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Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study

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Aims Availability of normative reference values for cardiac chamber quantitation is a prerequisite for accurate clinical application of echocardiography. In this study, we report normal reference ranges for cardiac chambers size obtained in a large group of healthy volunteers accounting for gender and age. Echocardiographic data were acquired using state-of-the-art cardiac ultrasound equipment following chamber quantitation protocols approved by the European Association of Cardiovascular Imaging.

Methods A total of 734 (mean age: 45.8 ± 13.3 years) healthy volunteers (320 men and 414 women) were enrolled at 22 collaborating institutions of the Normal Reference Ranges for Echocardiography (NORRE) study. A comprehensive echocardiographic examination was performed on all subjects following pre-defined protocols. There were no gender differences in age or cholesterol levels. Compared with men, women had significantly smaller body surface areas, and lower blood pressure. Quality of echocardiographic data sets was good to excellent in the majority of patients. Upper and lower reference limits were higher in men than in women. The reference values

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varied with age. These age-related changes persisted for most parameters after normalization for the body surface area.

Conclusion The NORRE study provides useful two-dimensional echocardiographic reference ranges for cardiac chamber quantification. These data highlight the need for body size normalization that should be performed together with age-and gender-specific assessment for the most echocardiographic parameters.

Keywords Two-dimensional echocardiography • Chamber size and function • Reference values

Introduction

Thanks to its versatility, the indications for echocardiography have progressively expanded. In fact, transthoracic echocardiography has become the standard imaging modality for the assessment of cardiovascular anatomy, function, and physiology in clinical practice. However, as for all imaging modalities the interpretation depends upon the availability of robust reference limits that define 'normalcy'.[1] Currently, available echocardiographic reference values are mostly based on cross-sectional studies including a mixture of published and unpublished reports or selected samples using a variety of mostly dated echocardiographic techniques.[2–4] The Normal Reference Ranges for Echocardiography (NORRE) study is the first European large multi-centre study involving accredited echocardiography laboratories of the European Association of Cardiovascular Imaging (EACVI).[5] The NORRE study provides a set of normal contemporary echocardiographic values obtained from a large cohort of healthy subjects over a wide range of ages acquired using recommended echocardiographic approaches. In this study, we report the reference ranges for all cardiac chamber sizes taking into account gender and age.

Methods

Patient population

A total of 865 normal European subjects were enrolled at 22 echocardiographically accredited collaborating European institutions. After exclusion of patients ($n = 131$) due to incompatible image format, poor image quality, high body mass index/abnormal glycaemia values, cardiac pathology detected by echocardiography, the final study population consisted of 734 healthy subjects with a mean age of 45.8 ± 13.3 years (range: 20–78). A comprehensive echocardiographic examination was performed in all patients. The study protocol was approved by the local ethics committees.

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 EACVI.[5,6] All Doppler-echocardiographic images were recorded in a digital raw-data format (native DICOM format) and centralized, after anonymization, at the EACVI Central Core Laboratory at the

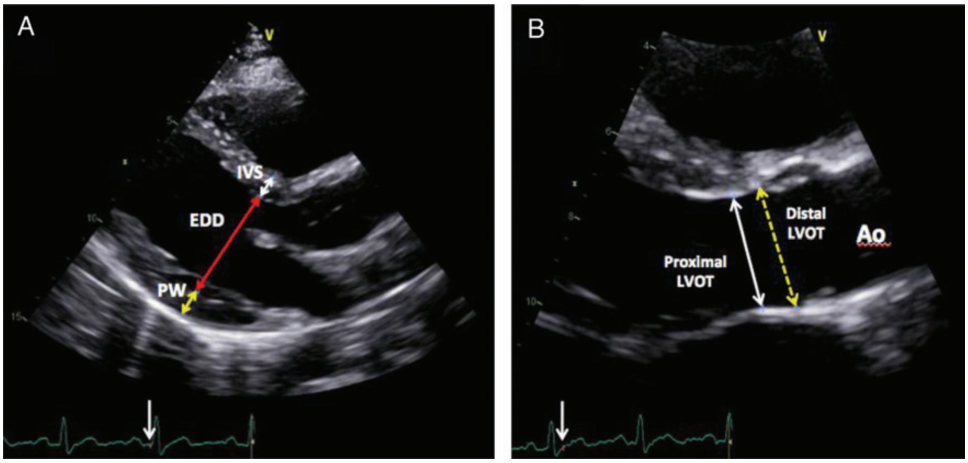

Figure 1 (*A*) Two-dimensional-guided measurement of left ventricle wall thickness in end-diastole from the left parasternal long-axis view. The interventricular septum thickness (white arrow), the left ventricle end-diastolic diameter (red arrow) and the posterior wall (PW; yellow arrow) thickness are measured just distal to the mitral leaflets tips, perpendicular to the long axis of the LV. (*B*) Proximal left ventricle outflow tract (LVOT) diameter was measured in mid-systole, using the trailing-edge-to-leading-edge method, 0.5–1 cm below the aortic cusps in a plane parallel to the aortic annulus (white arrow) from the zoomed parasternal long-axis view. The yellow dashed arrow represents the distal LVOT diameter measured just below the aortic annulus level.

