components global circumferential and longitudinal strains are then derived from the endocardial layer where they are computed based on the entire contour length of longitudes for global longitudinal strain and of latitudes for global circumferential strain as proposed from the ASE/EACVI task force for 2D strain. The actual 3D strain component is defined as the tangential main component of deformation consisting of circumferential and tangential components. Also called principal tangential strain, it describes the shortening of a surface element along the main contraction direction and may represent the

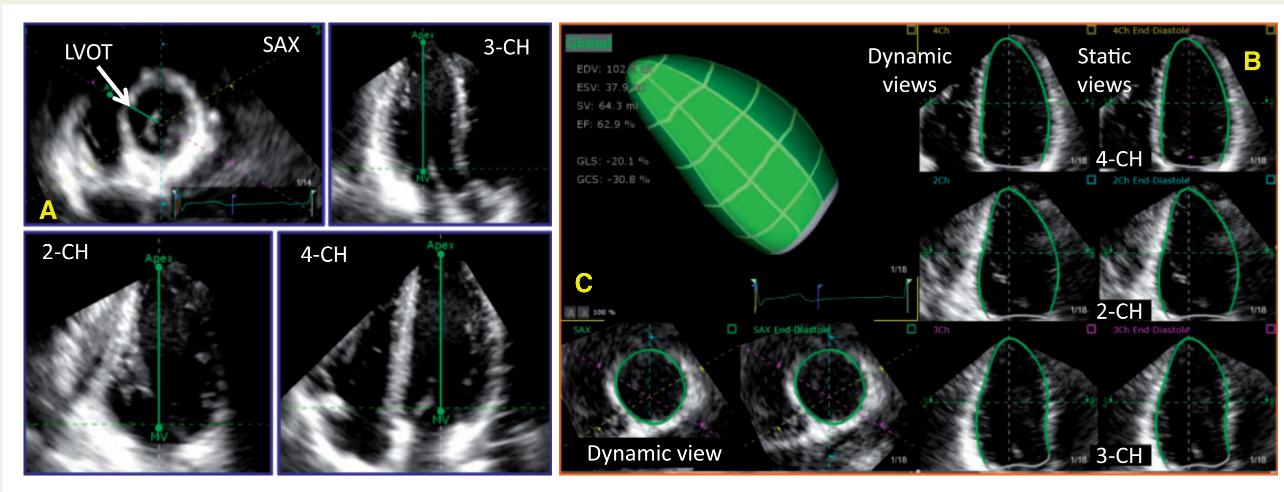

Figure 1 Orthogonal planes in the 4-, 2- and 3-chamber views were extracted from the 3D full-volume dataset (*A*). These cut-planes were manually adjusted to optimize the 2D planes and avoid fore-shortening of the left ventricle. End-diastolic and end-systolic endocardial contours were then automatically generated by the software and manually edited (*B*) to create an endocardial shell (*C*) from which end-diastolic, end-systolic volumes, ejection fraction and strain parameters could be derived. LVOT, left ventricular outflow tract; SAX, short-axis; CH, chamber.

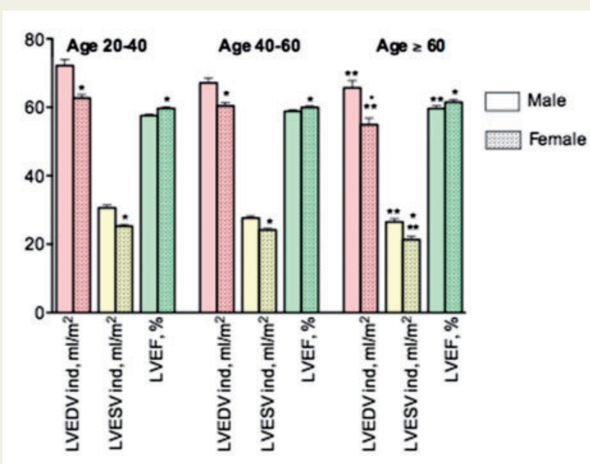

Figure 2 Bar graphs showing left ventricular indexed volumes and left ventricular ejection fraction values obtained by 3D echocardiography analysis according to gender and age categories. *P** differences between gender; *P*** differences between groups according to age category. Ind, indexed; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

resulting direction of the contraction of the muscle fibres, which are aligned in parallel/tangential to the myocardial surface. It is thus a measure of regional myocardial contractility, independent of longitudinal and circumferential direction (*Figure 3*).

