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RESEARCH ARTICLE

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Normal reference values of three-dimensional speckle-tracking echocardiography-derived mitral annular dimensions and functional properties in healthy adults: Insights from the MAGYAR-Healthy Study

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Abstract

Introduction: There is a limited number of echocardiographic studies determining mitral annular (MA) dimensions in healthy subjects. The present study aimed to establish normal reference values of three-dimensional speckle-tracking echocardiography-derived MA dimensions and functional properties in healthy adults in relation with age and gender.

Methods: The present study comprised 298 healthy adult subjects. From this population, 94 subjects were excluded due to inadequate image quality. Therefore the remaining group consisted of 204 subjects with the mean age of 33.88 ± 12.97 years (107 males). The population sample was further divided into age categories: 18-29 years (n = 105; mean age: 24.11 ± 2.98 years, 51 males), 30-39 years (n = 44; mean age: 33.80 ± 2.39 years, 31 males), 40-49 years (n = 19; mean age: 43.47 ± 3.18 years, 11 males) and ≥50 years of age (n = 36, mean age: 57.42 ± 6.11 years, 14 males).

Results: End-diastolic MA dimensions did not change significantly during the decades. End-systolic MA diameter, area, and perimeter were larger over the age of 50 years than in the 18-29 year-old group. MA fractional area change was found smaller over the age of 50 years than in 18-29-year-old group. While end-diastolic MA variables did not show gender-differences, end-systolic MA area and perimeter were lower in females in the 18-29-year-old group.

Conclusions: End-systolic MA dimensions change over decades, resulting in a special pattern of MA functional properties with significant reduction over the age of 50 years.

KEYWORDS

echocardiography, healthy, mitral annulus, three-dimensional

1 | INTRODUCTION

Three-dimensional (3D) speckle-tracking echocardiography (STE) is a new clinical method with capability of 3D chamber quantifications.[1,2] 3DSTE has been introduced in the first decade of the 2000s and is based on a block-matching algorithm allowing detailed simultaneous assessment of chamber volumes and functional properties (strains, rotational variables, etc.) along the cardiac cycle.[1,2] More and more 3DSTE-based clinical data are available in different pathological conditions together with normal reference values of left ventricular (LV),[3-5] left atrial (LA),[6] and right atrial (RA)[7,8] volumes/volume-based functional properties,[8] strains,[3,4,6,7] and rotational variables[5] in healthy adults, as well as their vendor-dependency.[9] Moreover, the clinical usefulness of 3DSTE in the assessment of mitral annular dimensions and its close relationship to LV function was also confirmed.[10] However, there is a limited number of transthoracic echocardiographic studies determining MA dimensions in healthy subjects.[11,12] Therefore, the present study aimed to establish normal reference values of 3DSTE-derived MA dimensions and functional properties in healthy adults in relation with age and gender.

2 | METHODS

2.1 | Subject population

The present study comprised 298 healthy adult subjects without any symptoms, conditions or diseases which could affect the results. None of them received any medication. Two-dimensional Doppler echocardiography was performed in all subjects and yielded normal findings, then was complemented with 3DSTE. From this population sample, 94 subjects were excluded due to insufficient image quality during 3DSTE. Therefore, the remaining group consisted of 204 subjects with the mean age of 33.88 ± 12.97 years (107 males). This subject population sample was further divided into age categories:

- 18-29 years (n = 105; mean age: 24.11 ± 2.98 years, 51 males),
- 30-39 years (n = 44; mean age: 33.80 ± 2.39 years, 31 males),
- 40-49 years (n = 19; mean age: 43.47 ± 3.18 years, 11 males),
- ≥ 50 years (n = 36, mean age: 57.42 ± 6.11 years, 14 males).

The presented work is a part of the **M**otion **A**nalysis of the heart and **G**reat vessels b**Y** three-dimension**A**l speckle-t**R**acking echocardiography in **Healthy** subjects **(MAGYAR-Healthy) Study;** of which one of the goals was to determine normal reference values of 3DSTE-derived variables in healthy adult subjects ('magyar' means 'Hungarian' in Hungarian language). The study was approved by the human research committee at the University of Szeged and complied with the Declaration of Helsinki. Informed consent was given by all subjects.