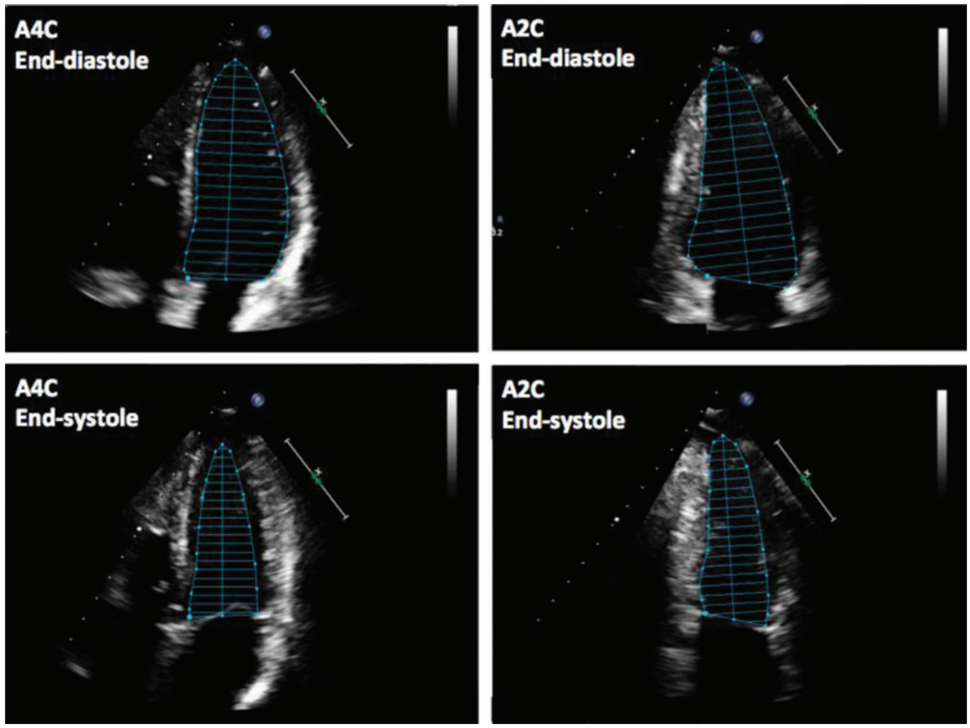

Figure 2 Two-dimensional measurements of left ventricle (LV) volumes using the biplane method of discs (modified Simpson's rule), in the apical four-chamber (A4C) and apical two-chamber (A2C) views at end-diastole (LV EDV) and at end-systole (LVESV). LV trabeculations and the papillary muscles should be excluded from the cavity in the tracing.

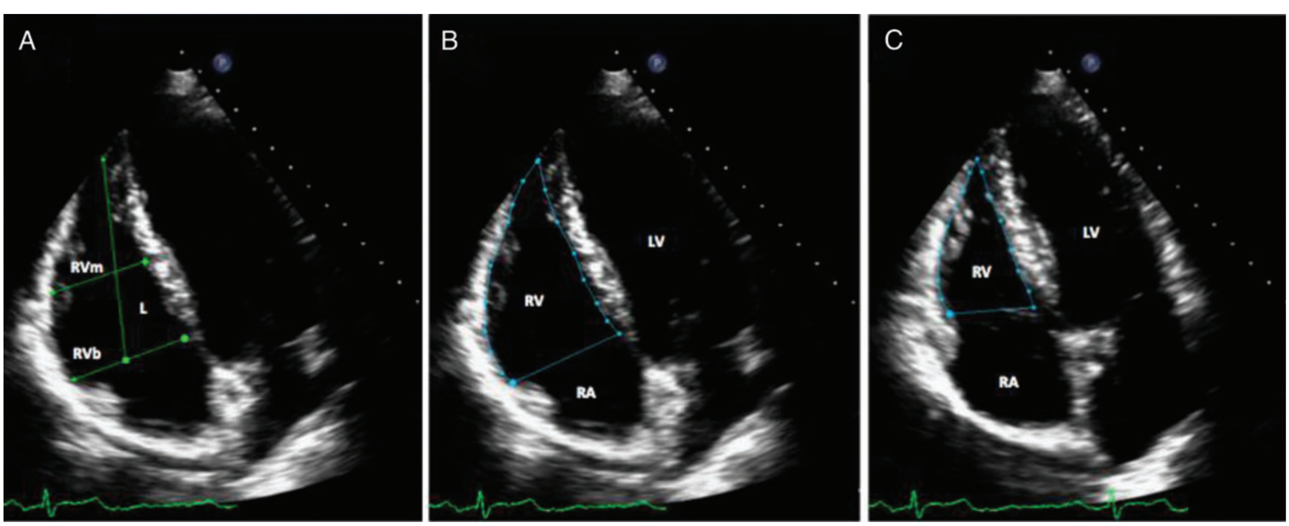

Figure 3 (*A*) Measurement of right ventricle (RV) linear dimensions from the apical four-chamber view showing the RV basal (RVb) and mid cavity (RVm) dimensions and the RV longitudinal dimension (L). Measurements were obtained at end-diastole. (*B*) Measurement of the right ventricle (RV) end-diastolic area in the apical four-chamber view. The endocardial border is traced in the apical four-chamber views from the tricuspid annulus along the RV free wall to the apex, then back to the tricuspid annulus, along the interventricular septum. Care should be taken to enclose trabeculation, tricuspid leaflets, and chords in this area. (*C*) Measurement of the right ventricle (RV) end-systolic area in the apical four-chamber view. The endocardial border is traced in apical four-chamber views from the tricuspid annulus along the RV free wall to the apex, then back to the tricuspid annulus, along the interventricular septum. Care should be taken to enclose trabeculation, tricuspid leaflets, and chords in this area.

