



Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study

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Aims

Reference values for Doppler parameters according to age and gender are recommended for the assessment of heart physiology, specifically for left ventricular (LV) diastolic function. In this study, we report normal reference ranges for Doppler parameters obtained in a large group of healthy volunteers. Echocardiographic data were acquired using state-of-the-art cardiac ultrasound equipment following Doppler acquisition and measurement protocols approved by the European Association of Cardiovascular Imaging.

Methods and results

A total of 449 (mean age: 45.8 ± 13.7 years) healthy volunteers (198 men and 251 women) were enrolled at the collaborating institutions of the Normal Reference Ranges for Echocardiography (NORRE) study. A comprehensive echocardiographic examination was obtained from all subjects following predefined protocols. The majority of the Doppler diastolic parameters (e' , E/e') as well as right ventricle systolic s' wave velocity were similar in men and women. Left ventricle s' wave velocity was higher in men than in women. E wave and e' were higher in younger subjects and decreased progressively in the older ones. E/e' ratio increased with ageing. Septal $e' < 8$ cm/s was present in 19.7% of the subjects in the 40–60 year group and in 55% of those in the ≥ 60 year group. However, the cut-off value of average E/e' or lateral E/e' remained < 15 or 13, respectively, in the majority of patients.

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Conclusion The NORRE study provides the reference values for the most useful Doppler parameters in the evaluation of heart physiology. These data highlight the need of using age-specific reference values especially for the diagnosis of LV systolic and diastolic dysfunction and for the estimation of LV filling pressures.

Keywords Doppler echocardiography • systolic and diastolic function • reference values • NORRE Study

Introduction

Doppler echocardiography has become the standard imaging modality for the assessment of heart valve disease severity and heart physiology, specifically diastolic function. However, due to the variability in Doppler parameters according to age, it is mandatory to establish reference limits that define normalcy¹ according to age and gender to be able to classify and differentiate normal vs. abnormal Doppler findings and patterns. Currently, available echocardiographic reference values are mostly based on cross-sectional studies including a combination of published and unpublished reports or selected samples using dated echocardiographic techniques.^{2–4} The Normal Reference Ranges for Echocardiography Study (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 aims to prospectively establish a set of normal echocardiographic values in a large cohort of healthy individuals over a wide range of ages. Recently, the 2D sub-study of the NORRE Study has been published providing normal 2D-echocardiographic reference values for left and right heart chambers according to gender and age.⁶ In the present study, we reported the reference ranges for normal Doppler parameters taking age and gender into account acquired using recommended echocardiographic approaches.

Methods

Patient population

A total of 449 European volunteers aged from 20 to 75 years (mean age: 45.8 ± 13.7 years) with high-quality echocardiographic images, compatible dataset format and no evidence of cardiac pathology detected by

echocardiography, were evaluated in the Doppler NORRE sub-study. All patients had comprehensive Doppler-echocardiographic examinations. The study protocol was approved by all local hospital ethics committee.

Echocardiographic examination

A comprehensive echocardiographic examination was obtained from all subjects using either a Vivid E9 (GE Vingmed Ultrasound, Horten, Norway) and/or iE33 (Philips Medical Systems, Andover, USA) ultrasound systems following a predefined protocol.^{5,7} All echocardiographic and Doppler images were recorded in a digital raw-data format (native DICOM format) and centralized, after anonymization, at the EACVI Central Core Laboratory at the University of Liège, Belgium. Colour flow Doppler images were obtained in all heart valves to exclude subjects with more than mild regurgitation of any valve. Pulse wave (PW) Doppler was obtained at the left and right ventricle outflow tract and continuous wave Doppler at the aortic and pulmonary valve. Transmitral flow pattern with E and A wave velocities was obtained with the sample volume positioned at mitral leaflet tips. PW Tissue Doppler Imaging (TDI) was obtained at the septal, lateral, inferior, anterior, and posterior annular ring of the mitral valve, measuring s', e', and a' peak velocities. PW TDI was also obtained at the lateral tricuspid annulus in the four-chamber view. All images and measurements were made according to the study protocol.⁵ LV ejection fraction and left atrial volume were calculated as previously reported by the NORRE group.^{5,6}

Statistical analysis

Doppler data were tested for distribution normality with the Kolmogorov–Smirnov test. Continuous variables were expressed as mean + SD and according to tertiles. Categorical variables were reported as percentages. Differences between groups were analysed for statistical significance with the unpaired t-test or the χ^2 test as appropriate. Comparisons of continuous variables according to age groups were done with one or

Table 1 Characteristics of the population

Parameters	Total Mean ± SD	Total 1st–3rd quartile	Male	Female	P-value
Age, years	45.8 ± 13.7	34.0–56.5	45.9 ± 14.0	45.7 ± 13.4	0.86
Height, cm	170.2 ± 9.6	163.0–177.0	176.6 ± 8.1	165.1 ± 7.3	<0.001
Weight, kg	69.8 ± 11.7	60.9–78.0	76.9 ± 10.6	64.2 ± 9.3	<0.001
Body mass index, kg/m ²	24.0 ± 3.0	21.8–26.0	24.6 ± 2.7	23.5 ± 3.2	<0.001
Body surface area, m ²	1.8 ± 0.2	1.65–1.93	1.93 ± 0.16	1.70 ± 0.14	<0.001
Systolic blood pressure, mmHg	120.6 ± 13.1	110.0–130.0	123.3 ± 10.9	118.5 ± 14.3	<0.001
Diastolic blood pressure, mmHg	74.5 ± 8.6	70.0–80.0	75.1 ± 8.4	74.0 ± 8.7	0.19
Glycaemia, mg/dL	94.6 ± 12.0	88.0–100.0	96.5 ± 11.0	93.1 ± 12.5	0.01
Cholesterol level, mg/dL	186.8 ± 34.5	162.3–209.0	187.5 ± 33.5	186.3 ± 35.4	0.76
LV ejection fraction biplane, %	63.6 ± 4.7	60.3–66.6	63.2 ± 4.8	63.9 ± 4.7	0.204

LV, left ventricular.

two-way ANOVA test. Correlations between continuous variables were performed with Pearson correlation test. $P < 0.05$ was considered as statistically significant. All statistical analyses were carried out using SPSS version 19 (SPSS Inc., Chicago, IL, USA).

Results

Demographic data

Table 1 summarizes the demographic data obtained in the entire population and according to gender. By inclusion criteria, patients had normal anthropometric and biological characteristics. A total of 198 men (44.1%) (mean age: 45.9 ± 14.0 years) and 251 women (55.9%) were included (mean age: 45.7 ± 13.4 years). There were no significant differences in age or cholesterol level between men and women. However, women showed significantly smaller body surface area, height, weight, and lower systolic blood pressure levels compared with men.

