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Normal reference values of left atrial volumes and volume-based functional properties using three-dimensional speckle-tracking echocardiography in healthy adults (Insights from the MAGYAR-Healthy Study)

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Abstract

Introduction: The present study was designed to define normal reference values of three-dimensional speckle-tracking echocardiography (3DSTE)-derived left atrial (LA) volumes, stroke volumes (SVs), and emptying fractions (EFs) with regard to the cardiac cycle.

Methods: The present study involved 256 healthy adult subjects in sinus rhythm who underwent complete two-dimensional Doppler echocardiography and 3DSTE at the same time. However, due to inferior image quality, 87 subjects have been excluded. The remaining population sample comprised of 169 patients who gave informed consent to participate in the study.

Results: While systolic maximum LA volume and early diastolic preatrial contraction LA volume did not change over age decades, late-diastolic minimum LA volume decreased and was lowest in subjects aged 40 to 49 years then increased after 50 years. Total atrial EF increased over age decades with a reduction after 50 years. Passive atrial EF showed a significant continuous increase over age decades. Active atrial EF did not change in younger ages and was the highest between ages 40 and 49 years with a significant impairment after 50 years.

Conclusions: This study shows the age- and gender-dependency of normal values of 3DSTE-derived LA volumes, stroke volumes, and emptying fractions with regard to the cardiac cycle in healthy adult subjects.

KEYWORDS

echocardiography, function, healthy, left atrium, speckle-tracking, three-dimensional, volume

1 | INTRODUCTION

Three-dimensional (3D) speckle-tracking echocardiography (STE) is a new promising imaging method based on block-matching algorithm.¹⁻³ It was found to be clinically useful in the 3D assessment of volumetric data and strain variables of different cardiac chambers.⁴⁻⁶ One of the most important benefits of this method is its ability to assess the

volumes and strains in various phases of the cardiac cycle at the same time using the same virtual 3D cast of a given heart chamber.¹ Although echocardiographic left atrial (LA) dimensions in healthy and in pathological subjects are known, no information is available regarding 3DSTE-derived normal reference values of LA volumetric variables.⁷ Therefore, the present study was designed to define normal reference values of 3DSTE-derived LA volumes, stroke volumes (SVs),

and emptying fractions (EFs) with regard to the cardiac cycle, and their age- and gender-dependency in healthy adults.

2 | PATIENTS AND METHODS

2.1 | Study population

The present study involved 256 healthy adult subjects in sinus rhythm, who underwent complete two-dimensional (2D) Doppler echocardiography and 3DSTE at the same time. All participants had no symptom, disease, or state that could affect results. None of them received any medication. Two-dimensional Doppler echocardiography proved to be normal in all subjects. However, due to inferior image quality, 87 subjects have been excluded. The remaining population sample comprised 169 subjects who gave informed consent to participate in the study. A study has been organized at our center to determine normal reference values of 3DSTE-derived parameters in healthy adult subjects among others named **MAGYAR-Healthy Study** (Motion Analysis of the heart and Great vessels bY three-dimensionAl speckle-tRacking echocardiography in Healthy subjects) ('magyar' means 'Hungarian' in Hungarian language). Institutional human research committee approved the study of which the protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2 | Two-dimensional Doppler echocardiography

According to recent guidelines, LA diameter, LV dimensions, volumes, and ejection fraction were measured by an Artida

echocardiographic tool (Toshiba Medical Systems, Tokyo, Japan) using a PST-30SBP (1-5 MHz) phased-array transducer.⁷ Significant valvular stenosis and regurgitations were excluded by Doppler echocardiography.