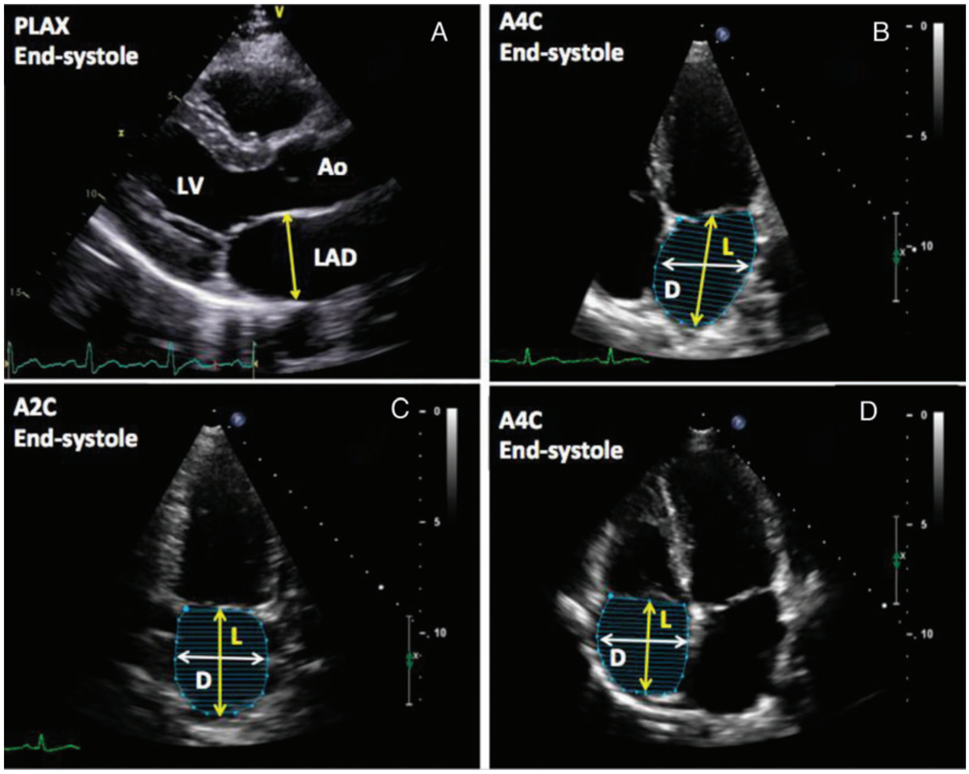

Figure 4 (*A*) Measurement of the left atrial diameter (LAD) from the parasternal long-axis view at end-systole. Measurement is done from trailing-edge-to-leading-edge from the posterior aortic wall to the posterior aspect of the left atrial wall in a plane parallel to the mitral annulus. (*B* and *C*) Measurement of left atrial volume using Simpson's biplane method from the apical four-chamber (A4C) and apical two-chamber (A2C) views at ventricular end-systole (maximum LA size). The LA length (L) is measured perpendicular from the mid-point of the segment that unifies the hinge points of the mitral leaflets, up to the ceiling of the LA. The LA minor dimension (D) is represented by the white line from the lateral wall to the interatrial septum. Care should be taken to exclude the pulmonary veins from the tracing the LA. (*D*) Measurement of the right atrial (RA) area end-systole from the parasternal four-chamber view. The right atrial major dimension (L) is represented by the yellow line from the tricuspid annulus plane centre to the superior RA wall, and the RA minor dimension (*D*) is represented by the white line from the antero-lateral wall to the interatrial septum.

Table 1 Characteristics of the population

Parameters	Total (n = 734)	Male (n = 414)	Female (n = 320)	*P*-value
Age, years	45.8 ± 13.3	46.3 ± 13.7	45.4 ± 13.1	0.387
Height, cm	169.8 ± 9.6	176.9 ± 7.8	164.4 ± 7.0	< 0.001
Weight, kg	69.5 ± 12.0	77.6 ± 10.4	63.3 ± 9.1	< 0.001
Body mass index, kg/m^2	24.0 ± 3.0	24.8 ± 2.6	23.4 ± 3.1	<0.001
Body surface area, m^2	1.8 ± 0.2	1.94 ± 0.6	1.69 ± 0.1	<0.001
Systolic blood pressure, mmHg	119.6 ± 12.7	123.5 ± 10.3	116.5 ± 13.5	<0.001
Diastolic blood pressure, mmHg	74.1 ± 8.5	75.7 ± 8.0	72.9 ± 8.7	<0.001
Glycaemia, mg/dL	92.5 ± 12.1	94.0 ± 10.7	89.0 ± 12.7	<0.001
Cholesterol level, mg/dL (n = 524)	184.1 ± 30.9	186.5 ± 29.6	182.1 ± 31.7	0.102

University of Liège, Belgium. A minimum of three cardiac cycles were recorded for analysis. All three standard left ventricular (LV) apical views (four-, two-, three-chamber views) were acquired avoiding LV foreshortening. The LV outflow tract (LVOT) diameters were measured at the aortic valve annulus (distal) and 0.5–1 cm below the aortic cups (proximal) from a zoomed parasternal long-axis acoustic window (*Figure 1*). Interventricular septal and posterior wall thicknesses at end-diastole and LV internal dimension at both end-diastole and