Left ventricular diastolic parameters

LV diastolic parameters are shown in Tables 2 and 3. *E* wave velocity was higher in women than in men, but there were no significant

differences between genders in *A* wave velocity, *E* wave deceleration time, and *E/A* ratio. At PW TDI study, *a'* wave velocity was higher in men in all mitral annulus positions (septal, lateral, inferior, anterior, and posterior annulus). Conversely, there were no significant differences in *e'* wave velocity between men and women, except in the inferior mitral annulus, where *e'* velocity was higher in women. Similarly, there were no gender differences for *E/e'* ratio at any place of measurement, *E/e'* ratio average in four-chamber view (septal and lateral), or *E/e'* ratio average of the five measurements.

Table 3 shows LV diastolic parameters according to gender and age categories (20–40 years, 40–60 years, and ≥ 60 years). *E* wave velocity and *E/A* ratio were lower in older patients (≥ 60 years) in both genders, and there was a negative significant correlation between these parameters and age ($r = -0.31$, $P \leq 0.001$ and $r = -0.61$, $P \leq 0.001$; respectively) in men. Conversely, *A* wave velocity and *E* wave deceleration time were increased in older patients (≥ 60 years) with a positive significant correlation with age ($r = 0.48$; $P < 0.001$ and $r = 0.23$; $P = 0.001$ respectively) in men. *e'* wave velocities were higher in 20–40 years category (septal e' 12.1 ± 2.5 cm/s) and lower in 40–60 years (9.8 ± 2.6 cm/s) and ≥ 60 years category (7.6 ± 2.3 cm/s), irrespectively of gender and annular place of

Table 2 Left ventricular diastolic parameters according to gender

Parameters	Total Mean \pm SD	Total 1st–3rd quartile	Total 95% CI	Male Mean \pm SD	Female Mean \pm SD	P*
Pulse Doppler at the mitral valve						
<i>E</i> wave velocity (cm/s)	0.76 ± 0.17	0.65–0.87	0.46–1.12	0.74 ± 0.16	0.79 ± 0.18	0.002
<i>A</i> wave velocity (cm/s)	0.60 ± 0.17	0.48–0.69	0.35–0.98	0.59 ± 0.17	0.61 ± 0.16	0.19
<i>E</i> wave deceleration time (ms)	188.0 ± 49.4	157.0–211.0	112.8–296.4	189.9 ± 55.6	186.5 ± 43.9	0.48
<i>E/A</i> ratio	1.37 ± 0.51	1.0–1.61	0.64–2.74	1.36 ± 0.49	1.38 ± 0.53	0.68
Tissue Doppler data						
Septal <i>e'</i> wave (cm/s)	10.3 ± 3.0	8.0–12.0	5.0–17.0	10.1 ± 3.1	10.3 ± 2.9	0.505
Septal <i>a'</i> wave (cm/s)	9.4 ± 2.0	8.0–11.0	6.0–13.0	9.9 ± 2.0	9.0 ± 1.9	<0.001
Lateral <i>e'</i> wave (cm/s)	13.5 ± 4.0	10.0–16.0	6.0–22.0	13.5 ± 4.0	13.5 ± 4.1	0.93
Lateral <i>a'</i> wave (cm/s)	9.2 ± 2.7	7.0–11.0	5.0–15.0	9.5 ± 2.7	9.0 ± 2.6	0.041
Average septal and lateral <i>Ea</i> wave (cm/s)	11.9 ± 3.3	9.25–14.0	6.0–18.5	11.8 ± 3.2	11.9 ± 3.3	0.73
Inferior <i>e'</i> wave (cm/s)	11.8 ± 3.6	9.0–14.0	5.0–19.0	11.3 ± 3.5	12.2 ± 3.6	0.008
Inferior <i>a'</i> wave (cm/s)	10.1 ± 2.3	8.0–12.0	6.0–15.0	10.5 ± 2.3	9.8 ± 2.3	0.001
Anterior <i>e'</i> wave (cm/s)	11.8 ± 3.6	9.0–14.0	5.3–19.0	11.7 ± 3.6	12.0 ± 3.7	0.45
Anterior <i>a'</i> wave (cm/s)	8.5 ± 2.2	7.0–10.0	5.0–14.0	8.8 ± 2.2	8.2 ± 2.2	0.01
Posterior <i>e'</i> wave (cm/s)	13.2 ± 3.7	11.0–16.0	7.0–21.0	13.2 ± 3.9	13.2 ± 3.5	0.93
Posterior <i>a'</i> wave (cm/s)	9.6 ± 2.8	8.0–11.0	5.0–16.0	10.1 ± 2.8	9.3 ± 2.7	0.012
Average <i>e'</i> wave (cm/s)	11.9 ± 3.1	9.8–14.2	6.4–18.4	11.8 ± 3.1	12.1 ± 3.1	0.43
<i>E/e'</i> ratio						
Septal <i>E/e'</i>	7.9 ± 2.4	6.1–9.2	4.5–13.6	7.8 ± 2.5	8.0 ± 2.3	0.38
Lateral <i>E/e'</i>	6.1 ± 2.1	4.6–7.3	3.4–11.7	6.0 ± 2.1	6.3 ± 2.2	0.10
Average septal and lateral <i>E/e'</i>	6.8 ± 2.1	5.4–7.9	4.0–12.0	6.7 ± 2.1	7.0 ± 2.1	0.15
Inferior <i>E/e'</i>	6.9 ± 2.4	5.3–7.8	3.7–13.4	7.1 ± 2.6	6.8 ± 2.1	0.27
Anterior <i>E/e'</i>	6.9 ± 2.7	5.1–8	3.7–13.5	6.9 ± 2.6	7.0 ± 2.8	0.64
Posterior <i>E/e'</i>	6.1 ± 2.1	4.8–7.0	3.3–11.3	6.0 ± 2.1	6.2 ± 2.2	0.33
Average <i>E/e'</i>	6.6 ± 2.0	5.3–7.5	3.9–11.9	6.6 ± 2.0	6.7 ± 2.0	0.51

CI, confidence interval.