2.2 | Two-dimensional Doppler echocardiography

2D echocardiography was performed by experts (P. D., A. K., Á. K., N. G.) using an Artida ultrasound system (Toshiba Medical Systems, Tokyo, Japan) with its PST-30SBP (1-5 MHz) phased-array transducer. First, 2D Doppler echocardiographic image acquisitions and chamber quantifications were performed according to the most recent guidelines.[13] Color Doppler echocardiography was used to exclude visually valvular regurgitations ≥grade 1. Doppler echocardiography was performed to exclude significant valvular stenoses and to determine early and late mitral inflow E and A.

2.3 | Three-dimensional speckle-tracking echocardiography

We performed 3DSTE examination with the same Artida echocardiographic system (Toshiba Medical Systems, Tokyo, Japan) and its PST-25SX matrix-array transducer.[1,2] Three-dimensional echocardiographic datasets were digitally acquired from the apical window within a single breath-hold. All subjects were in sinus rhythm with a constant RR interval. Six wedge-shaped subvolumes were acquired from which a full-volume ("pyramidal") 3D dataset was automatically created by the software. Analysis of this dataset was achieved with 3D Wall Motion Tracking software version 2.7 (Toshiba Medical Systems, Tokyo, Japan). Following optimization of image planes on lateral and septal MA endpoints on apical two- and four-chamber views, measurements were performed on the C7 short-axis view (Figure 1).[10]

The following MA dimensions were calculated in end-systole and end-diastole:

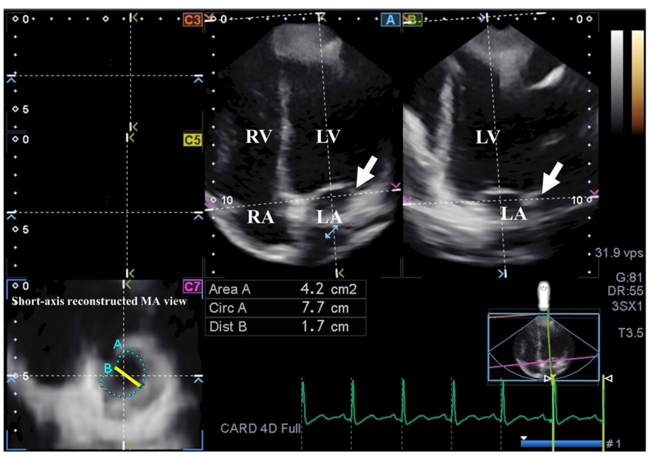

FIGURE 1 Extract from three-dimensional full-volume dataset showing mitral annulus (MA) in a healthy subject: A, apical four-chamber view; B, apical two-chamber view; and C7, a cross-sectional view at the level of the mitral annulus optimized in apical four- and two-chamber views. The white arrow represents the mitral annular plane on the long-axis, A and B, and short-axis, C7, images. Kidney-bean-shaped MA could be demonstrated on C7 image, on which while yellow line represents MA diameter. LA, left atrium; LV, left ventricle; MA, mitral annulus; RA, right atrium; RV, right ventricle; Area, MA area; Circ, MA perimeter; Dist, MA diameter

- MA diameter (MAD) defined as the perpendicular line drawn from the peak of MA curvature to the opposite side of the MA border was measured,
- MA area (MAA) was assessed by planimetry,
- MA perimeter (MAP) was obtained from planimetry determination.

The following MA functional variables were calculated using MAD and MAA data:

- MA fractional shortening (MAFS) = 100 × [end-diastolic MAD − end-systolic MAD]/end-diastolic MAD
- MA fractional area change (MAFAC) = 100 × [end-diastolic MAA − end-systolic MAA]/end-diastolic MAA.