2.3 | Three-dimensional speckle-tracking echocardiography

PST-25SX 1-4 MHz matrix phased-array transducer attached to the same Artida echocardiography machine (Toshiba Medical Systems, Tokyo, Japan) was used for a digital collection of six subvolumes from an apical window within a single breath-hold.¹ A pyramid-shape "full volume" 3D echocardiographic dataset was then created after stitching these subvolumes together. The 3D Wall Motion Tracking software version 2.7 (Toshiba Medical Systems, Tokyo, Japan) was used for analysis, displaying acquired 3D datasets in apical two- (AP2CH) and four-chamber (AP4CH) views and short-axis views at basal, mid-atrial, and superior LA levels (Figure 1). The complete digital 3D reconstruction of the LA started by defining the LA endocardial reference points in AP2CH and AP4CH views at the edges of the mitral annular ring and LA apex at end-diastole, then reconstruction was completed automatically. The user could correct manually the shape of the LA if needed, throughout the entire cardiac cycle. From the 3D datasets, time-global LA volume change curves were generated. End-systolic maximum LA volume (V_{\max} , just before mitral valve opening) and end-diastolic minimum LA volume (V_{\min} , just before mitral valve closure) were automatically obtained by the software. Early diastolic LA volume before atrial contraction (V_{preA}) was

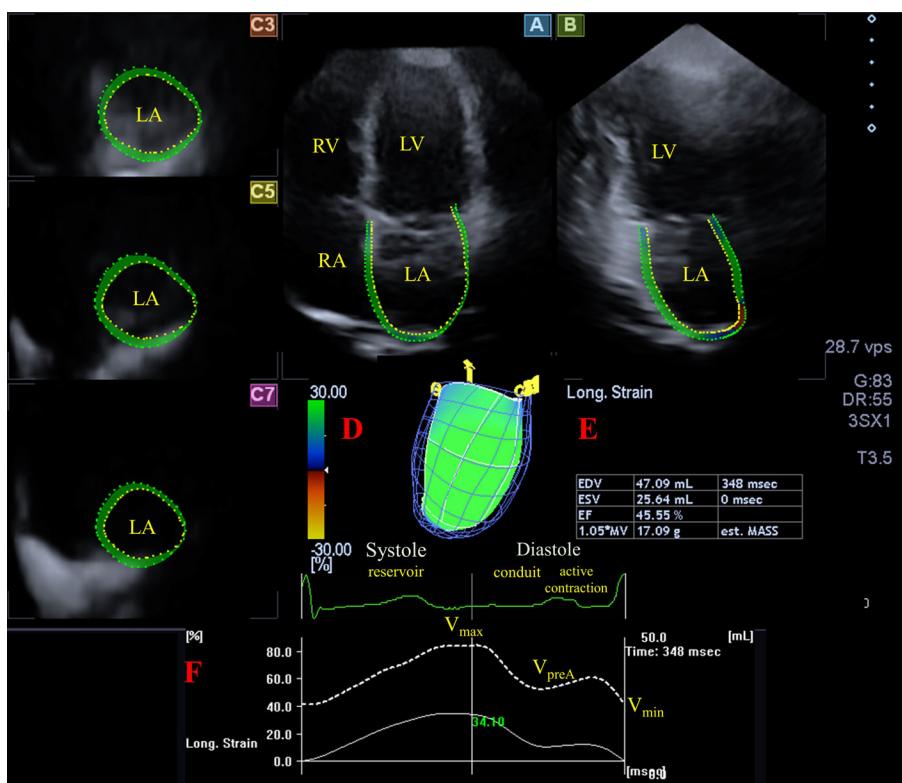


FIGURE 1 Three-dimensional (3D) echocardiography-derived 3D full volume dataset is presented in a healthy subject, displaying the left atrium (LA): apical four-chamber view (A), apical two-chamber view (B), short-axis views at basal (C3), mid-atrial (C5) and superior (C7) LA level. 3D cast of the LA (D), calculated LA volumetric data (E), time-global LA longitudinal strain (white line, F), and time-LA volume changes over time (dashed line, F) are also demonstrated. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; V_{\max} , end-systolic maximum LA volume; V_{\min} , end-diastolic minimum LA volume; V_{preA} , preatrial contraction LA volume

TABLE 1 The variables and calculations used for measuring left atrial stroke volumes and emptying fractions in each phase of left atrial motion

