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Echocardiographic reference ranges for normal left atrial function parameters: results from the EACVI NORRE study

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Aims To obtain the normal ranges for echocardiographic measurements of left atrial (LA) function from a large group of healthy volunteers accounting for age and gender.

Methods and results A total of 371 (median age 45 years) healthy subjects were enrolled at 22 collaborating institutions collaborating in the Normal Reference Ranges for Echocardiography (NORRE) study of the European Association of Cardiovascular Imaging (EACVI). Left atrial data sets were analysed with a vendor-independent software (VIS) package allowing homogeneous measurements irrespective of the echocardiographic equipment used to acquire data sets. The lowest expected values of LA function were 26.1%, 48.7%, and 41.4% for left atrial strain (LAS), 2D left

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atrial emptying fraction (LAEF), and 3D LAEF (reservoir function); 7.7%, 24.2%, and -0.53/s for LAS-active, LAEF-active, and LA strain rate during LA contraction (SRa) (pump function) and 12.0% and 21.6% for LAS-passive and LAEF-passive (conduit function). Left atrial reservoir and conduit function were decreased with age while pump function was increased. All indices of reservoir function and all LA strains had no difference in both gender and vendor. However, inter-vendor differences were observed in LA SRa despite the use of VIS.

Conclusion The NORRE study provides contemporary, applicable echocardiographic reference ranges for LA function. Our data highlight the importance of age-specific reference values for LA functions.

Keywords adult echocardiography • left atrial function • deformation imaging • reference values

Introduction

The left atrium is extremely sensitive to sustained volume and pressure overload secondary to increased left ventricular filling pressures,[1] and the stepwise backward effects of loss in left atrial (LA) functional properties are a reduction in lung vessel compliance and vascular remodelling that trigger right ventricular overload and dysfunction.[2] In contrast to left ventricular measures, there is a strong linear relationship between volumetric and longitudinal deformation indices of left atrium.[3] Early detection of subclinical LA dysfunction plays a crucial role in the evaluation of many cardiac diseases.[4–9] Although normal ranges of LA function have been reported in recent studies,[10–13] age related normal references remain unknown. The Normal Reference Ranges for Echocardiography (NORRE) study is the first European, large, prospective, multicentre study performed in 22 laboratories accredited by the European Association of Cardiovascular Imaging (EACVI) and in one American laboratory. The NORRE study has already provided reference values for all 2D echocardiographic measurements of the four cardiac chambers,[14] Doppler parameters,[15] aortic dimensions,[16] left ventricular strains,[17] and 3D echocardiographic measurements of LV volumes and strain.[18] This report aimed (i) to establish normal reference limits, using vendor-independent software (VIS), for 2D and 3D measurement of LA function in healthy adults and (ii) to examine the influence of age, gender, and vendor on the reference ranges.

Methods

Patient population

A total of 734 healthy European subjects constituted the final NORRE study population. The local ethics committees approved the study protocol. After the exclusion of patients that had incompatible image format and/or poor image quality, the final study population consisted of 371 normal subjects. Baseline clinical characteristics of patients included in and excluded from this study are shown in Supplementary data online, *Table S1*.

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.[19,20] All echocardiographic images were recorded in a digital raw-data format (native DICOM format) and centralized for further analysis, after anonymization, at the EACVI Central Core Laboratory at the University of Liège, Belgium.

LA functions and stiffness analysis

Based on previous validated studies and guidelines of the American Society of Echocardiography/EACVI, quantification of LA 2D strain, 2D volume, and 3D volume was performed using commercially available VIS (2D Cardiac Performance Analysis and 4D Cardio-View, TomTec Imaging System, Munich, Germany) (*Figure 1*).[10,21] 2D analyses were performed in the apical four- and two-chamber views. The most suitable cardiac cycle was chosen for each view. The reference point was set at the beginning of the QRS complex. Left atrial end-systole was identified as the time point in which the LA cavity was the smallest. The endocardial border was traced in end-systole. The accuracy of tracking was visually confirmed throughout the cardiac cycle and confirmed from the morphology of the strain curves. If necessary, the region of interest was readjusted. In the measurement of LA 3D volumes, end-diastole was identified as the time point in which the LA cavity is the largest and end-systole as the time point at which the cavity was the smallest. The definition of LA reservoir, pump, and conduit function in this study is demonstrated in *Figure 2*. Left atrial reservoir function was assessed using the left atrial strain curve (LAS), left atrial emptying fraction (LAEF) in both 2D and 3D. As shown in *Figure 2*, LA pump function was assessed using LAS-active: LA strain at the onset time of the P wave, LAEF-active: (LA volume at the onset time of the P wave - LA minimum volume)/LA volume at the onset time of the P wave and LA strain rate during LA contraction (SRa).[10] Left atrial conduit function was assessed by using LAS-passive: LAS - LAS-active, and LAEF-passive: (LA maximum volume - LA volume at the onset time of the P wave)/LA maximum volume. The ratio of mitral inflow *E*/e' to LA reservoir function (LAS, LAEF) was used to estimate LA stiffness.[22]