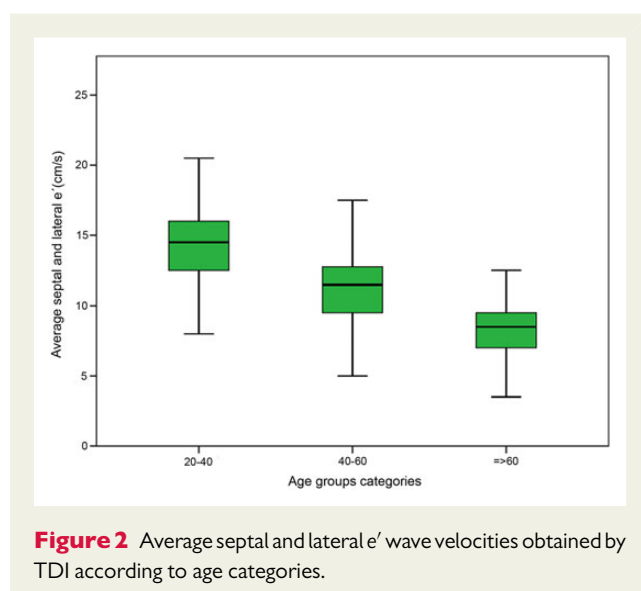
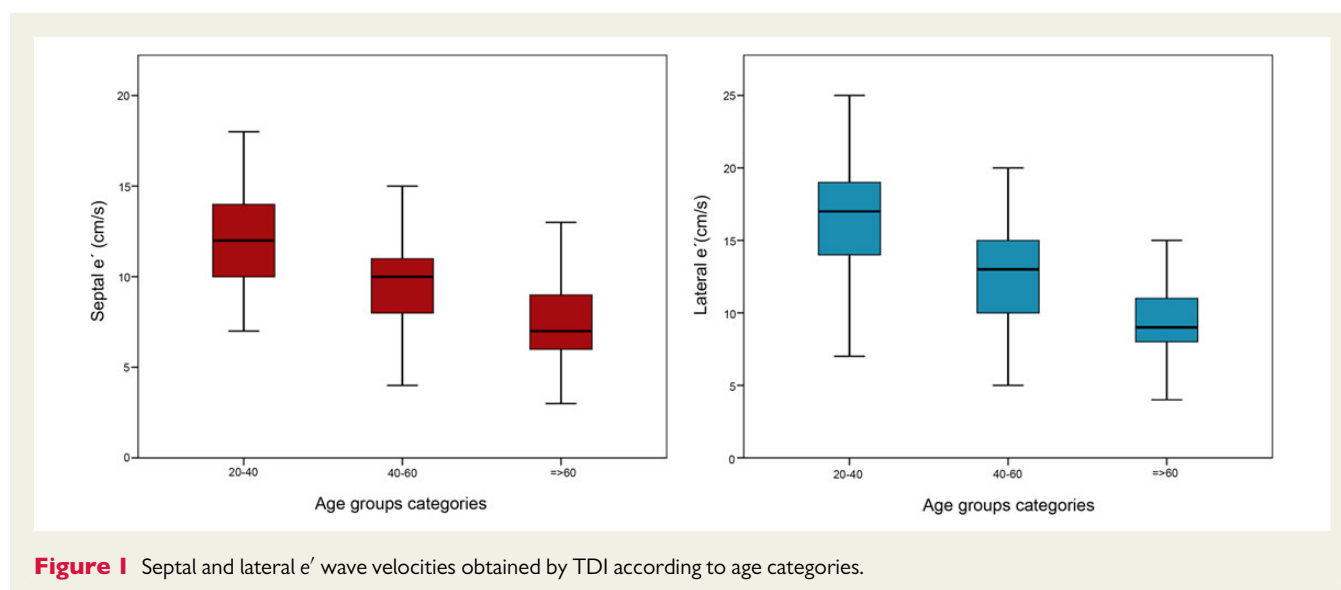
**P* differences between male vs. female.