Functions	Stroke volumes (mL)	Emptying fractions (%)
Reservoir	Total atrial $SV = V_{\max} - V_{\min}$	Total atrial EF = Total atrial SV/V_{\max}
Conduit function	Passive atrial $SV = V_{\max} - V_{\text{preA}}$	Passive atrial EF = Passive atrial SV/V_{\max}
Active contraction	Active atrial $SV = V_{\text{preA}} - V_{\min}$	Active atrial EF = Active atrial SV/V_{preA}

Abbreviations: EF, emptying fraction; SV, stroke volume; V_{\max} , maximum left atrial volume; V_{\min} , minimum left atrial volume; V_{preA} , left atrial volume before atrial contraction.

calculated from the time-volume change curve at the time of P wave on electrocardiogram. Featuring different phases of LA function, SVs, and EFs were calculated from LA volumes with regard to the cardiac cycle (Table 1).⁴

2.4 | Statistical analysis

All variables are expressed as mean \pm SD or number and percentage. Kolmogorov-Smirnov test was used for the normality of the distribution of datasets. An independent-sample Student's *t* test was utilized for comparison of datasets with the normal distribution. Datasets with non-normal distribution were tested with the Mann-Whitney-Wilcoxon test. Differences were considered to be statistically significant if $P < .05$. MedCalc software was used for statistical calculations (MedCalc, Mariakerke, Belgium).

3 | RESULTS

3.1 | Demographic parameters

Demographic data of 169 healthy adults are reported in Table 2. None of them had classic cardiovascular risk factors, including hypertension, hypercholesterolaemia, or diabetes mellitus. Healthy subjects are presented in the following age subgroups: 18 to 29 years ($n = 84$; mean age: 24.4 ± 2.7 years, 42 males), 30 to 39 years ($n = 37$; mean age: 34.0 ± 2.8 years, 24 males), 40 to 49 years ($n = 18$; mean age: 42.4 ± 4.7 years, 7 males), and > 50 years ($n = 30$, mean age: 56.7 ± 4.5 years, 11 males).

3.2 | Two-dimensional echocardiographic data

No abnormalities could be detected in any healthy adult subject by routine two-dimensional Doppler echocardiography (Table 2). None of them showed \geq grade one valvular regurgitations or had significant valvular stenosis.

TABLE 2 Clinical, two-dimensional, and volumetric three-dimensional speckle-tracking echocardiographic data of healthy subjects

	Data
n	169
Age (years)	33.2 ± 12.8
Male gender (%)	77 (46)
Weight (kg)	73.1 ± 18.1
Height (cm)	172.5 ± 10.9
Body surface area (kg/cm ²)	1.88 ± 0.22
Two-dimensional echocardiography	
Left atrium (mm)	37.5 ± 3.5
Left ventricular end-diastolic diameter (mm)	48.0 ± 3.1
Left ventricular end-diastolic volume (mL)	104.8 ± 22.5
Left ventricular end-systolic diameter (mm)	32.1 ± 3.0
Left ventricular end-systolic volume (mL)	37.8 ± 9.0
Interventricular septum (mm)	9.1 ± 1.2
Left ventricular posterior wall (mm)	9.3 ± 1.4
Left ventricular ejection fraction (%)	64.6 ± 4.0
E (cm/s)	80.3 ± 15.6
A (cm/s)	60.4 ± 16.0

3.3 | 3DSTE-derived LA volume changes over age decades

While systolic V_{\max} and early diastolic V_{preA} did not change over age decades, late-diastolic V_{\min} decreased over age decades and was lowest in subjects aged 40 to 49 years, then increased after 50 years (Table 3 and Figure 2). Indexed LA volumes are also presented. The rate of volume acquisition for 3DSTE-derived assessments was 24 ± 2 volumes per second.