Statistical analysis

Normality of the distribution of continuous variables was tested by the Shapiro–Wilk test. All data are presented as the mean ± standard deviation or median (interquartile range) as appropriate. Group differences were evaluated using the Student's *t*-test for normally distributed continuous variables and the Mann–Whitney *U* test for non-normally distributed continuous variables. Correlation between continuous variables was performed Pearson's or Spearman's correlation coefficient as appropriate. The lowest (2.5th percentile) and highest (97.5th percentile) expected values for left atrial parameters were estimated in 1000 bootstrap samples to generate sampling distributions. For each of these values, the mean and standard errors were estimated from the simulated sampling distribution. Multiple linear regression analyses were performed to examine the independent correlates between LA functions and baseline parameters including cardiovascular risk factors (age, gender, body mass index, systolic blood pressure, diastolic blood pressure, glycaemia, and cholesterol level) and vendor. Intra-observer (T.S.) variability was assessed in 20 randomly selected subjects using intraclass correlation coefficient (ICC). A *P*-value of <0.05 was considered as statistically significant. Data were analysed using open source statistical software, R version

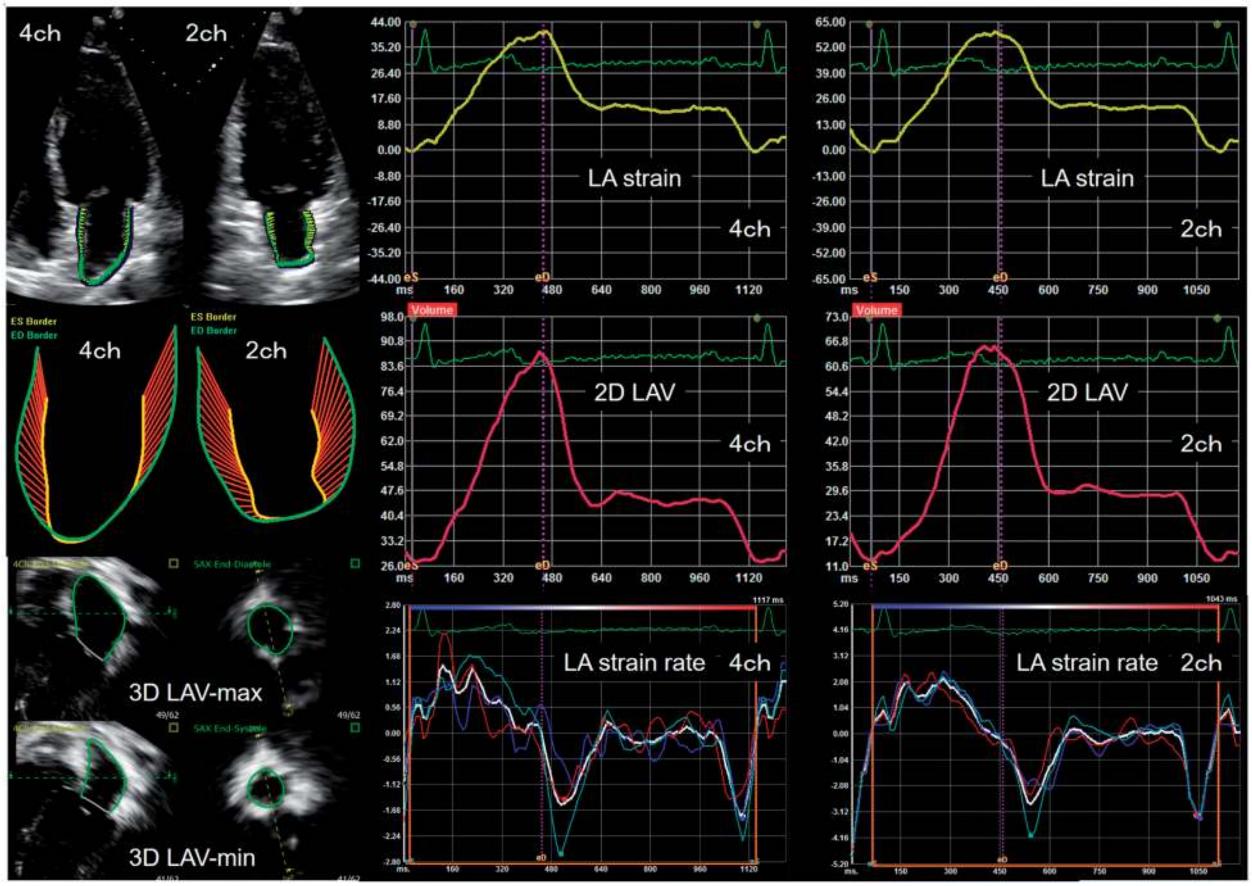

Figure 1 Measurements of LA strain and strain rate by 2D speckle-tracking echocardiography analysis and LA volume by 2D and 3D echocardiography analysis using VIS. VIS, vendor-independent software; LA, left atrial; LAV, left atrial volume.

3.3.2 (R Foundation for Statistical Computing, www.R-project.org) and SPSS 19.0 software (SPSS Inc., Chicago, IL, USA).

Results

Demographic data