Statistical analysis

Continuous variables were expressed as means SD and 2 SD range. Categorical variables were reported as percentages. The effect of the body surface area was accounted by normalizing the data to body size for morphological measurements. Differences between groups were analysed for statistical significance with the unpaired *t*-test or the Chi-square test as appropriate. Comparison of continuous variables according to age groups was done with the one-way ANOVA test. Data were tested for distribution normality with the Kolmogorov–Smirnov test. Correlation between continuous variables was performed using the Pearson correlation test. Intra-observer and inter-observer variability was assessed in 20 randomly selected subjects (A.B. and K.A.). Intra-class correlation coefficient (ICC) and the relative differences (mean ± SD) were reported. $P<0.05$ was considered as statistically significant. All statistical analyses were carried out using GraphPad Prism® (GraphPad Software, Inc).

Results

Demographic data

Table 1 summarizes the demographic data of the NORRE population analysed in the 3DE study. A total of 187 men (mean age 46 ± 14 years) and 253 women (mean age 45 ± 13 years) were included. Women had significantly smaller body surface areas.

Quality of the echo data

The quality of the 3D data sets was good in 51% and fair in 27% of the subjects (*Table 2*). Mean frame rate was 25 ± 6 vps. Signal-to-noise ratio was good in 44% of the subjects. The anterior wall was the most difficult myocardial segment to visualize particularly at end-diastole, whereas the septal and the inferolatero-septal segments were better seen.

LV volumes

3DE LV end-diastolic and end-systolic volumes, and LV ejection fraction obtained from the study population are displayed in *Table 3*. LV volumes were larger in men than in women, even after normalization for the body surface area. LV ejection fraction was higher in women compared with men (*Figure 2*). Lower limits of normality (2SD) for ejection fraction was 50% in men and 51% in women, 41 and 39 mL/m^2 for LV end-diastolic volume indexed, 16 and 14 mL/m^2 for LV end-systolic volume indexed, respectively. Upper limits of normality for ejection fraction were 67% in men and 69% in women, 97 and 82 mL/m^2 for LV end-diastolic volume, and 42 and 35 mL/m^2 for LV end-systolic volume, respectively.

LV myocardial strain

All strain components were higher in women than in men (*Figure 3*, *Table 3*). Lower range was −18.6% in men and −19.5% in women for 3D longitudinal strain, −27.0% and −27.6% for 3D circumferential strain, −33.2% and −34.4% for 3D tangential strain and 38.8% and 40.7% for 3D radial strain, respectively.

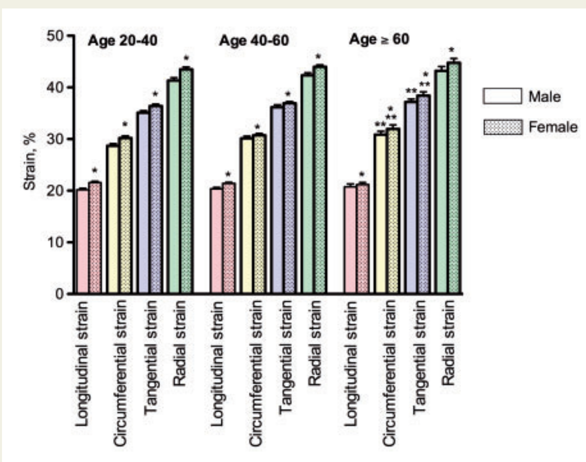

Figure 3 Bar graphs showing global longitudinal, circumferential, tangential, and radial strain values obtained by 3D speckle tracking echocardiography analysis according to gender and age categories. Longitudinal strain is displayed as an absolute value. *P** differences between gender; *P*** differences between groups according to age category.

Age and LV volumes and strains relationship

Relationships between age and LV volumes and strains are shown in *Tables 4 and 5*. LV end-diastolic volumes decreased with age in men ($r = -0.29$, $P < 0.001$) and in women ($r = -0.22$, $P < 0.001$). LV end-systolic volumes decreased with age in men ($r = -0.34$, $P < 0.001$) and in women ($r = -0.23$, $P < 0.001$). LV ejection fraction increased with age in men ($r = 0.18$, $P = 0.014$) but not significantly in women ($r = 0.11$, $P = 0.070$).