3 | STATISTICAL ANALYSIS

Normality of distribution was evaluated with Shapiro-Wilks test. Continuous data were expressed as mean ± SD, while categorical data were presented in frequencies and percentage. Statistical significance was considered if *P* was less than .05. All tests were two-sided. Levene's test was used to evaluate homogeneity of variances. For normally distributed data sets, Students *t* test was used, while Mann-Whitney Wilcoxon test was used for non-normally distributed datasets. Fisher's exact test was used for categorical variables. We used RStudio 2015 (RStudio: Integrated Development for R. RStudio, Inc., Boston, MA) for statistical analysis, MATLAB version 8.6 software package (The MathWorks Inc., Natick, MA) for data analysis, and Medcalc (Medcalc, Mariakerke, Belgium) for the assessment of measurement reproducibility.

TABLE 1 Demographic and two-dimensional echocardiographic data

	Data
Age (years)	33.88 ± 12.97
Male/female gender (n)	107/97
Two-dimensional echocardiography	
Left atrium (mm)	36.93 ± 3.89
Left ventricular end-diastolic diameter (mm)	48.29 ± 3.76
Left ventricular end-diastolic volume (ml)	108.33 ± 25.85
Left ventricular end-systolic diameter (mm)	38.78 ± 23.02
Left ventricular end-systolic volume (ml)	37.27 ± 9.81
Interventricular septum (mm)	9.04 ± 1.50
Left ventricular posterior wall (mm)	9.18 ± 1.55
Left ventricular ejection fraction (%)	65.58 ± 4.57
Three-dimensional speckle-tracking echocardiography	
End-diastolic MAD (cm)	2.43 ± 0.43
End-diastolic MAA (cm^2)	7.31 ± 2.26
End-diastolic MAP (cm)	10.22 ± 1.54
End-systolic MAD (cm)	1.59 ± 0.39
End-systolic MAA (cm^2)	3.44 ± 1.27
End-systolic MAP (cm)	7.08 ± 1.27
MAFAC (%)	51.50 ± 15.39
MAFS (%)	34.01 ± 15.06
LV-EF (%)	58.1 ± 4.9
LV-LS (%)	−16.7 ± 2.8

Abbreviations: MAD, mitral annular diameter; MAA, mitral annular area; MAP, mitral annular perimeter; MAFAC, mitral annular fractional area change; MAFS, mitral fractional shortening; LV-EF, left ventricular ejection fraction; LV-LS, left ventricular longitudinal strain.

4 | RESULTS

4.1 | Demographic and two-dimensional echocardiographic data

Conventional 2D echocardiographic data showed normal findings (Table 1). No subjects had ≥ grade 1 valvular regurgitation or significant valvular stenosis.

4.2 | Age-dependency of 3DSTE-derived MA variables

The rate of volume acquisition for 3DSTE-derived measurements was 26 ± 2 volumes per second. End-diastolic MA dimensions did not change significantly during the decades. End-systolic MAD, MAA, and MAP were greater over the age of 50 years than in the 18-29-year-old group. End-systolic MAD and MAA were greater in 30-39 year-old than in 18-29 year-old subjects. MAFAC was lower over the age of 50 years than in 18-29 years group. MAFS showed a decrease-increase-decrease pattern over decades due to end-systolic MAD changes (Table 2, Figures 2 and 3).

4.3 | Gender-dependency of 3DSTE-derived MA variables

While end-diastolic MA variables did not show gender-differences, end-systolic MAA and MAP were lower in females in the 18-29-year-old group. Some parameters variables changed over decades only in males/females. Moreover, MA functional variables were non-significantly higher in females (Figures 2 and 3).