Table 2 **Left ventricular chamber echocardiographic parameters**

Parameters	Total Mean ± SD	Total 2SD Range	Male Mean ± SD	Female Mean ± SD	*P*-value
Parasternal long-axis view					
Interventricular septal wall thickness, mm	8.6 ± 1.6	6.0–11.3	9.2 ± 1.6	8.2 ± 1.5	<0.001
Posterior wall thickness, mm	8.8 ± 1.5	6.5–11.4	9.3 ± 1.5	8.5 ± 1.5	<0.001
Diastolic LV internal dimension, mm	44.3 ± 4.8	36.8–52.7	46.2 ± 4.8	43.0 ± 4.1	<0.001
Systolic LV internal dimension, mm	29.9 ± 4.7	22.3–37.7	31.4 ± 4.6	28.8 ± 4.3	<0.001
LV mass, g	126.8 ± 37.4	72.1–197.0	145.6 ± 36.7	112.1 ± 30.6	<0.001
Proximal LVOT diameter, mm	20.3 ± 2.3	16.7–24.5	21.6 ± 2.3	19.3 ± 1.8	<0.001
Distal LVOT diameter, mm	21.0 ± 2.2	17.7–25.0	22.3 ± 2.1	20.0 ± 1.7	<0.001
Apical views					
Apical four-chamber view					
LV ejection fraction, %	63.8 ± 5.6	55.2–73.3	63.3 ± 5.6	64.1 ± 5.6	0.051
LV end-diastolic volume, mL	93.9 ± 27.0	58.5–146.3	107.1 ± 27.4	83.8 ± 21.8	<0.001
LV end-systolic volume, mL	34.3 ± 11.8	18.9–56.6	39.7 ± 12.2	30.2 ± 9.6	<0.001
Apical two-chamber view					
LV ejection fraction, %	64.4 ± 5.7	55.5–73.9	63.9 ± 5.5	64.8 ± 5.8	0.061
LV end-diastolic volume, mL	91.9 ± 26.8	54.0–142.3	102.6 ± 29.4	83.1 ± 20.1	<0.001
LV end-systolic volume, mL	32.7 ± 11.0	17.6–52.3	37.0 ± 12.0	29.2 ± 8.6	<0.001
Biplane					
LV ejection fraction, %	63.9 ± 4.9	56.5–71.7	63.3 ± 4.9	64.3 ± 4.9	0.009
LV end-diastolic volume, mL	92.8 ± 24.8	59.3–140.6	104.6 ± 25.9	83.3 ± 18.7	<0.001
LV end-systolic volume, mL	33.7 ± 10.9	19.0–53.9	38.5 ± 11.6	29.9 ± 8.4	<0.001
Normalized to BSA					
Parasternal long-axis view					
Systolic LV internal dimension, mm/m^2	16.7 ± 2.6	12.4 ± 21.1	16.2 ± 2.5	17.1 ± 2.6	<0.001
LV mass, g/m^2	69.9 ± 17.5	43.6–102.6	74.8 ± 17.5	66.1 ± 16.4	<0.001
Apical views					
Apical four-chamber view					
LV end-diastolic volume, mL/m^2	51.8 ± 12.5	34.0–75.0	55.1 ± 12.8	49.4 ± 11.7	<0.001
LV end-systolic volume, mL/m^2	18.9 ± 5.7	10.9–29.4	20.4 ± 5.8	17.8 ± 5.3	<0.001
Apical two-chamber view					
LV end-diastolic volume, mL/m^2	50.9 ± 12.9	31.3–73.9	52.8 ± 14.0	49.3 ± 11.8	0.001
LV end-systolic volume, mL/m^2	18.1 ± 5.3	9.9–27.8	19.0 ± 5.7	17.3 ± 4.9	<0.001
Biplane					
LV end-diastolic volume, mL/m^2	51.4 ± 11.4	34.2–70.7	54.1 ± 12.2	49.3 ± 10.4	<0.001
LV end-systolic volume, mL/m^2	18.6 ± 5.2	10.8–27.4	19.9 ± 5.5	17.7 ± 4.7	<0.001

LV, left ventricular; LVOT, left ventricular outflow tract.

end-systole were measured from the parasternal long-axis acoustic window. LV end-diastolic and end-systolic volumes were measured using the biplane method of discs' summation (modified Simpson's rule) using two-dimensional (2D) images from both the apical four- and two-chamber views (*Figure 2*). LV ejection fraction was then calculated from the respective 2D LV volumes. The LV mass was calculated from linear measurements obtained from parasternal views. Assessment of right ventricular (RV) size was performed by measuring RV end-diastolic and end-systolic areas as well as end-diastolic mid- and basal-cavity diameters from the apical four-chamber view (*Figure 3*). The RV fractional area change (FAC) was calculated by the equation 100 × (end-diastolic area − end-systolic area)/end-diastolic area. The 2D RV outflow tract diameters were measured from the parasternal long-axis (proximal) and the short-axis views (proximal and distal) at the level of the aortic valve. LA length and trasverse major and minor axis were measured from the apical four-chamber view. LA volume was measured at end-systole using the biplane discs' summation (Simpson's) method from dedicated 2D images of the left atrium acquired in both the apical

Table 3 Right ventricular chamber echocardiographic parameters

Parameters	Total Mean ± SD	Total 2SD Range	Male Mean ± SD	Female Mean ± SD	*P*-value
Parasternal long-axis view					
RV outflow tract, mm	31.9 ± 4.7	24.5–39.7	33.7 ± 4.4	30.6 ± 4.5	<0.001
Parasternal short-axis view					
Proximal RV outflow tract, mm	31.9 ± 5.5	23.0–41.3	33.5 ± 5.0	30.7 ± 5.5	<0.001
Distal RV outflow tract, mm	21.7 ± 3.4	16.2–27.5	22.6 ± 3.2	21.0 ± 3.4	<0.001
Apical views					
RV basal-diameter, mm	34.4 ± 5.7	25.0–43.7	36.8 ± 5.3	32.5 ± 5.3	<0.001
RV mid-diameter, mm	28.0 ± 5.5	19.7–37.5	30.4 ± 5.6	26.0 ± 4.5	<0.001
RV longitudinal diameter, mm	67.8 ± 8.0	54.5–81.4	70.7 ± 7.9	65.5 ± 7.4	<0.001
RV end-diastolic area, cm^2	17.1 ± 4.2	10.5–24.1	18.2 ± 4.3	14.8 ± 3.5	<0.001
RV end-systolic area, cm^2	8.6 ± 2.8	4.5–13.4	9.6 ± 2.8	7.3 ± 2.3	<0.001
FAC, %	49.7 ± 8.4	35.5–64.0	47.5 ± 8.6	50.9 ± 8.0	<0.001
Normalized to BSA					
Apical views					
RV end-diastolic area	9.5 ± 2.0	6.1–12.7	9.4 ± 2.1	8.8 ± 1.9	<0.001
RV end-systolic area	4.8 ± 1.4	2.6–7.0	4.9 ± 1.4	4.3 ± 1.3	<0.001

RV, right ventricular.

four- and two-chamber views. Right atrial (RA) size was assessed at end-systole by measuring the minor and major axes from the apical four-chamber view. RA volume was measured by the monoplane Simpson disc method (*Figure 4*).