Table 1 summarizes the demographic data of the cohort of the NORRE population analysed in this study. A total of 165 men and 206 women were included. There was no significant association between age and 3D LA volume index on univariable analysis ($R = 0.09$, $P = 0.07$) and no differences in 3D LA volume index for gender. Values for LA reservoir, pump, and conduit function obtained from analysis of LA volume and strain curves for the entire study population are summarized in *Table 2*. The lowest limits of normality were 26.1%, 48.7%, and 41.4% for LAS, 2D LAEF, and 3D LAEF (reservoir function), respectively; 7.7%, 24.2%, and -0.53/s for LAS-active, LAEF-active, and LA SRa (pump function), respectively; and 12.0% and 21.6% for LAS-passive and LAEF-passive (conduit function), respectively. All LA parameters except SRa were significantly associated with age. Gender differences were observed in LAEF-passive. Vendor differences were observed in 2D LAEF, LAEF-active, and LA SRa. Multivariable analysis for LA functions showed that LAS, 2D LAEF, 3D LAEF, LAS-passive, and LAEF-passive decreased whereas 3D LA volume index and LAS-active increased with age. After adjusting for variables including basic parameters and vendor, LAEF-passive was higher in women than in men and 3D LA volume index was higher and LA SRa was lower when acquired with GE platforms compared with Philips equipment, (*Table 3*). *Figure 3* shows two representative cases of LA functional assessments (middle vs. advanced age).

Age and LA functions relationship

Left atrial reservoir, pump, and conduit function and stiffness in the three subgroups according to age (20–40, 40–60, and ≥60 years) are displayed in *Table 4*. The lowest expected values for LAS were 31.1% in 20–40 years of age, 27.7% in 40–60 years, and 22.7% in ≥60 years. The highest expected values for LA stiffness calculated from LAS were 0.22 in 20–40 years of age, 0.42 in 40–60 years, and 0.55 in ≥60 years.

Vendor and LA functions relationship

Multivariable analysis showed that 3D LA volume index was higher [GE, 27.8 (24.2–32.2) mL/m^2, $n = 189$ vs. Philips, 25.5 (22.8–29.3) mL/m^2, $n = 184$, $P = 0.001$] and LA SRa was lower [GE, -0.98 (-1.16 to -0.73)/s vs. Philips, -1.99 (-2.42 to -1.58)/s, $P < 0.001$] with GE