4.4 | Reproducibility of 3DSTE-derived MA measurements

The mean ± SD difference in values obtained by two measurements of the same observer and by two independent observers for the measurements of 3DSTE-derived end-diastolic and end-systolic MA

TABLE 2 Mitral annular dimensions and functional variables in different age groups

	18–29 year-old (n = 105)	30-39 year-old (n = 44)	40–49 year-old (n = 19)	50+ year-old (n = 36)
End-diastole				
MAD (cm)	2.39 ± 0.46	2.51 ± 0.44	2.48 ± 0.27	2.41 ± 0.38
MAA (cm^2)	7.08 ± 2.36	7.76 ± 2.36	7.65 ± 1.26	7.28 ± 2.12
MAP (cm)	10.09 ± 1.62	10.53 ± 1.58	10.51 ± 0.91	10.13 ± 1.39
End-systole				
MAD (cm)	1.49 ± 0.36	1.77 ± 0.42*	1.54 ± 0.39	1.67 ± 0.34 *
MAA (cm^2)	3.16 ± 1.19	3.76 ± 1.33*	3.37 ± 1.17	3.92 ± 1.24*
MAP (cm)	6.87 ± 1.31	7.27 ± 1.23	6.96 ± 1.10	7.53 ± 1.14*
Functional variables				
MAFAC (%)	53.48 ± 15.22	50.42 ± 14.02	56.39 ± 15.15	44.52 ± 15.22*
MAFS (%)	36.43 ± 14.96	28.88 ± 15.30*	39.40 ± 15.54	30.38 ± 11.92*

Abbreviations: MAD, mitral annular diameter; MAA, mitral annular area; MAP, mitral annular perimeter; MAFAC, mitral annular fractional area change; MAFS, mitral fractional shortening.

*$P < .05$ vs data of 18-29 year-old subjects.

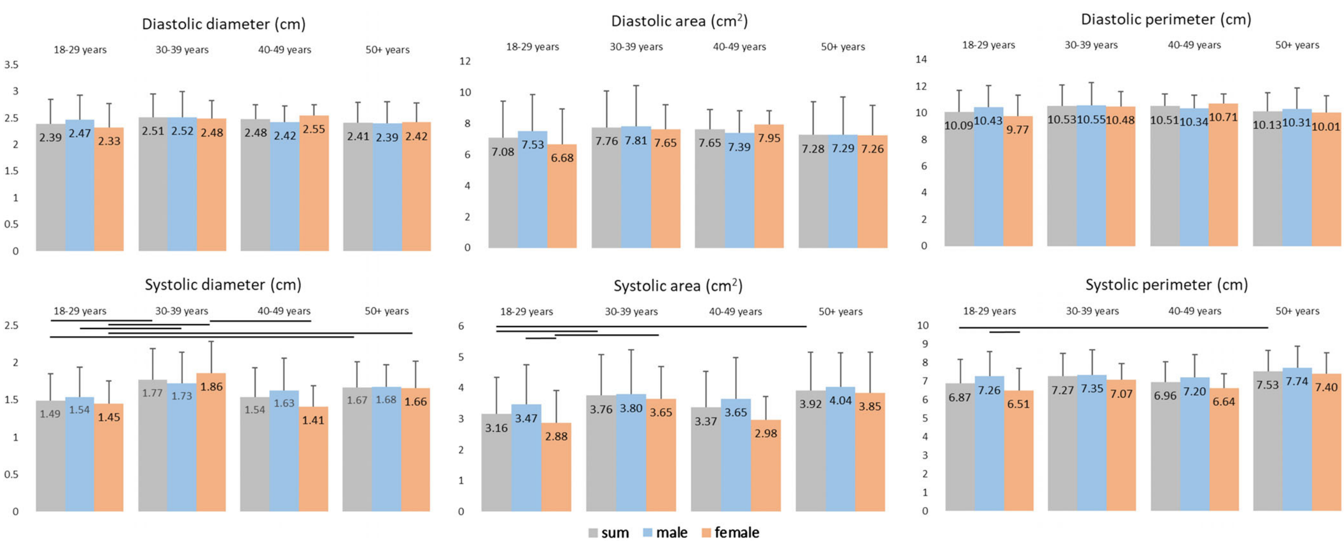

FIGURE 2 Gender-dependency of mitral annular end-diastolic and end-systolic diameter, area and perimeter data in different decades