Table 3 Left ventricular diastolic parameters according to age and gender

Parameters	20–40 years				40–60 years				≥60 years				P*			Male** r P	Female** r P
	Total Mean ± SD	Total 95% CI	Male Mean ± SD	Female Mean ± SD	Total Mean ± SD	Total 95% CI	Male Mean ± SD	Female Mean ± SD	Total Mean ± SD	Total 95% CI	Male Mean ± SD	Female Mean ± SD	Total	Male	Female		
Pulse Doppler at the mitral valve																	
E wave velocity (cm/s)	0.82 ± 0.16	0.53–1.22	0.79 ± 0.14	0.84 ± 0.17	0.75 ± 0.17	0.46–1.13	0.72 ± 0.16	0.77 ± 0.17	0.70 ± 0.16	0.39–1.03	0.67 ± 0.15	0.72 ± 0.17	<0.001	<0.001	<0.001	–0.31; <0.001	–0.29; <0.001
A wave velocity (cm/s)	0.50 ± 0.13	0.30–0.87	0.50 ± 0.13	0.51 ± 0.12	0.62 ± 0.15	0.37–0.97	0.61 ± 0.15	0.63 ± 0.14	0.74 ± 0.16	0.40–1.04	0.73 ± 0.16	0.76 ± 0.16	<0.001	<0.001	<0.001	0.49; <0.001	0.52; <0.001
E wave deceleration time (ms)	178.2 ± 43.1	105.2–269.0	179.8 ± 46.4	176.7 ± 40.1	187.6 ± 45.5	114.6–288.1	186.6 ± 52.8	188.2 ± 39.8	208.9 ± 62.7	114.0–385.9	217.5 ± 69.7	201.5 ± 55.7	<0.001	0.002	0.008	0.23; 0.001	0.18; 0.006
E/A ratio	1.71 ± 0.52	0.89–3.18	1.69 ± 0.52	1.72 ± 0.52	1.24 ± 0.39	0.71–2.27	1.22 ± 0.31	1.26 ± 0.43	0.98 ± 0.29	0.53–1.80	0.96 ± 0.27	0.99 ± 0.31	<0.001	<0.001	<0.001	–0.61; <0.001	–0.54; <0.001
Tissue Doppler data																	
Septal e' wave (cm/s)	12.1 ± 2.5	8.0–17.0	11.9 ± 2.7	12.3 ± 2.3	9.8 ± 2.6	5.0–16.0	9.8 ± 2.6	9.7 ± 2.5	7.6 ± 2.3	3.0–13.0	7.3 ± 2.2	7.9 ± 2.3	<0.001	<0.001	<0.001	–0.58; <0.001	–0.58; <0.001
Septal a' wave (cm/s)	8.5 ± 1.7	5.3–12.0	8.9 ± 1.6	8.1 ± 1.8	9.8 ± 2.0	6.9–14.0	10.6 ± 2.0	9.1 ± 1.8	10.5 ± 1.7	7.0–14.0	10.6 ± 1.9	10.4 ± 1.6	<0.001	<0.001	<0.001	0.40; <0.001	0.44; <0.001
Lateral e' wave (cm/s)	16.4 ± 3.4	10.0–23.0	16.2 ± 3.6	16.6 ± 3.2	12.5 ± 3.0	6.0–18.0	12.6 ± 3.0	12.4 ± 3.0	9.6 ± 2.8	4.0–17.0	9.5 ± 2.1	9.7 ± 3.2	<0.001	<0.001	<0.001	–0.65; <0.001	–0.65; <0.001
Lateral a' wave (cm/s)	8.2 ± 2.2	5.0–13.0	8.5 ± 2.0	8.0 ± 2.3	9.4 ± 2.6	5.0–15.0	9.8 ± 2.7	9.2 ± 2.5	10.6 ± 2.9	6.0–17.0	10.9 ± 3.0	10.4 ± 2.8	<0.001	<0.001	<0.001	0.36; <0.001	0.33; <0.001
Average septal and lateral e' wave	14.3 ± 2.7	9.1–19.5	14.0 ± 2.9	14.5 ± 2.4	11.1 ± 2.5	6.0–16.0	11.2 ± 2.4	11.1 ± 2.5	8.6 ± 2.3	3.5–15.0	8.5 ± 1.9	8.8 ± 2.6	<0.001	<0.001	<0.001	–0.66; <0.001	–0.66; <0.001
Inferior e' wave (cm/s)	14.2 ± 3.1	8.0–20.3	13.6 ± 3.0	14.7 ± 3.1	11.0 ± 2.9	6.0–17.0	10.5 ± 2.8	11.4 ± 2.9	8.4 ± 2.4	2.7–14.0	8.2 ± 2.6	8.6 ± 2.3	<0.001	<0.001	<0.001	–0.65; <0.001	–0.65; <0.001
Inferior a' wave (cm/s)	8.9 ± 1.8	5.0–13.0	9.3 ± 1.8	8.5 ± 1.7	10.5 ± 2.3	6.0–16.0	11.1 ± 2.2	10.1 ± 2.2	11.8 ± 2.0	7.7–16.0	11.8 ± 2.0	11.8 ± 2.1	<0.001	<0.001	<0.001	0.49; <0.001	0.49; <0.001
Anterior e' wave (cm/s)	14.5 ± 2.9	9.0–20.0	14.0 ± 3.0	15.0 ± 2.8	11.0 ± 2.8	6.0–18.0	11.1 ± 2.8	10.9 ± 2.8	8.0 ± 2.3	3.0–14.0	8.2 ± 2.8	7.9 ± 1.8	<0.001	<0.001	<0.001	–0.66; <0.001	–0.75; <0.001
Anterior a' wave (cm/s)	7.6 ± 1.7	4.0–11.0	8.1 ± 1.7	7.2 ± 1.6	8.7 ± 2.2	5.0–15.0	9.0 ± 2.3	8.5 ± 2.1	9.9 ± 2.4	5.0–14.3	9.9 ± 2.3	9.9 ± 2.4	<0.001	<0.001	<0.001	0.36; <0.001	0.39; <0.001
Posterior e' wave (cm/s)	15.9 ± 3.1	10.0–23.0	15.9 ± 3.5	15.9 ± 2.6	12.3 ± 2.9	7.0–18.1	12.3 ± 3.0	12.3 ± 2.8	9.8 ± 2.7	3.6–15.8	9.9 ± 2.7	9.7 ± 2.6	<0.001	<0.001	<0.001	–0.65; <0.001	–0.67; <0.001
Posterior a' wave (cm/s)	8.2 ± 2.0	4.0–13.0	8.6 ± 1.9	7.9 ± 2.1	10.0 ± 2.7	6.0–17.0	10.6 ± 2.7	9.7 ± 2.7	11.5 ± 2.8	6.3–20.1	11.7 ± 3.3	11.4 ± 2.3	<0.001	<0.001	<0.001	0.46; <0.001	0.45; <0.001
Average e' wave (cm/s)	14.5 ± 2.3	10.2–19.4	14.5 ± 2.6	14.9 ± 2.0	11.2 ± 2.3	6.5–15.5	11.0 ± 2.2	11.3 ± 2.3	8.6 ± 1.9	3.5–12.6	8.9 ± 2.0	8.3 ± 1.7	<0.001	<0.001	<0.001	–0.73; <0.001	–0.78; <0.001
E/Ea ratio																	
Septal E/e'	6.9 ± 1.6	4.4–10.6	6.9 ± 1.7	6.9 ± 1.6	8.1 ± 2.3	4.3–13.2	7.8 ± 2.4	8.2 ± 2.2	9.7 ± 2.8	5.0–16.9	9.8 ± 3.0	9.7 ± 2.6	<0.001	<0.001	<0.001	0.42; <0.001	0.41; <0.001
Lateral E/e'	5.1 ± 1.3	3.1–8.5	5.0 ± 1.3	5.2 ± 1.3	6.3 ± 2.2	3.7–12.0	6.1 ± 2.2	6.5 ± 2.3	7.8 ± 2.2	4.2–12.8	7.6 ± 2.1	7.9 ± 2.2	<0.001	<0.001	<0.001	0.43; <0.001	0.44; <0.001
Average septal and lateral E/e'	5.8 ± 1.3	3.6–9.1	5.8 ± 1.4	5.9 ± 1.3	7.0 ± 2.1	4.2–11.5	6.7 ± 2.1	7.2 ± 2.0	8.5 ± 2.2	4.6–13.5	8.4 ± 2.2	8.6 ± 2.2	<0.001	<0.001	<0.001	0.45; <0.001	0.46; <0.001
Average E/e'	5.6 ± 1.1	3.7–7.9	5.6 ± 1.2	5.5 ± 1.0	6.8 ± 1.8	4.0–11.6	6.7 ± 1.8	6.9 ± 1.9	8.3 ± 2.2	4.4–14.8	8.1 ± 2.3	8.6 ± 2.2	<0.001	<0.001	<0.001	0.50; <0.001	0.55; <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).



measurement (Figures 1 and 2). There was a significant negative correlation between e' wave velocity and age in both men (septal and lateral e' wave average velocity $r = -0.66$; $P \leq 0.001$) and women ($r = -0.66$; $P < 0.001$). Conversely, a' wave velocity and E/e' ratio increased with aging. Normal values of septal E/e' ratio and average septal and lateral E/e' ratio were 6.9 ± 1.6 and 5.8 ± 1.3 cm/s in 20–40 years category, 8.1 ± 2.3 and 7.0 ± 2.1 cm/s in 40–60 years, and 9.7 ± 2.8 and 8.5 ± 2.2 cm/s in ≥ 60 years, respectively. There was a negative and significant correlation between E/e' ratio and age in both men (Septal E/e' ratio $r = 0.42$; $P \leq 0.001$) and women ($r = 0.41$; $P < 0.001$) (Figures 3 and 4).