3D longitudinal strain did not change with age whereas 3D circumferential strain increased with age in men ($r = 0.20$, $P = 0.005$) and in women ($r = 0.16$, $P = 0.012$). 3D tangential strain increased with age in men ($r = 0.22$, $P = 0.002$) and in women ($r = 0.15$, $P = 0.015$). 3D radial strain increased with age in men ($r = 0.16$, $P = 0.030$) but not in women.

LV volumes and 3D strains relationship

LV end-diastolic volumes showed significant but weak correlations with 3D strain parameters: 3D longitudinal strain ($r = -0.13$, $P = 0.006$), 3D circumferential strain ($r = -0.14$, $P = 0.002$), 3D tangential strain ($r = -0.15$, $P = 0.001$), and 3D radial strain ($r = -0.18$, $P < 0.001$). LV end-systolic volumes showed moderate correlations with 3D strain parameters: 3D longitudinal strain ($r = -0.30$, $P < 0.001$), 3D circumferential strain ($r = -0.46$, $P < 0.001$), 3D tangential strain ($r = -0.44$, $P < 0.001$), and 3D radial strain ($r = -0.49$, $P < 0.001$). LVEF showed good correlation with 3D longitudinal strain ($r = -0.51$, $P < 0.0001$), and excellent correlation with 3D circumferential strain ($r = -0.91$, $P < 0.0001$), 3D tangential strain ($r = -0.84$, $P < 0.0001$), 3D radial strain ($r < 0.88$, $P < 0.0001$).

Reproducibility

Intra-observer and inter-observer reproducibility for 3D LV volumes and strains are summarized in *Table 6*. Intra-observer and inter-observer analysis showed good-to-excellent reproducibility (ICC varying from 0.62 to 0.99).

Discussion

The present prospective, EACVI, multicenter study provides normal references values for 3DE measurements of LV volumes and function

Table 1 Characteristics of the population

Parameters	Total (n = 440)	Male (n = 187)	Female (n = 253)	*p*-value
Age, years	45 ± 13	46 ± 14	45 ± 13	0.639
Height, cm	170 ± 10	177 ± 8	165 ± 7	<0.001
Weight, kg	69 ± 12	77 ± 10	63 ± 9	<0.001
BSA, m^2	1.8 ± 0.2	1.9 ± 0.1	1.7 ± 0.1	<0.001
Body mass index, kg/m^2	23.9 ± 3.0	23.8 ± 2.9	24.0 ± 3.0	0.422
Systolic blood pressure, mmHg	119 ± 13	118 ± 13	120 ± 13	0.108
Diastolic blood pressure, mmHg	74 ± 9	74 ± 9	74 ± 9	0.626
Glycaemia, mg/dL (n = 306)	91 ± 12	92 ± 11	91 ± 13	0.833
Cholesterol level, mg/dL	182 ± 29	183 ± 26	182 ± 31	0.813

Table 2 Image quality

Parameters	Total population (n = 440)
Global image quality, n (%)	
Excellent	94 (21)
Good	226 (51)
Fair	120 (27)
Signal to noise ratio, *n* (%)	
Good	192 (44)
Bad	248 (56)
Frame rate, vps	25 ± 6
Number of beats used	3.8 ± 1.6
Heart rate, bpm	65 ± 9
End-systole endocardial border visualization, %	89 ± 9
End-diastole endocardial border visualization, %	78 ± 11
End-systole endocardial border visualization, mean of segments	
Anterior wall (/3)	2.2 ± 0.8
Inferior wall (/3)	2.6 ± 0.5
Septal wall (/3)	2.9 ± 0.3
Lateral wall (/3)	2.7 ± 0.5
Antero-septal wall (/2)	1.9 ± 0.4
Infero-lateral wall (/2)	1.9 ± 0.3
End-diastole endocardial border visualization, mean of segments	
Anterior wall (/3)	1.6 ± 0.9
Inferior wall (/3)	2.3 ± 0.5
Septal wall (/3)	2.6 ± 0.5
Lateral wall (/3)	2.3 ± 0.6
Antero-septal wall (/2)	1.8 ± 0.5
Infero-lateral wall (/2)	1.8 ± 0.4

in a large cohort of healthy volunteers over a wide range of ages. 3DE analyses were performed using a vendor-independent software package in order to obtain homogeneous measurements regardless of the echocardiographic equipment used to record the 3DE data sets. 3DE upper and lower reference limits for LV volumes and strains were correlated with age and gender even after normalization for body surface area (for volumes). LV volumes decreased with age and were larger in men than in women, whereas LV strains increased with age but were lower in men.