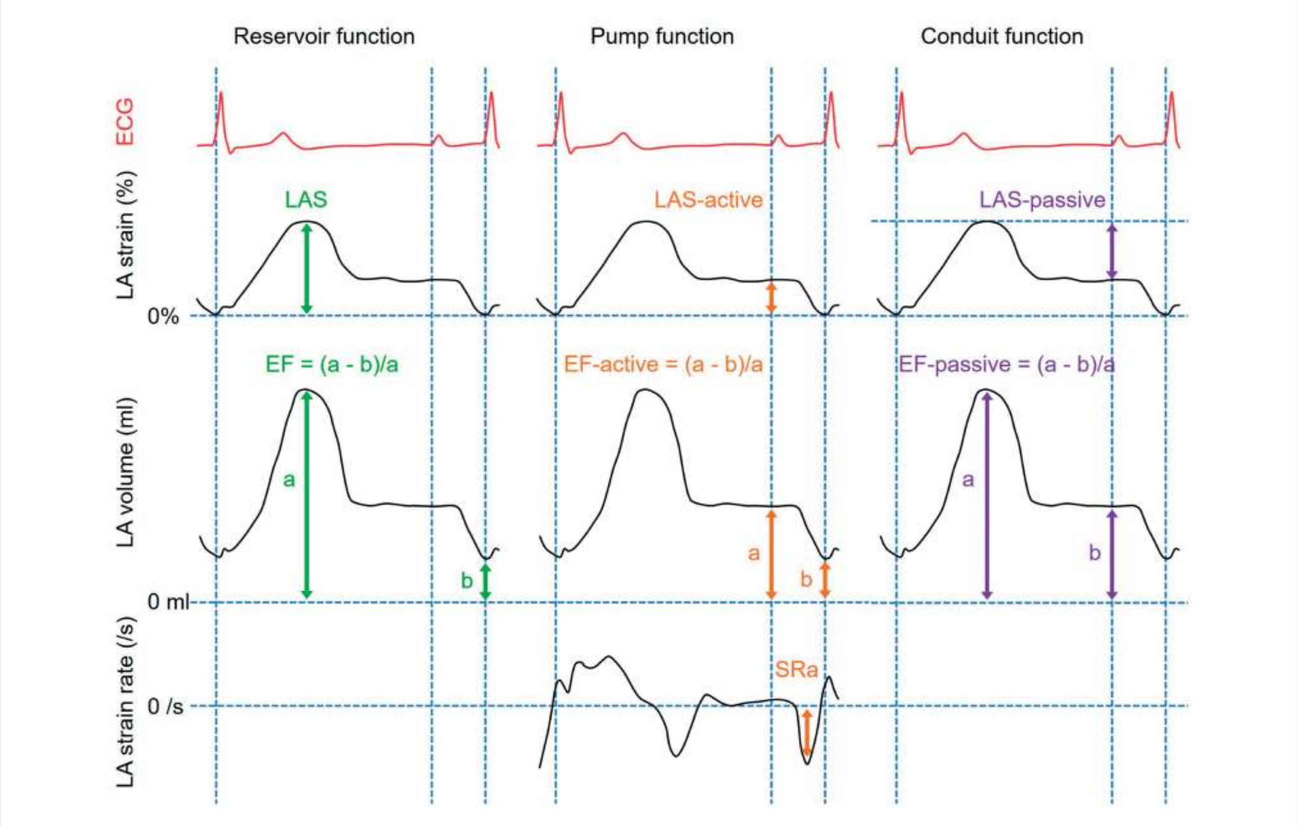

Figure 2 Assessments of LA reservoir, pump and conduit function using LA strain analysis and LA volume. EF, emptying fraction; LA, left atrial; LAS, left atrial strain; SRa, strain rate.

Table 1 Characteristics of the population

Parameters	Total ($n = 371$)	Male ($n = 165$, 44%)	Female ($n = 206$, 56%)	*P*-value
Age (years)	45 (34–55)	46 (33–57)	44 (34–54)	0.54
Height (cm)	170 ± 9	177 ± 7	165 ± 7	<0.001
Weight (kg)	69 (60–78)	77 (71–84)	63 (57–69)	<0.001
Body surface area (m^2)	1.79 (1.66–1.94)	1.94 (1.85–2.05)	1.68 (1.61–1.78)	<0.001
Body mass index (kg/m^2)	23.9 (22.0–26.0)	24.7 (23.2–26.4)	23.2 (21.1–25.4)	<0.001
Systolic blood pressure (mmHg)	120 (110–130)	121 (117–130)	116 (108–126)	<0.001
Diastolic blood pressure (mmHg)	75 (70–80)	77 (70–80)	73 (68–80)	0.002
Glycaemia (mg/dL)	90 (85–98)	91 (87–98)	90 (83–96)	0.017
Cholesterol level (mg/dL)	181 (163–197)	183 (160–197)	179 (164–196)	0.86

compared with Philips equipment for the total population. The same tendency was observed for the apical four-chambers [-0.84 (-1.12 to -0.65) vs. -1.81 (-2.28 to -1.32)/s, $P < 0.001$] and two-chambers [-1.11 (-1.31 to -0.82) vs. -2.25 (-2.65 to -1.70)/s, $P < 0.001$] LA SRa. The number of patients whose LA SRa could not be identified on LA strain analysis was significantly higher with GE than Philips (8% vs. 0% and 38% vs. 15% in apical four- and two-chambers view, $P < 0.001$, respectively). The lowest expected values for LA SRa were -0.47/s (GE) and -0.86/s (Philips). The highest expected values for LA volume index were 41.3 mL/m^2 (GE) and 39.6 mL/m^2 (Philips).

Repeatability

Intra-observer analysis showed excellent repeatability in LAS, LAS-active, LA SRa, and 3D LA volume (ICC = 0.85, 0.71, 0.79, and 0.90, $P < 0.01$, respectively).