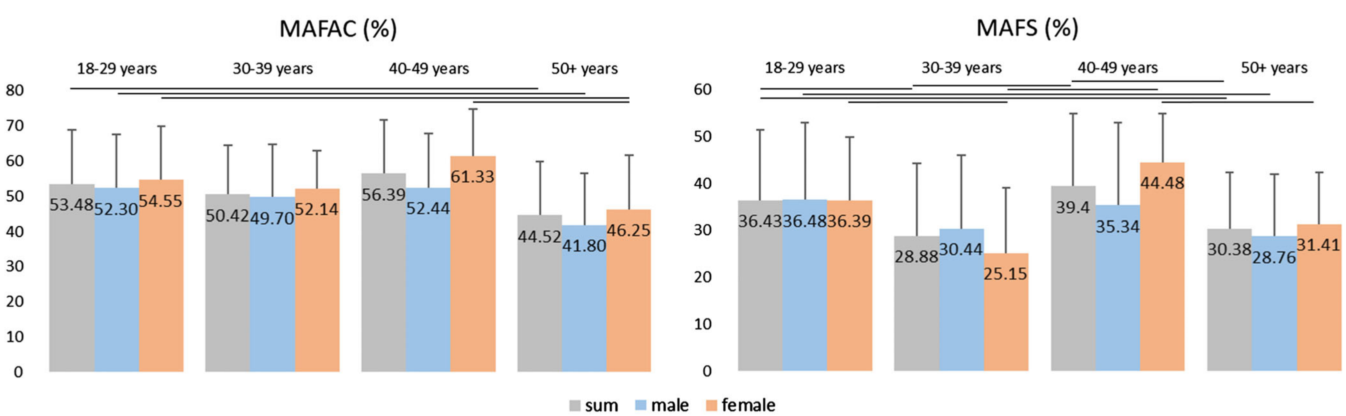

FIGURE 3 Gender-dependency of mitral annular functional properties in different decades

TABLE 3 Intra- and interobserver variability for the mitral annular dimensions and functional properties

	Intra-observer agreement		Inter-observer agreement	
	Difference in values obtained by two measurements by the same observer	Correlation coefficient between measurements by the same observer	Difference in values obtained by two observers	Correlation coefficient between measurements by two independent observers
End-diastolic MAD	0.01 ± 0.23 cm	0.94 (P < .0001)	0.03 ± 0.14 cm	0.96 (P < .0001)
End-diastolic MAA	−0.02 ± 1.01 cm^2	0.97 (P < .0001)	0.01 ± 0.81 cm^2	0.97 (P < .0001)
End-diastolic MAP	−0.03 ± 0.84 cm	0.95 (P < .0001)	−0.10 ± 0.89 cm	0.95 (P < .0001)
End-systolic MAD	−0.03 ± 0.15 cm	0.98 (P < .0001)	0.02 ± 0.21 cm	0.99 (P < .0001)
End-systolic MAA	−0.02 ± 0.30 cm^2	0.97 (P < .0001)	−0.05 ± 0.52 cm^2	0.96 (P < .0001)
End-systolic MAP	0.07 ± 0.51 cm	0.98 (P < .0001)	0.05 ± 0.45 cm	0.97 (P < .0001)

Note: Values are provided as mean ± SD.
Abbreviations: MAD, mitral annular diameter; MAA, mitral annular area; MAP, mitral annular perimeter.

dimensions and functional properties in 25 healthy subjects, along with the respective correlation coefficients, are presented in Table 3.

4.5 | Feasibility of 3DSTE-derived MA measurements

As mentioned before, 94 subjects from the original group of 298 healthy adults were excluded due to insufficient image quality from the subjects recruited between 2011 and 2017. The overall feasibility of measurements proved to be 68%, which improved to 90% in the last year (54 out of 60, P < .05).