Table 4 shows the proportion of patients with e' wave < 8 cm/s, $E/e' > 13$ or 15, and left atrial volume index (LAVi) > 34 or 37 mL/m² in each age category and gender. Only 1.2% of the patients in the 20–40 years category showed a septal and lateral e' wave < 8 cm/s

and none of them presented an averaged septal and lateral $E/e' > 15$ or lateral $E/e' > 13$. A total of 12.1% presented with a LAVi > 34 mL/m² and 6.7% had a LAVi > 37 mL/m². In the 40–60 age category, 19.7 and 5.7% of the study subjects showed a septal and lateral e' wave < 8 cm/s, respectively, but only 1.1 and 1.6% of them presented an averaged $E/e' > 15$ or a lateral $E/e' > 13$. Regarding LA volume, 17.8% of the subjects presented a LAVi > 34 mL/m² and 10.7% had a LAVi > 37 mL/m². In the group of ≥ 60 years, more than half of the patients (55.4%) showed a septal $e' < 8$ cm/s and 19.0% had a lateral $e' < 8$ cm/s. No patient of this group had an averaged $E/e' > 15$ or a lateral $E/e' > 13$ (Figures 5 and 6). However, 15.2 and 9.1% of them presented, respectively, a LAVi > 34 mL/m² or > 37 mL/m².

Left ventricular TDI systolic parameters

The LV TDI systolic parameters are shown in Tables 5 and 6. s' wave velocity was higher in men than in female in any mitral annulus location, except in the anterior mitral annulus (septal s' : 8.4 ± 1.4 vs. 7.9 ± 1.3 ; $P < 0.001$). Table 5 shows LV systolic TDI parameters according to age categories (Figure 7). s' wave velocity was lower in older patients (septal s' : 7.5 ± 1.3 cm/s) and higher in the younger ones (8.6 ± 1.3 cm/s). There was a significant negative correlation between average s' wave velocity and age ($r = -0.41$; $P \leq 0.001$).

Right ventricular TDI diastolic and systolic parameters

The RV TDI systolic parameters are shown in Tables 7 and 8. There were no significant differences in s' , e' , and a' wave velocities between male and female. Older patients (≥ 60 years) presented a significant lower e' wave velocity than younger patients (11.8 ± 3.8 vs. 14.6 ± 3.5 ; $P < 0.001$), whereas a' wave velocity was increased in the oldest age category. However, there was no significant difference in the s' wave velocity according to age categories. A significant negative correlation was found between e' wave velocity and age ($r = -0.32$; $P < 0.001$) and a positive correlation between a' wave velocity and age ($r = 0.35$; $P < 0.001$).

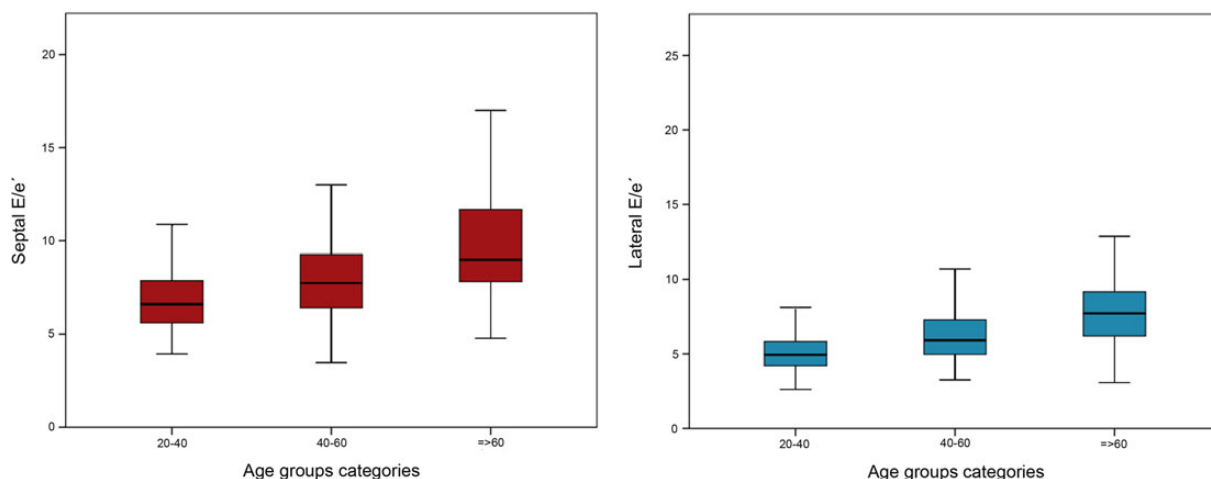


Figure 3 Septal and lateral E/e' obtained by TDI according to age categories.

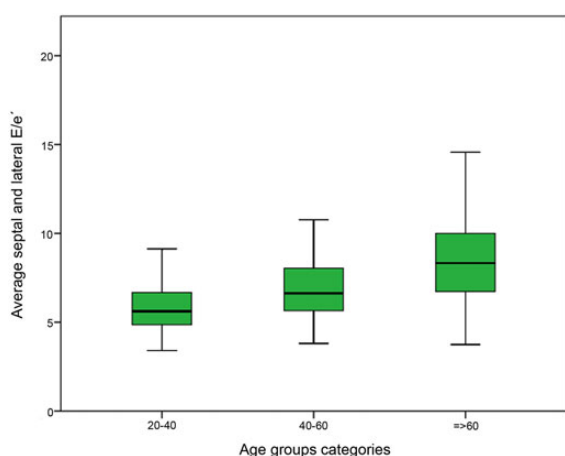


Figure 4 Average septal and lateral E/e' obtained by TDI according to age categories.

Discussion

This study provides a set of data with reference ranges for normal Doppler parameters according to age and gender using conventional recommended echocardiographic approaches and contemporary echocardiographic machines in a large cohort of healthy volunteers enrolled in the NORRE Study. Both genders were well represented with a slight predominance of women.