Table 2 **Left atrial reservoir, pump, and conduit function**

	Total		Age		Differences between gender	Differences between vender
	Mean ± SD or medial (IQR)	Limits of normality ± SE^{a,b}	*R*	*P*-value	*P*-value	*P*-value
3D LA volume (mL)	47.7 (40.8 to 57.1)	78.7 ± 2.2^{a}	0.10	0.06	<0.001	0.001
3D LA volume index (mL/m^2)	26.3 (23.1 to 31.1)	40.6 ± 1.1^{a}	0.09	0.07	0.07	0.001
Reservoir function						
LAS (%)	42.5 (36.1 to 48.0)	26.1 ± 0.7^{b}	-0.47	<0.001	0.49	0.47
2D LAEF (%)	68.5 (63.2 to 73.2)	48.7 ± 1.9^{b}	-0.31	<0.001	0.42	0.02
3D LAEF (%)	57.3 (52.4 to 61.9)	41.4 ± 1.1^{b}	-0.17	<0.001	0.53	0.76
Pump function						
LAS-active (%)	16.3 (12.9 to 19.5)	7.7 ± 0.3^{b}	0.15	0.003	0.34	0.35
LAEF-active (%)	43.1 ± 9.4	24.2 ± 1.4^{b}	0.14	0.008	0.13	0.002
LA SRa (/s)	-1.31 (-1.99 to -0.95)	-0.53 ± 0.03^{b}	-0.1	0.054	0.08	<0.001
Conduit function						
LAS-passive (%)	25.7 (20.4 to 31.8)	12.0 ± 0.5^{b}	-0.61	<0.001	0.06	0.98
LAEF-passive (%)	43.0 ± 10.3	21.6 ± 0.9^{b}	-0.55	<0.001	0.008	0.85

IQR, interquartile range; SD, standard deviation; SE, standard error; other abbreviations as in *Figure 2*.
[a] Highest expected values.
[b] Lowest expected values.

Table 3 **Multivariable analysis for left atrial functions**

Variables	Basic parameters^{a}		Basic parameters^{a} + vendor	
	β-coefficients ± SE	*P*-value	β-coefficients ± SE	*P*-value
3D LA volume index (mL/m^2)				
Age (years)			0.07 ± 0.03	0.029
Cholesterol level (mg/dL)	-0.03 ± 0.01	0.033	-0.03 ± 0.01	0.009
Male gender			1.62 ± 0.77	0.037
Vendor (GE as referent)			-3.94 ± 0.74	<0.001
LAS (%)				
Age (years)	-0.32 ± 0.04	<0.001	-0.33 ± 0.04	<0.001
Body mass index (kg/m^2)	-0.39 ± 0.18	0.03	-0.42 ± 0.18	0.02
Glycaemia (mg/dL)	-0.09 ± 0.04	0.049		
2D LAEF, (%)				
Age (years)	-0.20 ± 0.04	<0.001	-0.21 ± 0.04	<0.001
3D LAEF (%)				
Age (years)	-0.11 ± 0.04	0.008	-0.10 ± 0.04	0.013
LAS-active (%)				
Age (years)	0.06 ± 0.02	0.02	0.06 ± 0.03	0.02
Glycaemia (mg/dL)	-0.07 ± 0.02	0.005	-0.07 ± 0.02	0.006
LAEF-active (%)				
Body mass index (kg/m^2)	0.40 ± 0.20	0.047		
Glycaemia (mg/dL)	-0.10 ± 0.05	0.036	-0.10 ± 0.05	0.045
LA SRa (/s)				
Age (years)	-0.01 ± 0.004	0.01		
Vendor (GE as referent)			-1.08 ± 0.08	<0.001
LAS-passive (%)				
Age (years)	-0.37 ± 0.04	<0.001	-0.38 ± 0.04	<0.001
Body mass index (kg/m^2)	-0.53 ± 0.16	0.001	-0.56 ± 0.16	<0.001
LAEF-passive (%)				
Age (years)	-0.43 ± 0.05	<0.001	-0.43 ± 0.05	<0.001
Male gender			-2.42 ± 1.18	0.04
Body mass index (kg/m^2)	-0.52 ± 0.19	0.007	-0.55 ± 0.19	0.005

SE, standard error; other abbreviations as in *Figure 2*.
[a] Age, gender, body mass index, systolic blood pressure, diastolic blood pressure, glycaemia and cholesterol level.