3.4 | 3DSTE-derived changes in LA stroke volumes over age decades

Total atrial stroke volume (TASV) remained unchanged over age decades. Passive atrial stroke volume (PASV) showed a continuous increase over age decades, and a significant difference could be demonstrated between subjects aged 18 to 29 years and > 50 years. Active atrial stroke volume (AASV) did not change over age decades with a non-significant reduction in subjects aged > 50 years (Table 2 Figure 3). Indexed LA stroke volumes are also presented.

3.5 | 3DSTE-derived changes in LA emptying fractions over age decades

Total atrial emptying fraction (TAEF) increased over age decades with a reduction after 50 years. Passive atrial emptying fraction (PAEF)

TABLE 3 Age-dependency of left atrial volumes and volume-based functional properties as assessed by three-dimensional speckle-tracking echocardiography

LA volumetric data	All (n = 169)	Aged, 18 to 29 years (n = 84)	Aged, 30 to 39 years (n = 37)	Aged, 40 to 49 years (n = 18)	Aged, >50 years (n = 30)
Vmax (mL)	41.0 ± 13.2	41.9 ± 12.4	39.4 ± 14.0	39.5 ± 12.4	41.2 ± 15.0
Vmax-indexed (mL/m ²)	22.2 ± 7.9	23.1 ± 7.6	20.6 ± 8.5	22.1 ± 7.3	22.0 ± 8.6
VpreA (mL)	28.0 ± 11.9	29.7 ± 11.5	26.2 ± 11.7	25.7 ± 9.6	26.6 ± 14.0
VpreA-indexed (mL/m ²)	15.3 ± 7.1	16.4 ± 7.0	13.8 ± 7.3	14.4 ± 5.5	14.3 ± 8.0
Vmin (mL)	19.4 ± 8.2	20.8 ± 8.1	17.8 ± 7.7	16.7 ± 6.7 ^a	19.1 ± 9.3
Vmin-indexed (mL/m ²)	10.5 ± 4.8	11.4 ± 4.8	9.4 ± 4.5 ^a	9.3 ± 3.9	10.3 ± 5.3
LA volume-based functional properties					
TASV (mL)	21.6 ± 8.2	21.1 ± 7.8	21.6 ± 8.7	22.8 ± 8.1	22.1 ± 9.1
TASV-indexed (mL/m ²)	11.7 ± 4.8	11.6 ± 4.6	11.3 ± 5.2	12.7 ± 4.8	11.8 ± 5.0
PASV (mL)	13.0 ± 5.8	12.1 ± 5.6	13.3 ± 5.9	13.8 ± 6.5	14.6 ± 6.0 ^a
PASV-indexed (mL/m ²)	7.0 ± 3.2	6.7 ± 3.1	6.8 ± 3.1	7.7 ± 3.8	7.7 ± 3.1
AASV (mL)	8.6 ± 5.9	9.0 ± 6.1	8.3 ± 6.1	9.0 ± 4.4	7.5 ± 6.1
AASV-indexed (mL/m ²)	4.7 ± 3.5	5.0 ± 3.6	4.5 ± 3.8	5.1 ± 2.5	4.1 ± 3.4
TAEF (%)	52.8 ± 12.0	50.5 ± 11.4	54.8 ± 10.5 ^a	57.4 ± 9.5 ^a	53.8 ± 15.2
TAEF-indexed (%/m ²)	28.5 ± 7.3	27.8 ± 7.2	28.3 ± 6.5	32.2 ± 6.4 ^{a,b}	28.5 ± 8.2
PAEF (%)	32.7 ± 13.0	29.8 ± 12.1	34.8 ± 13.0 ^a	34.8 ± 10.9	37.1 ± 15.0 ^a
PAEF-indexed (%/m ²)	17.6 ± 7.1	16.4 ± 7.1	17.7 ± 6.7	19.4 ± 6.2	19.5 ± 7.7 ^a
AAEF (%)	29.6 ± 11.8	29.1 ± 12.4	30.3 ± 10.3	34.4 ± 11.6	27.5 ± 11.6 ^c
AAEF-indexed (%/m ²)	16.1 ± 7.1	16.0 ± 7.4	15.9 ± 6.7	19.4 ± 7.4	14.7 ± 6.4 ^c