Statistical analysis

Normal distribution of data was checked using Kolmogorov–Smirnov test. Continuous variables were expressed as means ± SD and 2 SD range. Categorical variables were reported as percentages. For morphological measurements, the effect of the body surface area was accounted by normalizing the data to body size. 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. Correlation between continuous variables was performed using the Pearson correlation test. Intra-observer and inter-observer variability was assessed in 30 randomly selected subjects. Intra-class correlation coefficient (ICC) with 95% confidence interval and the relative differences (means ± SD) were reported. $P<0.05$ was considered as statistically significant. All statistical analyses were carried out using SPSS version 17 (SPSS, Inc., Chicago, IL, USA).

Results

Demographic data

Table 1 summarizes the demographic data obtained in the entire population. A total of 320 men (mean age 46.3 ± 13.7 years) and 414 women were included (mean age 45.4 ± 13.1 years). There was no significant gender differences in cholesterol levels. Women had significantly smaller body surface areas, heights, weight, and lower blood pressure compared with men.

Quality of the echo data

The echocardiographic examinations were performed using either a Vivid E9 (General Electric, Vingmed Ultrasound, Horten, Norway) in 378 subjects and with a Philips iE33 (Andover, MA, USA) in 356 cases. Overall, the quality of the echocardiographic recordings was excellent. LV data sets for the quantitation of LV end-diastolic volumes were deemed fair to poor, poor in 17 subjects, for end-systolic volumes in 22 subjects, and for LA volumes in 10 subjects. In the remaining patients, the differences in LV longitudinal axes between the four- vs. two-chamber views were <10%. The quality of RV data sets for cardiac chamber quantitation was poor for the RV end-diastolic area in 27 subjects, for the RV end-systolic area in 24, and for RA volume in 16 subjects.

Ventricular sizes

The LV and RV measurements are shown in *Tables 2* and *3*. LV mass, dimensions, and volumes were larger in men compared with women, even after normalization for the body surface area. LV ejection fraction was significantly higher in women. The lower reference values (mean −2 SD) for ejection fraction were 55.8% in men and 57.3% in women, for LV end-diastolic volume 34.8 and 34.2 mL/m^2, for LV end-systolic volumes 11.7 and 10.5 mL/m^2, and for LV end-systolic dimension 12.4 and 12.4 mm/m^2, respectively. Upper reference values (mean ± 2 SD) for the LV mass were 104.1 g/m^2 in men and 100.1 g/m^2 in women, for ejection fraction were 71.3% in men and 72.6% in women, for LV end-diastolic volume 75.7 and 67.6 mL/m^2, for LV end-systolic volume 28.8 and 25.9 mL/m^2, and for LV end-systolic dimension 20.7 and 21.3 mm/m^2, respectively.

RV dimensions were larger in men compared with women, even after normalization for the body surface area. RV FAC was

Table 4 **Left atrial chamber echocardiographic parameters**

Parameters	Total Mean ± SD	Total 2 SD range	Male Mean ± SD	Female Mean ± SD	*P*-value
Parasternal long-axis view					
LA diameter, mm	33.6 ± 4.3	26.7–41.0	35.1 ± 4.1	32.4 ± 4.1	<0.001
Apical views					
Apical four-chamber view					
LA minor length, mm	39.2 ± 4.7	31.0–47.5	40.1 ± 4.5	38.5 ± 4.8	0.001
LA major length, mm	47.6 ± 5.5	38.5–57.0	48.8 ± 5.4	46.6 ± 5.4	<0.001
LA area, cm^2	16.5 ± 3.2	11.5–21.9	17.2 ± 3.1	15.8 ± 3.1	<0.001
LA volume area-length, mL	49.2 ± 15.0	26.5–78.2	52.7 ± 14.3	46.5 ± 15.0	<0.001
LA volume Simpson, mL	45.0 ± 13.5	25.2–70.0	47.8 ± 13.0	42.7 ± 13.5	<0.001
Apical two-chamber view					
LA minor length, mm	40.2 ± 5.0	32.5–49.0	41.8 ± 5.2	39.0 ± 4.6	<0.001
LA major length, mm	49.4 ± 4.5	42.0–57.0	50.7 ± 4.5	48.3 ± 4.3	<0.001
LA area, cm^2	17.1 ± 3.2	12.7–23.1	18.2 ± 3.4	16.2 ± 2.7	<0.001
LA volume area-length, mL	51.5 ± 16.3	30.2–80.9	56.8 ± 18.0	47.5 ± 13.6	<0.001
LA volume Simpson, mL	48.2 ± 15.2	27.6–75.0	53.2 ± 16.6	44.3 ± 12.7	<0.001
Biplane					
LA volume area-length, mL	51.8 ± 14.3	33.3–78.7	56.7 ± 14.9	48.1 ± 12.7	<0.001
LA volume Simpson, mL	46.6 ± 12.8	29.5–70.3	50.6 ± 13.3	43.5 ± 11.6	<0.001
Normalized to BSA					
Parasternal long-axis view					
LA diameter, mm/m^2	18.7 ± 2.4	15.0–22.8	18.1 ± 2.3	19.2 ± 2.4	<0.001
Apical views					
Apical four-chamber view					
LA area, cm^2/m^2	9.1 ± 1.6	6.5–11.8	8.9 ± 1.5	9.3 ± 1.7	0.008
LA volume area-length, mL/m^2	27.1 ± 7.5	14.9–40.3	27.0 ± 7.0	27.3 ± 7.9	0.733
LA volume Simpson, mL/m^2	24.8 ± 6.8	13.7–36.9	24.5 ± 6.4	25.1 ± 7.2	0.462
Apical two-chamber view					
LA area, cm^2/m^2	9.5 ± 1.5	7.1–12.1	9.3 ± 1.6	9.6 ± 1.4	0.126
LA volume area-length, mL/m^2	28.3 ± 7.8	17.5–43.1	28.9 ± 8.5	28.0 ± 7.3	0.263
LA volume Simpson, mL/m^2	26.6 ± 7.2	16.1–40.1	27.1 ± 7.9	26.1 ± 6.7	0.189
Biplane					
LA volume area-length, mL/m^2	28.6 ± 6.7	19.3–41.5	28.9 ± 7.0	28.3 ± 6.5	0.376
LA volume Simpson, mL/m^2	25.7 ± 6.1	16.7–36.9	25.9 ± 6.3	25.6 ± 6.0	0.704