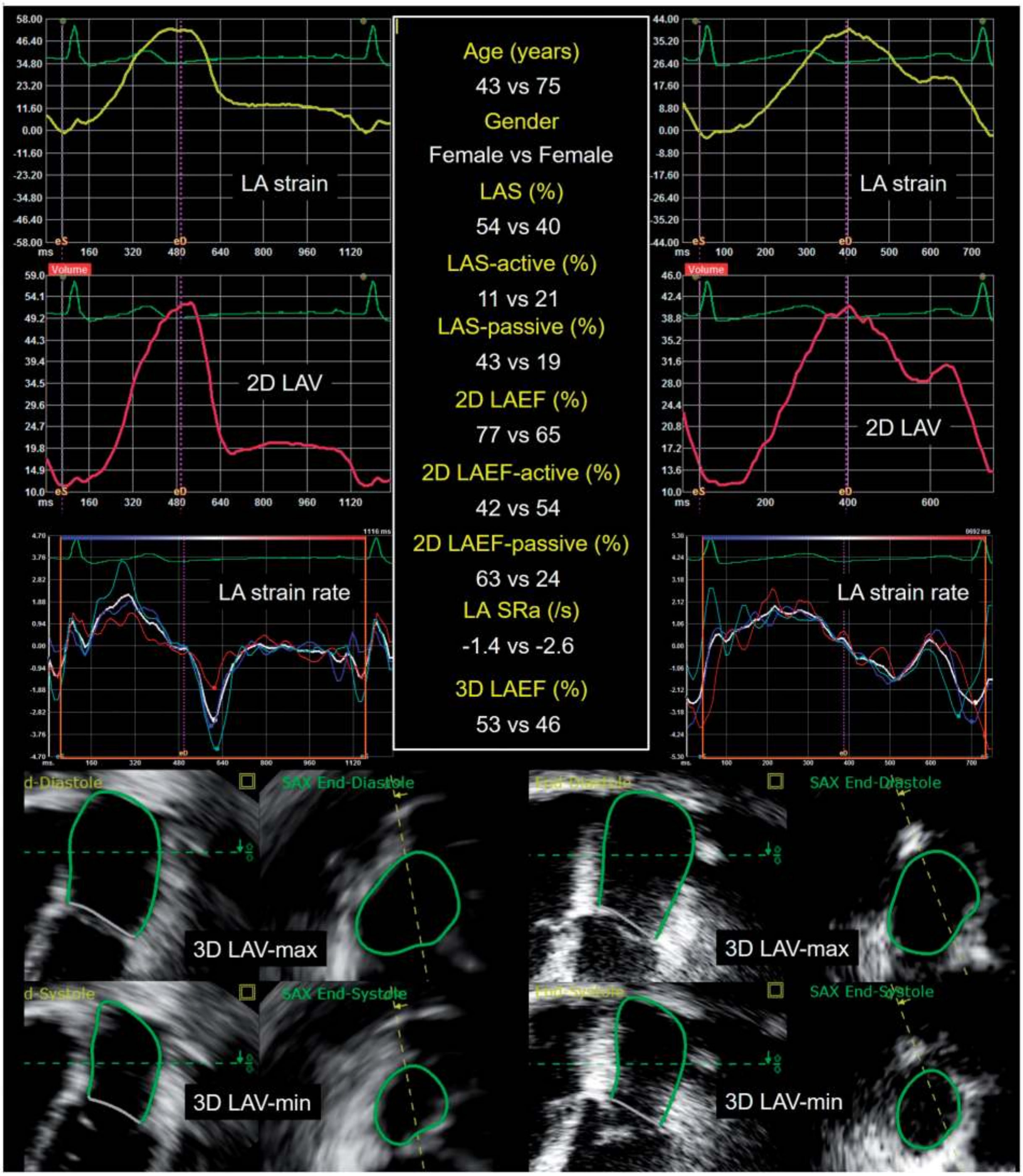

Figure 3 Two representative cases of LA functional assessments. LAV, left atrial volume; other abbreviations as in *Figure* 2.

Discussion

The present prospective, EACVI multicentre study provides contemporary normal reference values for LA function in a large cohort of healthy volunteers over a wide range of ages. 2DE analyses were performed using a VIS in order to obtain homogeneous measurements irrespective of the echocardiographic equipment used to acquire data. Left atrial reservoir and conduit function decreased with age while pump function increased. All indices of reservoir function and LA strains had no gender and vendor differences. Interestingly, inter-vendor differences were observed in 3D LA volume index and LA SRa despite the use of VIS software.