Left ventricular diastolic parameters

Regarding LV diastolic parameters, there was a higher E wave velocity in female than in males but without significant differences in E/A ratio and E wave deceleration times. There were also no significant

differences in most clinical parameters such as septal, lateral, and average e' wave velocities as well as in E/e' ratios between men and women. Interestingly, most diastolic parameters varied and changed according to age similarly for both genders. While E and e' wave velocities decreased progressively with age, there was an increase in A wave, in E wave deceleration time, and in E/e' ratios. These data are of paramount importance especially when using E/A ratio, e' wave, and E/e' ratio to either diagnose and classify the severity of diastolic dysfunction or identify an increase in LV filling pressures. Therefore, age reference values should be taken into account when analysing diastolic function or LV filling pressures according to current recommendations.⁸ Indeed, although only a small proportion of patients with 20–40 years had a septal or lateral $e' < 8$ cm/s, there was nearly 20% of patients in the 40–60 years group with a septal $e' < 8$ cm/s, and in the ≥ 60 years group, more than half of these healthy volunteers had a reduced septal $e' < 8$ cm/s. However, regarding the E/e' ratio, although there was a progressive increase in E/e' ratio with age, the cut-off value of average E/e' or lateral E/e' remained < 15 or 13 , respectively, in the majority of patients. None of the patients in the ≥ 60 years group had an elevated E/e' ratio and only a small proportion ($\sim 1\%$) in the 40–60 years group presented with an increased E/e' ratio. The LAVi, another parameter frequently used in the algorithm for the diagnosis of diastolic function, was increased in 12–18% of our volunteers, without significant differences according to age categories. Interestingly, no patients over all age categories had both a LAVi > 34 or 37 mL/m² and an increased lateral and average E/e' .

Left ventricular systolic parameters

Contrasting with mitral e' wave, no significant differences were found according to gender, mitral s' wave velocity was higher in men than in women. Notably, s' wave changed significantly with age in both sexes and older patients presented a lower s' wave than younger subjects. Therefore, normal reference values for s' should be interpreted according to age and gender.

Table 4 e' wave, E/e' ratio, left atrial volume (LA), and systolic pulmonary artery pressure (sPAP) according to age and gender

Parameters	20–40 years			40–60 years			≥ 60 years			Global cohort		
	Total (N = 172) n/ N (%)	Male (N = 79) n/ N (%)	Female (N = 93) n/N (%)	Total (N = 194) n/ N (%)	Male (N = 80) n/ N (%)	Female (N = 114) n/ N (%)	Total (N = 83) n/ N (%)	Male (N = 39) n/ N (%)	Female (N = 44) n/N (%)	Total (N = 449) n/ N (%)	Male (N = 198) n/ N (%)	Female (N = 251) n/N (%)
Septal e' < 8 cm/s	2/170 (1.2)	2/79 (2.5)	0/91 (0)	38/193 (19.7)	13/80 (16.3)	25/113 (22.1)	46/83 (55.4)	22/39 (56.4)	24/44 (54.5)	86/446 (19.3)	37/198 (18.7)	49/248 (19.8)
Lateral e' < 8 cm/s	2/167 (1.2)	1/76 (1.3)	1/91 (1.1)	11/192 (5.7)	4/80 (5.0)	7/112 (6.3)	15/79 (19.0)	5/36 (13.9)	10/43 (23.3)	28/438 (6.4)	10/192 (5.2)	18/246 (7.3)
Average sept-lat. E/e' > 15	0/158 (0)	0/75 (0)	0/83 (0)	2/184 (1.1)	1/76 (1.3)	1/108 (0.9)	0/78 (0)	0/36 (0)	0/42 (0)	2/420 (0.5)	1/187 (0.5)	1/233 (0.4)
Lateral E/e' > 13	0/159 (0)	0/75 (0)	0/84 (0)	3/184 (1.6)	1/76 (1.3)	2/108 (1.9)	0/78 (0)	0/36 (0)	0/42 (0)	3/421 (0.7)	1/187 (0.5)	2/234 (0.9)
LA volume > 34 mL/m ^{2a}	18/149 (12.1)	9/68 (13.2)	9/81 (11.1)	30/169 (17.8)	15/68 (22.1)	15/101 (14.9)	10/66 (15.2)	5/33 (15.2)	5/33 (15.2)	58/384 (15.1)	29/169 (17.2)	29/215 (13.5)
LA volume > 37 mL/m ^{2b}	10/149 (6.7)	6/68 (8.8)	4/81 (4.9)	18/169 (10.7)	8/68 (11.8)	10/101 (9.9)	6/66 (9.1)	3/33 (9.1)	3/33 (9.1)	34/384 (8.9)	17/169 (10.1)	17/215 (7.9)
LA volume > 34 mL/m ^{2c}	4/124 (3.2)	2/58 (3.4)	2/66 (3.0)	19/131 (14.5)	7/54 (13.0)	12/77 (15.6)	5/53 (9.4)	4/26 (15.4)	1/27 (3.7)	28/308 (9.1)	13/138 (9.4)	15/170 (8.8)
LA volume > 34 mL/m ^{2d}	10/117 (8.5)	4/53 (7.5)	6/64 (9.4)	18/127 (14.2)	7/51 (13.7)	11/76 (14.5)	3/50 (6.0)	2/24 (8.3)	1/26 (3.8)	31/294 (10.5)	13/128 (10.2)	18/166 (10.8)
LA volume > 37 mL/m ^{2e}	5/117 (4.3)	2/53 (3.8)	3/64 (4.7)	10/127 (7.9)	5/51 (9.8)	5/76 (6.6)	1/50 (2.0)	0/24 (0.0)	1/26 (3.8)	16/294 (5.4)	7/128 (5.5)	9/166 (5.4)
LA volume > 34 mL/m ^{2f}	20/117 (17.1)	8/53 (15.1)	12/64 (18.8)	33/127 (26.0)	16/51 (31.4)	17/76 (22.4)	8/50 (16.0)	6/24 (25.0)	2/26 (7.7)	61/294 (20.7)	30/128 (23.4)	31/166 (18.7)
LA volume > 37 mL/m ^{2g}	12/117 (10.3)	6/53 (11.3)	6/64 (9.4)	21/127 (16.5)	11/51 (21.6)	10/76 (13.2)	4/50 (8.0)	3/24 (12.5)	1/26 (3.8)	37/294 (12.6)	20/128 (15.6)	17/166 (10.2)
sPAP > 36 mmHg	1/106 (0.9)	1/48 (2.1)	0/58 (0.0)	0/131 (0.0)	0/57 (0.0)	0/74 (0.0)	0/57 (0.0)	0/24 (0.0)	0/33 (0.0)	1/294 (0.3)	1/129 (0.8)	0/165 (0.0)
sPAP > 45 mmHg	0/106 (0.0)	0/48 (0.0)	0/58 (0.0)	0/131 (0.0)	0/57 (0.0)	0/74 (0.0)	0/57 (0.0)	0/24 (0.0)	0/33 (0.0)	0/294 (0.0)	0/129 (0.0)	0/165 (0.0)

^aLA volume > 34 mL/m² by single plane area-length method (four-chamber view).^bLA volume > 37 mL/m² by single plane area-length method (four-chamber view).^cLA volume > 34 mL/m² by single plane Simpson method (four-chamber view).^dLA volume > 34 mL/m² by biplane Simpson method.^eLA volume > 37 mL/m² by biplane Simpson method.^fLA volume > 34 mL/m² by biplane area-length method.^gLA volume > 34 mL/m² by biplane area-length method.