LA, left atrial.

higher in men. Lower reference values (mean − 2 SD) for RV FAC were 33.0% in men and 38.7% in women. Upper reference values (mean ± 2 SD) for RV FAC were 62.3% in men and 64.9% in women.

LVOT and RVOT diameters were smaller in women (*Tables 2* and *3*).

Atrial sizes

The LA and RA measurements are shown in *Tables 4* and *5*. LA dimensions and volumes were larger in men than in women. After normalization for the body surface area, LA volumes were no longer different between groups. Upper reference values (means ± 2 SD) for LA volumes were 41.9 mL/m^2 in men and 41.5 mL/m^2 in women using the area-length method, and 37.2 mL/m^2 in men and 36.9 mL/m^2 in women with the Simpson method.

RA dimensions and volumes were larger in men compared with women, with differences mitigated after normalization for the body surface area. Upper reference values (means ± 2 SD) for the RA volume method were 36.7 mL/m^2 in men and 30.6 mL/m^2 in women using the area-length method, and 33.8 mL/m^2 in men and 29.3 mL/m^2 in women with the Simpson method.

Table 5 Right atrial chamber echocardiographic parameters

Parameters	Total Mean ± SD	Total 2 SD range	Male Mean ± SD	Female Mean ± SD	*P*-value
Apical four-chamber view					
RA minor axis, mm	36.1 ± 5.6	27.5–46.0	38.4 ± 5.4	34.2 ± 5.1	<0.001
RA major axis, mm	45.9 ± 5.4	38.0–54.5	48.1 ± 4.7	44.1 ± 5.3	<0.001
RA area, cm^2	14.5 ± 3.2	9.6–20.4	16.1 ± 2.9	13.2 ± 2.9	<0.001
RA volume area-length, mL	40.1 ± 14.7	20.0–68.6	46.9 ± 14.5	34.4 ± 12.4	<0.001
RA volume Simpson, mL	37.5 ± 13.5	19.1–63.4	43.8 ± 13.4	32.5 ± 11.4	<0.001
Normalized to BSA					
Apical four-chamber view					
RA minor axis, mm/m^2	20.0 ± 2.9	15.3–24.5	19.8 ± 2.8	20.2 ± 3.0	0.228
RA major axis, mm/m^2	25.5 ± 3.0	21.3–29.8	24.8 ± 2.5	26.1 ± 3.2	<0.001
RA area, cm^2/m^2	8.0 ± 1.5	5.6–10.4	8.3 ± 1.4	7.8 ± 1.6	0.003
RA volume area-length, mL/m^2	21.9 ± 7.1	12.3–35.2	24.1 ± 7.0	20.2 ± 6.7	<0.001
RA volume Simpson, mL/m^2	20.6 ± 6.5	11.5–32.9	22.5 ± 6.5	19.0 ± 6.2	<0.001

RA, right atrial.

Age and cardiac size relationship

Table 6 summarizes the relationship of chamber quantification parameters with age and genders. LV volumes and RV areas decreased with ageing in both genders, even after body surface area normalization. LV ejection fraction increased significantly with age in both genders. A significant correlation between age and LV mass or indexed LV mass was found in women but not in men. LA and RA volumes did not change significantly with age in both genders.

Reproducibility

Intra-observer and inter-observer reproducibility for cardiac chamber size measurements are summarized in *Table 7*. Intra-observer and inter-observer analysis showed good-to-excellent reproducibility (inter-class ICC varying from 0.78 to 0.99).

Discussion

The present study provides a comprehensive analysis of cardiac chamber quantification in a large cohort of healthy volunteers over a wide range of ages using state-of-the-art echocardiographic equipment enrolled in the NORRE study. Both genders were well represented with a slight predominance of females. Overall, upper and lower reference limits were higher in men compared with women with age-related changes, highlighting the importance of applying age-gender-specific reference values for reliable identification of cardiac chambers enlargement and dysfunction. Gender differences were maintained for most parameters after normalization for the body surface area and age. Quality of echo data sets was good to excellent in most patients, indicating the high-quality standards of EACVI accredited laboratories and consequently the high clinical relevance of the NORRE study results.