Previous single-centre studies with healthy subjects reported that the highest expected value for 3D LA volume index was: 33 mL/m^2 in

Table 4 **Left atrial functions and stiffness according to age**

	Age 20–40 ($n = 137$)		Age 40–60 ($n = 173$)		Age ≥60 ($n = 61$)	
	Medial (IQR)	Limits of normality ± SE[a,b]	Medial (IQR)	Limits of normality ± SE[a,b]	Medial (IQR)	Limits of normality ± SE[a,b]
Reservoir function						
LAS (%)	46.8 (42.3–52.4)	31.1 ± 2.6[b]	40.9 (35.4–46.1)	27.7 ± 1.5[b]	35.5 (30.9–41.9)	22.7 ± 2.0[b]
2D LAEF (%)	71.3 (67.3–74.9)	51.7 ± 2.0[b]	66.7 (62.8–72.4)	49.2 ± 2.7[b]	64.0 (58.1–69.5)	44.1 ± 1.7[b]
3D LAEF (%)	58.4 (53.1–63.1)	42.2 ± 2.3[b]	57.1 (52.2–61.3)	39.4 ± 1.9[b]	55.6 (50.6–60.4)	38.3 ± 2.5[b]
Pump function						
LAS-active (%)	15.6 (11.9–19.0)	7.2 ± 0.5[b]	16.3 (13.2–19.6)	9.3 ± 0.8[b]	16.8 (13.6–21.4)	7.7 ± 0.8[b]
Conduit function						
LAS-passive (%)	30.6 (26.8–36.5)	16.2 ± 1.6[b]	24.1 (19.7–29.3)	12.0 ± 1.0[b]	18.6 (14.7–22.6)	11.5 ± 0.1[b]
Stiffness						
E/e' divided by LAS	0.12 (0.10–0.15)	0.22 ± 0.01[a]	0.16 (0.13–0.22)	0.42 ± 0.04[a]	0.24 (0.18–0.29)	0.55 ± 0.09[a]
E/e' divided by 2D LAEF	0.08 (0.07–0.09)	0.15 ± 0.01[a]	0.10 (0.09–0.12)	0.23 ± 0.04[a]	0.14 (0.11–0.15)	0.24 ± 0.02[a]
E/e' divided by 3D LAEF	0.10 (0.08–0.12)	0.19 ± 0.01[a]	0.11 (0.10–0.15)	0.24 ± 0.04[a]	0.15 (0.13–0.17)	0.27 ± 0.02[a]
E/e'	5.6 (4.8–6.7)	9.0 ± 1.3[a]	6.8 (5.8–8.3)	13.4 ± 2.4[a]	8.3 (7.1–9.8)	13.3 ± 0.5[a]

CI, confidence interval; SD, standard deviation; other abbreviations as in *Figure 2*.

[a] Highest expected values.

[b] Lowest expected values.

the study of Wu *et al.*,[23] a Japanese cohort, using Philips equipment and software, 41 mL/m^2 in the study of Aune *et al.*,[24] a Norway cohort, using Philips equipment and software, and 43 mL/m^2 in the study of Badano *et al.*,[13] an Italian cohort, using GE equipment and TomTec software. This multicentre study with a Caucasian European population showed lower 3D LA volume index compared with single-centre studies in the Norway and Italy. The reasons for this difference may be caused by several factors: (i) lower temporal resolution of 3D echocardiographic data sets caused by a wide-angle 3D acquisition for the LA[13]; (ii) the difference in baseline blood pressure in male [systolic/diastolic blood pressure: 123/76 mmHg (mean) and 121/77 mmHg (median) in this study vs. 127/79 mmHg (mean) in the Norwegian cohort and 130/80 mmHg (median) in the Italian cohort]; and (iii) inter-vendor differences as demonstrated in this study.

A previous multicentre study reporting on a large cohort of healthy subjects showed that LAS and LAEF were negatively associated with age while having no differences in gender.[10] A meta-analysis of LA strain using 2D speckle tracking echocardiography has detected no difference in both gender and vendor.[11] These finding are consistent with the findings of this study. The mechanism of age-related changes in LA function, in particular pump function, may be explained by age-related changes in left ventricular diastolic performance from normal to diastolic dysfunction grade 1.[25] In fact, our data demonstrated the age-related increases in LA stiffness, an index that has been reported as a sensitive marker of diastolic dysfunction.[22,26] This study showed that the best concordance between the two major vendors was in LA strain whereas the major discordance was noted in 3D LA volume index and SRa. These data support the use of comparable values independently of the machine used to acquire LA images.