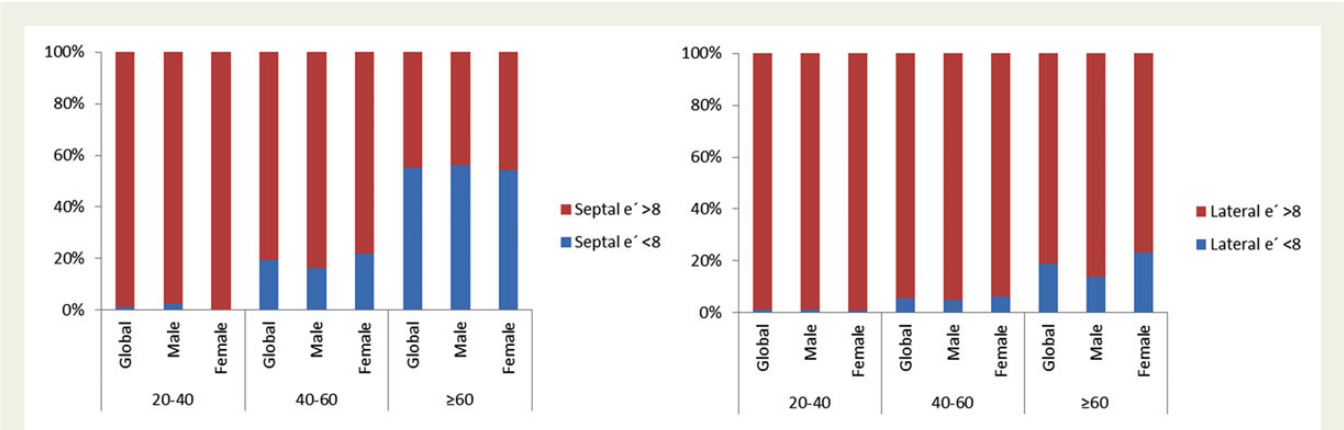


Figure 5 Percentage of patients with e' wave velocity < 8 cm/s according to age categories.

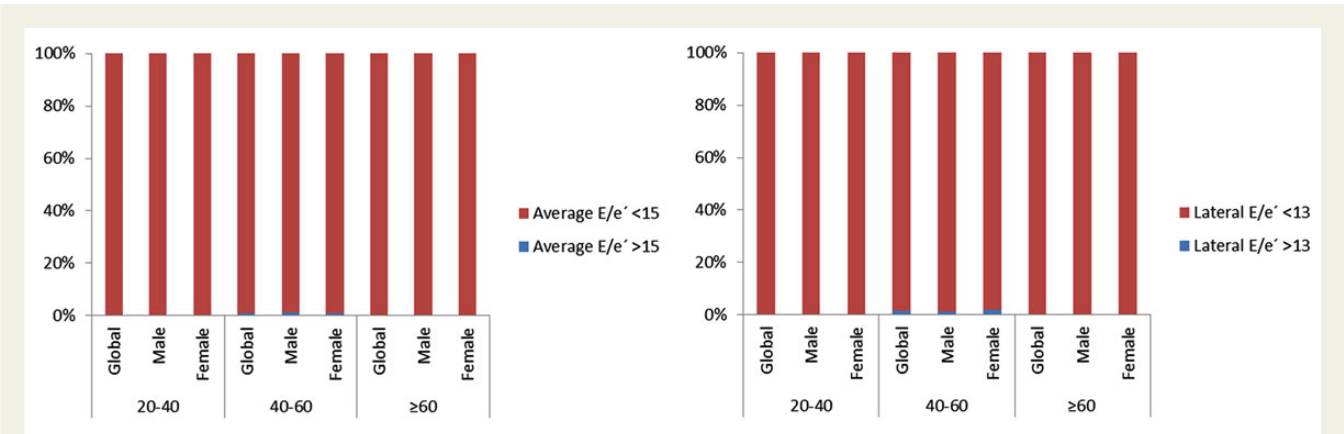


Figure 6 Percentage of patients with an average (septal and lateral) $E/e' > 15$ or lateral $E/e' > 13$ according to age categories.

Table 5 Left ventricular TDI systolic parameters according to gender

Parameters	Total Mean \pm SD	Total 1st–3rd quartile	Total 95% CI	Male Mean \pm SD	Male 95% CI	Female Mean \pm SD	Female 95% CI	P*
Septal s' wave (cm/s)	8.1 \pm 1.4	7.0–9.0	6.0–11.0	8.4 \pm 1.4	6.0–11.1	7.9 \pm 1.3	5.0–10.0	< 0.001
Lateral s' wave (cm/s)	9.8 \pm 2.4	8.0–12.0	5.0–14.1	10.1 \pm 2.6	5.0–16.0	9.5 \pm 2.3	5.1–14.0	0.028
Average septal and lateral s' wave (cm/s)	8.9 \pm 1.6	7.5–10.0	6.0–12.1	9.2 \pm 1.7	6.0–13.1	8.7 \pm 1.5	6.0–12.0	0.001
Inferior s' wave (cm/s)	8.9 \pm 1.5	8.0–10.0	6.0–12.0	9.2 \pm 1.6	6.0–12.0	8.7 \pm 1.4	6.0–12.0	0.001
Anterior s' wave (cm/s)	9.1 \pm 3.4	7.0–11.0	5.0–13.0	9.0 \pm 2.2	5.0–13.0	9.3 \pm 4.9	5.0–13.0	0.509
Posterior s' wave (cm/s)	9.5 \pm 2.1	8.0–11.0	6.0–14.0	10.0 \pm 2.3	6.0–14.1	9.1 \pm 1.9	6.0–13.0	< 0.001
Average s' wave (cm/s)	9.0 \pm 1.7	7.8–10.0	6.2–12.3	9.3 \pm 1.6	6.2–12.4	8.8 \pm 1.7	6.1–12.0	0.005

CI, confidence interval.

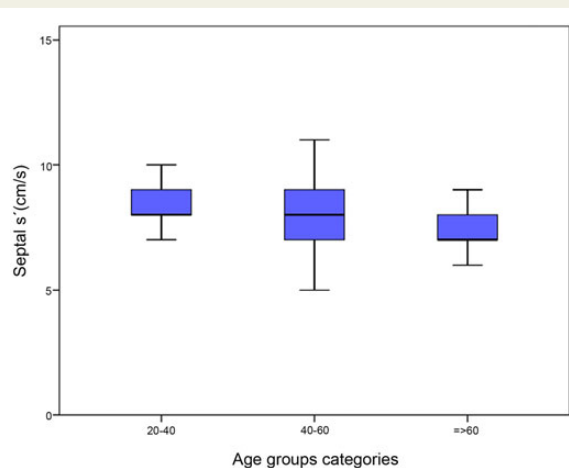
*P differences between male vs. female.