3D LV volumes

The NORRE study was the first study to provide normal reference ranges for 2D LV volumes and function.[8] In this initial study, care was taken to only analyse non-foreshortened high-quality views. Same precautions were applied to the present 3D study, only analysing data sets that included the entire LV with good visualization of the endocardial border and a good signal-to-noise ratio.[13] The very low variability obtained in this study highlights the high quality of the study data sets. In the present study, 3DE LV volumes were larger than 2D echocardiographic LV values published in our first study (i.e. for indexed LV end-diastolic volume +19 mL/m^2 in men and +13 mL/m^2 in women).[8] In addition, the reference values differ between men and women, even after normalization for body surface area, highlighting the need to define specific normal ranges for men and women. With age, LV volumes significantly decreased, though direct correlations with age were moderate in both men and in women. Although discordant with a few reports, these data are concordant with multiple other studies.[3,5,7,14] Of note, our data are close to the values reported by Muraru *et al.*[7] and Aune *et al.*,[6] which included European populations but differ from those obtained by Fukuda *et al.*[5] from Japanese subjects (*Table* 7). The importance of ethnicity on 3D volumes was partially confirmed by Chahal *et al.*[17] who showed that LV volumes were smaller among Asian Indians than among white Europeans. Beyond ethnicity, differences in echocardiographic

Table 3 3D left ventricular volumes and function

Parameters	Total, Mean ± SD	Interquartile range (25%–75%)	Male, mean ± SD	Interquartile range (25%–75%)	Female, mean ± SD	Interquartile range (25%–75%)	*P* value*
LV end-diastolic volume, mL	115.6 ± 29.6	93.1–132.3	133.3 ± 30.5	114.2–150.2	102.5 ± 20.8	87.4–114.2	<0.001
LV end-systolic volume, mL	47.1 ± 13.7	36.6–55.3	55.4 ± 13.9	45.4–63.0	41.0 ± 9.9	33.6–48.5	<0.001
LV ejection fraction, %	59.4 ± 4.6	55.9–62.5	58.5 ± 4.3	54.9–61.6	60.1 ± 4.6	56.7–63.2	<0.001
Stroke volume, mL	68.5 ± 17.6	55.8–77.4	78.0 ± 18.6	63.7–92.2	61.5 ± 13.0	53.1–69.3	<0.001
Normalized to BSA							
LV end-diastolic volume, mL/m^2	63.9 ± 12.9	54.8–72.0	68.7 ± 14.0	58.6–77.2	60.4 ± 10.8	52.7–67.1	<0.001
LV end-systolic volume, mL/m^2	26.0 ± 6.2	21.3–29.7	28.5 ± 6.5	24.4–32.6	24.1 ± 5.3	20.4–27.5	<0.001
Stroke volume, mL/m^2	37.9 ± 7.9	32.0–43.0	40.1 ± 8.7	34.1–46.5	36.3 ± 6.9	31.4–40.3	<0.001
Longitudinal strain, %	−21.0 ± 2.6	−19.0 to 22.7	−20.4 ± 2.7	−18.6 to 22	−21.4 ± 2.4	−19.5 to 22.9	<0.001
Circumferential strain, %	−30.3 ± 4.0	−27.4 to 33.0	−29.7 ± 3.9	−27.0 to 32.5	−30.7 ± 4.1	−27.6 to 33.3	0.012
Tangential strain, %	−36.5 ± 3.9	−33.8 to 39.2	−36.0 ± 3.9	−33.2 to 38.9	−37.0 ± 3.8	−34.4 to 39.4	0.008
Radial strain, %	43.2 ± 4.5	40.0 to 46.2	42.1 ± 4.6	38.8 to 45.2	43.9 ± 4.3	40.7–46.7	<0.001

*P** differences between gender.