Abbreviations: AAEF, late-diastolic LA emptying fraction; AASV, late-diastolic LA stroke volume; LA, left atrium; PAEF, early diastolic passive LA emptying fraction; PASV, early diastolic passive LA stroke volume; TAEF, systolic total LA emptying fraction; TASV, systolic total LA stroke volume; Vmax, end-systolic maximum LA volume; Vmin, end-diastolic LA volume; VpreA, early diastolic preatrial contraction LA volume.

^aP < .05 vs aged 18 to 29 years.

^bP < .05 vs aged 30 to 39 years.

^cP < .05 vs aged 40 to 49 years.

showed a significant continuous increase over age decades. Active atrial emptying fraction (AAEF) did not change in younger ages and was highest at ages 40 to 49 years with a significant impairment after 50 years (Table 2 Figure 4). Indexed LA emptying fractions are also presented.

3.6 | Gender differences in 3DSTE-derived LA variables

Females showed non-significantly higher LA volumes than males. A significant difference could be demonstrated in indexed V_{max} and indexed V_{preA} of females vs males at ages 30 to 39 years. No significant differences were found between genders in LA stroke volumes, while indexed TASV and indexed AASV was higher in females than in males at ages 30 to 39 years. Similarly, no significant differences were found between genders in LA emptying fractions, while indexed TAEF were higher in females than in males at ages 18 to 29 years and 30 to 39 years, indexed PAEF at ages 18 to 29 years, and indexed AAEF at ages 30 to 39 years (Figures 2–4).

3.7 | Correlations

No correlations could be demonstrated between transmitral flow E and A velocities as well as their ratio and any of LA volumes neither in younger age group (less than 50 years) nor in older age group (more than 50 years).

4 | DISCUSSION

In the current clinical practice, one of the most frequently used LA variable is its echocardiography-derived diameter. According to the American Society of Echocardiography guidelines, the largest LA diameter should be measured at LV end-systole by M-mode echocardiography from aortic posterior wall to posterior LA wall (leading edge to leading edge method).⁷ According to the recent publication, indexed LA volume is more strongly associated with the presence of cardiovascular diseases than indexed LA diameter following adjustment to age and gender.⁸ LA volumes could be calculated from LA area and LA longitudinal data with regard to the cardiac cycle, measured by 2D