Left ventricular size

LV dimensions, volumes, and ejection fraction are powerful predictors of morbidity and mortality in both clinical and population studies. However, these parameters are frequently limited by a number of circumstances, the most common being inadequate image quality and foreshortened LV apical views. In the present study, to circumvent these sources of errors only non-foreshortened high-quality LV apical views were analysed.[7] The reference values reported for most LV size parameters were gender specific and the simple normalization of LV volumes to the body surface area did not eliminate gender differences. LV volumes were smaller, and as a result LV ejection fraction was higher in women. With age, LV volumes decreased and LV ejection increased in both genders. Of note, a significant increase in the LV mass with age was only observed in women. These findings are in general consistent with previous studies.[8,9] However, as expected, independent of gender, the reported LV dimensions in the present study were lower than those obtained from three-dimensional (3D) echocardiographic studies (i.e. for indexed LV end-systolic volume −3.7 mL/m^2 in men and −1.9 mL/m^2 in women in the study by Muraru *et al.*[9]) The LV dimensions reported in the present study remained, however, larger than in the study of Chahal *et al.*[10] Interestingly, when using data not indexed for body size, data, our reference values for LV dimensions (i.e. for LV end-systolic volume −5.5 mL in men and −4.4 mL in women) and LV mass were higher than those reported in the JAMP study (normal values of echocardiographic parameters in relation to age in a healthy Japanese population), highlighting the importance of developing ethnicity-specific reference values for LV parameters.[11] Finally, lower and upper cut-off values for normal LV diameters reported in the NORRE study were significantly higher in men, suggesting that in patients with valvular heart disease indexing for the body surface alone might be insufficient to identify LV impairment. Moreover,

Table 6 Echocardiographic parameters according gender and age

Parameters	Age 20–40 (n = 262)		Age 40–60 (n = 341)		Age ≥ 60 (n = 131)		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	110.5 ± 26.5	86.9 ± 20.4	104.2 ± 25.1	83.8 ± 17.4	94.8 ± 24.7	72.0 ± 13.2	0.002	<0.001	−0.258	<0.001	−0.264	<0.001
LV end-systolic volume, mL	41.0 ± 11.5	31.9 ± 9.1	38.8 ± 11.2	29.7 ± 8.0	33.3 ± 11.6	25.1 ± 5.6	0.001	<0.001	−0.291	<0.001	−0.277	<0.001
LV ejection fraction, %	62.9 ± 4.7	63.5 ± 4.8	62.8 ± 4.8	64.7 ± 4.8	65.0 ± 5.3	65.1 ± 5.0	0.022	0.046	0.187	0.002	0.127	0.018
LV mass, g	142.9 ± 39.1	103.9 ± 28.3	148.2 ± 34.3	116.0 ± 29.3	144.5 ± 38.3	119.2 ± 35.4	0.516	<0.001	0.021	0.708	0.205	<0.001
RV end-diastolic area, cm^2	19.3 ± 4.6	15.1 ± 3.5	18.1 ± 3.9	14.9 ± 3.6	16.3 ± 3.8	13.8 ± 3.2	<0.001	0.046	−0.228	<0.001	−0.123	0.015
RV end-systolic area, cm^2	10.1 ± 3.0	7.7 ± 2.4	9.7 ± 2.6	7.3 ± 2.3	8.5 ± 2.6	6.6 ± 2.2	0.002	0.014	−0.165	0.004	−0.140	0.005
LA volume area-length, mL	55.5 ± 15.1	48.0 ± 13.2	58.8 ± 16.0	48.5 ± 12.9	54.0 ± 11.4	46.6 ± 10.9	0.303	0.784	−0.007	0.932	−0.320	0.665
LA volume Simpson, mL	49.6 ± 13.3	43.1 ± 11.5	52.5 ± 14.4	44.2 ± 12.0	48.2 ± 10.2	42.4 ± 10.6	0.300	0.707	0.001	0.995	−0.00	0.971
RA volume area-length, mL	47.9 ± 12.8	33.6 ± 11.8	47.4 ± 17.0	36.0 ± 13.0	43.6 ± 11.0	31.3 ± 11.1	0.440	0.180	−0.135	0.108	−0.008	0.914
RA volume Simpson, mL	44.1 ± 12.2	31.4 ± 10.8	44.5 ± 15.6	34.0 ± 11.9	41.1 ± 10.0	29.9 ± 10.2	0.538	0.156	−0.098	0.232	0.007	0.921
Normalized to BSA												
LV end-diastolic volume, mL/m^2	56.5 ± 12.0	51.6 ± 11.0	53.4 ± 11.8	49.4 ± 10.0	51.1 ± 12.8	43.0 ± 7.3	0.028	<0.002	−0.215	<0.001	−0.288	<0.001
LV end-systolic volume, mL/m^2	20.9 ± 5.2	18.9 ± 4.9	19.9 ± 5.3	17.5 ± 4.5	17.9 ± 6.0	15.0 ± 3.4	0.007	<0.001	−0.262	<0.001	−0.296	<0.001
LV mass, g/m^2	72.4 ± 18.0	61.5 ± 14.5	75.6 ± 16.1	68.2 ± 15.9	77.5 ± 20.0	70.6 ± 19.8	0.153	<0.001	0.105	0.065	0.219	<0.001
RV end-diastolic area, cm^2/m^2	9.8 ± 2.2	9.0 ± 1.9	9.3 ± 2.0	8.8 ± 2.0	8.8 ± 2.1	8.2 ± 1.7	0.006	0.027	−0.162	0.004	−0.149	0.003
RV end-systolic area, cm^2/m^2	5.1 ± 1.4	4.6 ± 1.3	5.0 ± 1.3	4.3 ± 1.3	4.5 ± 1.4	3.9 ± 1.2	0.039	0.005	−0.109	0.056	−0.163	0.001
LA volume area-length, mL/m^2	28.1 ± 6.8	28.6 ± 6.5	29.7 ± 7.5	28.3 ± 6.9	29.0 ± 6.2	27.4 ± 5.4	0.449	0.701	0.054	0.523	−0.70	0.343
LA volume Simpson, mL/m^2	25.1 ± 6.0	25.7 ± 5.6	26.6 ± 6.8	25.8 ± 6.4	25.9 ± 5.5	24.9 ± 5.2	0.448	0.777	0.063	0.457	−0.038	0.601
RA volume area-length, mL/m^2	24.3 ± 6.3	20.0 ± 6.7	24.0 ± 8.1	20.8 ± 6.9	23.6 ± 5.9	18.4 ± 6.0	0.908	0.272	−0.081	0.334	−0.036	0.635
RA volume Simpson, mL/m^2	22.5 ± 5.9	18.8 ± 6.1	22.6 ± 7.4	19.7 ± 6.4	22.2 ± 5.4	17.5 ± 5.5	0.973	0.266	−0.048	0.555	−0.027	0.716