Table 4 3D left ventricular volume and function according age and gender

Parameters	Age 20–40 (n = 156)		Age 40–60 (n = 211)		Age ≥ 60 (n = 73)		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
LV end-diastolic volume, mL	142.0 ± 33.2	106.2 ± 20.1	131.1 ± 27.5	102.7 ± 20.3	122.1 ± 27.7	92.7 ± 21.8	0.004	0.004	−0.29	<0.001	−0.22	<0.001
LV end-systolic volume, mL	60.2 ± 15.0	42.9 ± 9.5	54.0 ± 12.1	41.1 ± 9.5	49.4 ± 12.9	36.0 ± 10.7	<0.001	0.002	−0.34	<0.001	−0.23	<0.001
LV ejection fraction, %	57.5 ± 3.9	59.7 ± 4.4	58.8 ± 4.5	59.9 ± 4.6	59.6 ± 4.6	61.5 ± 5.1	0.045	0.130	0.18	0.014	0.11	0.070
Stroke volume, mL	81.7 ± 20.0	63.3 ± 12.7	77.2 ± 17.6	61.5 ± 12.9	72.7 ± 17.0	56.7 ± 13.0	0.054	0.034	−0.23	0.002	−0.18	0.004
LV end-diastolic volume, mL/m^2	72.2 ± 14.7	62.7 ± 9.8	67.1 ± 13.4	60.4 ± 10.7	65.6 ± 12.8	54.9 ± 12.0	0.028	0.001	−0.24	<0.001	−0.26	<0.001
LV end-systolic volume, mL/m^2	30.6 ± 6.7	25.3 ± 4.8	27.6 ± 6.1	24.2 ± 5.0	26.5 ± 6.1	21.3 ± 6.2	0.002	<0.001	−0.30	<0.001	−0.26	<0.001
Stroke volume, mL/m^2	41.5 ± 9.0	37.4 ± 6.4	39.5 ± 8.5	36.2 ± 7.1	39.1 ± 8.3	33.6 ± 7.0	0.246	0.020	−0.17	0.021	−0.20	0.001

P* differences between groups according to age category (one-way ANOVA).
P and r** correlation with age for both genders (Pearson correlation test).

Table 5 3D strain according age and gender

Parameters	Age 20–40 (n = 156)		Age 40–60 (n = 211)		Age ≥ 60 (n = 73)		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, %	−20.2 ± 2.5	−21.6 ± 2.4	−20.4 ± 2.5	−21.4 ± 2.4	−20.7 ± 3.3	−21.2 ± 2.6	0.580	0.717	0.10	0.194	−0.08	0.178
Circumferential strain, %	−28.7 ± 3.6	−30.2 ± 4.0	−30.1 ± 4.0	−30.7 ± 3.9	−30.8 ± 3.9	−31.9 ± 4.7	0.013	0.093	0.20	0.005	0.16	0.012
Tangential strain, %	−35.1 ± 3.4	−36.4 ± 3.7	−36.2 ± 4.2	−36.9 ± 3.6	−37.2 ± 3.5	−38.4 ± 4.5	0.029	0.026	0.22	0.002	0.15	0.015
Radial strain, %	41.3 ± 4.4	43.5 ± 4.1	42.3 ± 4.6	44.0 ± 4.2	43.2 ± 5.1	44.7 ± 5.1	0.135	0.334	0.16	0.030	0.10	0.124

P* differences between groups according to age category (one-way ANOVA).
P and r** correlation with age for both genders (Pearson correlation test).

Table 6 Reproducibility of 3D echocardiographic data

Variables	Intraobserver		Interobserver	
	Relative difference (%)	ICC	Relative difference (%)	ICC
LV end-diastolic volume, mL	1 ± 4	0.99	3 ± 3	0.96
LV end-systolic volume, mL	4 ± 5	0.98	9 ± 6	0.95
LV ejection fraction, %	3 ± 4	0.91	8 ± 5	0.74
Longitudinal strain, %	4 ± 8	0.81	1 ± 11	0.62
Circumferential strain, %	7 ± 9	0.81	12 ± 6	0.72
Tangential strain, %	9 ± 6	0.89	5 ± 8	0.70
Radial strain, %	6 ± 4	0.91	4 ± 7	0.77