5 | DISCUSSION

The mitral valve is an atrio-ventricular valve, which comprises MA, anterior and posterior leaflets, papillary muscles and chordae.[14] MA is an innervated fibrous ring affected by contractile forces of LV and LA, and supplying blood vessels to the leaflets.[14,15] Although MA resembles a kidney-bean front-wise, it has a dynamic motion during cardiac cycle and a non-planar 3D saddle-shape. Its 3D structure and dynamic function reduces leaflet tissue stress and is important for coaptation geometry.[14] MA dilation is also accompanied by MA flattening resulting in changes in leaflet stress and unfavorable mitral leaflet remodeling.[14] Therefore, MA is an important anatomical junction between the left heart chambers, and its clinical relevance is related to the etiology/mechanism of mitral regurgitation (MR) (primary or organic vs secondary or functional).[14,15]

Although knowledge of the normal ranges of MA dimensions would be essential in the clinical practice, they were provided so far by a limited number of echocardiographic studies.[11,12] Three-dimensional echocardiography opens new opportunities in assessing valves due to its potential for "en-face" measurements.[1,2,16] However, two different 3D echocardiographic techniques can be used in clinical practice: the volumetric real-time 3D echocardiography (RT3DE), widely available since 2003,[17] and 3DSTE, which encompasses benefits of 3D echocardiography and STE.[1,2] With 3DSTE, myocardial speckles are block-matched during their frame-to-frame motion, using an algorithms intrisically different from those of RT3DE.[1,2] Both methods are capable for volumetric measurements, but 3DSTE is useful for simultaneous assessments of strain and rotational variables using the same virtual 3D heart chamber cast. Moreover, both RT3DE and 3DSTE allow planimetric measurements, especially for determining MA dimensions.[10,18] Although many clinical studies are available with RT3DE, mainly with transesophageal approach,[19] clinical data related to 3DSTE are limited as regards the assessment of MA.[10]

Following 3D optimizations using valvular edges, the typical 2D projected D-shape of the MA could be depicted, allowing its accurate assessment with 3DSTE.[10] Thus, not only optimal MA diameter, but also MA area and perimeter by planimetry could be determined at the same time using the same 3D dataset.

To our best knowledge, the present study is the first to determine MA dimensions together with their age- and gender-dependency and MA functional properties by 3DSTE in healthy adult subjects. Although end-diastolic MA dimensions did not change over decades, we observed specific alterations in end-systolic MA dimensions, resulting in a special pattern of MA functional properties with significant reduction over the age of 50 years. The physiological base of these findings could be theoretically explained by aging-associated subclinical calcification, focal edema, and increased fluid accumulation capacity, but the role of deposition/infiltration of non-cardiomyocytes cannot be excluded either. Moreover, it is known that MA functions as a "sphincter" due to extrinsic contractile forces including LV and LA movements.[15] LA basal circumferential fibers are positioned in such a way that their contraction imparts a centripetal force onto the inner aspect of the adjacent fibrous MA, leading to its translation inward in late diastole. The superficial oblique fibers of the LV inlet lay on a torsional force onto the outer aspect of the MA, making it to translate inwards during systole.[15] Aging has also effects on these specific LA and LV functions and morphology of these heart chambers, which could have effects on MA dimensions as well.

There is a "learning curve" in measuring MA dimensions, as suggested by the feasibility findings, which could also affect results. However, further studies are warranted to confirm our findings together with comparisons between 2D echocardiography and 3DSTE.

6 | LIMITATIONS

- With recently available 3DSTE systems, image quality is better in 2D than in 3D mode, affecting the results.[1] Moreover, the results can only be applied to the Toshiba equipment we used.
- As mentioned above, only 2D MA projection was evaluated during 3DSTE analysis, not its real 3D saddle shape.[10]
- The present study did not aim to compare 2D- and 3DSTE-derived MA dimensions.
- We included a limited number of cases older than 50 years, and none over 60 years.
- Although 3DSTE could combine volumetric and strain assessments allowing more detailed analysis from the same 3D echocardiographic dataset[3-8] for MA featuring, no volumes or strains of other heart chambers were assessed in the present study.

7 | CONCLUSIONS

Changes in end-systolic MA dimensions appear to occur over decades, resulting in a special pattern of MA functional properties with significant reduction over the age of 50 years.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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