Table 6 Left ventricular TDI systolic parameters according to age

Parameters	Total						P*	r P**
	20–40 years		40–60 years		>60 years			
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI		
Septal s' wave (cm/s)	8.6 ± 1.3	6.0–12.0	7.9 ± 1.4	5.9–11.0	7.5 ± 1.3	5.0–10.0	<0.001	–0.30; <0.001
Lateral s' wave (cm/s)	10.7 ± 2.3	6.1–16.0	9.4 ± 2.2	5.0–14.0	8.5 ± 2.5	4.0–15.0	<0.001	–0.37; <0.001
Average septal and lateral s' wave (cm/s)	9.6 ± 1.6	7.0–13.0	8.7 ± 1.5	6.0–12.0	8.1 ± 1.6	5.5–12.5	<0.001	–0.39; <0.001
Inferior s' wave (cm/s)	9.3 ± 1.5	7.0–12.0	8.8 ± 1.5	6.0–12.0	8.2 ± 1.5	5.0–12.0	<0.001	–0.26; <0.001
Anterior s' wave (cm/s)	10.0 ± 2.1	6.6–13.4	8.6 ± 2.0	5.0–13.0	7.6 ± 2.1	4.0–12.0	<0.001	–0.45; <0.001
Posterior s' wave (cm/s)	10.2 ± 1.8	7.0–14.0	9.2 ± 1.9	6.0–13.2	8.8 ± 2.7	5.6–18.6	<0.001	–0.27; <0.001
Average s' wave (cm/s)	9.7 ± 1.7	7.2–12.9	8.7 ± 1.4	6.2–11.9	8.1 ± 1.6	5.7–12.7	<0.001	–0.41; <0.001

*P differences between groups according to age category (two-way ANOVA).

**P and r correlation with age for both genders (Pearson correlation test).

**Figure 7** Septal s' wave velocities obtained by TDI according to age categories.

Right ventricular TDI systolic and diastolic parameters

As for LV, no significant differences were found in s', e', and a' wave velocities according to gender. However, according to age categories, e' wave velocity was decreased and a' wave velocity was increased in older patients. Interestingly, and in contrast to the LV, the RV s' wave velocity was not affected by age. Therefore, normal reference values and cut-off values for s' can be used independently of age and gender.

Comparison with previous studies

Our study confirmed and extended some previous studies concerning European populations, which, however, were often of small sample size with limited ranges of ages and uncertainties about normality (no laboratory findings). The NORRE Doppler results emphasized the need for reference values for pulsed wave Doppler and TDI.⁹

As shown previously, E wave and E/A ratio decreased with age in healthy volunteers,^{10–12} and so, an inversion of E/A ratio should likely be considered as a physiologic pattern in elderly subjects in the absence of other abnormal findings. Conversely to some reports in paediatric populations^{13,14} but consistent with previous studies in adults,^{15–17} we found a negative correlation between s' wave and age, with a value being higher in younger and male volunteers. Nonetheless, Sun *et al.*¹⁸ described little influence of sex on s' wave. We also confirmed that s' was higher in the lateral wall,^{16,19} though these results were discordant with a few previous reports.¹⁵ Interestingly, we found similar impacts of age on s' wave velocities whatever the annulus site, whereas other studies reported better correlations with lateral s' wave velocity^{20,21} or even no impact of age on s' wave.^{12,22,23}

Discordant with a few reports^{15,16} but concordant with several studies, we did not find any significant differences in e' wave values according to gender,²⁴ but e' decreased with age in both women and men.^{12,16,17,20–22,24–28} Moreover, we showed that lateral e' remained <8 in all age categories in most patients. As previously reported, we also showed that E/e' ratio was correlated with age^{12,20,21,23,25,29} and remained <13 or <15 in almost all patients.^{20–22,24,29} Whether medial or lateral wall should be used in calculating E/e' ratio is still controversial. In accordance with previous studies, we found lateral E/e' ratio to be smaller than medial E/e' ratio in both sexes.^{22,24,29}

Regarding the RV, our study showed the absence of gender-related differences in TDI parameters and confirmed the previous findings of the absence of the influence of age on s' wave velocities, whereas the e' wave at the tricuspid annulus of the RV was decreased with age.¹⁷

Limitations

The NORRE study results pertain only to European individuals. Thus, conclusions concerning other ethnic populations could not be drawn. Despite all subjects were considered normal, we cannot exclude the possibility of subclinical coronary artery disease or cardiomyopathies, which can influence the values of systolic and diastolic parameters.

Table 7 Right ventricular TDI systolic and diastolic parameters according to gender

Parameters	Total Mean \pm SD	Total 1st–3rd quartile	Total 95% CI	Male Mean \pm SD	Female Mean \pm SD	P*
s' wave (cm/s)	13.3 \pm 2.5	12.0–15.0	9.0–18.0	13.6 \pm 2.8	13.1 \pm 2.1	0.055
e' wave (cm/s)	13.1 \pm 3.8	10.0–15.0	7.0–21.0	12.8 \pm 3.8	13.4 \pm 3.7	0.12
a' wave (cm/s)	13.1 \pm 3.9	10.0–15.0	7.0–23.0	12.9 \pm 3.8	13.2 \pm 4.0	0.44

CI, confidence interval.

*P differences between male vs. female.

Table 8 Right ventricular TDI systolic and diastolic parameters according to age

Parameters	Total						P*	r P**
	20–40 years		40–60 years		≥60 years			
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI		
s' wave (cm/s)	13.6 ± 2.3	9.0–18.1	13.1 ± 2.5	8.0–18.0	13.2 ± 2.9	8.0–20.0	0.169	−0.08; 0.085
e' wave (cm/s)	14.6 ± 3.5	8.0–23.0	12.5 ± 3.6	6.0–20.0	11.8 ± 3.8	6.0–20.0	<0.001	−0.32; <0.001
a' wave (cm/s)	11.5 ± 3.2	6.0–20.0	13.4 ± 3.6	7.7–21.3	15.1 ± 4.7	7.0–26.0	<0.001	0.35; <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).

Conclusion

The NORRE Study provides applicable Doppler and TDI echocardiographic reference ranges for left and right ventricle diastolic and systolic assessment. Our data highlight the need to use different normal reference values according to the age of the patient in most of the parameters and to gender in some of them.

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Appendix

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