LV, left ventricular; RV, right ventricular; LA, left atrial; RA, right atrial.
P* differences between groups according to age category (one-way ANOVA).
P and r** correlation with age for both genders (Pearson correlation test).

Table 7 Reproducibility of echocardiographic measurements

Variables	Intra-observer			Inter-observer		
	Relative difference (%)	ICC	95% of confidence intervals	Relative difference (%)	ICC	95% of confidence intervals
LV end-diastolic volume	5 ± 7	0.95	0.89–0.98	4 ± 2	0.99	0.95–0.99
LV end-systolic volume	1 ± 10	0.93	0.86–0.97	8 ± 6	0.95	0.83–0.99
LV ejection fraction	3 ± 7	0.83	0.62–0.92	2 ± 1	0.92	0.70–0.98
LV mass	4 ± 11	0.95	0.89–0.97	7 ± 2	0.95	0.84–0.99
RV end-diastolic area	1 ± 9	0.94	0.89–0.97	17 ± 8	0.78	0.33–0.94
RV end-systolic area	5 ± 17	0.84	0.69–0.92	22.5 ± 13	0.81	0.42–0.95
LA volume	2 ± 7	0.95	0.87–0.98	5 ± 4	0.89	0.64–0.87
RA volume	7 ± 13	0.89	0.75–0.96	7 ± 6	0.94	0.80–0.99

ICC, inter-class correlation coefficient; LV, left ventricular; RV, right ventricular; LA, left atrial; RA, right atrial.

measurements of LVOT diameter 0.5–1 cm below the aortic annulus result in smaller values compared with those measured at the insertion of the aortic cusps, suggesting that although the former approach is recommended,[12] it might lead to an underestimation of the LVOT cross-sectional area.[13]

Right ventricular size

The quantitation of RV size and function with conventional echocardiography is of importance but still not uniformly adopted in routine clinical practice.[14] Consistent with previous studies, RV size parameters were lower in women, even after normalization for the body surface area.[15,16] As a result, FAC was higher in women. Of note, RV areas decreased with age even after normalization for the body surface area. These data indicate that age, gender, and body size are important determinants of 2D echocardiographic RV dimensions reinforcing the need for age- and gender-specific RV reference values indexed to body surface area for the routine clinical assessment of the RV. Of note, non-indexed RV parameters were higher in our study compared with the JAMP Study[11] and slightly lower to those reported by Maffessanti *et al.*[16]

Left atrial size

LA volume is a validated marker of clinical and subclinical cardiovascular disease.[17] LA diameters and volumes often refer to indexed values for body size, but little is known about the potential influence of gender.[18,19] Our results showed significantly different LA size and volumes between men and women, but these differences did no longer persist after indexing for body size regardless of the method used to calculate them. Only, the indexed LA diameter (parasternal long-axis) and single-plane area (apical 4-chamber) remained different and paradoxically higher in women, suggesting that the complexity of LA shape is underappreciated by these approaches. Our data suggest that for LA volumes there is less need for checking for age-gender-specific references. Indeed, LA volume did not correlate with age. Importantly, the upper LA volume reference limits for defining an enlarged LA were larger than the currently recommended cut-off values, which were derived from population studies.[20] Of note, and as shown previously, the area-length method yielded systematically larger values compared with the Simpson method ($P<0.001$), suggesting that these methods are not fully interchangeable.[21]

RA size

There is increasing evidence that RA enlargement is an outcome predictor in various cardiac conditions.[22,23] To date, diameters and area measured in the apical four-chamber view are the only recommended methods to assess RA size, while RA volume computation is not included in routine clinical echocardiography due to the lack of reference data.[24] Consistent with previous data, our results showed significantly different RA volumes between men and women even after indexing for body surface area, suggesting the need for gender-specific reference values.[19,24] Of note, RA volume did not correlate with age. Thus, indexation of RA volume for age is not mandatory. As for LA, RA volumes were lower than 3D derived values.[19,24] However, our upper references limits for RA diameters for defining an enlarged RA were close to current recommended cut-off values.[14] Of note, as for LA, the single-plane area-length method provided larger values than the biplane discs' summation method ($P < 0.001$).

Limitations

The NORRE study results mainly pertain to white individuals. Thus, conclusions concerning other ethnic populations could not be drawn. Despite the fact that all subjects were considered normal subjects, the possibility of subclinical coronary artery disease particularly in older subjects cannot be excluded. Of note, the higher intra- and inter-observer variability for the assessment of RV parameters might affect the interpretation of our data.

Conclusion

The NORRE study provides applicable 2D echocardiographic reference ranges for cardiac chamber quantification. Our data highlight that normalization for body size should be performed along with age-gender-specific assessment for most echocardiographic parameters. This study is unique, because it provides chamber quantitation parameters data over a wide range of ages for all parameters measured in the same patient population. The data have been acquired using state of the art equipment following recommended protocols for chamber quantitation approved by the EACVI.

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