Table 7 Normal values for 3D LV volumes and LV ejection fraction

	NORRE study (2016)	Recommendations on chamber quantification[3]	Muraru *et al.*[7]	Fukuda *et al.*[5]	Aune *et al.*[6]	Cardiac magnetic resonance[18]
Number of sujects	440	–	226	410	166	288
Ethnic makeup of population	White European	–	White European	Japanese	Scandinavian	–
LV end-diastolic volume index, mL/m^2						
Male, mean (LLN-ULN)	69 (41-97)	ULN = 79	63 (41-85)	50 (26-74)	66 (46-86)	81 (ULN = 105)
Female, mean (LLN-ULN)	60 (39-82)	ULN = 71	56 (40-78)	46 (28-64)	58 (42-74)	76 (ULN = 96)
LV end-systolic volume index, mL/m^2						
Male, mean (LLN-ULN)	28 (15-41.5)	ULN = 32	24 (14-34)	19 (9-29)	29 (17-41)	26 (ULN = 38)
Female, mean (LLN-ULN)	24 (13-35)	ULN = 28	20 (12-28)	17 (9-25)	23 (13-33)	24 (ULN = 34)
LV ejection fraction, %						
Male, mean (LLN-ULN)	58 (50-67)	LLN = 52 (2D echo data)	62 (54-70)	61 (53-69)	57 (49-65)	67 (LLN = 57)
Female, mean (LLN-ULN)	60 (51-69)	LLN = 54 (2D echo data)	65 (57-73)	63 (55-71)	61 (49-73)	67 (LLN = 57)

Comparison between the NORRE study, recommendations on chamber quantification, previous published studies and with cardiac magnetic resonance (Kawel-Boehm *et al.* 2015)[22]
LLN, lower limit of normal; ULN, upper limit of normal.
LLN and ULN are defined as mean ± 2 SDs.

equipment, acquisition technique, and analysis software might explain the slight differences noted between the European studies. In the NORRE study, the acquisition of 3DE data sets was performed using contemporary machines with off-line analysis using vendor-independent software package (TomTec). This algorithm requires manual adjustment of the semi-automatically identified endocardial border. Therefore, the endocardial border tracing is much more precise allowing a better exclusion of trabeculae. When compared with cardiac magnetic resonance, 3DE is known to provide smaller LV volumes.[2] Although the NORRE Study was not designed to compare these imaging techniques, a similar observation could be expected.

3D LV function: ejection fraction and strain

Parameters of LV function were higher in women than in men, which is consistent with previous studies.[5,7,14] As in other studies, 3D LV ejection fraction was lower than the reported NORRE 2D LV ejection fraction (2D LV ejection fraction = 64 ± 5%).[8] Higher LV end-systolic volumes could explain this discrepancy. 3D LV ejection fraction correlated weakly with age which is consistent with the results of most of previous studies.[5,7,14]

Beyond assessing LV function using LV ejection fraction, 3DE also allows to obtain the various strain components from the same data set. Four strain components (longitudinal, circumferential, tangential, radial, and not the area strain) were obtained from a single data set using TomTec software. Longitudinal, circumferential, tangential, and radial strains differed significantly between men and women with higher (i.e. more negative) values in women. These results confirm the requirement of proposing different limits of normality for men and women. Overall, the magnitudes of strains were comparable but slightly larger than previously reported.[19,20] As for 2D longitudinal strain[21] or cardiac magnetic resonance-derived strain,[22,23] we found no correlation between age and 3DE longitudinal strain, whereas circumferential and tangential strains as LV ejection fraction increased with age in both genders. In addition, LV end-systolic volumes and strains were also correlated.[19] All these findings highlight the complexity of heart chamber size and function adaptation to aging.

Limitations

This study presents several limitations. First, the use of a neutral platform for 3D strain analysis with a common algorithm for strain analysis allows displaying reference values in the whole cohort of subjects irrespective of the machine used. However, some differences may be found using vendor-specific software for 3D strain analysis as found with 2D strain analysis.[24] It is likely too early to extrapolate these reference values to other software packages. Second, whether the NORRE study results can be extrapolated to non-Caucasian European individuals is still unknown.[16]

Conclusion

The NORRE study provides applicable 3D echocardiographic reference ranges for LV function assessment. Our data highlight the importance of age-gender-specific assessment for LV volumes and strains.

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