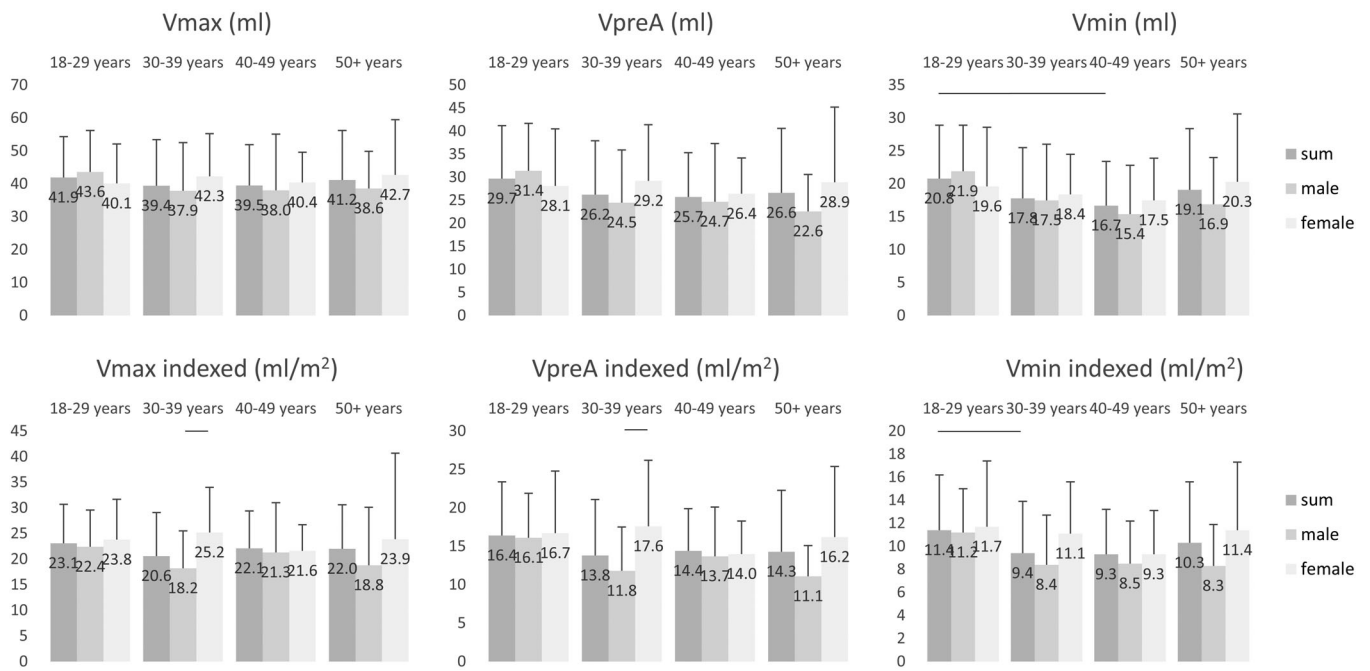


FIGURE 2 Gender-dependency of left atrial volumes over age decades as assessed by three-dimensional speckle-tracking echocardiography. Lines represents significant differences between the groups. V_{\max} , end-systolic maximum LA volume; V_{\min} , end-diastolic minimum LA volume; V_{preA} , preatrial contraction LA volume