Limitations

This study presents several limitations. First, only half of the patients included in the study were available for LA function analysis indicating that dependency on image quality is one of the main limitations for strain analysis by speckle tracking. Second, the existence of inter-vendor differences in 3D LA volume index and LA SRa was not confirmed by the direct comparison in the same patients. Further study is warranted to investigate the cause of the inter-vendor differences. Last of all, whether the NORRE study results can be extrapolated to non-Caucasian European individuals is still unknown.

Conclusion

The NORRE study provides applicable reference ranges for LA functions. Multivariable analysis showed that age is independently associated with all LAS components irrespective of gender and vendor. Our data highlight the importance of age-specific assessment for LA function.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Appendix of the list of contributors to the NORRE Study

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IMAGE FOCUS

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Longitudinal strain by speckle tracking echocardiography in constrictive pericarditis

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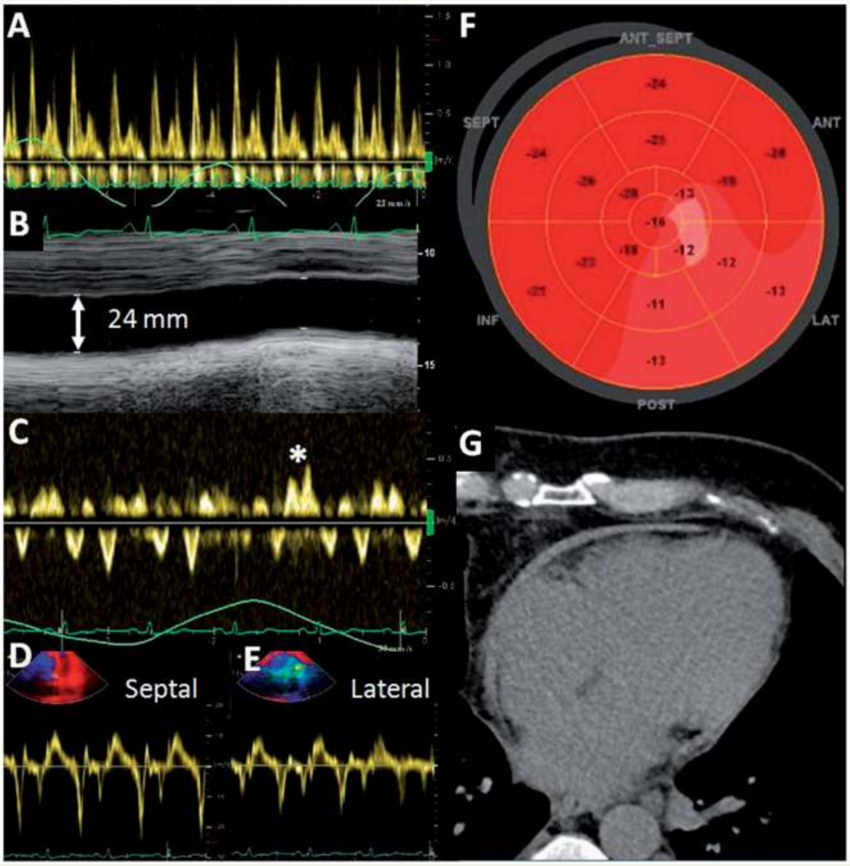
A 58-year-old patient presenting cholestasis was referred for cardiac evaluation following the detection of a 25 mmHg right atrial pressure during hepatic catheterization.

Echocardiography demonstrated a 65% left ventricular ejection fraction and a normal sized right ventricle, without tricuspid regurgitation. There was respiratory interventricular septal shift (Supplementary data online, *Video S1*), without pericardial effusion. Pulsed wave Doppler demonstrated a 36% expiratory increase in transmitral peak E wave velocity (*Panel A*), a dilated inferior vena cava (*Panel B*), and hepatic vein expiratory diastolic flow reversal (*, *Panel C*). Tissue Doppler imaging demonstrated higher medial than lateral early diastolic annulus velocities (23 cm/s and 15 cm/s, respectively) (*Panels D, E*). By speckle tracking imaging, global longitudinal strain was −17.6%; anterior, lateral, and inferolateral segments had on the average lower values (−14.0%) than septal segments (−22.6%), as depicted by the bull's eye representation (*Panel F*). These findings were deemed consistent with the diagnosis of constrictive pericarditis. Thickened pericardium (5 mm) was demonstrated by computed tomography (*Panel G*).



Unlike restrictive cardiomyopathies—where longitudinal strain is usually uniformly reduced, the typical longitudinal deformation pattern of constrictive pericarditis includes preserved septal and reduced longitudinal strain values in left ventricular free wall myocardial segments due to pericardial adhesions. This specific pattern can be easily appreciated by a bull's eyes map which may provide incremental information to ascertain the diagnosis of pericardial constriction.

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.