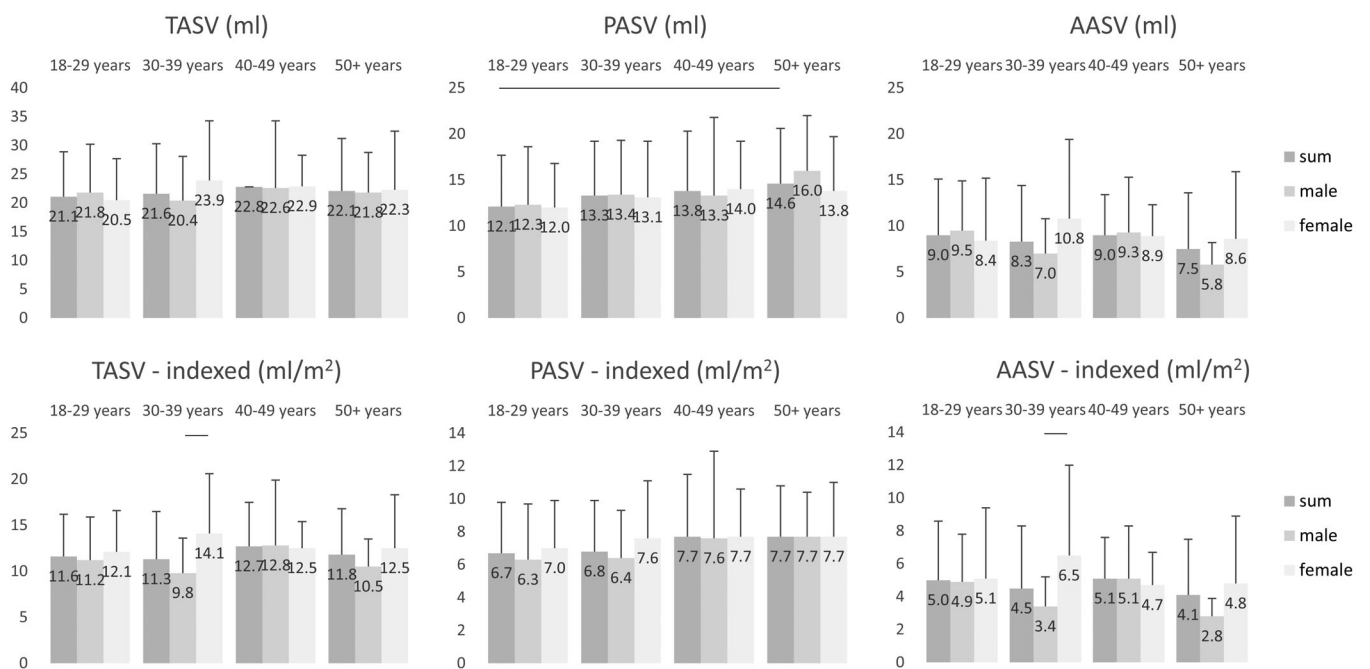


FIGURE 3 Gender-dependency of left atrial stroke volumes over age decades as assessed by three-dimensional speckle-tracking echocardiography. Lines represents significant differences between the groups. AASV, Active atrial stroke volume; PASV, Passive atrial stroke volume; TASV, Total atrial stroke volume

echocardiography in AP2CH and AP4CH using biplane area-length method.⁷ Speckle-tracking echocardiography (STE) is able to help assessment of LA volumes regardless of the fact whether

measurements are made on a 2D echocardiographic loop (2DSTE) or in a 3D volume (3DSTE).⁹ Real-time 3D echocardiography (RT3DE) sees the LA as it is, that is, a 3D organ with an almost always atypical

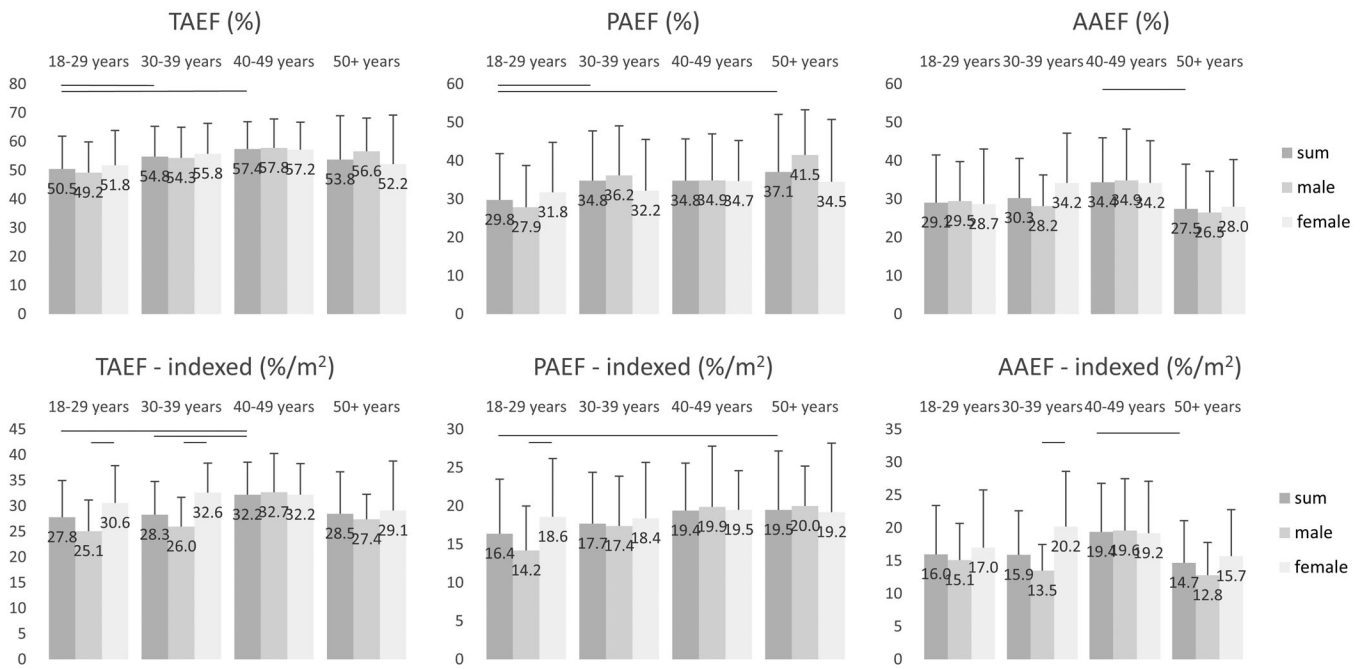


FIGURE 4 Gender-dependency of left atrial emptying fractions over age decades as assessed by three-dimensional speckle-tracking echocardiography. Lines represents significant differences between the groups. AAEF, Active atrial emptying fraction; PAEF, Passive atrial emptying fraction; TAEF, Total atrial emptying fraction

shape.^{10,11} Normal 3D echocardiographic LA volumetric variables have been demonstrated in adults^{12,13} and in elderly subjects.^{13,14} These variables were also defined in children by 3D echocardiography using a commercial speckle-tracking package.¹⁵ The 3DSTE technique takes one step forward: by using created virtual 3D cast, not only volumetric but also strain data can be measured at the same time.¹ Thus, 3DSTE was found to be suitable for measuring LA features according to the reservoir, conduction, and active contraction phases of the cardiac cycle in different pathological scenarios with different patterns.⁴ LA volumetric and strain analysis derived from 3DSTE have been validated against 2D echocardiography,¹⁶ RT3DE,⁵ and computer tomography.⁹ In a recent study, excellent correlations were found for 3DSTE-derived LA volumetric data and good correlations for LA strain variables.¹⁸ 3DSTE-derived LA strains have just been defined in healthy adult subjects.¹⁷

In the present study, LA-PAEF showed an increase after the age of 50 years, while LA-AAEF tends to decrease after the age of 50 years. These results are opposite to those obtained by Badano et al.¹² Differences could be explained by different selection bias and by the fact that the results of subjects over 50 years were managed together in our study. Moreover, different echocardiographic methodologies were used with different and not optimal image quality in all healthy subjects, which could theoretically affect results as mentioned in the cited paper.¹²

With the present study, normal values of 3DSTE-derived LA volumes, stroke volumes, and emptying fractions and their indexed versions have been defined in different age decades. The different behavior of LA volumetric variables over decades (increase vs no

change) could be theoretically explained by LA strains, and their non-uniformity in answer to volume changes together with aging-associated structural changes of LA wall could also not be excluded.¹⁷ Moreover, their gender-dependency was also examined with a predominance of higher values for females. According to these findings, it could be stated that special significant changes could be demonstrated in normal values of LA volumes and volume-based functional properties over age decades, which affects all three phases of the cardiac cycle.

4.1 | Limitation section

The most important limitations are listed below:

- 1 A limited number of 3DSTE-derived LA validation studies are available at this moment; therefore, further studies are warranted.
- 2 A high percentage of subjects (34%) were excluded from the study. It is known that 3DSTE suffers from inherently lower image quality than 2D echocardiography due to the low temporal and spatial image resolutions (low rate of volume acquisition, insufficient number of crystals, etc.); therefore, further technical improvements are warranted.
- 3 LA appendage and pulmonary veins were excluded from measurements, which could theoretically affect the results.
- 4 LA strains are important LA functional features.¹⁹ Although parallel LA strain measurements could be performed together with volumetric assessments at the same time from the same 3D

echocardiographic datasets, they were not presented. However, normal values of 3DSTE-derived LA strains have been recently published from the MAGYAR-Healthy Study population.¹⁷

- 5 Complex analysis of other heart chambers or the relationship between 3DSTE-derived LA volumetric data and other variables was not aimed to be examined.

5 | CONCLUSIONS

This study provides age- and gender-dependency of normal values of 3DSTE-derived LA volumes, stroke volumes, and emptying fractions with regard to the cardiac cycle in healthy adult subjects.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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